7TH SLOVENIAN PNEUMOLOGY, ALLERGOLOGY AND IMMUNOLOGY CONGRESS

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SLOVENIAN ASSOCIATION OF ALLERGY AND CLINICAL IMMUNOLOGY

Združenje pnevmologov Slovenije
Slovenian Respiratory Society

3 indikacije. 1 terapija.[1]

Zdravilo OFEV® (nintedanib) je indicirano za zdravljenje odraslih bolnikov z:[1]

- idiopatsko pljučno fibrozo (IPF),
- intersticijsko pljučno boleznijo, povezano s sistemsko sklerozo (SSc-ILD),
- drugimi kroničnimi fibrozirajočimi intersticijskimi pljučnimi boleznimi (ILD, interstitial lung diseases) s progresivnim fenotipom.

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

Ofev 100 mg mehke kapsule, Ofev 150 mg mehke kapsule
Kakovostna in količinska sestava: Ena kapsula vsebuje 100 mg (150 mg) nintedaniba (v obliki esilata). Vsebuje sojin lecitin. **Terapevtske indikacije:** Za zdravljenje odraslih bolnikov z idiopatsko pljučno fibrozo (IPF). Za zdravljenje odraslih bolnikov z drugimi kroničnimi fibrozirajočimi intersticijskimi pljučnimi boleznimi (ILD) s progresivnim fenotipom. Za zdravljenje odraslih bolnikov z intersticijsko pljučno boleznijo, povezano s sistemsko sklerozo (SSc-ILD). **Odmerjanje in način uporabe:** Zdravljenje mora uvesti zdravnik, ki ima izkušnje z obvladovanjem bolezni, za katere je zdravilo odobreno. *Odmerjanje:* Priporočeni odmerek je 150 mg nintedaniba dvakrat na dan, ki ga je treba jemati v približno 12urnem razmiku. Odmerek po 100 mg 2x/ dan se priporoča samo za uporabo pri bolnikih, ki ne prenašajo odmerka po 150 mg 2x/ dan. Največji priporočeni dnevni odmerek je 300 mg. *Prilagajanja odmerka:* Poleg simptomatskega zdravljenja, če je potrebno, lahko obravnava neželenih učinkov pri zdravilu Ofev vključuje zmanjšanje odmerka in začasno prekinitev, dokler specifični neželeni učinek ne bo izzvenel do ravni, ki omogoča nadaljevanje zdravljenja. Zdravljenje lahko nadaljujete s polnim odmerkom (150 mg 2x/ dan) ali z zmanjšanim odmerkom (100 mg 2x/ dan). Če bolnik ne prenaša odmerka po 100 mg 2x/ dan, je treba zdravljenje z zdravilom Ofev ukiniti. Če so driska, navzea in/ali bruhanje še vedno prisotni kljub ustrezni podporni oskrbi (vključno z antiemetičnim zdravljenjem), je morda treba odmerek zmanjšati ali zdravljenje prekiniti. Zdravljenje lahko nadaljujete z zmanjšanim odmerkom (100 mg dvakrat na dan) ali s polnim odmerkom (150 mg dvakrat na dan). V primeru, da huda driska, navzea in/ali bruhanje kljub simptomatskemu zdravljenju vztrajajo, je treba zdravljenje z zdravilom Ofev ukiniti. V primeru prekinitev zaradi zvišanja vrednosti AST ali ALT na > 3x zgornjo mejo normalnih vrednosti (ULN), se lahko zdravljenje po vrnitvi vrednosti aminotransferaz na izhodiščno raven nadaljuje z zmanjšanim odmerkom, nato pa se lahko poveča na polni odmerek. *Starejši:* Verjetnejе je, da bodo bolniki, stari 75 let ali več, potrebovali zmanjšanje odmerka za obvladovanje neželenih učinkov. *Ledvična okvara:* Varnosti, učinkovitosti in farmakokinetike nintedaniba pri bolnikih s hudo ledvično okvaro (očistek kreatinina < 30 ml/min) niso proučevali. *Jetrna okvara:* Izpostavljenost se je povečala pri bolnikih z jetrno okvaro (Child Pugh A, Child Pugh B). Pri bolnikih z blago jetrno okvaro (Child Pugh A) je priporočeni odmerek 100 mg dvakrat na dan. Zdravljenja bolnikov z zmerno (Child Pugh B) in hudo (Child Pugh C) jetrno okvaro se ne priporoča. *Pediatrična populacija:* Varnost in učinkovitost zdravila Ofev pri otrocih, starih 0 do 18 let, nista bili dokazani. Podatkov ni na voljo. *Način uporabe:* Zdravilo Ofev je namenjeno peroralni uporabi. Kapsule je treba zaužiti s hrano, pogoltniti cele z vodo; ne sme se jih žvečiti ali drobiti. **Kontraindikacije:** Nosečnost. Preobčutljivost na nintedanib, arašide ali sojo ali katero koli pomožno snov. **Posebna opozorila in previdnostni ukrepi:** *Driska:* V kliničnih preskušanjih je bila driska najpogostejši neželeni učinek prebavil, o katerem so poročali. Pri večini bolnikov je bil neželen učinek blag do zmeren in se je pojavil v prvih 3 mesecih zdravljenja. V obdobju trženja zdravila so poročali o resnih primerih driske s posledično dehidracijo in elektrolitskimi motnjami. Bolnike je treba zdraviti takoj, ko se pojavijo prvi znaki, včasih je treba zmanjšati odmerek ali zdravljenje prekiniti. Zdravljenje lahko nadaljujete z zmanjšanim odmerkom ali s polnim odmerkom. Pri trdovratni hudi driski, je treba zdravljenje ukiniti. *Navzea in bruhanje:* Pogosta neželena učinka prebavil sta bila navzea in bruhanje. Pri večini bolnikov z navzeo in bruhanjem je bil dogodek blag do zmeren. Pri trdovratnih simptomih, ki kljub podporni oskrbi ne izginejo, je morda treba odmerek zmanjšati ali zdravljenje prekiniti. Zdravljenje se lahko nadaljuje z zmanjšanim odmerkom ali s polnim odmerkom. Pri trdovratnih simptomih je treba zdravljenje z zdravilom Ofev ukiniti. *Delovanje jeter:* Zdravljenje za bolnike z zmerno (Child Pugh B) ali hudo (Child Pugh C) jetrno okvaro ni priporočljivo. Na podlagi večje izpostavljenosti se lahko poveča tudi tveganje za neželene dogodke pri bolnikih z blago jetrno okvaro (Child Pugh A). Bolnike z blago jetrno okvaro je treba zdraviti z nižjim odmerkom. Pri zdravljenju z nintedanibom so opazili poškodbe jeter, povzročene z zdravilom, vključno s hudo poškodbo jeter s smrtnim izidom. Zato je treba pred uvedbo zdravljenja in v prvem mesecu zdravljenja določiti raven jetrnih aminotransferaz in bilirubina. Bolnike je treba v naslednjih dveh mesecih zdravljenja spremljati v rednih intervalih, nato pa periodično ali kot je klinično indicirano. Če so izmerjene vrednosti aminotransferaz (AST ali ALT) > 3 x ULN, se priporoča zmanjšanje odmerka ali prekinitev zdravljenja, bolnika pa je treba natančno spremljati. Ko se aminotransferaze vrnejo na izhodiščne vrednosti, se lahko zdravljenje nadaljuje s polnim odmerkom ali z zmanjšanim odmerkom, nato pa postopoma zvišuje do polnega odmerka. Če so zvišane vrednosti jetrnih testov povezane s kliničnimi znaki ali simptomi poškodbe jeter, je treba zdravljenje trajno ukiniti. Raziskati je treba alternativne vzroke za zvečanje jetrnih encimov. Pri bolnikih z majhno telesno maso (<65 kg), bolnikih azijske rase in ženskah obstaja večje tveganje za povečanje ravni jetrnih encimov. Izpostavljenost nintedanibu se linearno veča z bolnikovo starostjo, kar lahko povzroči večje tveganje za povečanje ravni jetrnih encimov. Priporočljivo je skrbno spremljanje bolnikov s temi dejavniki tveganja. *Delovanje ledvic:* pri uporabi nintedaniba so poročali o primerih ledvične okvare/odpovedi, v nekaterih primerih s smrtnim izidom. Med zdravljenjem je treba bolnike spremljati, posebna pozornost pa je potrebna pri tistih bolnikih, ki imajo dejavnike tveganja za ledvično okvaro/odpoved. V primeru ledvične okvare/odpovedi je treba razmisliti o prilagoditvi odmerka. *Krvavitev:* Zaviranje receptorja vaskularnega endotelijskega rastnega faktorja VEGFR lahko poveča tveganje za krvavitev. V obdobju trženja zdravila so poročali o neresnih in resnih krvavitvah, od katerih je bilo nekaj s smrtnim izidom (vključno pri bolnikih, ki niso zdravljeni z antikoagulanti, in tistih, ki so zdravljeni z antikoagulanti ali drugimi zdravili, ki bi lahko povzročili krvavitve). Bolniki z znanim tveganjem za krvavitve, vključno z bolniki z redno nagnjenostjo h krvavitvam ali tisti, ki so pred začetkom zdravljenja z zdravilom prejemali polne odmerke antikoagulantov, niso bili vključeni v klinična preskušanja. Ti bolniki se lahko zdravijo le, če so pričakovane koristi večje od možnih tveganj. *Arterijski trombembolični dogodki:* Bolniki z miokardnim infarktom ali možgansko kapjo v nedavni anamnezi so bili iz kliničnih preskušanj izključeni. Pri zdravljenju bolnikov z večjim srčnožilnim tveganjem, vključno z znano koronarno arterijsko boleznijo, je potrebna previdnost. Če se pri njih pojavijo znaki ali simptomi akutne miokardne ishemije, je treba razmisliti o prekinitvi zdravljenja. *Anevrizme in disekcije arterij:* Uporaba zaviralcev poti VEGF pri bolnikih s hipertenzijo ali brez nje lahko spodbudi nastanek anevrizem in/ali disekcij arterij. Pred uvedbo zdravila Ofev je treba to tveganje skrbno preučiti pri bolnikih z dejavniki tveganja, kot sta hipertenzija ali anamneza anevrizme. *Venska trombembolija:* Zaradi mehanizma delovanja nintedaniba je lahko pri bolnikih tveganje za trombembolične dogodke večje. *Predrtje prebavil:* Zaradi mehanizma delovanja nintedaniba je lahko pri bolnikih tveganje za predrtje prebavil večje. V obdobju trženja zdravila so poročali o primerih predrtja prebavil, od katerih jih je bilo nekaj s smrtnim izidom. Posebno pozornost je treba nameniti zdravljenju bolnikov s predhodno abdominalno operacijo, peptično razjedo, divertikularno boleznijo v anamnezi ali bolnikom, ki sočasno jemljejo kortikosteroide ali nesteroidna protivnetna zdravila. Zdravilo Ofev se lahko uvede najmanj 4 tedne po abdominalni operaciji. Zdravljenje je treba trajno ukiniti pri bolnikih, pri katerih se pojavi predrtje prebavil. *Hipertenzija:* Dajanje zdravila Ofev lahko zviša krvni tlak. Sistemski krvni tlak je treba meriti periodično in kot je klinično indicirano. *Pljučna hipertenzija:* Podatkov o uporabi zdravila Ofev pri bolnikih s pljučno hipertenzijo je malo. Bolniki z resno pljučno hipertenzijo (srčni indeks ≤ 2 l/min/m² ali parenteralni epoprostenol/treprostinil ali resna odpoved desnega prekata) so bili izključeni iz preskušanjINBUILD in SENSCIS. Zdravila Ofev se ne sme uporabljati pri bolnikih s hudo pljučno hipertenzijo. Pri bolnikih z blago do zmerno pljučno hipertenzijo se priporoča pozorno spremljanje. *Zaplet s celjenjem rane:* Zaradi mehanizma delovanja lahko nintedanib poslabša celjenje ran. Zdravilo Ofev je dovoljeno uvesti ali v primeru perioperativne prekinitve nadaljevati njegovo jemanje le na podlagi klinične ocene ustreznega celjenja rane. *Sočasno dajanje s pirfenidonom:* zaradi podobnosti varnostnega profila obeh zdravil lahko pričakujemo kombinirane neželene učinke, vključno z neželenimi učinki prebavil in jetrnimi neželenimi učinki. Razmerje med koristjo in tveganjem pri sočasni uporabi s pirfenidonom ni bilo ugotovljeno. *Učinek na interval QT:* Previdnost je potrebna pri dajanju nintedaniba bolnikom, pri katerih se lahko razvije podaljšanje intervala QTc. *Alergijska reakcija:* Pri bolnikih z znano alergijo na arašidove beljakovine je tveganje za resne reakcije na izdelke s sojo povečano. *Vožnja:* Zdravilo ima blag vpliv na sposobnost vožnje in upravljanja s stroji. **Interakcije:** *Pglikoprotein (Pgp):* Sočasno dajanje z močnim zaviralcem Pgp, je povečalo izpostavljenost nintedanibu. Močni induktorji Pgp lahko zmanjšajo izpostavljenost nintedanibu. *Encimi citokroma (CYP):* Na podlagi presnove s CYP velja, da je verjetnost medsebojnega delovanja zdravil z nintedanibom majhna. Sočasno dajanje nintedaniba z posentanom ni spremenilo farmakokinetike nintedaniba. **Plodnost, nosečnost in dojenje:** Nintedanib lahko povzroči poškodbe ploda pri ljudeh. Ženskam v rodni dobi je treba svetovati, naj med zdravljenjem z zdravilom Ofev ne zanosijo. Svetovati jim je treba, naj med zdravljenjem z zdravilom Ofev in še najmanj 3 mesece po zadnjem odmerku uporabljajo visokoučinkovite metode kontracepcije. Trenutno ni znano, ali lahko nintedanib zmanjša učinkovitost hormonskih kontracepcijskih sredstev, zato morajo ženske, ki uporabljajo hormonska kontracepcijska sredstva, dodatno uporabiti tudi pregradno metodo kontracepcije. Ker lahko nintedanib pri ljudeh poškoduje plod, se ga med nosečnostjo ne sme uporabljati, pred zdravljenjem z zdravilom Ofev in med zdravljenjem, kot je ustrezno, pa je treba opraviti test nosečnosti. Če bolnica med uporabo zdravila Ofev zanosi, je treba zdravljenje ukiniti in bolnico seznaniti z možno nevarnostjo za plod. Med zdravljenjem z zdravilom Ofev je treba prenehati z dojenjem. Ni znakov vpliva na plodnost pri moških. **Neželeni učinki 1) IPF:** *Zelo pogosti:* driska, navzea, bolečine v trebuhu, zvečana vrednost jetrnih encimov. *Pogosti:* zmanjšana telesna masa, zmanjšan tek, krvavitev, bruhanje, zvečana vrednost ALT, AST in GGT, izpuščaj in glavobol. *Občasni:* trombocitopenija, dehidracija, miokardni infarkt, hipertenzija, pankreatitis, kolitis, poškodba jeter zaradi zdravila, hiperbilirubinemija, zvečana vrednost ALKP v krvi, pruritus in alopecija. *Neznana pogostnost:* anevrizme, disekcije arterij in ledvična odpoved. **2) ILD:** *Zelo pogosti:* zmanjšan tek, driska, navzea, bolečine v trebuhu, bruhanje, zvečana vrednost jetrnih encimov in zvečana vrednost ALT. *Pogosti:* zmanjšana telesna masa, krvavitev, hipertenzija, poškodba jeter zaradi zdravila, zvečana vrednost AST in GGT, zvečana vrednost ALKP v krvi, izpuščaj in glavobol. *Občasni:* trombocitopenija, dehidracija, miokardni infarkt, pankreatitis, kolitis, hiperbilirubinemija, pruritus, alopecija in ledvična odpoved. *Neznana pogostnost:* anevrizme in disekcije arterij. **3) SSc-ILD:** *Zelo pogosti:* driska, navzea, bolečine v trebuhu, bruhanje, zvečana vrednost jetrnih encimov. *Pogosti:* zmanjšana telesna masa, zmanjšan tek, krvavitev, hipertenzija, zvečana vrednost ALT, AST in GGT, zvečana vrednost ALKP v krvi in glavobol. *Občasni:* trombocitopenija, kolitis, poškodba jeter zaradi zdravila, izpuščaj, pruritus in ledvična odpoved. *Neznana pogostnost:* dehidracija, miokardni infarkt, anevrizme, disekcije arterij, pankreatitis, hiperbilirubinemija in alopecija. **Preveliko odmerjanje**: Zdravljenje je treba prekiniti in takoj uvesti ustrezne splošne podporne ukrepe. **Način in režim izdaje:** Rp/ Spec. **Imetnik dovoljenja za promet z zdravilom**: Boehringer Ingelheim International GmbH, Binger Strasse 173, D-55216 Ingelheim am Rhein, Nemčija. **Za podrobnejše informacije o zdravilu glejte** Povzetek glavnih značilnosti zdravila 07/2020.

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RARE PULMONARY DISEASES

Role of 18F-FDG PET/CT in Sarcoidosis

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Background: We tried to find out if 18F-FDG PET/CT (PET/CT) has a role in assessment of activity of sarcoidosis, in assessment of different organ involvement and in follow up of sarcoidosis, compared to other established methods.

Methods: We studied 104 sarcoidosis patients who underwent PET/CT scan at time of diagnosis between March 2010 and February 2018. 54 of them also had PET/CT at follow up. We aimed to assess the presence of inflammatory activity using PET/CT. Correlations between PET/CT findings (MAXSUV at any location, in lymph nodes and in parenchymal organs), different biomarkers (CTO, ACE, sIL2R, TNF-alpha), radiological evaluation (XrayScore, Scadding stage) and pulmonary function at the time of diagnosis (1) and at follow-up (2) were calculated.

Results: PET/CT more often showed involvement of mediastinal lymph nodes and lung than X-ray (XrayScore, Scadding stage). In addition PET/CT showed possible involvement of extra thoracic organs (whole body CT) and it provided possibility for robust quantitative assessment of metabolic activity of specific lesions. No correlations were found between PET/CT and pulmonary function tests. PET/CT findings at the time of diagnosis significantly correlated with X-ray score, ACE, CTO, sIL2R and TNF-alpha at time of diagnosis and only with CTO at follow up.

Conclusion: PET/CT is better diagnostic method for assessment of activity of sarcoidosis, assessment of different organ involvement and for monitoring of the effects of therapeutic interventions. As more frequent use of PET/CT is limited due to its availability, cost and radiation exposure, CTO has a place in follow up of patients with sarcoidosis.

PLEURAL DISEASES: INFECTIONS

Surgical treatment of empyema: timing and outcome

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Background: Main principles of acute stage (I and II) empyema treatment are appropriate antibiotic therapy, evacuation of pleural fluid and full lung reexpansion. If later two cannot be achieved by conservative means, surgical intervention is mandatory. VATS debridement is standard surgical procedure before the onset of organizing stage (III) empyema, when open decortication is mostly necessary. Therefore timely recognition of emypema is a keypoint of an effective surgical treatment of empyema that avoids thoracotomy.

Methods: We retrospectively analyzed patients who underwent surgery for empyema between January 2020 and November 2020 in our institution. All patients with stage II eympema were submitted to VATS approach. Primary goal of the study was to evaluate effectivness and complication rate of VATS debridement for parapneumonic empyema.

Results: Out of 51 patients, 37 (72,5 %) underwent surgery for parapneumonic empyema. Among them, 26 (70,2 %) underwent VATS debridement. Conversion rate was 3 (11,5 %), 1 for bleeding and 2 due to technical difficulties. There were 6 reoperations, 4 for bleeding, 1 for failed debridement and 1 for prolonged airleak. Among all revisions only 1 was performed through thoracotomy. The average ICU stay and hospital stay were 2,8 days (1-23) and 9,0 days (2-25), respectively. Average chest tube duration was 7,4 days (1-29). Postoperative complication rate was 8 (34,8%), the most common was bleeding (4). In-hospital mortality and readmission rate were 0.

Conclusions: Our VATS debridement program for empyema revealed to be effective and safe with only 1 procedure failure, low conversion rate and 0 in-hospital mortality. However, bleeding rate was not negligible and could have impact on the outcome. Therefore it is of utmost importance to employ early and effective reoperation that can be in expert hands mostly performed by minimally invasive VATS as shown in our study.

GENETICS IN PNEUMOLOGY

Genetics of pulmonary diseases – single centre experience

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Introduction: In pulmonology, as well as in other diseases, genetic testing is being increasingly used to identify the cause of different diseases.

Aim: To describe the experience with genetic testing in different disease settings in patients being referred to testing to Laboratory for Clinical Immunology and Molecular Genetics Golnik.

Methods and results: Genetic tests in our laboratory were performed in the context of alpha 1 antitrypsin deficiency (AATD) and in the context of Clinical Exome sequencing for different diagnoses. Six hundred and fifty eight patients had genetic test for AATD performed. In 398 (60.5%) Pi*MM, 189 (28.7%) Pi*MZ, 36 (5.5%) Pi*MS, 31 (4.7%) Pi*ZZ and 4 (0.6%) Pi*SZ genotypes were discovered respectively. Furthermore, we tested 68 patients using NGS with pulmonary disease as indication. In 13 patients (20 %) we found a causative variant namely i.) in 2 patients with Hermansky-Pudlak syndrome (HPS1, HPS4) ii.) in 1 patient with non Z/S AATD iii.) in 4 patients with primary ciliary deficiency (DNAH11, DNAH5, DNAI1, SPAG1) iv.) in 4 patients with idiopathic pulmonary fibrosis (TERC, 2*TERT, RTEL1) and v.) in 2 patients with Birt-Hogg-Dube (FLCN). In two patients with idiopathic pulmonary fibrosis we found rare missense variants (absent from GNOMAD control population) in genes associated with IPF (namely RTEL1 and PARN), however we were not able to classify them as pathogenic/likely pathogenic, therefore they were classified as variants of unknown significance (VUS).

Conclusions: Our single centre experience shows that molecular genetic testing is a valuable tool for establishing/confirming diagnosis in patients with pulmonary diseases. High rate of positive diagnoses in NGS testing (roughly 20%) in an adult population shows that clinical suspicion to consider a genetic test is too high and should be lowered (to achieve 10% rate of positive diagnoses).

Genetic variants and clinical parameters of asthma treatment outcome in adults

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Background: The aim of our study was to evaluate the success of long-term inhaled corticosteroids (ICS) controller therapy in adult asthmatics. Genetic variants important for the biologic action of corticosteroids might be responsible for different treatment response.

Patients and methods: A prospective study involved 208 adult patients with newly diagnosed ("glucocorticoid naïve") mild to moderate asthma. The chosen treatment outcome parameters were: changes in FEV_1, PD20 for methacholine, Asthma Control Test (ACT) and Asthma Quality of Life Questionnaire (AQLQ) scores. We wanted to evaluate correlations between changes in all four parameters after at least 3 years of treatment with ICS.

In the genetic part of the study, variants rs9910408 in *TBX21*, rs37973 in *GLCCI1*, rs242941 and rs1876828 in *CRHR1* gene, identified in previous studies to predict the therapeutic response to ICS, were genotyped in all 208 patients. Genotypic distribution and allelic frequencies in »good« and »poor« responders were compared.

Results: Despite the fact that all four parameters of asthma treatment outcome showed a significant improvement, we only found significant correlation between the two "subjective" outcome parameters: change in asthma control and change in asthma-related quality of life.

Variant rs9910408 in *TBX21* gene was associated with response to ICS treatment. In good responders, assessed by increase in PD20, the frequency of AA genotype was significantly higher than in poor responders. With regard to changes in PD20 and in FEV_1 this genotype related response was even more evident in the subgroups of non-smokers and in non-atopic patients. Furthermore in non-atopic patients AA genotype was overrepresented among good responders regarding changes in AQLQ score.

Genotype dependent difference in FEV_1 improvement for variant rs37973 in *GLCCI1* gene was highly influenced by smoking and atopy. We were unable to confirm the association of variants rs242941 and rs1876828 in *CRHR1* gene with therapeutic reponse to ICS.

Conclusion: There is only weak correlation between changes in subjective and objective treatment outcome parameters after long-term treatment with ICS in adult asthmatics. Our results suggest that genotyping for rs9910408 in *TBX21* gene and rs37973 in *GLCCI1* gene may allow the identification of patients that are more or less likely to respond to ICS therapy.

Fibrotic Processes in Lungs – Meta-analysis of the Transcriptome Data

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Introduction: Pulmonary fibrosis occurs when excessive deposition of extracellular matrix appears in lungs. It is characteristic for idiopathic pulmonary fibrosis (IPF), but it can also happen as complication of systemic sclerosis (SSc) and progressive fibrotic sarcoidosis. Our goal was to identify common mechanisms of these diseases and propose novel candidates for therapeutic targets, as well as disease-specific mechanisms possibly explaining different course of the studied diseases.

Methods: The study included transcriptome data on primary lung fibroblasts from patients with SSc, IPF and normal donors(1) and from patients with progressive fibrotic sarcoidosis and self-limiting sarcoidosis(2). Using bioinformatics tools BRB-ArrayTools, String and BioVenn we performed a differential gene expression analysis and gene set enrichment analysis based on KEGG and BioCarta pathways and transcription factors (TF) target genes.

Results: We found 7 differentially expressed (DE) genes, leukocyte transendothelial migration KEGG pathway and 2 TF (CEBPA, JUN) in all studied diseases. SSc and IPF shared 541 (53 %) of all identified DE genes including various proteins of extracellular matrix and matrix metaloproteinases. Steroid biosynthesis was the most significantly changed KEGG pathway and Cell cycle G1/S checkpoint was common perturbed pathway of SSc and IPF according to BioCarta. On the contrary, sarcoidosis showed lesser, but more interconnected number of DE genes, as observed by high number of enriched pathways and involved TF. Only there HLA genes and T cell surface proteins were noticed. Enriched pathways belonged to cytokine-receptor, Jak-STAT signaling pathway by KEGG and to 18 different B and T cell signaling and polarization pathways by BioCarta. Additionally, we showed that TF RARG/RARA and Oct-1/Oct-2 are involved in expression of DE genes at intersections of different combinations of studied diseases, resulting in covering of DE genes in all three.

Conclusion: Findings suggest that the number of mutual DE genes and enriched pathways between SSc and IPF is markedly larger than if comparing them to sarcoidosis. Changes in sarcoidosis transcriptomics expectedly confirm predominant involvement of immune cells in disease pathology. While RARG/RARA were already examined in different models of fibrosis, our further experiments will examine role of until now non-described Oct-1/Oct-2 in development of fibrotic disease pathology.

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PULMONARY HYPERTENSION – NOVEL INVASIVE PROCEDURES AND NOVEL RISK FACTORS

Pulmonary embolism, atherogenesis and inflammation markers in metabolic syndrome

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Background: Metabolic syndrome is a new worldwide epidemic and leading cause of the cardiovascular disease, including pulmonary embolism. Previously described as a degenerative disease, atherosclerosis is now described as inflammatory immunological disease. The mechanisms of pulmonary embolism in patients with metabolic syndrome have not been fully established. The aim of the study is to determine the incidence of pulmonary embolism in patients with metabolic syndrome in our conditions and to evaluate the values and significance of atherogenesis and inflamamation biomarkers (CRP, fibrinogen, uric acid, lipid profile) in patients with pulmonary embolism in metabolic syndrome.

Method: A retrospective study enrolled 30 patients with pulmonary embolism in metabolic syndrome selected by the International Diabetes Federation (IDF) criteria who were hospitalized at the Clinic for Pulmonary Disease UKC Tuzla from January to December 2019. The patients included in the study were determined the following parameters: history and physical examination, anthropometric parameters (age, sex, weight, height, body mass index, waist circumference), pulmonary artery CT angiography and biochemical parameters (CRP, fibrinogen, uric acid, total serum cholesterol, serum HDL cholesterol, serum LDL cholesterol, serum triglycerides).

Results: Standard methods of descriptive statistics were used in the statistical processing of results. The results showed significantly higher incidence of metabolic abnormalities, elevated CRP, fibrinogen, uric acid and more frequent lipid profile disorders in patients with pulmonary embolism in the metabolic syndrome compared to the general population.

Conclusion: The effects of metabolic syndrome on the respiratory system are often underestimated. Metabolic syndrome may play a key role in the pathogenesis of pulmonary embolism. Significant proportion of patients who show an increased risk of pulmonary embolism in metabolic syndrome remain unrecognized. Very often there is no clinical suspicion of pulmonary embolism in patients with metabolic syndrome. The results of this study will contribute to the identification of individuals at increased risk for pulmonary embolism in the metabolic syndrome.

Pulmonary hypertension in intermediate risk patients with acute pulmonary embolism, patient outcomes – our single center results

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Introduction: Although pulmonary embolism (PE) is quite common, there is limited information about the prevalence, management and outcomes of intermediate-high risk patients with PE in routine clinical practise. The incidence of chronic thromboembolic pulmonary hypertension (CTEPH) in this group of patients is expected to be low, but due to unstructured ambulatory follow-up the true number of patients is unknown.

Methods: Intermediate-risk PE is characterized by initially normal hemodynamics and evidence of right ventricle dysfunction on echocardiography or CTPA and/or positive cardiac biomarkers. In UMC Ljubljana these patients are admitted to our level 2 intensive care unit for monitoring and further treatment. A retrospective analysis was performed of all these patients treated in the year 2018 and a thorough review of all available electronic medical records until November 2020 was then used to check for dedicated outcomes.

Results: In the year 2018 we treated 95 intermediate risk PE patients with a wide age range of 25 to 95 years (average 67 years). 45% of patients were female. Most were overweight, with a mean body weight of 85 kg (min 54 kg, max 160 kg).

61% of patients presented with hypoxia, 50% with tachycardia, 25% with hypotension and 17% with syncope. D-dimer levels (ref. < 500 µg/L) were measured at admittance in 79% of patients, all were elevated with values ranging between 1480 and 41105 (average 12490). Troponin I values were negative (<100) in 36% of patients. NTproBNP values were measured in 70% of patients, out of those 15% were negative (below 500 ng/L). All PE were confirmed by CTPA, 94% had radiologic evidence of right ventricle overload, and 67% had dilated pulmonary arteries. 86% of patients had an echocardiographic assessment, out of those 62% had signs of right ventricular strain. The average peak systolic pulmonary pressure was 45 mmHg and ranged between 25 and 105 mmHg. 76% of patients were assessed for concomitant lower limb deep vein thrombosis, of which only 20% had none.

17% of patients had a prior venous thromboembolic event (VTE), 13% had active cancer, 15% had a history of malignancy, 9% were hospitalized in the prior 3 months, 8% had prior surgery and 5% were immobilized due to prior trauma.

10% of patients were treated with systemic intravenous thrombolysis and 7% received an IVC filter.

Patients received different forms of anticoagulant treatment according to their underlying medical conditions. 19% were prescribed LMWH, 27% VKA, 31% apixaban,

11% dabigatran and 10% rivaroxaban. 64% of patients were advised to receive indefinitive anticoagulant treatment. Out of the group of patients treated with NOACs 19% continued with the lower dose of NOAC after 6-12 months of treatment.

During hospitalization and follow up 12% of patients experienced a major bleeding event and a further 10 % a clinical relevant non-major bleed. 9,5% of patients had a recurrent VTE, all after anticoagulant discontinuation. 10% died in the first 30 days and a further 14% during follow up. Most common cause of death was malignant disease and sepsis.

38% of patients had an echocardiographic follow up and 36% of these patients had evidence of pulmonary hypertension. 7 of the 95 patients after intermediate high risk PE had signs compatible with CTEPH on echo and further lung imaging, 2 of those died of malignancy and the remaining 5 patients were evaluated at a specialist ambulatory clinic for pulmonary hypertension. All were deemed unsuitable for pulmonary endarterectomy or pulmonary artery balloon dilatation, three are receiving riociguat, one has not received specific vasodilatator treatment and one is still awaiting further evaluation. 5 of the 7 CTEPH patients had an echocardiographic estimated sPAP values over 60 mmHg on admittance and 3 out of 7 had a history of prior VTE. None received thrombolytic therapy.

Conclusions: Patients with intermediate risk pulmonary embolism are a heterogenous group with a higher than expected rate of diagnosed CTEPH on follow-up. Improving education of PE caretakers, higher awareness for CTEPH and further evaluation, validation and implementation of clinical/radiological algorithms for earlier CTEPH diagnosis will likely help ensure earlier referral to expert centres and improved prognosis.

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TRANSITION BETWEEN PEDIATRIC AND ADULT PNEUMOLOGY

The prevalence of respiratory diseases in schoolchildren in Ljubljana health region area due to public health perspectives

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Background: There is a mixture of different pollutants present in indoor and outdoor air, which may have adverse effects on health. Children are the most vulnerable population group due to their behavioral and pathophysiological characteristics in relation to the effects of air pollution on health. The purpose of the study is to examine the association between air quality in the school environment and diseases of respiratory system including allergic diseases considering confounding factors.

Methods: In the period between September and December 2017 there was HIS-type cross-sectional study conducted in Ljubljana health region area. Considering the protocol of InAirQ project, which was implemented across Europe, there were 12 elementary schools enrolled in the study. The observed population group is represented by third grade pupils, age interval of 7 to 9 years. The data regarding the characteristics of school building, school surrounding and school happening were assessed by interview with school officials. Completing the questionnaire by parents the data about health status regarding the diseases of respiratory system, about pre-, peri-, postnatal period and home environment of the child were assessed. Association between explanatory factors and observed health outcome was analyzed with univariate and multivariate logistic regression models. The study was approved by Medical Ethics Authority of Slovenia.

Results: Results of univariate association analysis for observed population group yielded statistically significant influence of respiratory illness in the first year of life on respiratory system diseases in last 12 months (p=0.017). The frequency of allergic respiratory diseases using the same methods is statistically significantly associated with the use of carpet in the child bedroom (p=0.025) and with the presence of moisture and mold in the child bedroom (p=0.050). Multivariate logistic regression model yielded statistically significant influence of settlement type (p=0.017) and respiratory illness in the first year of life (p=0.009) on respiratory disease. Considering allergic respiratory disease, the use of carpet in child bedroom (p=0.032) appeared as statistically significant variable. The total responsiveness of the study was 83.75%.

Conclusions: There were numerous methodological public health challenges identified in the study, which offer good foundation for more comprehensive data analysis.

Lung ultrasound in the diagnostics and etiological definition of community-acquired pneumonia in children

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Background: Community-acquired pneumonia (CAP) still represents an important cause of morbidity. The aetiology of community-acquired pneumonia (CAP) is not easy to establish. Respiratory viruses are the most common cause of CAP in preschool children, followed by bacteria (especially *Streptococcus pneumoniae*). Atypical bacteria *Mycoplasma pneumoniae* and *Chlamydiophila pneumoniae* prevail in schoolchildren and adolescents. Lung ultrasound (LUS) has only recently been considered as an alternative to the chest x-ray (CXR) for diagnosing CAP. Less is known about the usefulness of LUS for the establishment of the etiological diagnosis of CAP.
Therefore, we first compared the sensitivity of chest x-ray (CXR) and LUS for the diagnosis of CAP. In addition, we analyzed and compared the LUS characteristics of different etiological types of CAP in children.

Methods: We performed a prospective study and included 166 children with CAP, who were admitted to hospital. LUS and CXR were performed in all patients at admission. Nasopharyngeal swab was taken for the detection of respiratory viruses and atypical bacteria with the polymerase chain reaction (PCR). Blood tests and sputum analysis were done for further stratification of patients.

Results: Subjects were stratified into bacterial (n = 80), atypical bacterial (n = 32) and viral (n = 54) CAP subgroups. Pneumonia was detected with LUS in 161 (97.0 %) patients and with CXR in 137 (82.5 %) patients ($p < 0.01$). Sensitivity of LUS was calculated as 97.0% and sensitivity of CXR as 82.5% ($p < 0.01$). LUS-detected consolidations in viral CAP were significantly smaller, with a median diameter of 15 mm, compared to 20 mm in atypical bacterial CAP ($p = 0.05$) and 30 mm in bacterial CAP ($p < 0.01$). Multiple consolidations were detected in 65.4 % of patients with viral CAP and in 17.3 % of patients with bacterial CAP ($p < 0.01$). Bilateral consolidations were also more common in viral CAP than in bacterial CAP (51.9 % vs. 8.0 %, $p < 0.01$). At follow-up, a regression of consolidations was observed in 96.6 % of patients with bacterial CAP and in 33.3 % of patients with viral CAP ($p < 0.01$).

Conclusion: We determined that LUS is an excellent tool for diagnosing the CAP in children. We found LUS to be especially suitable for differentiating bacterial CAP from CAP due to other aetiologies. However, LUS must be interpreted in the light of clinical and laboratory findings.

Comparison of efficacy between penicillin and broad-spectrum beta-lactam antibiotics in the treatment of community-acquired pneumonia in children

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Background: Bacterial community-acquired pneumonia (CAP) is still a common cause of morbidity in children in the developed world. Bacterial CAP is mostly caused by *Streptococcus pneumoniae*. The resistance of pneumococci against penicillin is increasing in Slovenia and worldwide. However, most guidelines still prefer treatment with narrow-spectrum antibiotics. Therefore, we compared the effect of intravenous treatment with penicillin and broad-spectrum beta lactam antibiotics in children with CAP.

Methods: We performed a prospective study and included 136 children hospitalized because of bacterial CAP, diagnosed with lung ultrasound (LUS). Patients were treated intravenously either with penicillin G or broad-spectrum beta lactam antibiotic monotherapy. The size of lung consolidations was measured with LUS. White blood cell (WBC) count and C-reactive protein (CRP) were determined in venous blood at admission and after two days of treatment. Follow-up LUS was performed after two days of treatment in 64 (47.1 %) of patients. The time interval from the application of antibiotic to the permanent defervescence was recorded.

Results: 87 (64.0 %) of patients were treated with penicillin G, and 49 (36.0 %) with broad spectrum beta-lactam antibiotics. The median time to the persistent defervescence was 5 hours in penicillin-treated patients and 8 hours in broad-spectrum group ($p = 0.18$). There were no significant differences between both treatment regimens regarding the effect on the consolidation size and CRP decrease. However, the decrease of WBC count was greater in the penicillin treatment group ($p < 0.01$).

Conclusions: We have shown that penicillin is at least as effective as broad-spectrum antibiotics in the treatment of bacterial CAP in children. Despite the resistance of bacteria (including pneumococci) to antibiotics is increasing, clinicians should still adhere to national guidelines, which promote the use of penicillin and other narrow-spectrum beta lactams in the treatment of bacterial CAP in children.

LUNG INFECTIONS / TUBERCULOSIS

Challenges in Diagnosis and Management of Endobronchial Tuberculosis: A Case Report and Review of the Literature

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The diagnose of endobronchial tuberculosis is still challenging.

In February 2018 28-year-old female pharmacist due to pneumonia was treated with antibiotic, when good chest X ray resolution was noticed. In July 2018 an occasional, dry cough was still present. Lungs' CT lung was done in December 2018, and showed sequel of pneumonic infiltration in the right lower lobe. In July 2019 sputum smear microscopy for acid-fast bacilli was negative, but her Quantiferon TB test was positive. In September 2019 the culture on Mycobacterium tuberculosis from July 2019 was was positive. Bronchoscopy was done in October 2019 and revealed the fine-grained changes of distal part of trachea and right main bronchus together with necrotic changes of bronchus for right basal lobe. Bronchoaspirate was negative for acid-fast bacilli, but positive for culture on Mycobacterium tuberculosis and TB-polymerase chain reaction. Standard TB treatment was prescribed due to endobronchial tuberculosis. In December 2019, control chest X ray showed very significant regression of the shading in right lung. In April 2020 the patients was asymptomatic. Last chest X ray was normal. Control sputum smear microscopy for acid-fast bacilli and the culture on Mycobacterium tuberculosis from December 2020 were negative. TB therapy was finished after 6 months (from October 2019 to April 2020).

The diagnosis of endobronchial tuberculosis is still complicated because of nonspecific respiratory symptoms, often normal chest X ray and variable diagnostic yield with sputum microscopy. However, endobronchial tuberculosis should be considered as differential diagnosis in cases of long-term nonspecific respiratory symptoms, particularly in the countries with high and middle TB incidence. This should be considered even in low risk patients. On the end the bronchoscopy is the most reliable method for confirmation of endobronchial tuberculosis.

Chronic obstructive lung disordes and infections with nontuberculous Mycobacteria Xenopi - case report

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Introduction: The manifestation of respiratory infection involves a series of diagnostic procedures to determine the cause of cough change and / or insite cough, fever, shortness of breath. Results: in 4 persons / 2 M, 2 F, mean age 52.4 years and chronic obstructive pulmonary disease accompanuing with smoking habits /. HIV infection was not determined. Extensive changes and destruction/ veryfied billateral patterns as centrilobular emphysema, cavities, consolidations / of the lung parenchyma and airways were presented radiographically - chest CT scans M.xenopi were isolated from the sputum in 4 persons during the analysis. Treatment controlled according to ATS / IDSA recommendations, were performed during the 12 months. Satisfactory clinical and radiographic responses achieved.

Conclusion: Nowadays, clinical doubts can be confirmed by modern technology in the aim of healthy population.

OBSTRUCTIVE LUNG DISEASES

T2-high asthma, classified by sputum mRNA expression of *IL4*, *IL5* and *IL13*, is characterized by eosinophilia and severe phenotype

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Asthma is a common, highly heterogeneous inflammatory disease. Identification of asthma endotypes, that reflect highly variable response to conventional treatment, will lead to a more precise asthma management. T2 asthma is characterized by airway inflammation driven by T2 cytokines including interleukins IL-4, IL-5 and IL-13. The aim of this study was to determine whether induced sputum samples can be used for gene expression profiling and if T2-high endotype can be classified based on *IL4*, *IL5* and *IL13* profiling.

Induced sputum samples were obtained from 44 subjects, among them 36 asthmatic patients and 8 controls. Immediately after collection, samples were processed with Sputolysin and cell pellets were stored in Qiazol reagent. Following total RNA extraction, RNA quantity and quality measurement, mRNA expression levels of *IL4*, *IL5*, *IL13*, were quantified by RT-qPCR.

Gene expression levels of *IL4*, *IL5*, and *IL13* were significantly increased in asthmatic patients' samples compared to controls. High correlation between *IL4*, *IL5* and *IL13* expression was also observed. We calculated T2 gene mean by combining the expression levels of IL4, IL5 and IL13 and set the T2-high/T2-low asthma cutoff value based on the expression of T2 gene mean in controls. Twenty four (67%) asthmatic patients had T2-high asthma. T2 gene mean inversely correlated with FEV_1, and positively correlated with blood and sputum eosinophils. Patients with T2-high asthma had significantly higher eosinophil blood and sputum counts, as well as lower albeit not statistically significantly FEV_1. Furthermore, T2-high asthma was characterized as a more severe, difficult-to-treat asthma, and T2-high asthma patients more often received biological therapy to control their asthma symptoms/exacerbations.

In this study we found that interleukins transcripts can be easily detected in sputum from asthmatic patients. mRNA expression levels of *IL4*, *IL5* and *IL13* are increased in sputum cells from asthmatic patients and can be used as molecular biomarkers to categorize patients into T2-high endotype, characterized by eosinophilia, and severe, difficult-to-treat asthma, often requiring biological treatment.

Vitamin D and COPD – Missed Opportunities

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A male, aged 70 years, patient was presented due to 9 moderate/severe COPD exacerbations with 3 hospitalizations during last year. He was treated with triple inhaled therapy (Salmeterol/Fluticasone proprionate 100/1000 mcg BID + Aclidinium bromide 800 mcg, BID), together with long-term oxygen therapy (5L/min.; 14 hours/day). After addition of Roflumilast (500 mg/day, orally; for 2 months) and later of Azithromycin (500 mg/day, orally; for 5 months) exacerbations were still present. At presentation oxygen saturation on room air was 88% and he was with respiratory insufficiency type II. Hematocrit was 61%. Diffusion capacity for carbon monoxide was 62%. High resolution computed tomography revealed centrilobular and paraseptal emphysema with traction adhesions and borderline bronchiectasis. Additional diagnostics excluded asthma, alpha 1 antitrypsin deficiency, tuberculosis and severe cardiac disease. Vitamin D concentration was 7.2 nmol/L (range: 36.8 - 171.0). After 6 months with vitamin D3 (4000 I.U. per day) supplementation mMRC and CAT score, as well as FEV1 improved. The therapy was de-escalated to Aclidinium (800 mcg, BID) + Indacaterol (150 mcg, once daily). He experienced only one mild egzacerbation in next one year.

The clinical outcomes in COPD are markedly heterogeneous. Identification of reliable, predictive biomarkers of COPD outcomes is imperative. Some studies have shown that vitamin D deficiency was associated with increased risk of COPD and severe COPD. Systematic reviews and meta-analysis from randomised controlled trials (RCT) showed that vitamin D supplementation protected against acute respiratory tract infection and may reduce inflammation in hospitalized COPD patients, but also, increase the quality of life. 8 cohort, 5 case-control, and 5 RCTs showed that vitamin D supplementation may prevent COPD exacerbations. But, it has been shown that vitamin D3 supplementation reduced the rate of moderate/severe COPD exacerbations, only when baseline levels were <25 nmol/L or <50 nmol/L. Although, some meta-analysis found certain evidence for the association between low serum vitamin D levels and COPD, the association between serum vitamin D and COPD is not well studied and further research is warranted.

Peripheral blood cell counts as a prognostic biomarker in COPD

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Introduction: This study aimed to determine the association between peripheral blood cell counts and exacerbations of COPD.

Methods: This observational prospective study comprised 97 patients (44 females) with COPD. Their clinical characteristics and a history of exacerbations in the last 12 months were noted. Upon inclusion, all patients had to be in a stable state, at least 4 weeks after the last COPD exacerbation and not receiving systemic corticosteroids. Peripheral blood cell counts were determined upon the first visit. Patients were followed up for 12 months, and the number of moderate and severe exacerbations during this period was recorded.

Results: Patients who had at least one moderate or severe exacerbation during the observational period had lower BMI (24.5 [4.0] vs. 26.4 [4.8], $p = 0.046$), lower age (65 [9] vs. 68 [7] years, $p = 0.037$), worse lung function (FEV_1: 45 [17] vs. 63 [21] %, $p < 0.001$ and FVC: 75 [16] vs. 86 [20] %, $p = 0.005$) and more frequent history of at least one exacerbation in previous 12 months (50.0 vs. 26.2 %, $p = 0.027$), while there was no difference in sex, smoking history or CAT. Peripheral blood cell counts showed higher relative and absolute eosinophil counts in patients with at least one exacerbation as compared to patients without exacerbations (3.01 [2.60] vs. 1.91 [1.27] %, $p = 0.006$ and 225 (190) vs. 154 (99) cells/µL, $p = 0.017$) but there were no significant differences in other parameters. Multivariate analysis using Cox regression model identified lung function (FEV_1) as the only independent predictor of future exacerbations (HR [95% CI]: 0.976 [0.956 - 0.996], $p = 0.019$).

Conclusion: In our cohort of patients with COPD, higher relative and absolute eosinophil counts were seen in patients with at least one observed moderate or severe exacerbation. However, the multivariate analysis confirmed only lung function as an independent predictor of exacerbations.

ALLERGY

Drug Allergy

Skin Allergy

Združenje pnevmologov Slovenije
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DRUG ALLERGY

Radiocontrast media hypersensitivity

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Introduction: Many patients are prevented from radiocontrast examination due to so called „iodine allergy ". Only a minority of them rightfully. True radiocontrast hypersensitivity can be confirmed or ruled out by allergy work up.

Clinical manifestation: Hypersensitivity reactions (HR) to radiocontrast media (RCM) are classified as immediate or nonimmediate. Immediate reactions start within one hour from RCM application while nonimmediate reactions start usually within several hours or days. Urticaria, angioedema, bronchospasm and anaphylaxis are typical clinical pictures of immediate reactions. Maculopapular exanthema is the most frequent nonimmediate manifestation.

Diagnosis and management: The most significant risk factor of HR is a past reaction to RCM. Contact or irritant dermatitis after iodine disinfection or fish/seafood allergy is not considered a risk factor of RCM hypersensitivity anymore. Laboratory tests can confirm the diagnosis of anaphylaxis (acute and basal tryptase) or detect an immediate type of allergy mediated by IgE to the respective RCM (basophil activation tests). Skin tests (ST) can confirm an immediate allergy (prick and intradermal tests with evaluation in 20 minutes) as well as a nonimmediate allergy (intradermal or patch tests with evaluation in 24-96 hours). Negative results of ST do not predict tolerance as approximately half of HR to RCM are mediated by direct mast cell degranulation without specific immune response. Some centres use drug provocation tests (DPT) to confirm allergy or tolerance to the respective RCM, in appropriate settings due to a risk of inducing HR. The current approach to the management of RCM HR is based on risk stratification, according to the type and severity of index reaction. Main measures are a change of RCM with respect to allergy test results and a premedication.

Conclusion: Proper allergy evaluation helps to de-label false diagnosis of iodine allergy and find safe RCM for future use. Total avoidance of all RCM is necessary in a very low proportion of patients.

SKIN ALLERGY

Predictive factors of response to omalizumab treatment in chronic spontaneous urticaria

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Omalizumab represents an effective treatment for chronic spontaneous urticaria (CSU). However, the response to treatment is variable, as some CSU patients respond to treatment within days of their first omalizumab injection, others respond within weeks, and a subgroup of patients do not respond to omalizumab at all. Currently, it is difficult to predict which patients will benefit most from omalizumab treatment. The aim of this study was to evaluate the predictive value of different markers, measured before starting omalizumab treatment, for the response to omalizumab in patients with CSU.

We enrolled 43 patients with active CSU, whose symptoms were not controlled with high doses of H1 antihistamines and were consequently treated with omalizumab. The rate of clinical response to omalizumab treatment (CSU-R) was 84% (36/43). Seven (16%) patients were nonresponders (CSU-NR). CSU-NR had significantly lower absolute numbers of circulating basophils and basophil CD63 activation, higher CD63 activation of donor basophils after incubation with sera of CSU patients, lower FcεRI and IgE densities on the basophils, and lower whole-blood relative gene expression of FCER1A and HDC, and a lower basophil gene mean (calculated as the mean of standardized gene expression variables of *FCER1A*, *CPA3* and *HDC*). As indicated by the estimated area under the ROC curve, the absolute blood basophil count (AUC = 0.99), followed by the FcεRI density per basophil (AUC = 0.95), *FCER1A* gene expression (AUC = 0.95) and the basophil gene mean (AUC = 0.95), showed the highest accuracy in discriminating between CSU-R and CSU-NR. Similarly, the number of circulating basophils was the most significant predictor of CSU-NR (The optimal cut-off was 1.7 basophils/μL with the OR of 144.

In conclusion, the most important finding of our study is that a very low number of circulating basophils, in addition to the corresponding low whole blood gene expression of basophil related markers, especially *FCER1A* and the basophil gene mean, showed the highest accuracy in discriminating between CSU-R and CSU-NR, and in predicting the response to omalizumab therapy. Therefore, we speculate that the baseline absolute basophil count represents a promising and feasible laboratory approach for predicting the clinical response to omalizumab.

IMMUNOLOGY

Immune Deficiences

Innate Immunity

Cancer Immunotherapy

Autoimmunity

Development of Advanced Therapies

Antigen Presenting Cells and T Cell Response

SLOVENIAN ASSOCIATION OF ALLERGY AND CLINICAL IMMUNOLOGY

Združenje pnevmologov Slovenije
Slovenian Respiratory Society

IMMUNE DEFICIENCIES

Selective IgA deficiency: our experience

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Background: Selective IgA deficiency (sIgAD) is defined as an isolated deficiency of serum IgA in an individual older than four years of age in whom other causes of hypogammaglobulinemia have been excluded. It is the most common primary immunodeficiency.

Methods: The clinical manifestations of pediatric patients seen at our clinic in the last 5 years were retrospectively analyzed.

Results: 45 patients were enrolled. The results are presented in table.

Clinical manifestation, n (%)	Partial deficiency, n=9	Complete deficiency, n=36	Total, n=45	P -value
Recurrent otitis media	5 (55.5)	7 (19.4)	12 (26.7)	0.043
Pneumonia	3 (33.3)	6 (16.6)	9 (20)	0.354
Sinusitis	0	2 (5.5)	2 (4.4)	1.000
Gastrointestinal infections	3 (33.3)	6 (16.6)	9 (20)	0.354
Urinary infections	1 (11.1)	2 (5.5)	3 (6.7)	0.497
Autoimmune diseases	2 (22.2)	5 (13.8)	7 (15.6)	0.614
Food allergy	3 (33.3)	7 (19.4)	10 (22.2)	0.393
Asthma	3 (33.3)	8 (22.2)	11 (24.4)	0.666
Atopic dermatitis	1 (11.1)	3 (8.3)	4 (8.9)	1.000
Celiac disease	0	4 (11.1)	4 (8.9)	0.569
Positive autoantibodies	0	10 (27.7)	10 (22.2)	0.173
Asymptomatic	2 (22.2)	4 (11.1)	6 (13.3)	1.000

Average age was 6.4 years. 23 patients (51%) were male. 36 patients (80%) had complete sIgAD. The most common infections were recurrent otitis media. Asthma and autoimmune diseases were also common. Mostly, there were no significant differences between patients with partial and complete IgA deficiency. None of our patients had serious invasive infection and none progressed to common variable immunodeficiency. In most patients sIgAD was persistent, whereas in 1 patient severe deficiency resolved over time. In 1 patient partial deficiency progressed to severe deficiency. Most of our patients were symptomatic, even those with partial deficiency which is probably due the fact that we included only patients who were examined in our clinic because of health problems.

Conclusion: Children with sIgAD are at risk of recurrent infections, allergic, autoimmune and other diseases. Therefore, they should be followed up regularly.

INNATE IMMUNITY

Molecular mechanisms of NLRP3 inflammasome activation and its regulation

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NLRP3 inflammasome is a multiprotein complex mediating inflammatory response in a variety of autoinflammatory, metabolic and degenerative diseases. Upon activation with diverse triggers NLRP3 oligomerizes, recruits adaptor protein ASC and pro-caspase-1. Active caspase-1 processes IL-1β and IL-18 cytokines to their mature form and gasdermin D to a pore-forming protein that induces pyroptotic cell death. Although the role of NLRP3 in various pathologies has been described, not much is known about the molecular mechanism of NLRP3 inflammasome activation.

In order to define the role of particular domains of NLRP3 in inflammasome trigger sensing, assembly and autoregulation systematic truncation of NLRP3 and reconstitution of NLRP3 variants in NLRP3-deficient macrophages was performed. We demonstrate that LRR domain is dispensable for NLRP3 activation and self-regulation. A minimal NLRP3 truncation variant was found fully responsive to various canonical NLRP3 activators. Substitution of the pyrin domain of NLRP3 with the CARD domain of NLRC4 or ASC led to a constitutive activation, demonstrating that the pyrin domain restricts NLRP3 in an inactive conformation.

NLRC4 inflammasome is formed by self-catalytic polymerization of NLRC4 initiated with bacterial ligand/NAIP complex. We were interested whether similar process is involved in NLRP3 activation. We show that pathological mutations of NLRP3 failed to engage wild-type NLRP3 in a self-catalytic oligomerization, demonstrating that the activating signal is not enhanced at the level of NLRP3 oligomerization, representing an additional level of NLRP3 regulation.

These results contribute to the understanding of the molecular basis of NLRP3 inflammasome activation and demonstrate the versatility of recognition and regulation mechanisms of the innate immune receptors.

Reference: Hafner-Bratkovic et al. (2018) Nature Communications 9, article no. 5182

Inhibition of the NLRP3 inflammasome by peptide inhibitors

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NLRP3 inflammasome is a multiprotein complex which forms within cells in response to various microbial and self-derived stress-associated triggers in order to activate the production of pro-inflammatory cytokines such as IL-1β and pyroptotic cell death. Mutations in the gene encoding NLRP3 cause rare cryopyrin-associated periodic syndromes (CAPS) and growing evidence links NLRP3 inflammasome to common diseases such as Alzheimer´s disease. The mechanism of NLRP3 inflammasome activation is not fully understood, which hinders the design of effective and specific NLRP3 inflammasome inhibitors. In order to modulate different stages of NLRP3 inflammasome assembly we selected a set of peptides whose sequences correspond to segments of the inflammasome proteins NLRP3 and ASC. The design was based on the crystal structures of the PYD and CARD interaction domains and on the pathological mutation hotspots in the NLRP3 NACHT domain. We identified peptides that were inhibiting the activation of caspase-1, the release of IL-1β and ASC oligomerization in response to soluble and particulate NLRP3 triggers. Modulatory peptides also attenuated IL-1β release from the cell lines with NLRP3 mutations linked to CAPS. One of the peptide inhibitors selectively inhibited NLRP3 inflammasome and also effectively dampened neutrophil infiltration in the mouse model of silica-induced peritonitis. When equipped with peptide sequence which allows transfer through the blood-brain barrier the peptide localised inside the cells as well as within the brain of mice after intravenous injection showing its potential as an NLRP3 inflammasome inhibitor in a neurological setting. Designed peptides provide an insight into the mechanism of NLRP3 inflammasome assembly and the basis for the development of novel anti-inflammatory strategies.

The role of cystatins in inflammasome activation and sepsis

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Progressive myoclonus epilepsy of Unverricht–Lundborg type (EPM1) is an autosomal recessively inherited neurodegenerative disease, characterized by the cerebellar granule neurons apoptosis, progressive ataxia and myoclonic epilepsy. Mutations in the cysteine proteinase inhibitor stefin B/cystatin B (CTSB) are found in patients with EPMI. A mouse model of the EPM1 disease, stefin B deficient mice, recapitulates the principal symptoms of EPM1, myoclonic seizures and progressive ataxia.

Stefin B deficient mice were found more sensitive to lipopolysaccharide (LPS) induced sepsis as a consequence of increased expression of caspase 11 and nucleotidebinding oligomerization domainlike receptor 3 (NLRP3) inflammasome activation and higher levels of mitochondrial reactive oxygen species (ROS). In addition we determined that the lack of stefin B leads to a significant increase in the expression of the mitochondrial antioxidant proteins to LPS challenge [3]. In our study we used stefin B deficient mice (StB KO), as well as mice with an additional copy of stefin B gene, stefin B trisomic mice (StB 3n). In macrophages from stefin B trisomic mice we determined lower caspase 11 expression and non canonical inflammasome activation. Stefin B suppressed mammalian target of rapamycin (mTOR) activity and induced autophagic activity for mitophagy by increase of unc51 like autophagy activating kinase 1 (Ulk1) phosphorylation. As a conclusion, we propose that stefin B plays an important role in regulation of autophagy and non canonical inflammasome activation.

Development of NOD2 agonists as vaccine adjuvants

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Muramyl dipeptide, a fragment of bacterial peptidoglycan, has long been known as the smallest fragment possessing adjuvant activity, on the basis of its agonistic action on the nucleotide-binding oligomerization domain-containing protein 2 (NOD2). There is a pressing need for novel adjuvants and NOD2 agonists provide an untapped source of potential candidates. Here, we present the design, synthesis and characterization of a series of novel acyl tripeptides. A pivotal structural element for molecular recognition by NOD2 has been identified, culminating in the discovery of the most potent desmuramylpeptide NOD2 agonist to date, albeit solely in *in vitro* conditions. Further pharmacokinetic optimization afforded an *in vivo* active compound, which was able to significantly induce ovalbumin-specific IgG titers in a mouse model of adjuvancy. Our findings provided deeper insights into the structural requirements of desmuramylpeptides for NOD2-activation and highlight the potential use of NOD2 agonists as adjuvants for vaccines.

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Extracellular vesicles as modulators of innate immune response

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Extracellular vesicles (EVs) are submicron membrane-contained vesicles that are released from cells. The significance of EVs lies in their capacity to transmit the information from donor to recipient cells thus influencing their function. The information can be proteins, nucleic acids, lipids or sugars. The amount of released EVs increases under stressful conditions and increased concentrations of EVs are detected in the peripheral blood of patients with chronic inflammatory diseases, cancer or infection.

Atherosclerosis and RA are chronic diseases with inflammatory characteristics involving oxidative stress, where lipids with unsaturated fatty acids chains are particularly prone to oxidation with reactive oxygen species and might be released from cells with EVs. These oxidized species represent endogenous damage associated endogenous ligands (DAMPs), which can be recognized by innate immune receptors. We showed that EVs from patients with RA or produced under oxidative stress in cell cultures activated Toll-like receptor 4 (TLR4/MD-2) receptor complex. The activity of EVs was oxidation related. 15-lipoxygenase oxidized lysoPLs were identified as TLR4 ligands. Their generation was dependent on 15-LO and $sPLA_2$ activity, which we detected in the synovial fluid from patients. Injection of sPLA2-IIA into mice promoted K/BxN serum induced arthritis in TLR4-dependent manner. As both 15-LO and $sPLA_2$ are induced during inflammation, therefore these results imply the role of oxidized lysoPLs in stressEVs in promoting sterile inflammation through TLR4 signaling.

Link between activation of inflammatory signaling pathways and cancer is particularly evident in Waldenström macroglobulinaemia (WM), where more than 90% of patients harbor a mutant of MyD88. MyD88 is a signaling adapter protein involved in TLR signaling through myddosome formation. $MyD88^{L265P}$ constitutively activates the signaling pathway and provides a survival signal to cancer cells, thus chronic inflammation may contribute to the tumor` microenvironment. We identified an alternative mechanism to the transmission of inflammatory mediators by transfer of the myddosome via EVs. Constitutively active $MyD88^{L265P}$ was transferred to other recipient cells, where $MyD88^{L265P}$ recruited the endogenous $MyD88^{wt}$ to trigger cell activation without receptor activation. *In vivo* internalization of EVs containing MyD88 occurred and the changes to the bone marrow microenvironment were observed. MyD88-containing EVs were detected in the bone marrow aspirates of WM patients. This process may play an important role in WM cancer development by triggering inflammation in the nontransformed cells independently of the membrane receptors.

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Cardioprotection against simulated ischemia/reperfusion injury mediated by calcium ionophore-induced extracellular vesicles

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Introduction: Adaptive response is an important defense function, which helps cells to fight against oxidative stress. Studies showed that low levels of oxidized species (among them also oxidized phospholipids) enhance defense capacity of cells by inducing the expression of antioxidant enzymes such as heme oxygenase 1 (HO-1) as well as by triggering transient activation of Toll-like receptors (TLRs). We investigated the capability of extracellular vesicles (EVs), released after oxidative stress (stressEVs), to induce TLR dependent signaling in H9c2 and AC16 heat-derived proliferating cell lines. We wanted to assess if such EVs are capable of inducing cardioprotection against acute ischemia/reperfusion injury.

Methods: StressEVs were produced in HEK293 cells exposed to 10 μM calcium ionophore A23187 and isolated using ultracentrifugation. StressEVs were characterized by DLS, NTA, WB and electron microscopy. Changes in gene expression and signaling after stressEV stimulation were determined by dual luciferase assay, qPCR, WB and ELISA. Cytotoxicity after hypoxia/reoxygenation was assessed by LDH activity assay and by calcein staining.

Results and discussion: Our results show that EVs released from cells cultured *in vitro* as a consequence of calcium ionophore treatment can be utilized as a treatment option against simulated I/R injury in cardiac myocytes. Even though stressEVs were capable of activating TLR dependent signaling, the cardioprotection resulted from induction of antioxidant pathways, which were triggered in a TLR-independent manner. Based on these results, we suggest that calcium ionophore-induced stressEVs may reveal novel avenues for cardioprotective treatments against ischemic cardiac disease such as myocardial infarction.

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CANCER IMMUNOTHERAPY

Interleukin-12 gene therapy for treatment of cutaneous tumors

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Interleukin-12 (IL-12) is cytokine with potent antitumor effectiveness. Its action is mediated by cellular and humoral immune system stimulation and antiangiogenic action. The first clinical studies with recombinant proteins were terminated due to its high toxicity, although the good antitumor effectiveness was evident in some patients. New technologies, though, enable sustained and controlled local or systemic release of IL-12 by gene therapy approach. Transfection of cells, tumor or normal in the skin enable local release of the transgene (IL-12) and direct antitumor effectiveness on targeted tumors. Specific delivery system, by electroporation enables also plasmid DNA transfer, with no side effects. Thus, naked plasmid coding for IL-12 transfection by electroporation is feasible and effective as demonstrated on preclinical level and on clinical level. Studies on mouse tumors demonstrated its effectiveness on various tumors, in veterinary oncology on mast cell tumors and oral malignant melanoma, and in the clinical study conducted in USA on melanoma metastases. We tested this system on various levels and want to further develop it into use in clinical oncology. Our aim is to develop combined treatment of electrochemotherapy with adjuvant intratumoral IL-12 gene electrotransfer. With such approach, we anticipate to transform the local effectiveness of either of the approaches into the locoregional and systemic effect. This is also the purpose of the SmarGene.Si project that will be developing this treatment approach from the bench to bedside.

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Gene electrotransfer for cancer immunotherapy

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Gene electrotransfer (GET) is one of the most efficient non-viral gene therapy approaches for localized gene transfer into tumors *in vivo*. It is especially promising for delivering different cytokines that are toxic if administered systemically. Currently, GET of plasmids encoding the cytokine interleukin 12 (IL-12) is approaching clinical use for treatment of various superficial solid tumors. Plasmids used in ongoing IL-12 GET clinical trials in the USA, contain antibiotic resistance genes and are, thus, according to safety recommendations of the European Medicines Agency, not suitable for clinical trials in the EU. Hence, in our group we are striving to prepare plasmids without antibiotic resistance genes. Moreover, we are investigating different immunological capacities of GET: from using GET as an adjuvant to local ablative therapies or tumor-based vaccines, to investigating the adjuvant effect of plasmid DNA itself.

In one of the immunological GET based approaches, we are utilizing concomitant intratumoral GET of two plasmids: a plasmid encoding a cytotoxic cytokine tumor necrosis factor alpha (TNFα) to induce *in situ* vaccination and a plasmid encoding an immunostimulatory cytokine IL-12 to boost the primed local antitumor immune response into a systemic one. Our initial results confirmed the feasibility and effectiveness of the approach in eliciting a potent and durable antitumor response in a mouse melanoma tumor model. In furthers studies, our aim was to prove the systemic, *i.e.*, abscopal, effectiveness of the approach. Furthermore, we tested the approach in two additional tumor models, since *in situ* vaccination has the potential to be effective in different cancer types, considering it utilizes the tumors own antigens. It turned out that both local and abscopal effectiveness of *in situ* vaccination by intratumoral GET of TNFα and IL-12 very much depend on the immune status of the tumor. While the abscopal effectiveness was higher in more immunogenic tumor model, local was lover. Currently, we are investigating the mechanisms of observed differences in the effectiveness of the described and similar approaches.

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Retrospective analysis of treatment-naive Slovenian patients with metastatic melanoma treated with pembrolizumab

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Background: Based on recent data from clinical trials, the immune checkpoint inhibitor pembrolizumab prolongs survival and has a good toxicity profile in patients with advanced or metastatic melanoma: However, the question remains whether these results are transmitted into daily clinical practice: The aim of this study was to assess the efficacy and toxicity of pembrolizumab in treatment-naive patients with metastatic melanoma in everyday clinical practice in Slovenia and compare it to the results from clinical trials.

Patients and methods: From January 2016 to December 2018, 138 metastatic treatment-naive melanoma patients treated with pembrolizumab at the Institute of Oncology Ljubljana in Slovenia were included in our observational retrospective study: Patient and treatment characteristics were retrospectively collected from hospital data base: Statistical data was obtained using the SPSS software version 22: Survival rate was calculated with the Kaplan-Meier method: Observation period took place between January 2016 and the end of June 2019.

Results: The estimated median overall survival (OS) was 25.1 months (95% CI, 14.6-35.6) and the median progression-free survival (PFS) was 10.7 months (95% CI, 5.9-15.4): Among all patients, 29 (21.0%) achieved complete response, 31 (22.5%) partial response and 23 (16.7%) reached stable disease: The number of organs with metastatic involvement and the level of baseline lactate dehydrogenase (LDH) concentration had significant influence on survival rates: Immune-related adverse events (irAE) were reported in 88 (63%) patients, while grade 3-4 irAE occurred in 12 (8.7%): Due to toxicity, 16 (11.6%) patients discontinued the treatment.

Conclusions: Our real-world data from single centre retrospective analysis of treatment-naive metastatic melanoma patients treated with pembrolizumab showed inferior median OS and similar median PFS, compared to the results from clinical trials: However, patients with normal serum levels of LDH and a small number of organs with metastatic involvement had comparable survival outcomes: Toxicity rates of pembrolizumab were quite similar: These results further support the use of pembrolizumab for metastatic treatment-naive melanoma patients.

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^{18}F-FDG PET immunotherapy radiomics signature (iRADIOMICS) predicts response of NSCLC patients treated with anti-PD-1

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Background: Immune checkpoint inhibitors have shown impressive results in patients with various malignancies. However, non-invasive biomarkers of response are still needed to identify candidates for non-responders. We investigated whether immunotherapy 18F-FDG PET radiomics signature (iRADIOMICS) predicts response of non-small-cell lung cancer patients better than the current clinical standards.

Methods: Thirty patients were treated with pembrolizumab and scanned with 18F-FDG PET/CT at baseline, month 1 and month 4. Six robust radiomics features of primary tumours were analysed. The Mann-Whitney U-test (MWU), Cox proportional hazards regression analysis, and receiver operating characteristic (ROC) curve analysis were used to study the impact of radiomics features on overall survival (OS). The iRADIOMICS signature was constructed using univariate and multivariate logistic models of the most promising radiomics feature(s). Its predictive power was compared to PD-L1 tumour proportion score (TPS) and iRECIST signatures using ROC curve analysis. Accuracy of predictions were assessed with repeated 5-fold cross validation.

Results: The most predictive were baseline radiomics features, e.g. Small Run Emphasis (MWU, p = 0.001; Hazard Ratio (HR) = 0.46, p = 0.007; area under the ROC curve (AUC) = 0.85 (95% Confidence Interval 0.69-1.00)). Multivariate iRADIOMICS signature was found superior to the current standards, both in terms of predictive power, as well as timewise: iRADIOMICS (baseline), AUC = 0.90 (0.78-1.00), accuracy = 78% (standard deviation 18%); PD-L1 TPS (baseline), AUC = 0.60 (0.37-0.83), accuracy = 53% (18%); iRECIST (month 1), AUC = 0.79 (0.62-0.95), accuracy = 76% (16%); iRECIST (month 4), AUC =0.86 (0.72-1.00), accuracy = 76% (17%).

Conclusions: Pre-treatment multivariate iRADIOMICS signature was identified as a promising imaging biomarker of response to anti-PD-1 immunotherapy. iRADIOMICS signature could improve the management of patients on immunotherapy considerably. For example, patients identified as non-responders could receive additional therapy besides immunotherapy (e.g. chemotherapy) to improve their OS.

Real-world efficacy of immunotherapy in advanced non-small cell lung cancer: a single centre experience

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Background: Immunotherapy with checkpoint inhibitors (CPIs) changed the standard of treatment for advanced non-small cell lung cancer (NSCLC). In the clinical trials, monotherapy with CPIs resulted in incredibly high 1-year OS rates of up to 55% - 70% in second-line (SL) and first-line (FL) setting. Our study aimed to evaluate the efficacy of monotherapy with CPIs in advanced NSCLC.

Methods: This was a retrospective observational study of 66 consecutive patients (pts) treated at a single academic centre, from August 2015 to November 2018. Clinical, pathological, treatment and survival characteristics were retrieved from the hospital registry, with prospective data collection. By Kaplan-Meier estimator progression-free survival (PFS) was calculated from the start of treatment until progression (according to RECIST 1.1 criteria), death or last follow-up, while overall survival (OS) was calculated until death or last follow-up date.

Results: The main characteristics were: median age 63 (42 – 77), 55% male, 82 % current or former smokers, 83% adenocarcinoma, 94% with performance status (PS) 0 – 1. Six percent had PS ≥ 2 and 33% had controlled CNS metastases at baseline. The characteristics did not differ between the SL cohort of 40 pts treated with atezolizumab, nivolumab or pembrolizumab (PD-L1 expression 0%-100%) and the FL cohort of 26 pts (PD-L1 ≥ 50 %) treated with pembrolizumab.

Median PFS was 3.5 months (95% CI: 1.9 – 6.6) in the SL cohort and 9.3 months (95% CI: 3.5 – ∞) in the FL cohort. Median OS was 9. 9 months (95% CI: 4.9 – 16.2) in the SL cohort, and has not yet been reached (95% CI: 7.1 – ∞) in the FL cohort. Of note, 1-year OS was 38% (95% CI: 25 – 56%) and 62% (95% CI: 45 – 83%) in the SL and FL cohorts, respectively.

Conclusion: In our real-world study, mono-immunotherapy with CPIs demonstrated very similar PFS and OS rates to those observed in the pivotal clinical trials, despite including some patients with PS ≥ 2. Even though our cohort was small, these data support the efficacy of CPIs in a real-world setting.

Outcomes and safety in patients with metastatic urothelial cancer receiving atezolizumab at the Institute of Oncology Ljubljana

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Introduction: Data from non-randomized and randomized studies show that atezolizumab (AT), a PD-L1 inhibitor, improves prognosis of chemotherapy-naive (CTn) patients whose tumors are PDL-1 positive and of chemotherapy pre-exposed (CTe) patients with metastatic urothelial cancer (mUC). The response rates, survival outcomes and safety of patients with mUC treated with AT in real-world practice were investigated.

Methods: 62 patients with mUC, who received at least one cycle of AT at the Institute of Oncology Ljubljana between May 8, 2018, and Dec 31, 2019, were included. The best overall response rates as defined by RECIST and immune-related adverse events (irAE) as assessed by treating oncologists were obtained from patient's data charts. Median overall survival (mOS) times using the Kaplan–Meier method are reported for the cohort of CTn versus CTe patients.

Results: Of 62 patients, 5 (8.1%) have not been evaluated yet and 20 (32%) died prior to first radiologic evaluation. Clinical benefit was obtained in 15 (26%) cases, objective response in 12 (21%) and complete response in 5 (11%). Of all patients, 18 (29%) were CTn and 44 (71%) were CTe. PDL-1 testing was not performed in 6 (33%) CTn patients and all of them, but one, died or had progressive disease. At 5.2 months median follow-up, the mOS was 8.7 months for CTn (CI 95%:0.8-16.5) and 6.8 months for CTe (CI 95%:3.7-10). For patients with clinical benefit the mOS was 23.1 months.

IrAE occurred in 20 (32 %) patients, of those 7 (11%) had grade 3-4 by CTCAE version 5.0. Systemic corticosteroids for irAE were used in 5 (8%) patients. AT was discontinued because of irAE in 7 (11%) patients. One patient suffered presumably autoimmune encephalitis that caused severe functional impairment.

Conclusion: Patients with clinical benefit on AT have long disease remission. However, the mOS of all CTn and CTe patients was shorter than the mOS of similar patient groups reported in prospective studies. Noteworthy, not all of our CTn patients have been tested for PDL-1 as this was not initially required.

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And a significant percentage of our patients received AT near the end of life. The types and the frequency of irAE were as expected.

AUTOIMMUNITY

Systemic sclerosis-where do we stand?

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Background: Systemic sclerosis (SSc) is a chronic autoimmune disease, currently still considered incurable. It is characterized by widespread vascular dysfunction, immune dysregulation and progressive fibrosis of the skin and internal organs. The diagnosis is based primarily upon the presence of characteristic clinical findings and supported by specific serologic abnormalities. SSc still carries the highest mortality of all the rheumatic diseases.

Methods: A systematic PubMed search for papers regarding systemic sclerosis between 1st January 2010 and 1st January 2020 with search terms "systemic sclerosis", "diagnosis" and "treatment " was performed. Eleven articles corresponded to the pre-specified search terms.

Results: SSc is classified into two subsets based on the extent of skin involvement: 1) limited cutaneous SSc with skin involvement restricted to distal limbs below elbow and knees with or without facial involvement and 2) diffuse cutaneous SSc occurring proximally to the elbows and knees. Diffuse SSc is usually characterized by more rapid onset of skin and internal organ involvement. In addition to puffy fingers or skin thickening, systemic manifestations of SSc are myopathy, joint involvement and contractures, interstitial lung disease, gastro-intestinal dysmotility and cardiac involvement. Vascular manifestations of SSc include Raynaud's phenomenon, digital ulcers, scleroderma renal crisis and pulmonary hypertension. SSc has the highest mortality, mainly due to the development of lung complications. The two most important lung complications in SSc are lung fibrosis (50-70 % of patients with interstitial lung disease) and pulmonary arterial hypertension (9-12% SSc patients). Current therapeutic options mainly manage vascular disease and fibrotic manifestations (skin disease and ILD). None of the therapies is curative, and treatment response rates vary.

Conclusions: Diagnosis and follow-up of patients with systemic sclerosis has to be systematic, while treatment must be adapted to organ manifestations. Although specific therapies for gastrointestinal, pulmonary or vascular complications exist, patients respond only partly to these and new therapeutic approaches are still needed.

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Integrative approaches in systemic sclerosis

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Gene expression microarrays and RNA-Seq data of transcriptomic profiling are published in public repositories, such as Array Express or Gene Expression Omnibus, containing 2.5 and 3.5 million assays respectively. This is in line with open science policy of EU Commission and FAIR (Findable, Accessible, Interoperable and Reusable) open access data policy recommendation for publicly funded research. Accessibility of transcriptomic data allows secondary analyses to answer novel questions, test reproducibility of published data, perform meta-analyses and compare gene expression profiles across different studies and to stratify clinical responses retrospectively. Integrative analysis of skin biopsy molecular signatures divided systemic sclerosis (SSc) patients into four subgroups with divergent mechanistic features. Peripheral blood mononuclear cell gene expression re-analysis suggested that the fibroproliferative subgroup of SSc patients benefits most from autologous hematopoietic stem cell transplantation (1), while modified Rodnan skin score improves most in inflammatory subgroup of patients after mycophenolate mofetil therapy (2). No such studies are published on SSc lung tissue datasets, although pulmonary fibrosis is life threatening complication of SSc.

We used deposited lung fibroblasts dataset of SSc patients with interstitial lung disease vs. controls (GSE40839) and lung tissue vs. control (GSE76808) to analyze differentially expressed gens, processes, transcription factors and miRNA importantly implicated in development of lung fibrosis in fibroblasts, the main effector cells and the rest of lung cell populations. We found 843 differentially expressed genes in fibroblasts and 549 in lung tissue, with 66 overlapping genes. Apoptosis and response to cytokines were shared in both groups, while growth factors, cell cycle and proliferation pathways were only upregulated in fibroblasts. Only in lung tissue, but not in fibroblasts 42 immunoglobulin genes were increased, pointing towards B cell involvement. Other upregulated genes only in tissue showed central involvement of insulin growth factor (IGF), complement and DNA damage pathways. PI3K/Akt pathway and FOXO1 transcription factors, already known therapeutic targets in some metabolic diseases, were suggested to regulate perturbed genes and mir-132 was suggested as regulator of their expression. Leveraging existing datasets offered us a convenient and cost-effective avenue to identify novel hypotheses for further experimental work.

Funding: This study was supported by Slovenian research agency (Systemic autoimmune diseases P3- 0314 and Z3-9261 to KL).

Resources:

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Can we predict gastrointestinal and/or renal complications in adult IgA vasculitis?

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Background: IgA vasculitis (IgAV) is an immune complex vasculitis, characterized by deposition of immunoglobulin A in vessel wall, and clinically by skin, joint, gastrointestinal (GI) and renal involvement. It is still poorly defined disease in the adult population, particularly markers, predicting visceral involvement have not been extensively. The aim of our study was to determine the predictors of GI or renal involvement in adult IgAV.

Methods: The prospective study included histologically proven adult IgAV cases diagnosed between January 2013 and July 2019 at Department of Rheumatology, UMC Ljubljana. We evaluated the role of several clinical and the laboratory parameters as markers predicting the GI or renal involvement in IgAV, using the multiple logistic regression analysis.

Results: During the observation period, we identified 214 incipient adult IgAV cases (59.3% males, median (interquartile range) age 64 (57–76) years). Skin involvement was present in all patients (necrotic lesions developed in 98 (45.8%) patients and vasculitic lesions above the waistline (i.e. generalized purpura) were observed in 109 (50.9%) patients). Seventy-two (33.6%) patients reported arthralgia, and 29 (13.6%) patients had arthritis. The GI tract and renal involvement developed in 58 (27.1%) and 83 (38.8%) cases, respectively (concurrently in 26 cases). In the multivariate logistic regression analysis, generalized purpura (OR 6.74 (95%CI 3.18–14.31)), the pre-treatment neutrophil to lymphocyte ratio (NLR) >3.5 (OR 2.78 (95%CI 1.34–5.75)), and elevated serum IgA levels (OR 0.40 (95%CI 0.20–0.79)) emerged as factors associated with GI involvement, whereas current smoking (OR 3.23 (95%CI 1.50–6.98)), generalized purpura (OR 1.98 (95%CI 1.08–3.61)), elevated serum IgA (OR 2.25 (95%CI 1.21–4.18)), NLR >3.5 (OR 1.96 (95%CI 1.02–3.77)), and age (1.02 (95%CI 1.01–1.04)) emerged as factors associated with renal involvement.

Conclusion: Generalized purpura and pre-treatment NLR predicted both GI and renal involvement, and active smoking was associated with renal involvement. The serum IgA level had a divergent effect on renal and GI involvement in adult IgAV. The presented findings could help clinicians to identify patients, who need a vigilant monitoring during the acute IgAV.

Serum microRNA profile in adult patients with IgA vasculitis

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Background: Immunoglobulin A vasculitis (IgAV) is a small vessel, immune complex vasculitis, involving skin, joints, gastrointestinal tract and kidney. Currently, no serum diagnostic or prognostic biomarkers exist for IgAV. Circulating microRNAs (miRNAs) can be used as noninvasive biomarkers of various diseases, since they are stable in serum and their expression signatures can reflect the disease-specific pathology. Our aim was to investigate the serum miRNA profile in IgAV patients and healthy blood donors (HBDs), as well as explore in silico their gene targets and biological pathways.

Methods: Small RNAs were isolated from sera of therapy-naive IgAV patients and from age- and sex-matched HBDs (n=6 each) using the novel TRAPR method. Small RNA libraries, prepared with Lexogen kit, were sequenced (Illumina4000) and reads mapped onto human genome (GRCh38). We used the miRror database to predict target genes of differentially expressed miRNAs ($\log_2$ fold change $\geq |1|$ and $p_{adj} < 0.05$) between IgAV patients and HBDs and the enrichment of target genes in biological pathways was analysed using the STRING protein networks platform.

Results: In total, 88 miRNAs were identified as differentially expressed ($\log_2$ fold change $\geq |1|$ and $p_{adj} < 0.05$) between IgAV patients and HBDs. Specifically, 28 miRNAs were elevated in the serum of IgAV patients (e.g. miRNA-128, -937, -30c, -328, -26a, $p_{adj} < 0.005$), whereas 60 miRNAs were decreased (e.g. miRNA-22, -146a, -185, -320a/b/c, -378a, -423, -3184; $p_{adj} < 10\text{-}10$). These miRNAs thus represented the IgAV-associated serum miRNA signature. miRror analysis identified 426 protein-coding genes as predicted targets of IgAV-associated miRNAs. These genes, as analyzed by STRING, were enriched in distinct molecular networks including "Regulation of actin cytoskeleton" (FDR 0.008), "Fcgamma receptor dependent phagocytosis" (FDR 0.01) and "Proteoglycans in cancer" (FDR 0.009). Additionally, three distinct molecular clusters were identified as enriched in miRNA-target genes, specifically "Chemokines and their receptors", "Ubiquitination process" and "Vesicle, endocytosis, lysosomes and their trafficking".

Conclusions: An IgAV-associated serum miRNA signature was identified in adult IgAV patients that clearly discriminated IgAV patients from HBDs, and might play a key role in the pathogenesis of IgAV. Our study sets the basis for the identification of novel, serum-based disease biomarkers in IgAV.

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Detection of anti-drug antibodies improves therapeutic drug monitoring in patients treated with TNF-α inhibitors

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Background and aim: The treatment of inflammatory bowel and chronic rheumatic diseases has changed dramatically since the development of TNF-α inhibitors. However, despite evidences of high efficacy, many patients do not respond or fail to respond to the treatment, and the immunogenicity, formation of anti-drug antibodies (ADA), could be the major reason. Therefore, the importance of therapeutic drug monitoring of TNF-α inhibitors, such as infliximab (IFX) and adalimumab (ADL) has been increasingly recognized in the recent years, thus also establishing a demand for developing appropriate assays. Many different assays used in routine analysis of ADA differ in their reported levels and types of the detected antibodies.

We aimed to investigate which method for ADA detection best improves the therapeutic drug monitoring of IFX and ADL.

Methods: 134 samples of patients on IFX therapy (IFX group) and 68 samples of patients on ADL therapy (ADL group) from the Departments of Rheumatology and Gastroenterology, University Medical Centre Ljubljana, with undetectable drug levels were tested for ADA with *in-house* competitive ELISA (cELISA), *in-house* bridging ELISA (bELISA) and Reporter Gene Assay (RGA). Samples were collected between August 2016 and October 2019. Agreement between assay results was quantified with Kappa coefficient.

Results: In IFX group 22/134 (16%) and in ADL group 12/68 (18%) samples negative in bELISA tested positive in cELISA. The Kappa coefficients between bELISA and cELISA were 0.597 (95%CI 0.466–0.728) for anti-IFX assays and 0.597 (95%CI 0.416–0.777) for anti-ADL assays. The results of cELISA were confirmed with RGA.

In IFX group we have samples of 28 patients and in ADL group samples of 17 patients available at different time points. In samples of 10/28 (IFX group) and 6/17 (ADL group) patients cELISA could detect ADA earlier than bELISA. In samples of 18 (IFX group) and 11 (ADL group) patients cELISA and bELISA yielded the same result, negative or positive.

Conclusions: Our results show that cELISA could be superior in clinical practice because it detects ADA earlier and in up to 18% more samples than routinely used bELISA.

Extracellular vesicles in antiphospholipid syndrome

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Antiphospholipid syndrome (APS) is a systemic autoimmune disease, characterized by thromboses and/or obstetric complications and persistence presence of antiphospholipid antibodies (aPL) (1). aPL, cause activation of vascular cells (endothelial cells, platelets, monocytes) and release of extracellular vesicles (EVs). EVs are submicron particles constitutively released from all cells. Increased numbers of EVs are released in response to stimuli such as cellular activation and/or apoptosis. EVs circulate in plasma at concentrations approaching 10^9/mL. Frequencies of plasma EVs of different cellular origin may be altered in disease states.

The last decade has seen a sharp increase in the number of scientific publications describing physiological and pathological functions of extracellular vesicles (EVs), a collective term covering various subtypes of cell-released, membranous structures, called exosomes, microvesicles, microparticles, ectosomes, oncosomes, apoptotic bodies, and many other names. The International Society for Extracellular Vesicles (ISEV) proposed Minimal Information for Studies of Extracellular Vesicles ("MISEV") guidelines for the field (2). According MISEV2018 guidelines EVs can be divided into subsets according to their a) physical characteristics, such as size ("small EVs" (sEVs) and "medium/large EVs" (m/lEVs), with ranges < 100nm or < 200nm for sEV and > 200nm as m/lEV) and density (low, middle, high); b) biochemical composition (protein marker positivity) or c) descriptions of conditions or cell of origin.

EVs, particularly endothelial m/lEVs, have been studied in antiphospholipid syndrome (APS) (3). Compared with healthy controls, patients with aPL have significantly higher levels of circulating endothelial and platelet m/lEVs. On the other hand, no data till now has been provided for exosomes or sEVs (<100nm), secreted vesicles of endosomal origin. Our research group first determined plasma levels of sEVs in APS patients and investigate their surface protein profiles. Altered sEVs levels as well as different exosomal surface marker profile between APS and healthy controls were found. These findings show that a complex systemic network existing in the form of cell-cell communication via sEVs is altered in APS patients.

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DEVELOPMENT OF ADVANCED THERAPIES

Adoptive Cell Therapy and chimeric antigen receptor – T cells

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Adoptive T-cell therapy can be divided mostly to therapies with tumor-infiltrating lymphocytes (TIL) and to therapies using T-cells genetically modified with transgenic T-cell receptors (TCR) or chimeric antigen receptors (CAR). All of these therapies are exclusively personalized and are at the moment based on the autologous transplant of the patient's own cells. Therapeutic cells are prepared for each patient individually, which carries a great impact on the processes of their development and production, as well as the logistics and costs involved. The new mode of therapies with CAR-T, for specific diseases at the moment the only registered mode of ATC, causes revolutionary breakthroughs in the development of such advanced therapeutics and, consequently in clinical oncology. CAR-T therapy is achieving an incredible success in clinical practice especially in combat against hematological cancers, while the treatment of patients with solid tumors it has not been as successful. Along with that, due to great complexity of the CAR-T therapy, it is accompanied by frequent and severe side effects, which can be fatal in worst cases. By adopting adequate measures, these effects can be controlled and partially mitigated. CAR-T therapy is being introduced to Slovenia through registered, commercially accessible therapeutics of this kind, while the access to other ATC is still pending. At the same time, in Slovenia in this field, we are developing our own knowledge and technology, hoping that new, efficient treatment modalities become accessible to a wider population of patients as soon as possible.

Nobel Prize in Chemistry 2020

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In Year 2020, Nobel Prize Committee awarded 12 laureates a Nobel Prize for different discoveries with important benefit for humankind. Their findings range from the formation of black holes to important tools for genome editing.

The Nobel Committee awarded The Nobel Prize in Chemistry 2020 two scientists, which pioneered the revolutionary genome editing technology CRISPR/Cas9. Emmanuelle Charpentier, born in 1968 in France and Jennifer Doudna, born in 1964 in USA, share the prize for their important work on developing a powerful gene-editing tool CRISPR/Cas that derives from majority of species of archaea and bacteria. Emmanuelle Charpentier who works at Max Planck Unit for the Science of Pathogens in Germany discovered that CRISPR/Cas system constitute a variety of immune systems that offers bacteria and archaea protection against invading phages and plasmids. Key feature of her finding, which was published in year 2011 in Nature, is tracrRNA mediated maturation of short CRISPR RNA (crRNA) that silence foreign nucleic acid in a sequence specific manner, therefore offering RNA-mediated immunity against invaders.

Shortly after this discovery, she began her collaboration with Jennifer Doudna from University of California, Berkeley in USA. Their joint effort led to the rise of CRISPR/Cas9 system, which comprises a dual base-paired small RNAs (crRNA+tracrRNA) and an endonuclease Cas9. Pairing of crRNA to tracrRNA forms a two-RNA structure that directs CRISPR-associated protein Cas9 to introduce a site-specific DNA double-stranded break. This latter can be exploited for programmable genome editing via intrinsic cell repair mechanism. Repair mechanisms are exploited to introduce the desired changes. Using CRISPR/Cas9 system, knockout models by introducing indel mutations can be made or knock in models by codelivery of a donor DNA can be established. Work describing the discovery of CRISPR/Cas system was published in 2012 in Science.

CRISPR/Cas technology allows a precise way to alter genome and influence gene expression. Although the genome-wide specific CRISPR/Cas9 system has some possible disadvantages regarding off-target effects, the wide range of applicability offers tremendous progress in time and efficiency in development of various cell lines, animal models for human illnesses and gives a possible treatment choice for human genetic-derived diseases and that represents a revolution in personalized medicine.

CRISPR method modification for enhanced genome editing

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Background: The CRISPR/Cas system is a highly potent tool, which has revolutionized genome engineering and regulation of gene transcription in various cells and organisms. This gene-editing tool consists of a guide RNA (gRNA), which targets the Cas9 endonuclease to the desired genomic site. Cas9 catalyzes the formation of double-strand DNA breaks, which are then repaired by different cell mechanisms. Depending on the size (tens of base pairs) of indel mutations, higher rates of "knock-out" can be achieved. To achieve greater indel mutations, CRISPR system can be coexpressed in cells with DNA exonucleases, which cause increased recessions of DNA following DNA breaks. We show that joint action of the CRISPR system with different exonucleases significantly increases the percentage of indel mutations at various targeted genes. Of the different exonucleases tested, the E.coli-derived exonuclease III (EXOIII) exhibited the best performance in terms of indel formation.

Material and methods: K562 cells, model for Philadelphia chromosome positive cells and chronic myelogenous leukemia (CML) patient cells were used. Constructs, expressing BCR- ABL1 targeting gRNA and Cas9, tethered via coiled-coil forming peptides to E.coli exonuclease EXOIII, were nucleofected into target cells. T7E1 assay to detect genome modifications was carried out. TUNEL assay, FACS analysis with bioluminescence measurement were used for cell death determination. SCID mice were used for a subcutaneous K562 cancer model.

Results: Of the different exonucleases tested, the EXOIII exhibited the best performance in terms of indel formation. To improve the rate of indel mutations, we connected Cas9 and EXOIII via coiled-coil forming peptides, bringing the two enzymes into close proximity. This resulted in increased indel formation compared to the classical CRISPR/Cas system. We performed a case study for the use of our novel CRISPR system as a potential anti-cancer therapeutic tool. In the case of our new system, we showed significant increase in cell death due to higher genome modification in BCR-ABL1 region. Later, these findings were confirmed also in animal cancer model, where animals with tumors, electroporated with CRISPR-EXO system showed 100% survival and drastic reduction in tumor size.

Conclusion: Our de novo upgraded CRISPR system by tethering Cas9 protein to exonuclease EXOIII by heterodimeric coiled-coil forming peptides, resulted in higher editing of BCR- ABL1 fusion gene, leading to enhanced death of CML cancer cells.

Regulatory T cells for immunotherapy of autoimmune diseases

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Background: Autoimmune diseases affect people of all ages often greatly aggravating their quality of life. Regulatory T cells (Treg) are crucial for the maintenance of homeostasis and the prevention of immune responses against self-antigens. They can employ direct and indirect mechanisms such as the expression of anti-inflammatory cytokines or via co-inhibitory receptors. They can even promote tissue repair. Clinical trials demonstrated that polyclonal Tregs can control autoimmune responses following adoptive transfer. In preclinical models, antigen-specific Tregs were superior to polyclonal ones, which has driven the field towards the development of antigen-specific Tregs for cell-based therapies. However, such cells are rare end difficult to isolate. This could be overcome by engineering the polyclonal Tregs into antigen-specific ones by T cell receptor (TCR) gene transfer.

Methods: We used a preclinical model of experimental autoimmune encephalomyelitis (EAE), which is an animal model for demyelinating diseases of the central nervous system (CNS) including multiple sclerosis. The EAE is triggered by immunization with encephalitogenic peptides like peptide from myelin oligodendrocyte glycoprotein (MOG). Tregs engineered to express TCR that recognizes MOG peptide protect mice from the development of EAE. To understand molecular mechanisms involved in the protective function of engineered autoreactive Tregs we silenced or overexpressed several proteins shown to be overexpressed in the CNS of EAE mice.

Results: We have shown that engineered antigen-specific Tregs employ IL-10, LAG-3, and CTLA-4 to inhibit disease in recipient mice while the expression of the tissue repair factor AREG has no effect. Antigen-specific Tregs can intercept EAE progression when administered at the disease onset but not at the peak of the disease. Engineered cells also persist in the animals and, compared to endogenous Tregs, display activated phenotype.

Conclusions: This study greatly contributes to the understanding of the features that control the efficacy of Treg cell therapy. Engineered autoreactive Tregs protect from CNS autoimmunity via multiple immune mechanisms and they block disease progression upon administration at clinical onset underscoring their immense potential for intercepting autoimmune responses and the development of cell-based therapies.

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Next-generation Chimeric Antigen Receptor (CAR) T Cells

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Background: T cell-intrinsic dysfunctions and immunosuppressive tumor microenvironment (TME) influence clinical efficacy of CAR T cells. We recently discovered that inducible expression of transcription factors or immunostimulatory molecules improved functional qualities and augmented anti-tumor activity of CAR T cells in preclinical *in vivo* models.

Methods: We have developed genetic approach that combines autonomous antigen-triggered production of an accessory molecule, along with constitutive CAR expression in a single lentiviral vector - *Uni-Vect*. By knocking out the endogenous TCR we render CAR signaling an exclusive activator of the system. To modulate CAR T cell-intrinsic features we implemented Uni-Vect for transient, activation-inducible transcription factor expression (iTF-CAR T). In a second model, we introduced inducible expression of IL-12 (iIL-12-CAR T) to overcome immunosuppressive TME. We analyzed phenotype, expansion, and anti-tumor activity of "upgraded" CAR T cells *in vitro* and *in vivo*.

Results: *iTF-CAR T* cells demonstrated enhanced antigen-dependent proliferation and a less differentiated phenotype following repeated stimulations with cancer cells *in vitro*. CyTOF analysis of iTF-CAR T cells showed that antigen-inducible expression of a single TF favorably affected T cell markers of efficacy. Finally, we tested activity *in vivo* in tumor xenografts models where iTF-CAR T cells demonstrated significantly increased expansion in the blood compared to control CAR T cells. Importantly, T cells expansion was transient and ultimately contracted to the normal levels after tumor was cleared. iTF- CAR T approach addresses challenges related to intrinsic CAR T cell dysfunctions, however, it may not directly counteract immunosuppressive TME. Therefore, we have developed an *iIL-12-CAR T* system and demonstrated that only iIL-12- secreting, and not conventional CAR T cells, were capable of eradicating solid tumors *in vivo*.

Conclusions: First, we demonstrated that inducible TF expression equips CAR T cells with improved therapeutically relevant T cell states, which translates into improved *in vivo* T cell expansion. Second, iIL-12 expression remarkably enhanced anti-tumor responses in established solid tumors *in vivo*. With these contributions, we have established a foundation for more effective next- generation cellular immunotherapies.

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ANTIGEN PRESENTING CELLS AND T CELL RESPONSE

Safety and immunogenicity of varicella vaccine in children with juvenile idiopathic arthritis treated with anti-cytokine therapy

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Background: Children with juvenile idiopathic arthritis (JIA) on immunosuppressive therapy are at risk for more severe course of varicella infection. Vaccination against *Varicella zoster virus* (VZV) is the most effective method for protection against varicella, but data on live attenuated vaccines in patients treated with anti-cytokine therapy are scarce. The aim of this study is to evaluate long-term safety and immunogenicity of varicella vaccine in children with JIA, treated with anti-cytokine therapy.

Methods: VZV-naive patients with JIA on anti-cytokine therapy, who were at risk for contracting varicella, had stable disease and normal values of immunoglobulins and lymphocyte populations, were vaccinated against VZV. Adverse events and disease activity after vaccination were followed. One month and then every 6-12 months after second vaccination VZV-specific humoral and cellular immunity were measured by ELISA and intracellular cytokine staining, respectively. Control group includes children with JIA who had varicella, healthy children who had varicella and healthy children after varicella vaccination.

Results: To date, 15 patients were vaccinated. At the time of vaccination, 11 patients were treated with anti-TNFα therapy, 3 with anti-IL6 therapy and 1 with anti-IL1 therapy. There were no serious adverse events, no increase in disease activity and no varicella infection after vaccination. Twelve patients developed VZV-specific humoral immunity and 10/12 patients VZV-specific cellular immunity following vaccination. Cellular immunity persisted for longer time than humoral. Three patients had a mild case of varicella 4 months – 4.5 years after vaccination. Further 5 patients had a documented contact with varicella but did not contract it.

Conclusion: Vaccination against varicella appears to be safe, but not always immunogenic and also not effective in some children with JIA, treated with anti-cytokine therapy. VZV-specific cellular immunity could offer additional insight into immunogenicity of the vaccine.

Optimization of THP-1 cell line differentiation to macrophages for *in vitro* studies of macrophage immune response to infection with different strains of group B *Streptococcus*

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Macrophages are mononuclear phagocyte cells that are part of innate immunity and the first line of defence against pathogenic microbes. They also play a key role in the maintenance of tissue homeostasis and repair and are as such extremely heterogeneous. In order to fulfil all of their functions they are capable to adopt different activation states by polarization from basic M0 state, which differ in metabolic phenotype. The so-called M1 macrophages are associated with inflammatory responses and acquire ATP by aerobic glycolysis while M2 macrophages produce anti-inflammatory mediators and depends mainly on oxidative phosphorylation. Studies show that infection with pathogens induce specific M1 or M2 programs in macrophages and therefore indicate that their immune functions are directly related to metabolic reprogramming. We have therefore set to determine immune response of macrophages following infection with different Group B *Streptococcy* strains on the level of macrophage immunometabolism. *Streptococcus agalactiae* is a Gram-positive pathobiont that can thrive and live in a healthy host without causing any problems but due to many virulence factors that allow him to avoid host immune responses it remains one of the most invasive pathogens that can cause serious illnesses such as sepsis, pneumonia, meningitis and death in newborns and immunocompromised elderly people. THP-1 monocytic cell line has been shown to be a good model for *in vitro* studies of macrophages. As part of our study we first optimized the process of differentiation of THP-1 monocytes into macrophages. For this purpose, cells were treated with 3 different concentrations of mitogen PMA (30 nM, 100 nM, 162 nM) and allowed to differentiate for 24 and 72 hours, followed by 1 or 5-days rest in medium without PMA. Using the flow cytometry, we sought to determine the viability of the cells and the presence of surface markers CD14, CD16, CD163, CD11c and intracellular CD68. Differentiation lasting for 72 hours with 100 nM PMA and 5-day rest resulted in significantly higher cell viability, while the expression of markers was comparable between the treated cells. Successful differentiation into macrophages was confirmed by bright-field microscopy and confocal microscopy.

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Difference in the dendritic cell function in intestinal immunity and inflammation

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The intestine is a complex environment that is constantly exposed to antigens derived from food, microbiota, and metabolites. Intestinal dendritic cells (DC) have the responsibility of establishing oral tolerance against these antigens while initiating immune responses against mucosal pathogens. In the intestine, DC are a heterogeneous population of innate immune cells composed of conventional cDC (classical and monocyte-derived DC, Langerhans cells), and plasmacytoid pDC. We were studying function of gut DC and T lymphocytes in the context of intestinal homeostasis and inflammation. Breakdown of tolerance against the commensal micro-flora is believed to be a major factor in the pathogenesis of inflammatory bowel disease. Dendritic cell (DC) function is believed to be of critical importance for the pathogenesis of IBD. Intestinal biopsies (inflamed and uninflamed areas) were obtained from 30 patients with IBD before and after the treatment with TNF inhibitors (infliximab 13 patients, adalimumab 17 patients) and 10 healthy controls.

Intestinal lamina propria cDCs were identified as lineage (CD3, CD19, CD56 and CD14)-negative cells that express CD11c and plasmocytoid pDCs that express CD123 and CD303. Conventional DCs were further analysed on the expression of costimulatory molecules CD80, CD86, and HLA-DR, CD83, CD103. To determine the proportions of different subtypes of T lymphocytes cells were stained with CD103/CD28/CD3/CD8 and FoxP3/CD127/CD4/CD25/CD3. The analysis was performed on BD FACS Canto II using FlowJo software. Disease activity was endoscopically assessed at baseline and after treatment induction. We found a significantly higher frequency of plasmacytoid DCs and conventional DCs in the inflamed colonic mucosa compared with uninflamed mucosa. Moreover, the proportion of CD80+, CD83 and HLA-DR expressing myeloid DCs were significantly higher in inflamed mucosal tissue compared to a uninflamed mucosal tissue. IBD patients compared to control group had higher expression of costimulatory CD28 molecules on cytotoxic T lymphocytes and they had more activation molecules HLA-DR+. Helper T cells expressed more IL-2RA (CD25+) receptor and had regulatory properties (FoxP3+CD25hiCD127low/-). 18/30 (60%) patients responded to treatment at week 12. Responders had significantly higher proportion of cDCs with higher expression of HLA-DR in inflamed mucosa before treatment compared with non-responders. After the treatment, the responders to showed lower frequency of cytotoxic T lymphocytes expressing CD28 molecules and HLA-DR+, as well as lower frequencies of cytotoxic T lymphocytes expressing integrin αEβ7 (CD103+). Understanding these processes should help target individual subsets for 'fine tuning' immunological responses within the intestine, a process that may be of relevance for the treatment of inflammatory bowel disease (IBD).

Immunometabolism - targeting metabolism of antigen presenting cells

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Warburg presented the first evidence that cancer cells produce lactate from glucose under normoxic conditions, a phenomenon known as the 'Warburg effect.' Recently, many studies have explored the modulation of cancer cell metabolism as a therapeutic strategy.

Similarly as cancer cells, immune cells use different metabolic pathways to support their differentiation and specific functions. The metabolic pathways change depending on the differentiation and activation of the immune cells and at the same time, they are critically dependent on the microenvironment.

For example, naive T cells in quiescence are fueled by fatty acid oxidation (FAO), cytotoxic CD 8+ T lymphocytes mainly depend on glycolysis while regulatory T lymphocytes (Treg cells) rely on FAO and oxidative phosphorylation (OXPHOS). Recently, metabolic reprogramming of antigen presenting cells (APC) has been also implicated in regulating their phenotype and function and the studies show that metabolism of monocytes, macrophages and dendritic cells (DC) is altered in case of different autoimmune diseases and cancer. Studies suggested that DC activation also requires an increase in glycolysis, while FAO is important in tolerogenic DCs. The reduction of glycolytic capability significantly impairs DC effector functions including antigen presentation, co-stimulatory molecule expression, cytokine secretion, and T lymphocyte stimulatory capacity.

For macrophages, it was demonstrated that the metabolic profile of M1 macrophages shift to glycolysis, which is crucial for production of mediators such as NO, whereas M2 macrophages rely on mitochondrial OXPHOS. Importantly, glycolysis itself drives inflammatory macrophage responses, while OXPHOS supports M2 activation.

Altogether, the mechanisms behind metabolic regulation of macrophages polarisation and DC activity are still being explored and only very recently, unexpected non-metabolic functions for metabolic enzymes were identified in the context of inflammation. Specifically, there are several open questions of metabolic alterations of different types and subtypes of APC cells because of pathological changes in autoimmune diseases. Metabolic phenotype of APC cells could for example present a potential biomarker for predicting the response to specific treatments in autoimmune diseases such as rheumatoid arthritis.

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ZDRAVSTVENA NEGA

Kronične pljučne bolezni

Astma

Alergijske bolezni

Pljučni rak

Bolnik s covidom-19

SLOVENIAN ASSOCIATION OF ALLERGY AND CLINICAL IMMUNOLOGY

Združenje pnevmologov Slovenije
Slovenian Respiratory Society

KRONIČNE PLJUČNE BOLEZNI

Safety culture at the University Clinic Golnik

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Between 2005 and 2019, a total of 1,001 reports of medication-related adverse events and near misses were collected at the University Clinic Golnik. In 2005, 5 medication-related adverse events were reported (5,436 hospitalizations). In 2014, the number rose to 52 events, 15 of which were near misses (6,843 hospitalizations); and in 2015, there were 112 reports, 20 of which were those of near misses (7,271 hospitalizations). Reports were mostly submitted by nurses. In 2015, only a few reports were submitted by physicians, but in 2018, there were 19 physicians and 10 pharmacists who reported of adverse events and/or near misses. There were 152 adverse events (9,203 hospitalizations) in 2016. In 2017, we collected reports of 128 adverse events (8,844 hospitalizations). There were 197 adverse events (9,095 hospitalizations) in 2018. In 2019, we collected reports of 229 adverse events, most of which (108 adverse events) were medication-related, and the least adverse events occurred in the area of work organization (16). The number of adverse events is increasing each year. We believe that this is due to the increased commitment to report such events.

The main two goals of adverse event reporting and control are to analyze causes and to implement corrective measures. We follow the PDCA cycle and evaluate the outcome of implemented changes. This is also where the staff get their chance to be active in implementing the necessary changes. It is our goal for the employees to realize that making a mistake does not result in a punishment, but rather that correct steps will reduce damage to the patient or the staff, and prevent future recurrence of such mistakes by finding the appropriate solution to the problem.

An experimental e-registry of adverse event reporting has been set up in 2020. Its emphasis is on following up analyses of causes and corrective measures. Each person who is assigned tasks receives these by email. Only up-to-date contents that regularly follow the analysis of adverse events in practice enable continuous development of the staff, case-based learning and problem solving.

Zavedanje medicinskih sester o vlogi na področju nadzora nad tobakom

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Uvod: Povečati znanje, odgovornost in zavedanje medicinskih sester o nekadilskem vedenju ter izobraževanju pacientov o opuščanju kajenja predstavlja pomembno področje v okviru promocije nekajenja med medicinskimi sestrami. Nekadilski status zdravstvenih delavcev je ključni element za zagotavljanje učinkovite pomoči pri opuščanju kajenja.
Glavni namen raziskave je bil ugotoviti mnenje medicinskih sester o zavedanju lastnega pomena nekadilskega vedenja.

Metode: Uporabljena je bila kvantitativna metoda dela, kot instrument smo uporabili strukturiran vprašalnik. Raziskava je bila izvedena med medicinskimi sestrami na vseh treh nivojih zdravstvenega varstva, ki so se udeležile delavnic v okviru mednarodnega projekta Tobacco Control v obdobju od leta 2017 - 2018. Uporabljen je bil priročni vzorec. V raziskavo je bilo vključenih 79 medicinskih sester, ki so se udeležile delavnic. Anketo je izpolnilo 66 medicinskih sester. Podatki so analizirani s pomočjo programa SPSS 20.00.

Rezultati: Statistično pomembnih razlik o vplivu lastnega kajenja in zglednega delovanja glede na starost in delovno dobo nismo ugotovili. Rezultati so pokazali na enotno, stabilno in pozitivno mnenje o vplivu lastnega kajenja in zglednega delovanja (PV = 1,4; SO = 0,7), o vlogi medicinskih sester pri aktivni pomoči pacientom pri opuščanju kajenja (PV = 1,4; S= 0,8) ter o potrebi po dodatnem znanju na področju nadzora nad tobakom (PV = 1,5; SO = 0,8).

Diskusija in zaključek: Ugotovitve raziskave kažejo nato, da se anketiranci v veliki meri zavedajo, da lastno kajenje vpliva na poslanstvo in delo na področju promocije zdravja, promocijo nekajenja in pomoč pri opuščanju kajenja, kar vsekakor lahko predstavlja oviro za učinkovito izvajanje nadzora nad tobakom. Glede na rezultate raziskave o pridobivanju znanja, menimo, da je potrebno medicinske sestra opolnomočiti na področju opuščanja kajenja z uvedbo različnih metod dela ter krepiti programe promocije nekadilskega vedenja med zdravstvenimi delavci. Različne iniciative po vzorih iz tujine (npr. "Medicinske sestre proti kajenju") bi lahko delovale s ciljem zmanjševanja kajenja v tej skupini zdravstvenih delavcev.

Kaj mora medicinska sestra vedeti o neinvazivni mehanski ventilaciji?

Ditka Benedičič Katona

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Neinvazivna mehanska ventilacija (NIMV) je temeljni del obravnave pri pacientih s poslabšanjem kronične obstruktivne pljučne bolezni (KOPB), saj zmanjša število intubacij, hospitalizacij in smrti (Fisher, 2018), hkrati pa kot kronična NIMV dokazano učinkuje pri hiperkapničnih pacientih s KOPB (Duiverman, 2019). Študije primerov akutne uporabe NIMV so pokazale, da rezultati doseženi v kliničnem okolju pogosto ne dosegajo rezultatov pridobljenih z raziskavami. Dejavniki vključujejo neprimerno izbiro pacientov in neučinkovito uporabo NIMV. (Elliott, 2018).

Pri obravnavi pacientov na NIMV je potreben multidisciplinarni pristop in formalno izobraževanje zaposlenih, ki ga dopolnjuje usposabljanje na delovnem mestu. Uspešen NIMV team mora imeti posameznike z veliko različnimi znanji (Elliott, 2018), zlasti s profesionalnimi in tehničnimi veščinami (Escarrabill, 2015). Eni osebi ni potrebno storiti vsega, toda tim zahteva vodjo, ki prevzame odgovornost. Predvsem se mora znati odločati kateri pacienti morajo prejemati zdravljenje z NIMV in kako hitro je potrebno ukrepati (Elliott, 2018).

Ključni dejavniki, ki jih je potrebno upoštevati za uspešno NIMV (British Thoracic Society Reports- BTS, 2018):

1. Zdravljenje pravih pacientov: Ali je indicirana NIMV?
   Študija NCEPOD (National Confidential Enquiry into Patient Outcome and Death) je pokazala, da zdravljenje z NIMV ni bilo primerno ali ni bilo indicirano pri skoraj 20% pacientih. Razlogi za to so bili zdravljenje hipoksemije namesto hiperkapnije ali zdravljenje metabolične acidoze. Skoraj dve tretjini pacientov, pri katerih NIMV ni bila indiciran ali je bil neustrezna, je umrlo. Zato je zdravljenje pravih pacientov z ustrezno indikacijo nujno.
2. Načrt in potek zdravljenja z NIMV.
   Pomembno je načrtovanje zdravljenja, saj NIMV uspe v dveh tretjinah primerov. Ko z NIMV ne izboljšamo hiperkapnije, je tveganje za smrt veliko. Vnaprejšnje načrtovanje ukrepov, ki jih je treba sprejeti, če je NIMV neuspešna, lahko izboljša izid zdravljenja.
3. Dokumentiranje in prilagajanje nastavitev NIMV kot odziv na nove informacije (npr. izvid plinske analize arterielne krvi).
   Študije so pokazale, da tam, kjer so bile nastavitve NIMV ustrezno dokumentirane, je bila umrljivost nižja. Dokumentacija nastavitev je bila v 50% primerov slaba, kljub temu da je več kot dve tretjini bolnišnic imelo načrt za izvajanje NIMV in več kot 80% z določeno NIMV kontrolnim obrazcem.

4. Začetek NIMV v 60 minutah po odločitvi za zdravljenje z NIMV.
   Klinično poslabšanje zaradi zamujenega zdravljenja lahko povzroči poslabšanje acidoze. Pri meritvah plinov v krvi pred NIMV je poslabšanje acidoze povezano s povečano umrljivostjo.
5. Neprekinjeno spremljanje pacienta v prvih 24 urah ali dokler začetna respiratorna acidoza ne izzveni.
   Študije so pokazale, da pacienti, ki so bili zdravljeni z akutno NIMV, v prvih 24 urah niso bili dovolj pozorno spremljani, kar bi lahko povzročilo zapoznelo prepoznavanje poslabšanja ali prekinitve NIMV. BTS in NCEPOD priporočata neprekinjeno spremljanje pulzne oksimetrije, frekvenco dihanja in pulza v prvih 24 urah ali do razrešitve acidoze.
6. Usposabljanje in usposobljenost osebja.
   Vsi zgoraj navedeni ukrepi se do neke mere opirajo na dobro klinično znanje, razumevanje NIMV in usposobljenost za vodenje pacientov na NIMV. To velja za vse člane tima NIMV. Za zagotavljanje visokokakovostne in učinkovite storitve standardi kakovosti BTS od bolnišnic zahtevajo, da lahko dokažejo stopnjo usposobljenosti osebja.

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Prehransko stanje pulmološkega bolnika

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Bolniki z različnimi respiratornimi obolenji: s kronično obstruktivno pljučno boleznijo, s cistično fibrozo, s tuberkulozo, s pljučnim rakom, z idiopatsko pljučno fibrozo in bolniki po transplantaciji pljuč so v veliki meri podhranjeni. Izjema so bolniki z motnjami dihanja v spanju, ki se običajno spopadajo s morbidno debelostjo in tudi potrebujejo prehransko obravnavo.

Izguba telesne mase, predvsem puste telesne mase je pogost spremljevalec kroničnih respiratornih bolezni. Pljučna bolezen s svojimi simptomi povzroči zmanjšan vnos hrane na drugi strani pa povečane energijske in beljakovinske potrebe, kot posledica same bolezni, vodijo v podhranjenost. Pljučni bolniki s podhranjenostjo imajo daljšo ležalno dobo, slabši izid zdravljenja in slabšo prognozo, zato je pomembno, da podhranjenost prepoznamo čim prej in jo poskušamo obravnavati individualno. Samo ITM ni zadosten kriterij za diagnosticiranje podhranjenosti, zato uporabimo vprašalnike za presejanje. Prehranska obravnava obsega oceno prehranskega stanja, pomembna je meritev telesne sestave in s tem določitev indeksa puste telesne mase. Prehranski ukrepi, ki sledijo, so individualno prilagojeni posameznemu bolniku. Timski pristop z vključitvijo različnih strokovnjakov v obravnavo je za uspešnost zdravljenja zelo pomemben. Z rednim spremljanjem prehranskega stanja in presnove nadzorujemo uspešnost prehranskih ukrepov in po potrebi prilagajamo ukrepe.

Prehranska podpora pozitivno vpliva na uspešnost zdravljenja in kakovost življenja bolnika s pljučno boleznijo.

Aplikacija pospeševalca izdihanega zraka (Free Aspire) ali izkašljevanje s pozitivnim tlakom (Cough Assist) v respiratorni fizioterapiji pri pljučnem bolniku

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Uvod: Respiratorna fizioterapija velik poudarek namenja čiščenju in predihavanju pljuč. Pri vseh bolnikih z oteženim ali onemogočenim izkašljevanjem je respiratorna fizioterapija ključnega pomena. Poznamo mnogo tehnik za pomoč pri izkašljevanju, zato je odločanje o pravilni zelo pomembno.

Namen: je predstaviti in primerjati novo tehniko izkašljevanja s pomočjo pospeševalca ekspiratornega tlaka - Free Aspire, z že veljavno tehniko izkašljevanja – Cough Assist glede na izkušnje na Univerzitetni Kliniki Golnik.

Metode dela: Free Aspire je pospeševalec ekspiratornega pretoka, ki omogoča bolniku lažje izkašljevanje. Prilagojena je glede na bolnikov naravni vzorec dihanja. Bolniki se med terapijo počutijo prijetno in udobno. Gre za popolnoma varno tehniko brez znanih kontraindikacij. Tehnika neinvazivno odstranjuje sluz, kjer ni pritiska na pljuča, tlak pa je minimalen. Način odstranjevanja izločkov s tehnologijo Free Aspire se doseže povečanim pretokom med izdihom. V ustniku pretok zraka zaokroži in se nato prenese v pljuča, kjer seže za sluzni čep in ga pomakne proti velikim dihalom. Postopek deluje v fazi izdiha ter sledi naravnem ritmu dihanja bolnika, zato to tehniko uporabljamo tudi pri nesodelujočemu bolniku, ki samostojno diha vsaj eno uro. Učinkovit je za drenažo spodnjih dihalnih poti. Free Aspire uporabljamo pri bolnikih s KOPB, z bronhiektazijami, po OP pljuč, s pljučnico itd. Uporaba Cough Assist-a za pomoč pri izkašljevanju je že zelo uveljavljena. Temelji na uporabi pozitivnega tlaka. V dihalnih poteh bolnika spodbudi vdih (insuflacija), nato omogoči hiter vklop in prehod na negativen tlak (eksuflacija). Prisilni tlak izdiha je tolikšen, da omogoča odstranjevanje izločkov, ki so v dihalnih poteh bolnika. Za predpis se odločamo na podlagi meritev moči kašlja (PCF) in/ali moči dihalnih mišic (MIP/MEP). Indikacije: živčno mišična obolenja, pljučna obolenja, bolniki s traheostomo, huda izčrpanost in slaba učinkovitost kašlja. Kontraindikacije: povišan intrakranialni tlak, nedreniran pnevmotoraks, bulozni emfizem, nesodelujoči bolniki, slaba toleranca bolnika ali odklonilnost, aktivne hemoptize,…

Zaključek: Free Aspire je nova tehnika za pomoč pri izkašljevanju, kjer zaenkrat še primanjkuje število kvalitetnih raziskav z velikim vzorcem preiskovancev. Kaže se, da dela podobno kot že uveljavljen Cough Assist. Zaenkrat še ne obstaja študija, ki bi primerjala obe tehniki. Glede na pregled študij obeh pripomočkov zgleda, da je Free Aspire varnejša tehnika za izkašljevanje, saj še zaenkrat nima znanih kontraindikacij, prav tako pa je manj utrujajoča za bolnika, saj ne deluje na spremembi tlaka. Predvidevamo, da je kombinacija obeh tehnik najboljša. Free Aspire se izvaja pri šibkih,

slabo sodelujočih bolnikih, ki imajo KOPB, pljučnico, bronhiektazije, in so po operaciji pljuč. Cough Assist se uporablja pri tistih bolnikih, kjer je zelo zmanjšana moč kašlja in so dobro sodelujoči. To so bolniki z živčno mišičnimi obolenji (Auger et al., 2017) in pljučnimi obolenji. Obe tehniki se lahko dopolnjujeta, saj Free Aspire čisti male dihalne poti, medtem ko Cough Assist očisti centralno dihalno pot. Aparat Kalos združuje obe tehniki izkašljevanja. Uporaba je v določenih primerih zelo dobrodošla.

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ASTMA

Samonadzor bolnikov z astmo

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Uvod: Pravilen samonadzor bolezni izboljšuje kakovost življenja pacienta z astmo. Z ustrezno zdravstveno vzgojo se omogoči njihovo samostojnost in boljši nadzor nad boleznijo. Cilj raziskave je bil ugotoviti kako pacienti vodijo samonadzor astme doma.

Metode: Kvantitativna raziskava je bila izvedena na priročnem vzorcu 58 pacientov, ki so bili obravnavani v pulmološki ambulanti v Kliniki Golnik zaradi astme, od začetka maja do konca aprila . Podatki so bili zbrani s pomočjo strukturiranega vprašalnika. Za obdelavo rezultatov je bila uporabljena statistična analiza (t-test, Hi-kvadrat in korelacijsko analizo).

Rezultati: Pacienti ocenjujejo, da delno obvladujejo svojo bolezen (75,86%). Ustrezno uporabo inhalacijskih zdravil ocenjujejo kot dobro (84,48%), ampak so neodločni glede uporabe PEF-a (81,03%). Nekadilci bolje poznajo dejavnike, ki poslabšajo astmo (51,72%) v primerjavi s kadilci (31,03%). Pacienti ocenjujejo, da je zdravljenje astme zamudno (87,93%), vendar zaupajo inhalacijskim zdravilom (89,66%) in so pripravljeni spremeniti življenjski stil (86,21%). Večina je je spremenilo življenjske navade zaradi astme (85,96%). Menijo, da je zdravstvena vzgoja pomembna in ocenjujejo, da imajo dovolj znanja, da se astma ne poslabša (82,76%). Ugotavljali smo moč povezanosti med znanjem o astmi, obvladovanjem bolezni ter merjenjem PEF-a doma. Ugotovili smo statistično značilno povezanost med meritvami PEF-a doma in razumevanjem namena merjenja PEF-A vsak dan Povezava je pozitivna ($r = 0{,}898$, $p < 0{,}001$), kar pomeni, da pacienti, ki si doma merijo PEF tudi bolj razumejo namen merjenja PEF-a. Prav tako smo ugotovili statistično značilno povezanost med dejavniki, ki poslabšajo astmo in meritvami PEF-a ($r = 0{,}300$, $p = 0.041$). Povezava je srednje visoka in pozitivna, kar pomeni da pacienti, ki si doma merijo PEF bolj poznajo dejavnike, ki poslabšajo astmo.

Zaključek: Rezultati so primerljivi podobnim raziskavam drugih avtorjev. Za nadaljnjo natančnejšo obdelavo bi bila priporočljiva raziskava, v katero bi bil zajet obsežnejši vzorec pacientov z astmo.

SAQ (Severe Asthma Questionary)-vprašalnik za težko astmo. Multisdiciplinarni pristop za validacijo prevoda

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Uvod: Trenutni vprašalniki, ki jih uporabljamo za oceno urejenosti astme, kot so na primer ACT (Asthma Control Test), so bili razviti predvsem za bolnike z blago do srednje težko astmo. Bolniki s težko astmo predstavljajo najmanjši delež (4-10%) vseh pacientov z astmo, vendar pa imajo nesorazmerno najvišjo stopnjo obolevnosti, komorbidnosti in tudi najvišje stroške zdravljenja.

Na kakovost življenja bolnikov s težko astmo ne vplivajo samo vsakodnevne omejitve zaradi respiratornih simptomov, imajo tudi več in težja poslabšanja, več in pogostejše hospitalizacije, ki motijo življenje bolnikov in njihovih svojcev. Kakovost življenja zniža tudi breme sistemskih steroidov. Neželeni učinki steroidov so povezani s številnimi težavami, vključno s spremembami razpoloženja, samopodobe, težavami s prehranjevanjem, motnjo spanja in spremembami videza. Te neželene učinke lahko izboljšamo z zmanjšanjem peroralnih kortikosteroidov, kar lahko dosežemo, ko bolniki začnejo biološko zdravljenje. Posege, ki izboljšujejo kakovost življenja, povezanih z zdravjem, je mogoče natančno oceniti le, če se uporabijo ustrezna orodja za oceno specifičnih zdravstvenih težav, ki jih imajo ljudje težko astmo.

Vprašalnik za težko astmo SAQ (Severe Asthma Questionary) je bil zasnovan s perspektive bolnika, tako, da odkrije vpliv simptomov astme in stranskih učinkov zdravil, breme jemanja sistemskih steroidov, na kakovost življenja. Zajema vsa področja življenja od težav v službi do zasebnega življenja, spolnosti, prostega časa, vpliva bolezni na odnose s svojci in na lastno samopodobo.

Potek validacije: Za prevod SAQ v slovenski jezik smo se držali protokola skupine Plymouth SAQ. Potreben je bil dvostopenjski postopek, ki je vseboval prevode in kvalitativno analizo razumevanja vprašalnika s strani bolnikov. Sodelovala je interdisciplinarna ekipa medicinskih sester, zdravnikov in kliničnega psihologa.

Udeleženi sta bili dve fokusni skupini bolnikov, ki so bili izbrani tako, da so predstavljali obravnavano populacijo, tj. Bolniki s hudo astmo v skladu s smernicami GINA. Zaželeno je bilo ravnovesje med moškimi in ženskami, starostjo. Povprečna starost udeležencev fokusnih skupin je bila 54,4 let. Sodelovalo je 7 moških in 6 žensk.

Moderator je pridobil soglasje bolnikov. Seja smo zvočno posneli in anonimizirano prepisali. Bolniki so bili seznanjeni s ciljem seje, to je izboljšanje besedila vprašalnika. Prebrali so in izpolnili vprašalnik. Na vsako vprašanje je moderator sprožil razpravo o tem, kako bolniki razumejo, kaj je napisano. Spodbujal jih je, da so opisali, kaj mislijo. Opis vsakega bolnika je postal osnova za razpravo z drugimi udeleženci. Moderator je popisal vse predloge.

Postopek se je nato ponovil z drugo fokusno skupino. Moderator je pripravil priporočilo o končnem besedilu vprašalnika. Skupne predloge smo upoštevali in vprašalnik popravili, dopolnili.

Končno prevedena različica s potrditvijo izvedenih postopkov in kratkim povzetkom vseh vprašanj, ki so jih postavili bolniki je bila predstavljena skupini Plymouth SAQ, ki je prevod odobrila in objavila na svoji spletni strani.

SAQ vprašalnik lahko sedaj uporabljamo za sledenje uspeha zdravljenja težke astme z biološkimi zdravili in tudi za primerjavo z drugimi državami.

Uporaba olajševalcev pri bolnikih s težko astmo na biološki terapiji

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Uvod: Zdravljenje bolnikov s težko astmo je namenjeno nadzoru astme. GINA (Globalna iviciativa za astmo) prepoznava visoko porabo SABA in nepravilne tehnike vdihavanja, kot pomembne dejavnike tveganja za poslabšanje astme.

Cilj: Cilj naše raziskave je bil preučiti tehniko vdihavanja olajševalca pri bolnikih s težko astmo. Preverili smo, ali je bila velika poraba olajševalca povezana z neprimernimi tehnikami vdihavanja.

Metode: Multidisciplinarna skupina (medicinska sestra, farmacevt in zdravnik) je analizirala in ocenila tehniko vdihavanja pri 80 bolnikih s težko astmo na bioloških zdravilih. Vprašali smo bolnika o uporabi olajševalcev in izmerili inspiratorni pretok pri vdihavanju z napravo In-Check Dial®. Primerjali smo podatke bolnikov, ki porabijo 1 do 3 kanistre na leto, s tistimi, ki so porabili 5 ali več.

Rezultati: Med 80 bolniki (30 moških, mediana starosti 55 let) jih je bilo 26 (11 moških, mediana starosti 55,5), ki so porabili 5 ali več kanistrov/leto in 17 (5 moških, mediana starosti 53) z do 3 kanistrov/leto. Samo pri 12 bolnikih smo ugotovili klinično učinkovit pretok (razpon od 30 do 60 l/min). Bolniki z visoko porabo SABA so imeli slabšo inhalacijsko tehniko v primerjavi s tistimi z nizko porabo (pravilno le pri 31 % oziroma 53 %), zavrgli so pol prazen kanister pogosteje (31% v primerjavi z 24 %) in so po nepotrebnem uporabljali vdihovalnik (53% v primerjavi s 35 %).

Zaključki: Več kot polovica bolnikov s težko astmo, olajševalcev ne uporablja pravilno. Visoka poraba olajševalca je povezana z neustrezno tehniko vdihavanja, prezgodaj zavrženimi kanistri in pogosto nepotrebno uporabo zdravila. Izboljšanje tehnike vdihavanja in multidisciplinarni pristop pri obravnavi bolnika, privede do boljšega nadzora nad astmo.

Multidisciplinarna obravnava bolnika s težko astmo v ambulanti za biološko terapijo na Kliniki Golnik

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Astma je bolezen, ki jo spremlja poslabšanje simptomov. Bolnikom s težko obliko astme je namenjeno podporno zdravljenje z biološkimi zdravili. Za zdravljenje težke astme so trenutno v Sloveniji na voljo štiri biološka zdravila. Bolnik s težko astmo je najprej napoten na ambulantni pregled na Kliniko Golnik s strani področnega pulmologa. Na podlagi pregleda se bolnika predstavi na zdravniškem obstruktivnem konziliju za pljučne bolezni, ki tudi sprejme indikacijo za samo zdravljenje ter se določi, katero biološko zdravilo bi bilo za bolnika najbolj primerno. Ob prvi aplikaciji biološkega zdravila je bolnik obvezno hospitaliziran, nato pa zdravljenje nadaljuje ambulantno. Kontinuirana in koordinirana ambulantna obravnava je osnova za zagotavljanje varne in kakovostne oskrbe. Na Univerzitetni Kliniki Golnik poteka ambulantno zdravljenje bolnikov s težko astmo v ambulanti za biološko terapijo. Namen te ambulante je najboljša možna ambulantna oskrba in vodenje te skupine bolnikov, ki imajo lahko pridružene tudi druge kronične bolezni. V zadnjih letih smo reorganizirali način dela v biološki ambulanti in razširili tim poklicnih strokovnjakov z namenom učinkovitejšega vodenja bolnikov s težko astmo. Poleg zdravnika in diplomirane medicinske sestre se v multidisciplinarno obravnavo aktivno vključujejo tudi respiratorni fizioterapevt, dietetik, klinični farmacevt in psiholog. Vsi izvajalci delujejo povezano z učinkovito medsebojno komunikacijo. Diplomirana medicinska sestra ima pomembno vlogo tako pri naročanju bolnikov, izvaja zdravstveno vzgojno delo in samostojno pripravi ter aplicira zdravilo. Bolnika napoti predhodno k zdravniku samo v primeru odstopanj. Respiratorni fizioterapevt bolnika po potrebi nauči ali preveri pravilno tehniko izvajanja dihalnih vaj ter čiščenja dihalnih poti. Prav tako je pomembna tudi prehranska obravnava s strani dietetika pri bolnikih, ki so prepoznani kot prehransko ogroženi. Klinični farmacevt se vključi takrat, ko je potrebno preverjati, koliko zdravil je bolnik dejansko prevzel v lekarni in preveri razumevanje vloge posameznih zdravil. V primeru, da se pri bolnikih opazi izguba motivacije, brezvoljnost in znaki depresije, se vključi tudi psihologa. Naše izkušnje potrjujejo, da se večina vseh bolnikov zelo dobro vključuje in aktivno sodeluje v timskem procesu zdravljenja v biološki ambulanti in imajo bolj urejeno osnovno bolezen ter izboljšano kvaliteto življenja.

ALERGIJSKE BOLEZNI

Timsko sodelovanje in predaja pacienta z anafilaksijo iz alergološke enote v enoto intenzivne terapije - predstavitev kliničnega primera

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Specifična imunoterapija (VIT) s strupi žuželk je edino učinkovito vzročno zdravljenje za paciente, ki so preobčutljivi za pik kožekrilca. VIT izvajamo po konvencionalni (angl. convencional), hitri (angl. rush) ali zelo hitri (angl. ultra-rush) shemi, zdravljenje pa traja približno 5 let. Med zdravljenjem se lahko pojavi približno 12 do 30 odstotkov sistemskih preobčutljivostnih reakcij (Kołaczek et al., 2017; Ludman in Boyle, 2015). Med najpogostejše dejavnike, ki lahko vplivajo na večjo verjetnost in težji potek sistemske preobčutljivostne reakcija spada mastocitoza (Przybilla et al., 2011). Pomembna naloga diplomirane medicinske sestre med zdravljenjem z VIT je zagotavljanje varnosti pacientov, zgodnje prepoznavanje prvih znakov preobčutljivostne reakcije in hitro ukrepanje po smernicah za obravnavo anafilaksije (Košnik et al., 2015; Rezelj, 2012).

Predstavitev primera: 54-letni pacient je septembra 2018 po piku sršena utrpel sistemsko preobčutljivostno reakcijo z dolgotrajno hipotenzijo in izgubo zavesti. V diagnostičnem postopku smo pri pacientu potrdili senzibilizacijo s stupom ose in čebele in glede težo sistemske reakcije ocenili, da potrebuje zdravljenje s specifično imunoterapijo z obema strupoma. Pacient ima potrjeno indolentno mastocitozo, zdravi pa se zaradi arterijske hipertenzije. Do sistemske preobčutljivostne reakcije IV. stopnje je prišlo 20 minut po aplikaciji vzdrževalnega odmerka strupa čebele. Pacient je oba strupa prejemal v intervalu 30 minut. Pacient je kolabiral, bil poten in slabo odziven. Prvi krvni tlak 84/70 je bil izmerjen po aplikaciji adrenalina 0.5mg intramuskularno. Pacient je v skupnem odmerku prejel 2mg adrenalina (4x 0.5mg) intramuskularno, v vmesnih fazah tlak občasno ni bil merljiv. Aplicirali smo tudi 0.2 mg adrenalina subkutano na mesto, kjer je prejel injekcijo specifične imunoterapije, inhalacije adrenalina zaradi pokašljevanja in intravenozno 1000ml fiziološke raztopine. Vmes je prehodno prihajal k zavesti, vendar ni komuniciral. Pacienta smo nato premestili v intenzivni oddelek. Pred premestitvijo je prejel tudi 0.1 ml razredčenega adrenalina intravenozno, nato je adrenalin prejemal v kontinuirani infuziji.

Ob sprejemu Na Oddelek za intenzivno nego in terapijo je bil pacient normotenziven, normokarden, prejemal je infuzijo Adrenalina v 100 ml FR s hitrostjo 30 ml/h, kasneje se je pretok znižal na 15 ml/h, nato smo do večera infuzijo postopoma prekinili. Sprva je imel 2l kisika apliciranega preko nosnega katetra, postopoma smo kisik odstranili. Tekom dneva je bil vitalno stabilen, zaradi hemodinamskega nadzora je bil izvajan neinvazivni monitoring. Vzorec triptaze (20.9) je bil odvzet 120 minut po začetku

sistemske preobčutljivostne reakcije, kar potrjuje, da je šlo za anafilaksijo.

Pacient je bil zaradi sistemske preobčutljivostne reakcije 24 ur zadržan v intenzivni enoti. Predpisan ima recept za dva avtoinjektorja adrenalina Epipen. Ob odpustu je prejel natančna navodila o izogibanju kožekrilcem in navodila kako ukrepati ob morebitnem ponovnem piku. O načinu uporabe avtoinjektorja adrenalina smo poučili tudi pacientove svojce.

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Zdravljenje alergijskih bolezni s specifično imunoterapijo

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Specifična imunoterapija z alergeni je metoda zdravljenja, pri kateri pri alergičnih osebah z aplikacijo ponavljajočih odmerkov alergena skušamo vzpostaviti imunsko toleranco. Gre za etiološko zdravljenje alergijskih bolezni.

Z imunoterapijo zdravimo tiste alergijske bolezni, ki jih posredujejo IgE. Odločitev o IT sprejmemo po prepričljivi anamnezi, dokazani senzibilizaciji (kožni testi alergije, serološki testi, celični testi) in jasni povezavi med simptomi alergijske bolezni in izpostavitvijo.

Natančni imunski mehanizmi specifične imunoterapije niso poznani. Med imunoterapijo se zmanjša koncentracija sIgE, poveča koncentracija sIgG4, poveča koncentracija Tr1 celic s posledičnim povečanjem koncentracije IL-10.

Indikacije za zdravljenje s specifično imunoterapijo so: alergijski rinokonjunktivitis z ali brez astme, alergijska astma, anafilaksija po piku kožekrilcev, redko tudi atopijski dermatitis in alergija na hrano.

Kontraindikacije za zdravljenje s specifično imunoterapijo so slabo nadzorovana astma in resne kardiovaskularne bolezni (težka ishemična bolezen srca, nestabilna AP, nezdravljena AH), slaba komplianca bolnika. Relativne kontraindikacije so zdravljenje z beta-blokerji, avtoimune in maligne bolezni, nosečnost.

Alergen lahko apliciramo subkutano (subkutana IT) ali sublingvalno (sublingvalna IT). Subkutano IT izvajamo z inhalacijskimi alergeni (pršica, pelodi) in strupom kožekrilcev, subkutano IT pa samo z inhalacijskimi alergeni.

Med subkutano IT bolniku s podkožnimi injekcijami vbrizgamo alergen, na katerega je preobčutljiv. Na začetku je količina alergena majhna, postopno jo večamo do vzdrževalnega odmerka. Sprva je razmak med aplikacijami kratek, postopno ga daljšamo. Obdobje večanja odmerka imenujemo uvodna faza, obdobje aplikacije vzdraževalnega odmerka pa vzdrževalna faza. Med vzdrževalno fazo bolniku vbrizgamo vzdrževalni odmerek vsake 4 tedne, nato razmak postopno daljšemo na 8-12 tednov. Specifično imunoterapijo z inhalacijskimi alergeni izvajamo 3 leta, s strupom kožekrilcev pa 5 let.

Zapleti med zdravljenjem z inhalacijsko IT so zelo redki. Med IT s strupom kožekrilcev približno 20% bolnikov doživi zaplet v obliki sistemske preobčutljivostne reakcije. IT zato poteka v ustrezno opremljenih prostorih, s pripravljenimi zdravili za zdravljenje sistemskih zapletov, v bližini EIT.

Pri sublingvalni IT bolnik kapljice ali tablete alergena na tešče aplicira sublingvalno,

zadrži 2 minuti in preostanek pogoltne. Uvodna faza, med katero odmerek alergena postopno večamo do vzdrževalnega odmerka, poteka v ambulanti pod zdravniškim nadzorom, nato si bolnik aplicira alergen dnevno v domačem okolju. Bolnik s perzistentnim rinokonjunktivitisom prejema alergen vsak dan tri leta. Bolniki z intermitentnim rinokonjunktivitisom pričnejo z jemanjem alergena 12-16 tednov pred sezono polinacije in z jemanjem nadaljujejo do konca sezone, nato prekinejo in po enaki shemi nadaljujejo 3 sezone.

Pri sublingvalni IT so lokalni zapleti zelo pogosti, praviloma so blagi in ne potrebujejo zdravljenja, sistemski zapleti pa izjemno redki.

Za uspešno vodenje IT je pomembno, da pravi bolnik prejme pravi alergen v pravem odmerku. Bolniku pred aplikacijo preverimo identiteto, ga pregledamo, povprašamo o spremembi terapije, zdravstvenem stanju, cepljenju, težavah ob predhodni aplikaciji alergena, morebitnih pikih, preverimo obdobje od zadnje aplikacije. Nato preverimo alergenski produkt, koncentracijo, odmerek, rok uporabe. Po vsaki aplikaciji bolnika opazujemo 30 minut. Bolniki morajo biti obveščeni, da med opazovanjem ne zapuščajo oddelka in takoj obvestijo osebje o pojavu zapletov. Bolnik mora dobiti tudi navodila o ukrepih ob poslabšanju po odhodu iz bolnišnice.

S specifično imunoterapijo dosežemo izboljšanje klinične slike, manjšo porabo zdravil in izboljšanje kakovosti življenja. Specifična imunoterapija je pri preobčutljivih za strup kožekrilcev edina učinkovita profilaksa pred ponovnimi težkimi sistemskimi preobčutljivostnimi reakcijami po piku.

Vloga multidisciplinarnega tima pri izvajanju intravenozne desenzibilizacije za zdravila

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V zadnjih letih je povečanje uporabe novih zdravil za zdravljenje raka in sistemskih vezivnotkivnih bolezni ter zdravljenje z uporabo monoklonskih protiteles povezano s povečanjem preobčutljivostnih reakcij za tovrstna zdravila (3). Desenzibilizacija je postopek, ki spremeni imunski odziv in povzroči začasno toleranco na določeno zdravilo. Različni desenzibilizacijski protokoli omogočajo bolnikom, da prejmejo celoten odmerek zdravila, za katerega so imeli predhodno preobčutljivostno reakcijo. V kolikor zdravljenje z zdravilom prekinemo, se bolnikova preobčutljivost za zdravilo vrne (2). Za aplikacijo zdravil po desenzibilizacijskem postopku se odločimo, ko za izboljšanje zdravstvenega stanja nimamo no voljo boljših nadomestnih zdravil oziroma, ko je učinkovitost zdravljenja z določenim zdravilom po postopku desenzibilizacije bistveno večja od tveganja za poslabšanje bolnikovega zdravstvenega stanja (1; 5).

Desenzibilizacijski postopek izvaja multidisciplinarni tim, ki vključuje zdravnika specialista alergologa, diplomirano medicinsko sestro s specialnimi znanji iz področja alergologije ter kliničnega farmacevta. Na Univerzitetni kliniki za pljučne bolezni in alergijo Golnik je bilo od leta 2014 do 2020 po protokolu intravenoznih desenzibilizacij zdravljenih 18 bolnikov. Približno 73 odstotokov je bilo izvedenih po 12 ali 16 - stopenjskemu desenzibilizacijskem protokolu, 27 odstotkov pa je bilo izvedenih po protokolu počasne intravenozne aplikacije. Od vseh izvedenih desenzibilizacij jih je 66 odstotkov potekalo brez zapletov, pri 22 odstotkih (n=4) smo zabeležili SR z generalizirano urtikarijo ter 11 odstotkov (n=2) SR s padcem krvnega tlaka. Prekinjenih zdravljenj s postopkom desenzibilizacije smo zabeležili 22 odstotkov. Dva bolnika sta se na lastno željo odločila za prekinitev zdravljenja, dva bolnika pa sta zdravljenje prekinila zaradi spremembe načina zdravljenja po posvetu z lečečim revmatologom oziroma onkologom. Od vseh izvedenih desenzibilizacij je bilo 78% uspešno zaključenih.

Dobro medsebojno sodelovanje in prizadevanje različnih strokovnjakov pripomore k učinkovitemu izvajanju desenzibilizacij, izboljša pa tudi psihično počutje bolnika, da se ob samem izvajanju zdravljenja počuti varno. Razvoj ekipe, ki skrbi za natančno ter kakovostno zdravljenje po desenzibilizacijskh protokolih in ob tem zagotavlja najsodobnejšo oskrbo bolnikov, pa je možno le z usklajenim multidisciplinarnim timskim delom (4).

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Kako znajo epipen uporabljati bolniki, ki dobijo predpis na urgenci

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Uvod: Uporaba samoinjektorja adrenalina je prva linija zdravljenja anafilaksije. Zgodnja in pravilna raba izboljša klinične izide, kot sta obolevnost in umrljivost. Samoinjektor se predpiše pacientu z anamnezo anafilaktične reakcije in tveganjem, da se anafilaksija ponovi ob ponovnem kontaktu z alergenom.

Za pravilno uporabo samoinjektorja je pomembno, da je pristop k edukaciji bolnikov celovit, kar pomeni, da vključuje vsa starostna obdobja od otroka naprej, družino, šolo, športne dejavnosti in da izobraževanje vključuje tudi nadzor bolnikov glede prepoznavanja anafilaksije in ukrepanja v primeru pojava.

V raziskavi smo želeli ugotoviti, kako so uporabe samoinjektorja adrenalina vešči bolniki, ki so dobili prvi predpis recepta v okviru urgentne obravnave anafilaktične reakcije oziroma pri svojem osebnem zdravniku. Želeli smo ugotoviti dejavnike, ki vplivajo na sposobnost pravilno uporabiti samoinjektor in ugotoviti v katerih korakih največkrat storijo napako.

Metode: Raziskava je bila izvedena v specialistični ambulantni dejavnosti terciarne ustanove. V raziskavo so bili vključeni bolniki z anamnezo anafilaksije, ki so bili napoteni na prvi alergološki pregled v specialistično alergološko ambulanto zaradi anafilaksije in so že v urgentnem centru ali pri osebnem zdravniku dobili predpis samoinjektorja adrenalina. Zaprošeni so bili, naj pokažejo uporabo samoinjektorja z uporabo vadbenega pripomočka. Medicinska sestra je bolnika opazovala 1 minuto in po tem času presodila, ali si je bolnik uspel učinkovito aplicirati zdravilo.

Uporabniki, ki so ključne korake (odstranjevanje modrega varnostnega pokrova, postavitev konice za injiciranje stegno in držanje injekcijskega peresa nekaj sekund) izvedli pravilno, so bili označeni kot kompetentni pri uporabi samoinjektorja. Bolnike smo razdelili v dve skupini; skupina, ki zna uporabiti samoinjektor in skupina, ki ga ne zna.

Za statistično analizo obdelave podatkov smo uporabili program Microsoft Excel 2013.

Rezultati: Vključili smo 41 bolnikov (24% žensk), ki so na pregled prišli 116 ± 145 dni po tem, ko so dobili predpis recepta za samoinjektor adrenalina. Ob predpisu recepta sta 26 bolnikom (63,4 %) zdravnik ali medicinska sestra razložila navodila o uporabi samoinjektorja, 13 bolnikov (31,7%) je uporabo samoinjektorja vadilo z uporabo vadbenega pripomočka. V lekarni je bilo devetim bolnikom (22,0%) razloženo glede uporabe samoinjektorja, trije od njih so vadili z uporabo vadbenega pripomočka. V času obiska v alergološki specialistični ambulanti je imelo 25 bolnikov (61%) samoinjektor pri sebi. Bolniki z višjo izobrazbo so pogosteje znali uporabiti samoinjektor (p= 0,02564).

Razprava: Glavna ugotovitev raziskave je, da kljub temu, da so bolniki dobili samoinjektor adrenalina, velik delež ni bil deležen pouka glede njegove uporabe. Le dobra polovica (54%) bolnikov je ob obisku specialistične alergološke ambulante učinkovito izvedlo ključne faze uporabe samoinjektorja. Ukrep: predlagamo redno spremljanje in ponavljanje usposabljanja bolnikov, pošiljanje opomnika, če pozabijo na obisk, in ob obisku preverjanje pravilne rabe samoinjektorja.

PLJUČNI RAK

Diagnostika pljučnega raka

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Uvod: Pljučni rak je najpogostejši rak, za katerim ljudje po svetu in pri nas zbolevajo in umirajo. Večja obolevnost sledi predvsem spremenjenim kadilskim navadam, izpostavljenosti škodljivim snovem na delovnih mestih in bivanju v onesnaženem okolju. Prav poznavanje teh dejavnikov tveganja in preventivni ukrepi lahko pripomorejo k manjši obolevnosti v prihodnosti. Pomemben del izboljšanja in vzdrževanja zdravja nasploh je v zadnjih desetletjih pripisati tudi uspešni realizaciji preventivnih zdravniških pregledov in pa izobraženosti ljudi, da v primeru zdravstvenih težav čimprej obiščejo osebnega zdravnika. Možnost hitre diagnostične obravnave in sodobne terapevtske sheme pa omogočajo zgodnjo postavitev diagnoze, uspešnejše zdravljenje in obvladovanje bolezni.

Najpogostejše invazivne preiskave: V Univerzitetni kliniki za pljučne bolezni in alergijo Golnik, je dokaj pogosta pot diagnostike pljučnega raka, najprej pregled v ambulanti za pljučne infiltrate, kamor so napoteni s strani triažnega pulmologa znotraj klinike, kjer opravijo osnovne preiskave (biokemične preiskave krvi, elektrokardiogram, preiskava pljučne funkcije, rentgen pljuč, ev. tudi globinsko slikanje prsnega koša, trebuha, glave, nato pa so pacienti v nekaj dneh s strani oddelčnega koordinatorja klicani za sprejem na oddelek za interventno pulmologijo, kjer se jih obravnava za nadaljnjo diagnostiko. Pacient ob tem prejme tudi navodila glede jemanja nizko molekularnega heparina, antikoagulantne, antiagregacijske ter diabetične terapije

Spremljajoče bolezni pacienta in njegova telesna kondicija sta osnovna podatka za opredelitev ocene tveganja za zaplete med invazivnimi preiskavami in poznejšim kirurškim ali ne kirurškim zdravljenjem, še pomembneje pa je oceniti funkcionalno stanje bolnika po končanem zdravljenju (Boc, idr., 2019).

Diagnostični postopki si sledijo v jasnem in enostavnem zaporedju od manj invazivnih do bolj invazivnih, vse do jasne histopatološke diagnoze in natančne ugotovitve razširjenosti bolezni. Diagnostični postopek indicira zdravnik glede na splošno stanje pacienta, vrsto in lego tumorja ali morebitnih drugih sumljivih sprememb. (Kržišnik & Koren, 2012).

Plevralna punkcija: je prva invazivna diagnostična metoda v diagnostiki plevralnega izliva. Namen je pridobitev plevralnega izliva za nadaljne preiskave. Pri plevralni punkciji zdravnik po predhodno ultrazvočno določenemu mestu punkcije, z iglo in brizgo zabode skozi prsno steno in aspirira plevralni izliv. Plevralni izliv po naročilu zdravnika pošljemo na različne analize, kot so biokemična, citološka in mikrobiološka analiza ter laboratorij za tuberkulozo (Kržišnik & Koren, 2012). Gre za izključitev ali potrditev malignega plevralnega izliva.

Ugotavlja se, ali gre za eksudat ali transudat. Eksudat je tekočina s serumskimi proteini in nastane zaradi povečane prepustnosti plevre ali kapilar. Najpogostejši vzrok eksudata v plevralnem prostoru je vnetje in maligna bolezen. Transudat pa je tekočina, ki jo najdemo v telesnih votlinah in nastane zaradi spremenjenih hidrostatskih sil v plevralnem prostoru, medtem ko prepustnost plevre in kapilar nista bistveno spremenjeni. Diagnozo transudat največkrat postavimo že na podlagi klinične slike in izvidov drugih preiskav (Štupnik, 2013).

Bronhoskopija: osnovna invazivna preiskava za biopsijski odvzem tkiva je bronhoskopija, ki jo opravimo brez ali v sedaciji. Material je navadno odvzet z biopsijskimi kleščami in igelno punkcijo, ker kombinacija obeh metod poveča možnost za postavitev diagnoze.

Pljučna punkcija je preiskava pri kateri po predhodni lokalni anesteziji kože, podkožja in parietalne plevre punktiramo spremembe v prsnem košu. Preiskava poteka pod nadzorom rentgena, računalniške tomografije ali ultrazvoka. Vzorce za citološke oz. histološke preiskave dobimo z iglami različnih dimenzij. Indikacije za preiskavo so sumljive, rentgensko vidne spremembe v pljučih, mediastinumu, plevralnem prostoru in prsni steni (Triller, 2013).

Torakoskopija je endoskopski pregled prsne votline oziroma plevralnega prostora. Izvede se v lokalni anesteziji z dodatkom intravenske sedacije, medtem ko pacient spontano diha. Navadno se uporablja le eno, največ dve vstopni mesti (Rozman, et al., 2011). Indikacije za poseg so: plevralni izliv – eksudat, ki ni bil diagnosticiran z manj invazivnimi metodami, spremembe po plevri, plevrodeza, delno septiran plevralni izliv, pnevmotoraks itd. (Rozman, 2013). Torakoskopija je pogosta invazivna preiskava za potrditev ali izključitev mezotelioma.

Vloga medicinske sestre: Pacienti s pljučnim rakom so posebna skupina pacientov, ter imajo navadno posebna, z zdravjem povezana vprašanja. So ranljivi in tudi občutljivi. Zdravstvena nega takšnih pacientov zahteva veliko strokovnega znanja in izkušenj medicinskih sester (Bishop, 2009).

Pomembna vloga medicinske sestre je spremljanje pacienta skozi diagnostiko pljučnega raka. S svojim strokovnim znanjem in izvedenimi diagnostično medicinsko-tehničnimi posegi zagotavlja varno in hitro obravnavo, preprečuje in prepozna morebitne zaplete ter mu nudi celostno psihosocialno oporo ob soočenju s strahom, ki ga prinaša sum na maligno bolezen ter kasneje tudi samo soočenje z boleznijo. Medicinska sestra mora poleg strokovnega znanja s področja diagnostično-terapevtskih postopkov obvladovati tudi znanja s področja komunikacije, čustvene inteligence in empatije (Kržišnik & Koren, 2012). Pacientu je vedno treba dati možnost, da opiše občutke v zgodbi, kot jo doživlja le on. Zelo pomembno je, da pacientovo stisko prepoznamo in se nanjo odzovemo. Izražajo jo na različne načine, nekateri z verbalno, drugo z neverbalno komunikacijo, nekateri z jezo, besom, drugi z jokom. Ob tem je pomembno vključevanje psihologinje, če se pacient s tem strinja. Ena od pomembnih vlog medicinske sestre pa je tudi prepoznavanje zapletov po invazivnih posegih.

Zaključek: Pri obravnavi bolnika s pljučnim rakom je ključnega pomena hitra diagnostika. Bolniki s pljučnim rakom, odkritim v zgodnjem stadiju, imajo boljšo prognozo in boljše možnosti zdravljenja. S tem namenom načrtujemo invazivne

preiskave na način, da biopsijski material dosežemo na najlažje dostopnem mestu in, če je možno z isto preiskavo potrdimo tako bolezen kot tudi njen stadij. Za izboljšanje odkrivanja bolezni bo potrebno v prihodnosti izobraževati zdravstveno osebje ter ozaveščati in opozarjati prebivalstvo na škodljivost in posledice kajenja ter simptome te zahrbtne bolezni. Smiselna pa bi bila tudi uvedba presajalnega programa.

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Sodobni pristopi v sistemskem zdravljenju pljučnega raka

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V zadnjem desetletju smo priča ogromnemu napredku v sistemskem zdravljenju pljučnega raka, predvsem pri bolnikih z napredovalo boleznijo – zdravljenje gre v smeri personalizirane medicine, ko za vsakega bolnika poiščemo najbolj optimalen način zdravljenja.

Pri omejeni bolezni, ko je še možno radikalno zdravljenje, to poteka z operacijo in nato glede na značilnosti in stadij tumorja še s pooperativno kemoterapijo in/ali radioterapijo. Vedno več pa je podatkov tudi glede uporabe imunoterapije ali tarčne terapije tudi pooperativno.

Pri razsejani bolezni, ki je praviloma neozdravljiva, je cilj onkološkega zdravljenja podaljšanje bolnikovega življenja, ki naj bo čimbolj kvalitetno. Torej je cilj tako zmanjšanje simptomov raka, kot tudi čim manj neželenih učinkov s terapijo, ki jo uporabljamo. Še pred dobrim desetletjem smo lahko bolnikom z napredovalim pljučnim rakom ponudili le zdravljenje s kemoterapijo na bazi platine, ob kateri je bilo povprečno preživetje bolnikov okoli 12 mesecev, ob tem pa so imeli bolniki kar nekaj neželenih učinkov kot posledica citostatskega zdravljenja.

Danes se kemoterapija kot samostojno zdravljenje pri napredovalem raku pljuč umika drugim, bolniku bolj prijaznim možnostim zdravljenja. Ena od teh je tarčna terapija in je usmerjena proti točno določeni tarči (izraz, ki se za ta zdravila pogosto uporablja, so biološka zdravila, vendar biološka nakazuje samo na način njihove izdelave, ne pa na način učinkovanja). Poleg že rutinsko dostopnih zdravil, usmerjenih proti EGFR, ALK in ROS-1, imamo preko posebnih programov na voljo tudi zdravila, usmerjena proti BRAF, MET, NTRK, RET, HER-2 itn. Tarčna terapija je uperjena proti točno določeni tarči – deluje na sistemu ključ - ključavnica. Zato je tarčna terapija tudi zelo učinkovita in ima bistveno manj neželenih učinkov, saj deluje večinoma samo na rakavo spremenjene celice in ne na ostale celice organizma. Taka terapija torej omogoča bolnikom dobro kvaliteto življenja z malo neželenimi učinki in bistveno daljšimi preživetji – tudi do 5 - 7 let.

Še veliko bolj revolucionarna je bila uvedba zdravljenja z inhibitorji nadzornih točk (angl. immune checkpoint inhibitors) ali na kratko imunoterapije za zdravljenje raka pljuč. Onkologija se je že od nekdaj spogledovala tudi z imunoterapijo oz. terapijo, ki bi uspešno aktivirala imunski sistem z namenom uničevanja rakavih celic. Imunoterapija ne učinkuje direktno na tumorske celice, ampak omogoča bolnikovim lastnim limfocitom, da prepoznajo tumorsko celico in jo uničijo. Pričakovano ima zdravljenje z zaviralci imunskih nadzornih točk večinoma neželene učinke, ki posnemajo avtoimunska dogajanja in posnemajo kakršnokoli vnetje kjerkoli v telesu.

V tem primeru je razpoznava in hitro ukrepanje ključnega pomena, saj so sicer lahko taki neželeni učinki tudi smrtno nevarni. V kolikor rakava bolezen dobro reagira na zdravljenje z imunoterapijo, lahko pričakujemo zelo dolge zazdravitve bolezni; tudi do te mere, da bolnik ne potrebuje več nobene terapije in ga lahko samo spremljamo.

Vsekakor so možnosti zdravljenja raka pljuč danes veliko bolj obetavne kot še samo desetletje nazaj in kot kaže, bo v prihodnosti teh možnosti še veliko več, saj gre razvoj v pravi smeri z neverjetno hitrostjo.

Organizacijski vidik zdravstvene oskrbe bolnika s pljučnim rakom

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Na Univerzitetni kliniki za pljučne bolezni in alergijo Golnik(Klinika Golnik) vsako leto odkrijemo 600-700 novih bolnikov s tumorji torakalnih organov, najpogosteje je to pljučni rak, redkeje pa mezoteliom in rak priželjca. Večino novo-odkritih bolnikov po postavitvi diagnoze nadaljuje obravnavo na Kliniki Golnik. V Enoti za internistično onkologijo (EIO) zdravimo bolnike, ki potrebujejo sistemsko terapijo, bodisi kot dopolnilno zdravljenje po operaciji, ali v okviru zdravljenja razsejane bolezni.

Za optimalno obravnavo bolnikov s pljučnim rakom, je potrebno sodelovanje strokovnjakov različnih področij. Delo, ki ga opravijo zdravniki, se prepleta z delom medicinskih sester, socialnih delavcev ter psihologov in drugih služb. Na Kliniki Golnik smo po vzoru onkoloških centrov v tujini, razvili organizacijski model, ki zajema sodelovanje vseh omenjenih služb.

Ob sumu na raka poskušamo ugotoviti izvor in vrsto rakave bolezni, razširjenost in morebitne molekularne označevalce, saj so vsi ti podatki pomembni za odločitev o zdravljenju. Po zaključku diagnostičnih postopkov dokumentacijo predstavimo na multidisciplinarnem Konziliju za torakalne tumorje, kjer so prisotni pulmologi, internisti onkologi, kirurgi, patologi, radiologi in radioterapevti.

Bolnike, ki potrebujejo zdravljenje v EIO, kontaktira koordinator EIO. Obvesti jih o manjkajoči dokumentaciji, napotnici in da osnovne informacije o poteku prvega pregleda pri onkologu. Ob prvem pregledu je priporočljivo, da je prisoten nekdo od svojcev, ker se pogovorimo o načinu in poteku zdravljena v naši enoti. Vsakemu bolniku, damo pisna in ustna navodila o poteku zdravljenja, učinkih in stranskih učinkih ter telefonsko številko, na katero lahko pokliče za informacije. Bolniki izpolnijo vprašalnik o psihološkem stanju na osnovi katerega jim svetujemo glede obravnave pri psihologu. Prejmejo tudi informacije o možnosti vključitve v obravnavo socialne službe.

Pri uvedbi kemoterapije diplomirana medicinska sestra (DMS) izvede zdravstveno vzgojno šolo. Pri naslednjem pregledu pa oceni koliko bolnik podana navodila razume in oceno pisno zabeleži.

Pri zdravljenju z imunoterapijo po prvem pregledu, bolnike napotimo na pregled k tirologu. , Po potrebnih preiskavah in prejetih izvidih bolniki pridejo na ponovno kontrolo in pričnejo z imunoterapijo. Pri prvi aplikaciji so bolniki še dve uri po končani terapiji na monitorju in opazovanju. Med aplikacijo terapije DMS opravi zdravstveno vzgojno šolo in po potrebi vključi kliničnega farmacevta. Pri imunoterapiji ki jo apliciramo na 6 tednov, po 3 tednih DMS pokliče pacienta in povpraša o splošnem stanju in neželenih učinkih in glede na to tudi dalje ukrepa, poda nasvete ali če je potrebno obvesti tudi lečečega onkologa.

Pri zdravljenju s tarčnimi zdravili, poleg omenjenih navodil zdravnika in DMS, ob prvem pregledu vključimo kliničnega farmacevta, ki se z bolnikom pogovori o sočasni terapiji, alternativi in prehranskih dodatkih.

Vloga koordinatorja in skupnih sestankov: Koordinator pokliče za prvi pregled, sprejema klice in bolnikove težave skupaj z zdravnikom rešuje. Svetuje kako ukrepati ob pojavu neželenih učinkov. Vse klice zabeleži. Vsak četrtek je skupni sestanek EIO, kjer poteka predaja bolnikov. V te sestanke so vključeni farmacevti, klinični psiholog, socialna delavka.

S takim načinom dela bolnike spremljamo v celotnem procesu zdravljenja. Delo je bolje organizirano, s telefonskimi svetovanjem o neželenih učinkih, le te pravočasno prepoznamo, uspešno in hitro rešujemo ter zmanjšujemo število obiskov v bolnišnici. Poleg boljših rezultatov zdravljenja, se bolniki počutijo varno, saj v vsakem trenutku vedo kam se za nasvet lahko obrnejo.

Diagnostika in zdravljenje bolnikov s pljučnim rakom morata biti hitra, učinkovita in varna. Da bi to dosegli, bolnike čim bolj celostno obravnavamo.

Obvladovanje neželenih učinkov pri bolniku na sistemskem zdravljenju pljučnega raka

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Zdravljenje raka pljuč je v zadnjem desetletju močno napredovalo. Na voljo imamo več zdravil, ki so bolj učinkovita. Pojav neželenih učinkov je nemogoče napovedati. Vendar pa pri posameznih zdravilih poznamo možne neželene učinke. Ti podatki so nam v pomoč, ko poučujemo bolnika, ki mu uvajamo sistemsko zdravljenje raka pljuč.

Pri obravnavi bolnika z pljučnim rakom se med seboj močno prepletajo vloge zdravnika, farmacevta in medicinske sestre. Nujno je, da smo pri obravnavi bolnikov usklajeni o vsebini nasvetov, ki jih dajemo bolnikom.

Sistemsko zdravljenje pljučnega raka obsega kemoterapijo, imunoterapijo, kemoimunoterapijo in zdravljenje s tarčnimi zdravili. Vsako od naštetih zdravljenj ima lahko specifične neželene učinke, ki jih moramo pri delu z bolniki dobro poznati. Zelo pomembno je pravočasno prepoznavanje neželenih učinkov in pravilno ukrepanje ob njihovi pojavitvi.

Neželene učinke delimo na pogoste, manj pogoste in redke. Glede na jakost jih ocenjujemo s pomočjo poenotenih kriterijev: Common Terminology Criteria for Adverse Events (CTCAE).

Neželeni učinki se lahko pojavijo kadarkoli med zdravljenjem ali pa tudi po že zaključenem zdravljenju.

Ob uvedbi sistemske terapije ocenimo bolnikovo sposobnost razumevanja navodil, sposobnost samooskrbe, socialno okolje, potrebo po psihološki pomoči ter prepoznamo večja tveganja za neželene učinke (denimo že prizadeta ustna sluznica/ nevarnost stomatitisa).

Ob uvedbi sistemske terapije mediciska sestra pouči bolnika glede splošnih navodil za preprečevanje neželenih učinkov, ki zajemajo skrb za sluznice, kožo, prehrano, gibanje, izogibanje okužbam ipd. ter predstavi najpogostejše neželene učinke posamezne sistemske terapije in ukrepanje ob njihovi pojavitvi. Bolnik se mora naučiti, kako mora v času zdravljenja skrbeti sam zase, da prepreči tiste neželene učinke, na katere lahko vpliva. Poučen mora biti, kdaj mora k zdravniku. Poleg ustnega informiranja dobi bolnik tudi pisna navodila.

Ob vsakem obisku v ambulanti preverimo neželene učinke in jih tudi zabeležimo.

Kadar so neželeni učinki zdravljenja resni, je pogosto potreben sprejem bolnika v bolnišnico. Resni neželeni učinki pogosto vodijo v prekinitev trenutnega onkološkega zdravljenja.

Poučitev bolnika o preprečavanju neželenih učinkov in ukrepanje ob njihovi pojavitvi je ključno za varno obravnavo onkoloških bolnikov.

Zdravstvena nega bolnika s trajnim plevralnim drenažnim katetrom – šola praznjenja plevralnega izliva

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Bolniki z malignim plevralnim izlivom v napredovalem stadiju bolezni potrebujejo celostno paliativno obravnavo. Vstavitev trajnega plevralnega drenažnega katetra (TPDK) je ena izmed možnosti paliativnega zdravljenja malignega plevralnega izliva.

TPDK kateter se bolnikom lahko uvede ambulantno v lokalni anesteziji. Bolnikom z malignim plevralnim izlivom (MPI) posredno lajša dihalno stisko in izboljšuje kakovost življenja. Ne posega v bolnikove običajne dnevne aktivnosti. Bolniku omogoča, da kljub svoji osnovni bolezni, večino časa preživi v svojem domačem okolju. Medicinske sestre imajo ključno vlogo pri izobraževanju bolnikov, njihovih svojcev in patronažnih medicinskih sester o praznjenju plevralnega izliva preko trajnega plevralnega drenažnega katetra.

Prvi TPDK je bil v Univerzitetni kliniki za pljučne bolezni in alergijo Golnik (Klinika Golnik) vstavljen leta 2009. Od aprila 2010 do konca oktobra 2020 smo vstavili 201 TPDK. V Kliniki Golnik na Oddelku za endoskopijo dihal in prebavil, kjer ustavljamo bolnikom z MPI TPDK, redno od decembra 2013 izvajamo individualno šolo učenja rokovanja in praznjenje plevralnega izliva preko TPDK za bolnike in njihove svojce. Za patronažne medicinske sestre pa izvajamo Šolo zdravstvene oskrbe bolnika s trajnim plevralnim drenažnim katetrom.

Medicinske sestre imajo ključno vlogo pri izobraževanju bolnikov in svojcev o uporabi TPDK in izpraznitvi MPI. Medicinske sestre, ki educirajo bolnike z vstavljenim TPDK in njihove svojce si postavijo vzgojni cilj: usposobiti bolnika oziroma njegove svojce za aktivno praznjenja MPI preko TPDK na bolnikovem domu in s tem izboljšati kakovost bolnikovega življenja.

V šoli učenja rokovanja in praznjenje plevralnega izliva preko TPDK se bolnik, svojci, patronažna medicinska skozi šest faz učenja seznanijo: kaj je TPDK in kakšen je njegov namen, poznajo set z vakuumsko bučko za praznjenje plevralnega izliva, so sposobni izvesti in prikazati praznjenje plevralnega izliva, znajo namestiti novo obvezo, znajo odstraniti uporabljeno vakuumsko bučko in ostali obvezilni material, dokumentirajo datum, količino in barvo izpraznjenega izliva in vedo kdaj poklicati medicinsko sestro ali zdravnika.

BOLNIK S COVIDOM-19

Bolnik s covidom-19

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Uvod: SARS-CoV-2 je nov koronavirus, ki so ga prvič identificirali v kitajski provinci Vuhan decembra 2019, ko so zaznali več primerov pljučnic, ki niso bile povzročene z običajnimi povzročitelji pljučnic oz. respiratornih okužb. Bolezen, ki jo virus povzroča, so poimenovali covid-19.

Bolezen se kaže s slabim počutjem, utrujenostjo, bolečinami v mišicah in sklepih, glavobolom, nahodom, z vročino, kašljem, drisko in pri težjih oblikah z občutkom težke sape. V lažji obliki poteka pri približno 80 % okuženih. Težji potek, za katerega je značilna pljučnica, naj bi imelo približno 20 % zbolelih. Smrtnost po okužbi z novim koronavirusom je približno 2-4%. Večina umrlih je starejših s pridruženimi kroničnimi boleznimi srca, pljuč, sladkorno boleznijo,…

Okužbo z novim koronavirusom potrdimo ali izključimo z mikrobiološkim testiranjem. Okužbe z novim koronavirusom zaradi podobne klinične slike namreč ne moremo ločiti od okužb z ostalimi povzročitelji akutnih okužb dihal. Koronavirus lahko dokažemo v brisu nosno-žrelnega prostora, v brisu žrela, izmečku dihal in še v drugih kužninah.

Zdravljenje je v večji meri simptomatsko. Od specifičnih zdravil uporabljamo protivirusno učinkovino remdesivir, kot učinkovito pa se je izkazalo tudi protivnetno zdravilo deksametazon, še posebno pri težko bolnih intubiranih bolnikih in bolnikih na ECMO. Podatkov o učinkovitosti D vitamina ter cinkovih preparatov zaenkrat še ni.

Naše izkušnje s covid-19 bolniki v 1. valu: Od marca do junija je bilo v naši bolnišnici hospitaliziranih 48 bolnikov, razlike med spoloma v številu ni bilo. Povprečna starost hospitaliziranih bolnikov je bila 67,9 let, najstarejši bolnik je imel 95 let, najmlajši 35 let. 15 bolnikov je bilo oskrbovancev DSO. Bolniki so imeli pridružene bolezni (arterijsko hipertenzijo, srčno popuščanje, sladkorno bolezen, astmo/KOPB), le 7 bolnikov je bilo brez znanih kroničnih bolezni. 36 bolnikov je bilo sprejetih zaradi virusne pljučnice, dodatek kisika je potrebovalo 31 bolnikov. 23 bolnikov je bilo zdravljenih s takrat uveljavljeno eksperimentalno terapijo (hidroksiklorokin/azitromicin/lopinavir+ritonavir), ostali so bili zdravljeni simptomatsko. Sekundarno bakterijsko pljučnico smo ugotavljali pri 16 bolnikih. 7 bolnikov je potrebovalo intenzivno zdravljenje. 11 bolnikov je umrlo. Obdukcija je bila opravljena pri 6 bolnikih, pri večini bolnikov je bila vzrok smrti respiratorna odpoved, ki je posledica covid-19 pljučnice z razvojem difuzne alveolarne okvare. Prisotnost IgG protiteles proti SARS-CoV-2 smo dokazali pri 32 bolnikih.

Priprave na zdravstveno obravnavo bolnikov z zelo nalezljivo boleznijo in covidom-19

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V obdobju vsakoletnih priprav na obvladovanje večjega števila obolelih zaradi gripe in respiratornih okužb se v zdravstvenih ustanovah vedno soočimo z dejstvom, da se lahko pojavi okužba, ki bo imel epidemične razsežnosti kot se je to zgodilo v času španske gripe leta 1918. V času od 1918 smo se soočali z manjšimi izbruhi gripe in nekaterih drugih nalezljivih bolezni za katere je na začetku kazalo, da bi lahko šlo za okužbe širših razsežnosti, vendar so se zadeve ali omejile na določena področja ali pa precej hitro umirile in za zdravstveni sistem in širšo skupnost niso imela hujših posledic.

Leta 2003 so veliko pozornosti vzbudile okužbe s koronavirusi na Kitajskem. Okužba, ki so jo kasneje poimenovali SARS se je razširila v 29 držav. Na možnost pojava smo se pripravljal tudi v Sloveniji. Spomladi leta 2009 se je v svetu pojavil podtip virusa prašičje gripe H1N1, ki je dobil ime nova gripa. Zaradi hitrega širjenja je Svetovna zdravstvena organizacija junija 2009 uradno razglasila, da gre po njenih kriterijih za pandemijo, ki se je končala dobro leto kasneje.

V letu 2013 se je na območju nekaterih zahodno afriških držav pojavilo večje število oseb obolelih za Ebola virusno boleznijo. Z večanjem števila okuženih, obolelih in tudi umrlih se je bojazen pred možnim stikom z okužbo razširila tudi na evropske države. V skladu s priporočili mednarodnih organizacij smo tudi v Sloveniji začeli s pripravami na možnost pojava primerov s to zelo kužno nalezljivo. Koordinacijska skupine za obvladovanje nalezljivih bolezni pri Ministrstvu za zdravje Republike slovenije je aktivno spremljala dogajanje v svetu in pripravila priporočila za obvladovanje okužbe v Sloveniji. Pri Nacionalnem inštitutu za javno zdravje je bila imenovana posvetovalna skupina, ki je pripravila krovni dokument: Smernice pripravljenosti in odzivanja ob sumu na nalezljivo bolezen, ki lahko predstavlja tveganje za javno zdravje. Klinika za infekcijske bolezni in vročinska stanja v Ljubljani je pričela z usposabljanjem kadra in zagotavljanjem prostorov in opreme za namestitve bolnika z ZNB.

Izdelani protokoli, smernice in izvedena uposabljanja so predstavljala pomembno izhodišče za obvladovanje razmer v času pojava SARS-COV-2 v začetku leta 2020.

Doživljanje in izkušnje medicinskih sester urgentne ambulante med epidemijo covida-19

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Uvod: Proti koncu leta 2019 pa se je v mestu Wuhan na Kitajskem pojavila nova vrsta virusne okužbe katere podatki o genomskem zaporedju tega virusa kažejo na nov sev koronavirusa imenovan SARS-CoV-2 (covid-19). Zaradi hitrega prenosa iz človeka na človeka preko tesnih stikov, govorjenjem ter kihanjem in kašljanjem je bolezen privedla do pandemije v letu 2020. S pojavom okužb v svetu v kratkem času je bilo potrebno za obvladovanje bolezni in preprečitve prenosa le-te narediti veliko sprememb pri obravnavi pacientov v bolnišnicah in ambulantah. Zaradi visoke kužnosti obravnava pacienta poteka v posebej opremljenih izolacijskih sobah, zdravstveno osebje pa ves čas uporablja popolno osebno varovalno opremo. Namen naše raziskave je bil ugotoviti, kako se medicinske sestre v urgentni ambulanti srečujejo z izzivi epidemije covida-19, ter kako je le-ta spremenila delo v urgentni ambulanti.

Metode: Naša raziskava temelji na empirično kvalitativni metodologiji s tehniko intervjuja. Intervju je vključeval pet osrednjih tematskih vprašanj in pet podvprašanj s področja proučevane teme. V raziskavi smo uporabili neslučajnostni namenski vzorec, ki je zajemal 10 diplomiranih medicinskih sester in zdravstvenikov urgentne ambulante Klinike za pljučne bolezni in alergijo Golnik. Po pridobitvi podatkov in transkripciji intervjujev je sledila kvalitativna vsebinska analiza podatkov s kategoriziranjem, kodiranjem in oblikovanjem osrednjih tem.

Rezultati: Bolezni covid-19 ter dela z okuženimi pacienti se naši intervjuvanci ne bojijo, po večini pa je prisoten strah, da bi okužbo nehote prinesli v domače okolje. Njihovo delo se je zelo spremenilo. Z vsakim pacinetom v urgentni ambulanti se obnašajo kot potencialno kužnim in obravnavo pacienta opravijo v posebej urejenih izolacijskih sobah, oblečeni v osebno varovalno opremo. Zaposleni so mnenja, da se za paciente obravnava od prejšnih razmer najbolj razlikuje v večurnem čakanju na PCR test na covid-19. Z nastopom epidemije je bila potrebna reorganizacija dela znotraj zdravstvenega tima in na splošno. Prav tako se je prilagodila namembnost prostorov v sami urgentni ambulanti. Poleg novosti pri samem neposrednem delu s pacienti, pa je epidemija prinesla veliko nepričakovanega tudi našim sodelujočim. Tudi sami so se srečevali z lastnimi okužbami in obolevnostjo svojih najbljižnjih, karantenami in prigoditvami v domačem okolju.

Razprava in zaključek: Epidemija covida-19 je prinesla v svet veliko novega. Zdravstveni delavci so izpostavljeni vsakodnevnim izzivom in morajo biti pri svojem delu zelo organizirani in biti voljni improvizacije novim razmeram. Naši intervjuvaci iz urgentne ambulante so mnenja, da je epidemija prinesla veliko slabega, saj imajo vsakodnevno stik s pacienti s hudimi poslabšanji, prav tako pa so izpostavili, da je izredno stanje pripomoglo k večji povezanosti kolektiva njihove urgentne ambulante.

Zelo veseli so tudi hvaležnosti svojih sodelavcev, družine in širše javnosti, ki v teh kriznih časih začenja razumeti kako pomembni in nezamenljivi so zdravstveni delavci v kriznih razmerah.

Ključne besede: Coronavirus Disease, symptoms covid-19, epidemic, Emergency nursing.

Izzivi zdravstvene nege pri obravnavi pacienta s covidom-19

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Z epidemijo covida-19 smo bili zdravstveni delavci postavljeni pred veliko izzivov. Zaradi reorganizacije dela in pomanjkanja medicinskih sester na Kliniki Golnik smo morali sprejeti 12-urni delavnik. Zaposleni v zdravstveni negi smo se morali na hitro prilagoditi novim, izrednim razmeram, se poglobiti v nove specialnosti ter nehote prilagoditi standarde za izvajanje zdravstvene nege, na katerih smo v zadnjih letih gradili sistem za zagotavljanje varne in kakovostne obravnave pacientov. Glede na reorganizacijo dela smo primorani delati z na novo sestavljenimi timi. Nadvse spodbudno je, da nam je priskočilo na pomoč veliko študentov zdravstvene nege, medicine in prostovoljcev Rdečega križa, ki so zelo motivirani za delo, čeprav so povečini še brez izkušenj. Zagotovo pa je izziv za prihodnost zdravstvene nege, kako mlade motivirati, da bi se odločili za poklice v zdravstveni negi in v njih tudi vztrajali.

V času epidemije covida-19 se je pod vprašajem znašla tudi varnost medicinskih sester na delovnem mestu, strah pred pomanjkanjem osebne varovalne opreme ter zaskrbljenost pred okužbo ter posledično prenos le te na družinske člane in sodelavce.

Ko smo vzpostavili izolacijske enote, čisto območje (bela cona); območje, kjer so nameščeni pacienti s sumom na covid-19 (siva cona) in območje, kjer so pacienti s covidom-19 (rdeča cona), smo se srečali z vrsto težav v komunikaciji, ki se dogajajo med pacienti in zaposlenimi, med zaposlenimi, ki delajo v različnih izolacijskih conah ter med pacienti, ki so izolirani in njihovimi bližnjimi.

Večina pacientov, ki so hospitalizirani zaradi okužbe s covidom-19, je v slabem zdravstvenem stanju, tako je pogostejši slab izid zdravljenja, nekateri tudi umrejo. Posledično smo medicinske sestre pogosteje v stiku z umirajočimi in umrlimi in njihovimi bližnjimi, kar zagotovo vpliva na počutje zaposlenih in negativno doživljanje svojega dela. Prav gotovo je izziv za prihodnost uvedba supervizije, ki bi bila v podporo zaposlenim v zdravstveni negi, da bi lahko prepoznavali osebne in čustvene odzive na delo in jih opremili z znanjem za premagovanje stresa.

Poseben izziv pri obravnavi pacientov s covidom-19 predstavlja zdravstvena dokumentacija, ki medicinski sestri v coni izolacije ni dostopna. Tako je pri sprejemanju informacij o zdravljenju pacienta, pri sporočanju informacij o pacientu, o negovalnih intervencijah in pri dokumentiranju odvisna od sodelavcev v beli coni. Z namenom točnosti in dostopnosti informacij, sprotnega dokumentiranja naročenih in izvedenih intervencij se oblikujejo vedno novi dokumenti, ki pa zaradi že obstoječega velikega števila dokumentov bolj povečujejo obseg dela, kot pa zagotavljajo varnost in informiranost. V dobi digitalizacije, ki se je izkazala kot zelo koristna še posebno v času epidemije, bi bila edina dobra rešitev obstoječega problema digitalna dokumentacija.

Kako spoznati bolnika s COVID 19, ki potrebuje intenzivno obravnavo

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Uvod: Infekcija z novim koronavirusom povzroči pri 80% okuženih blago bolezen, med njimi jih je od 20 do 40% takih, ki so »asimptomatski« torej niti ne pomislijo na okužbo. Do 10% okuženih potebuje bolnišnično obravnavo in od teh 25% intenzivno zdravljenje. V prispevku se bomo osredotočili na slednje.

Sprejem bolnika v bolnišnico: Sprejem je indiciran takrat, ko ima bolnik potrebo po zdravljenju s kisikom, ima RTG potrejno COVID pljučnico ali je zaradi prizadetosti ostalih organov (srca, prebavil, metabolnih bolezni) potreben sprejem. Ob sprejemu se pomerijo vitalni znaki in takoj doda kisik v takem odmerku, da se saturacija popravi na 90%. Pomemben podatek je koliko časa je bolnik bolan oziroma kdaj je bil bris pozitiven, to pa zato, ker se večina poslabšanj covid pljučnice zgodi v prvih 10. dneh poteka bolezni. Ker moramo z bolnikom, ki je sum na COVID in pozitivnim delati v polni OVO opremi in bolnika imeti v izolaciji (siva cona ali covid oddelek), je pomembno, da že v tem izolacijskem prostoru lahko začnemo z vsem zdravljenjem (kisik, nadzor vitalnih funkcij, parenteralna terapija, video nadzor). Dobra praksa je tudi taka, da se ob sprejemu pozitivnega bolnika v bolnišnico le-tega ne namešča v prostore sprejemne ambulante ali sive cone, pač pa se takoj naredi RTG PC, pomeri vitalne funkcije (saturacija, tlak, pulz, temperatura) kar na transportnem vozičku in se pred prelaganja bolnika takoj odpelje na covid izolacijski oddelek, kjer ga pregleda zdravnik in se odvzame kri ter začne zdravljenje. S tem se verjetnost kontaminacije in prenosa okužbe v sprejemni ambulanti, kjer se sprejemajo tudi ne-COVID bolniki, občutno zmanjša.

Zdravljenje na oddelku (ali v sivi coni) – kateri je tvegan bolnik?

Potreba po kisiku je v dobri korelaciji z težo pljučnice, še posebej, če potreba nastane zgodaj v razvoju bolezni (prve dni do enega tedna). Primer: bolnik, ki že ob sprejemu potrebuje več kot 35% kisikovo masko ali se mu v osmih urah od sprejema potreba po kisiku podvoji in doseže vrednosti več kot 50% maska, so ZELO ogroženi. Potrebno se je odločiti, ali je bolnik v svojem splošnem telesnem stanju primeren za intenzivno zdravljenje (to je odločitev lečečega zdravnika in ob odgovoru NE tudi konzilija treh zdravnikov, seznanitev svojcev in bolnika). Za bolnika, pri katerem pridejo v poštev vsi ukrepi je primeren konstantni monitoring vitalnih funkcij (npr. Midray monitorji). Če tega ni na voljo pa meritve vitalnih funkcij na 3 ure.

Podporno zdravljenje s kisikom (bolezen povzroča HIPOKSEMIČNO respiracijsko odpoved, brez hiperkapnije) omogoča, da bolnik prebrodi najbolj aktivno fazo bolezni in jo tako premaga; sam kisik pa ne zdravi virusa ali pljučnice. Najbolj pogosti spremljajoči zapleti pri teh bolnikih so metabolna iztirjenost (acidoze in alkaloze) in pljučni embolizmi. Manj je ob okužbi sproženih srčnih popuščanj.

Bolniki s preeksistentnimi pljučnimi boleznimi so še posebej ogroženi, ker imajo manjšo rezervo v delovanju pljuč. Sem spada predvsem KOPB in intersticijske pljučne bolezni. COVID okužba NE poslabšuje astme in pri astmatikih potek ni slabši kot pri zdravih. Trajanje potrebe po zdravljenju s kisikom je pri takih bolnikih daljša.

Bolnikom, ki akutno fazo bolezni preživijo in zaradi COVID pljučnice vsaj tri dni hospitalizacije potrebujejo konstantno 1 do 3 litre kisika za vzdrževanje saturacije na 90% imajo možnost predpisa in zdravljenja s koncentratorjem kisika na domu do trajanja treh mesecev. S tem skrajšujemo hospitalizacijo, organizem potrebuje vsaj dva meseca da se stanje povsem normalizira. Podatov o trajnih posledicah prebolele COVID pljučnice pa še ni zadosti.

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Diagnostika okužb s SARS-CoV-2

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Od decembra 2019 se človeštvo ponovno spopada s pandemijo, ki jo tokrat povzroča beta-koronavirus, SARS-CoV-2. SARS-CoV-2 je respiratorni virus, ki povzroča gripi-podobno bolezen, lahko pa tudi težko obliko bolezni, kjer virus ne prizadene le pljuča, ampak tudi druge organe. Bolezen, ki jo povzroča SARS-CoV-2 so poimenovali covid-19 (ang. Coronavirus disease 2019). Ob vsaki pandemiji je ključnega pomena hitra identifikacija povzročitelja, tako biološka kot genetska in ugotovitev, kakšen imunski odziv sproži okužba. Za diagnostiko covida-19 imamo na voljo teste, ki neposredno dokazujejo prisotnost (delčkov) virusa. To lahko izvedemo s pomočjo kultivacije virusa na celičnih kulturah, z dokazovanjem različnih površinskih beljakovin virusa, kar nam omogočajo hitri antigenski testi in z najpogosteje uporabljenimi metodami molekularne biologije in sicer direktnim dokazovanjem virusnih nukleinskih kislin ali detekcijo s pomnoževanjem nukleinskih kislin virusa. Druga možna diagnostična pot je ugotavljanje imunskega odgovora gostitelja na okužbo z virusom s pomočjo detekcije specifičnih protiteles proti SARS-CoV-2.

Diagnostiko covida-19 lahko izvajamo za različne namene kot so:

- triaža simptomatskih oseb,
- triaža presimptomatskih in simptomatskih oseb z dejavniki tveganja za,
- diagnostika simptomatskih oseb,
- diferencialna diagnostika,
- potrditveno testiranje,
- testiranje oseb s predhodno izpostavljenostjo virusu,
- presejanje določenih skupin ali okolij,
- pojasnjevanje preteklih ali potencialnih izbruhov,
- okoljski (epidemiološki) monitoring.

Glede na naš diagnostični cilj uporabimo teste oz. kombinacijo testov, od katerih pričakujemo optimalen diagnostični izplen. Da bi znali optimalno izbirati teste, moramo poznati njihove tehnične prednosti in pomanjkljivosti, optimalno časovno okno, v katerem so najbolj uporabni ter njihovo odvisnost od prevalence bolezni v populaciji.

Izkušnje epidemiologov s SARS-Cov-2

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Uvod: Koronavirusi zavzemajo pomembno mesto v zgodovini 21. stoletja. V tem stoletju so izolirali pet od sedmih človeških koronavirusov. Zadnji trije so v naše življenje prinesli strah pred izbruhom, pandemijo in smrtjo. Najnovejši človeški koronaviruski je izšel iz Kitajske Wuhan, imenuje se SARS CoV-2 in povzroča bolezen covid-19.

Epidemiologija bolezni covid-19 ima nekatere svoje značilnosti širjenja in obnašanja, kar do sedaj nismo poznali. Prenaša se kapljično in kontaktno s človeka na človeka. Prenos preko zraka še ni popolnoma dokazan. Bolezen je zelo kužna. Paleta bolezni covid-19 je opredeljena kot asimptomatska, blaga, zmerna, huda in kritična. Čeprav so o covidu-19 poročali od bolnikov vseh starosti, se starejši pacienti zdijo bolj dovzetni za okužbo. Pri otrocih bolezen ponavadi poteka brez simptomov, pri ostalih v blagi obliki.

V Sloveniji smo prvi val epidemije uspešno obvladali. Dejavnosti smo začeli sproščati že po 7 tednih od prvega pozitivnega primera. S hitrimi ukrepi smo preprečili prekomerno širjenje epidemije in s tem povečano smrtnost. Konec maja je število okuženih znova naraščalo zaradi primerov vnesenih iz tujine, in sicer iz Bosne in Hercegovine, Srbije in Kosova. V začetku avgusta smo zaznali povečano število obolelih predvsem mladih, ki so se vrnili iz Hrvaške. Kako se bo dogajanje odvijalo v prihodnosti je ugibanje. Epidemija sama in ukrepi za njeno zajezitev so povzročili gospodarsko škodo, škodo na zdravju številnih pacientov zaradi odlaganja zdravljenja, psihične stiske prebivalstva. Kljub omenjenim težavam je bilo obvladovanje prvega vala epidemije covida-19 v Sloveniji uspešno. Sedaj v začetku novembra smo v sredini drugega vala, ki je po številu obolelih in umrlih večkratnik prvega.

Zaključek: Kako se bo dogajanje odvijalo v prihodnosti je ugibanje. Epidemija sama in ukrepi za njeno zajezitev so povzročili gospodarsko škodo, škodo na zdravju številnih pacientov zaradi odlaganja zdravljenja, psihične stiske prebivalstva.

Prehranska podpora pri bolniku s covidom-19

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Bolniki z okužbo covidom-19 SARS imajo lahko blage, srednje ali hude respiratorne simptome in veliko jih potrebuje tudi specialno zdravljenje in zdravstveno nego v bolnišnici zaradi respiratorne odpovedi.

Covid-19 je nova bolezen, zato so bile smernice za prehransko podporo povzete po priporočilih, ki se uporabljajo za bolnike, ki imajo težko respiratorno obolenje. Simptomi in znaki okužbe z virusom SARS-COV-2 pripomorejo k slabšemu apetitu in posledično k nezadostnemu vnosu energije in posameznih hranil. Nezadostna prehrana v času okužbe pripomore k izgubi funkcionalne telesne mase in vpliva na razvoj vnetnih procesov pri okužbi, kar še dodatno vpliva na podhranjenost, ki lahko povzroči dodatne zaplete.

Energijske potrebe bolnikov s covidom-19 se določa individualno, cilj je nekje 30 kcal/kg telesne mase za podhranjene bolnike in starostnike. Ta cilj je potrebno doseči postopno. Potrebe po beljakovinah so 1-1,2 g na kg telesne mase. V primeru nezadostnega energijskega vnosa (manj kot 60% potreb) in pri podhranjenih bolnikih, se svetuje uporaba oralnih prehranskih dodatkov, ki naj bi jih bolniki jemali vsaj en mesec. V primeru da tudi to ne zadošča, se uvede enteralna prehrana preko sonde. Zgodnja uvedba enteralne prehrane lahko zavira vnetje in pripomore k zmanjšanju zapletov. Sondna hrana se uporablja tudi v primeru disfagije, ko tudi hrana ustrezne/modificirane teksture ni več primerna. Dopolnilno parenteralno prehrano uvedemo, če z enteralno ne zagotovimo zadostnega vnosa. Pomembo je preprečevati in zdraviti pomanjkanje mikronutrientov, medtem ko ni dokazov, da bi rutinsko dodajanje le teh imelo vpliv na izid zdravljenja.

Za bolnike s covid-19 pljučnico, ki so mehansko ventilirani in se zdravijo v enoti intenzivne terapije, se najprej, če se le da, uporabi enteralna prehrana, šele nato, če to ne gre, začnemo s parenteralno prehrano. Bolnike hranimo po nasogastrični ali nasojejunalni sondi. Tekom zdravljenja na intenzivni enoti se priporoča višji vnos beljakovin: 1,3 g/kg beljakovin na dan, pri bolnikih z debelostjo se upošteva prilagojena telesna masa.

Raziskave navajajo, da je dolgotrajna hospitalizacija v ICU enoti vzrok za podhranjenost z izgubo puste telesne mase in funkcionalnosti in vodi v slabšo kakovost življenja, nefunkcionalnost in številne polimorbidnosti.

Pomembna je tudi prehranska podpora v času okrevanja in rehabilitacije bolnikov po odpustu iz bolnišnice v domače okolje.

Zagotavljanje ustrezne prehranske podpore je pomembno v vseh korakih zdravljenja, kjer je potrebno upoštevati individualne posebnosti starostnikov, njihovo krhkost in polimorbidnost. Dobra prehranjenost in hidracija sta pomemben del zdravljenja bolnikov s covid-19 boleznijo.

Izzivi medicinskih sester pri delu z bolniki okuženimi s SARS-CoV-2 v enoti intenzivne terapije

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Uvod: V začetku leta 2020 se je bolezen covid-19 pričela nenadzorovano širiti iz Kitajske. Tako velikega navala bolnikov ni pričakoval noben zdravstveni sistem, zato je obremenitev le-tega postala zelo velika. Posledično so obremenjeni tudi zdravstveni delavci.

Metode: Raziskava temelji na metodi kvantitativnega raziskovanja, s pregledom strokovne literature. Pregled literature je bil opravljen s pomočjo podatkovnih baz. Ključne iskalne besedne zveze po katerih smo iskali zadetke so bile: "Nursing in ICU while covid-19 pandemic", "Nursing workload in ICU", "Nursing workload in covid-19 ICU's", "Obremenitev medicinskih sester v EIT". Za izključitvene kriterije smo določili: vsi viri, ki niso strokovni, nestrokovni spletni viri, neetične raziskave, zastareli viri, ki so potrjeni z novimi spoznanji, nepopolna besedila oziroma izvlečki. Dobljene rezultate pregleda literature smo nato primerjali z rezultati prikaza ocenjevalnega seznama TISS – 28, ki smo ga vodili tekom epidemije.

Rezultati: Rezultati so nam prikazali, da se večina medicinskih sester, ki so jih zajele raziskave po svetu, srečuje z nekaj osnovnimi problemi oziroma vprašanji. Velika večina medicinskih sester opozarja na to, da občutijo strah in nemoč zaradi nepoznavanja delovnega okolja in procesov, ki so nastali tekom sprejemanja bolnikov okuženih z virusom SARS-CoV-2. Anksioznost, ki jo občutijo medicinske sestre izvira predvsem iz nepoznavanja in neizkušenosti pri delu z bolniki, ki imajo nalezljive oblike bolezni. Prav tako je prisotna skrb, da se nebi okužile z virusom SARS-CoV-2 ali le-tega iz delovnega okolja prenesle domov oziroma bližnjim. Veliko avtorjev pri tem doda, da medicinske sestre navajajo veliko delovno obremenitev in posledično dolgoročno izčrpanost zaradi preobilice dela. Nekateri avtorji dodajajo, da so medicinske sestre v enotah intenzivne terapije, kjer so hospitalizirani bolniki okuženi s SARS-CoV-2 virusom, skrbele tudi za 9 bolnikov naenkrat, kar je privedlo do zelo velikih delovnih obremenitev ter posledično slabše obravnave bolnikov. Dobljene rezultate avtorjev smo nato primerjali z rezultati, ki jih prikazuje orodje TISS - 28 za vrednotenje težavnosti obravnave zdravstvene nege bolnikov v enoti intenzivne terapije, ki prav tako prikaže veliko delovno obremenitev medicinskih sester.

Zaključek in diskusija: Velika delovna obremenitev in novosti pri obravnavi bolnikov okuženih z SARS-CoV-2 virusom medicinskim sestram prinašajo veliko novih izzivov. Vsekakor je pomembno, da v teh časih velikih delovnih naporov in nemalokrat osebnih stisk ustrezno poskrbimo za zdravje medicinskih sester in ostalih zdravstvenih delavcev.

Doživljanje stresa zaposlenih v zdravstvu pri delu s covid-19 obolelimi pacienti

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Uvod: Stres je vsako dejanje, ki človeku postavlja posebne psihološke zahteve in mu poruši njegovo ravnovesje. Stres povezan z delom je zaskrbljujoč pri zdravstvenih delavcih. Povezan je z zmanjšanim zadovoljstvom z delom, tesnobo, depresijo, strokovnimi napakami in nesrečnimi dogodki. Izbruh covida-19 je povzročil veliko breme ter psihološki stres za zdravstvene delavce. Cilj raziskave je bil ugotoviti kako so doživljali stres zdravstveni delavci pri delu s covid-19 pacienti.

Metode: Za izvedbo raziskave smo uporabili prevedeni vprašalnik DASS-21 (cronbach alfa=0.88). V raziskavi je bilo skupno udeleženih 99 anketirancev zaposlenih na Univerzitetni kliniki za pljučne bolezni in alergijo Golnik. Za analizo smo uporabili 93 pravilno izpolnjenih anketnih vprašalnikov. Za statistično obdelavo podatkov smo uporabili program Excel in GraphPad Prism. Srednje vrednosti oziroma povprečja nenormalno razporejenih spremenljivk smo med skupinami primerjali z uporabo Mann-Whitney U testa. Kot statistično značilno smo uporabili p vrednost nižjo od 0.0001.

Rezultati: Raziskava je pokazala statistično pomembne razlike ($p<0.0001$) v doživljanju stresa, tesnobe in depresije med izpostavljeno skupino (povprečje=10.33) in ne izpostavljeno skupino (povprečje=5.71) ter statistično pomembne razlike glede na čas izvajanja aktivnosti pri pacientih s covidom-19. Statistično visoko pomembne razlike ($p<0.0001$) smo dokazali med skupino, ki je bila izpostavljena do 2 uri (povprečje=6.93) in skupino, ki je bila izpostavljena 5 ur ali več (povprečje=13.96). Ravno tako smo dokazali statistično pomembne razlike ($p=0.0013$) med skupino, ki je bila izpostavljena od 3 do 5 ur (povprečje=7.84) ter skupino, ki je bila izpostavljena 5 ur ali več. Na vprašanja o trenutnih epidemioloških delovnih razmerah 61 odstotkov udeleženih meni, da so v službi bolj pod stresom, kot običajno, 84 odstotkov udeleženih skrbi, da bi okužili druge, 63 odstotkov jih navaja, da njihove svojce in znance skrbi, da bi se okužili preko njih in 53 odstotkov udeleženih navaja, da se jih zaradi trenutnega področja dela ljudje izogibajo.

Zaključek: Rezultati so dokazali, da je časovna izpostavljenost pri delu s covid-19 obolelimi pacienti pomemben dejavnik, ki vpliva na občutek stresa, tesnobe in depresije. Udeleženci skupin, ki so bili izpostavljeni dlje časa, so ocenjevali višjo stopnjo občutka stresa, tesnobe in depresije v primerjavi z udeleženci, ki je bili izpostavljeni manj časa. Po mnenju anketirancev je delo v trenutnih epidemioloških razmerah vplivalo na njihovo socialno življenje. Skoraj večina se jih je soočala s skrbjo, da bi okužili druge, več kot polovica pa je navajala, da se jih je zaradi narave dela širša družba izogibala.

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ALLERGY - DIAGNOSTICS

Diagnostic relevance of IgEs to recombinant allergens Api m 1 and Ves v 5 determined by the multiplex test ImmunoCAP ISAC

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Background: ImmunoCAP ISAC (ISAC, Phadia, Uppsala, Sweden) is a multiplex allergen test that enables the measurement of IgE antibodies to a fixed panel of 112 components from 51 allergen sources in a single step, including two major venom components, honeybee rApi m1 and yellow jacket rVes v5 and two additional marker allergens, Api m4 and Pol d5. Both components are markers of genuine (species-specific) sensitization and are important for molecular diagnosis, which may permit the identification of bees and/or yellow jackets as culprit insects in venom-sensitized subjects. We conducted a multicentre study and the first methodological comparison of IgE measurements for rApi m1 and rVes v5 between ImmunoCAP singleplex (CAP, Phadia, Uppsala, Sweden) and ISAC testing, and evaluated the possible clinical utility of ISAC in Hymenoptera venom allergy.

Methods and results: We included 3001 subjects, who were routinely tested with ISAC from 2012 to 2017 at University Clinic Golnik, Slovenia, or at Charles University Faculty of Medicine, Pilsen, Czech Republic (801 subjects from Golnik, Slovenia, and 2200 subjects from Pilsen, Czech Republic). Positive ISAC results (≥0.30 ISU-E; ISAC Standardized Units) for rApi m1 and/or rVes v5 were observed in 342 (11.4%) subjects; 83 (24.3%) were sensitized to rApi m1, 232 (67.8%) to rVes v5, and 27 (7.9%) to both components. Of those 342 subjects, 93 subjects were methodologically and clinically analysed in detail. By ISAC, 8 (8.6%) of those subjects were positive for rApi m1, 74 (79.6%) for rVes v5 and 11 (11.8%) for both components. The ISAC results showed a high concordance with standard quantitative CAP testing, 90.3% for rApi m1 and 96.8% for rVes v5. Furthermore, there was a significant positive correlation between semi-quantitative ISAC and quantitative CAP values, both for rApi m1 ($R=0.79$, $p<0.0001$) and for rVes v5 ($R=0.69$, $p<0.0001$). Discordant results were observed in 12 subjects; nine for rApi m1 and three for rVes v5. Eight subjects showed negative ISAC and positive CAP rApi m1 results, and only one subject showed positive ISAC and negative CAP rApi m1 results. Three subjects had positive ISAC and negative CAP rVes v5 results.

A detailed clinical evaluation showed that 29 of 93 subjects (31.2%) had a positive

history of Hymenoptera venom allergy. For honeybee allergy, one (1.1%) subject had a systemic reaction and five (5.4%, 5/93) subjects had LLR. For *Vespula* allergy, 9 (10.3%) subjects had systemic reactions, 10 (10.8%) had LLRs after yellow jackets sting, two (2.2%) had a history of double-positive systemic reactions to both honeybee and yellow jacket stings, one subject had a systemic reaction after honeybee sting and LLR after yellow jacket sting, and one subject had LLRs after both stings. In the other 64 (68.8%) subjects, rApi m1 and rVes v5 sensitization seemed to be asymptomatic. According to the clinical data, ISAC and CAP rApi m1 were positive in 5 of 6 (83%) honeybee-allergic subjects. For rVes v5, ISAC and CAP were positive in all (100%, 19/19) yellow jacket–allergic subjects. In subjects allergic to both honeybee and yellow jacket venom, rApi m1 was positive by ISAC in one (25%) and CAP in 3 (75%) subjects; for rVes v5, both ISAC and CAP were positive in all 4 (100%) subjects.

Conclusions: With this study, we showed that, for measuring specific IgEs for rApi m1 and rVes v5, ISAC and CAP are methodologically comparable methods. Additionally, a high correlation between the measured values was observed, although the ISAC system measures semiquantitatively. ISAC displayed lower sensitivity regarding rApi m1, whereas the correlation for rVes v5 was optimal. ISAC is a diagnostic test that is generally not used for the detection of sensitization to Hymenoptera venom in routine practice. Nevertheless, patients, regardless of the clinical indication, needs to have their positive results precisely interpreted regarding the Hymenoptera allergy.

Comparison of ImmunoCAP ISAC and ALEX multiplex assay

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Background: The introduction of ImmunoCAP ISAC (ISAC) in 2009 was a major breakthrough in allergy diagnostic since the multiplex enables to determine specific IgE to 112 different allergen components. Recently another multiplex platform Allergy Explorer (ALEX) became available. It can detect specific IgE against 157 allergen extracts and 125 allergen components, based on a nano-bead technology. The objective of this study was to compare the methodological concordance between ISAC and ALEX assay.

Method: We included 20 patients in the analysis and we compared the results for 69 allergen components present in both assays. When discordant result between ISAC and ALEX was found sample was tested with singleplex ImmunoCAP test. Positive cutt-off values for ISAC was 0.30 ISU-E, for ALEX 0.30 kUA/L and for ImmunoCAP 0.35 kUA/L.

Results: Out of 1380 measurements for sIgE (20 patients x 69 components), concordant result for both multiplex systems was found in 96% (1327/1380) cases. The discordance was demonstrated for 34 allergen components. For nOle e 1 the discordance was 25% (5/20) and for rPol d 5, rAra h 8 and nJug r 2 15% (3/20). For 9 allergens discordance was 10% (2/20) and for 21 allergens 5% (1/20). Total agreement between both results were found among all patients for 35 (51%) allergens. 15 discordant measurements for 9 allergens (rApi m 1, rVes v 5, rPol d 5, rAra h 8, rAra h 9, nCor a 9, rBet v 1, rDer p 10 and rHev b 5) were additionally tested with ImmunoCAP singleplex assay. ISAC result was confirmed with ImmunoCAP in 9 cases (60%) and ALEX in 6 (40%). On the level of single patient, concordance of sIgE results are varying from 85.5% to 100.0%. Total agreement was observed in four (20%) patients, one patient had discordant result in 10 allergens (85.5%), one patient in 6 (91.3%), one patient in 5 (92.8%), three patients in 4 (94.2%), four patients in 3 (95.7%), two patients in 2 (97.1%) and four patients had discordant result in one allergen (98.6%).

Conclusion: There is a high level of concordance between ISAC and ALEX multiplex assay. When comparing results of both multiplexes with singleplex ImmunoCAP, ISAC showed slightly higher correlation in contrast to ALEX. Nevertheless, before starting using novel multiplex assay in a diagnostic routine setting, larger studies are needed and results should be interpreted carefully according to the clinical data.

Fluorescent labeling of major honeybee allergens Api m 1 and Api m 2 with Quantum dots and the development of a multiplex basophil activation test

Development of a multiplex BAT

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Introduction: Basophil activation test (BAT) represents a useful tool to detect immediate hypersensitivity reactions, whereas the labelling of allergens with fluorescent probes may represent a major step in development of multiplex BAT, which would enable analysis of the basophil activation by various allergens with a significantly smaller number of test probes. In this study we undertook initial validation and assessment of multiplex BAT, by using two major bee venom allergens Api m 1 and Api m 2 labelled with Quantum dot (Qdot) nanocrystals of two different sizes and surface chemistries.

Methods: nApi m 1 and rApi m 2 were conjugated to Qdot® ITK™ quantum dots (705 nm and 800 nm) with an amino (PEG) or carboxyl functionalized polymer coating. The IgE reactivity of the Qdot-labeled allergens was assessed by an immunodot assay. The allergenic activity was determined with BAT using CD123-PE/HLA-DR-APC/CD63-FITC labelled antibodies. Usefulness of Qdot-labelled allergens for multiplex BAT analysis was tested in 17 bee venom-allergic patients and in 6 controls.

Results: The amino and carboxyl Qdot-labeled Api m 1 (NQ705-Api m 1 and CQ705-Api m 1) and Api m 2 (NQ800-Api m 2 and CQ800-Api m 2) allergens bound IgE in patient samples in the immunodot assay regardless of their conjugation and size, whereas the unconjugated Qdots showed no interaction with serum IgE. The amino but not the carboxyl Qdot-labeled Api m 1 and Api m 2 were able to activate basophils, as reflected in the dose-response curves of basophil CD63 in the presence of NQ705-Api m 1 and NQ800-Api m 2, which were comparable to the responses to Api m 1 and Api m 2. We further tested the NQ705-Api m 1 and the NQ800-Api m 2 in the multiplex BAT by analyzing CD63 expression in a subpopulation of basophils according to the binding of the fluorescent allergen. We found a strong positive correlation between native and NQ-labeled Api m 1 or 2 ($r \geq 0.88$, $P < 0.0001$). Considering the threshold value of 15% for CD63-positive basophils, 15 out of 17 patients and 6 out of 6 controls had matching results for the multiplex BAT and BAT.

Conclusion: This is the first study describing the labeling of allergens with fluorescent probes, the evaluation of their IgE reactivity and their performance in the BAT. This approach will provide novel diagnostic possibilities and enable further studies of the role of the surface distribution of allergen-specific IgEs in the responses of effector cells.

Allergic conditions along rural-urban gradient in the study of Croatian school population

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Background: Urbanisation delays postnatal maturation of adaptive immunity. Interplaying with genetical determinants it is drammatically increasing the risk for all types of allergy, especially among children. Rural living comprises protective (not fully understood) immunomodulatory factors inducing immunotolerance. The main aim of our study was to investigate prevalence differences in asthma (A), rhinitis (AR) and atopic dermatitis (AD) symptoms between three age groups of children living in the city of Zagreb and children living in Natural Park Lonjsko Polje, complex of lowland riparian forests with 1500 species living there. Second, we intend to get insight into differences of some urban/rural early-life environmental exposures assessed from ISAAC questionnaires.

Patients and methods: In the schoolyear 2017/2018 total of 1745 schoolchildren aged 6-14 years (6-7 yrs, 10-11 yrs and 13-14 yrs age groups), from 39 randomly selected elementary schools, were included. Questionnaires were answered by parents. The results were compared with the study in Zagreb in year 2002.

Results: Regarding allergic rhinitis, children from rural setting showed lower risk for current AR (last 12-months symptoms) (OR 0,373; 0,563; 0,172 for all age groups respectivelly) in comparison to the children from the urban area who reported more drugs usage for current AR (X2 Yates corect 0,46, p <0,0001), and more often pharmacies visits (p<0,046).

The responses for asthma are different from the data seen in rhinitis. There was no difference between rural and urban three-age-groups-children current and *ever in lifetime asthma*. However, the meaning of more frequent urban *wheezing ever in a lifetime* in the oldest, 13-14 years old age group, is not clear.

There are literature evidences of strong genetic relationship in AD. Our study showed different environmental influences on current AD symptoms which are strongly associated with urban life-style and medication consumption. That is opposite in children living in rural area of Lonjsko Polje for all age groups. History of allergic diseases in both parents (mother´s AR and father´s AD) are risk factors for current AD in the city while cooked green vegetables were protective.

Conclusion: Comparisson of rural/urban risks for AR, A and AD symptoms has shown complex and different patterns of environmental associations with distinct type of allergic disease.

FOOD ALLERGY

Alpha-gal syndrome

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Background: Alpha-gal syndrome or. mammalian meat allergy, is an allergy to galactose-α-1,3-galactose. Alpha-gal is an oligosaccharide in the saliva of ticks and meat of four-legged non-primate animals. Allergic sensitization with alpha-gal appears to occur through a tick bite. Sensitization to this allergen is common (10% of rural individuals), but fortunately most sensitized individuals are asymptomatic. The characteristic clinical picture of this allergy is late anaphylaxis after eating red meat, especially offal. In patients with sIgE against alpha-gal, allergic reactions may also occur when using medicines containing gelatin (certain vaccines, antivenoms, cetuximab). Alpha-gal may be present in recombinant proteins derived from mammals, heparin, bioprosthetic heart valves.

Methods: The data refers to patients who are in the hospital information system of clinic Golnik. We looked for patients who, based on their anamnesis, the presence of sIgE against alphaGAL and a good response to diet, had a diagnosis of red meat allergy in a two year period from 2018 to 2020.

Results: Over a two-year period, the diagnosis was made in 15 patients (8 women), at the age of 44 (17-69). The concentration of sIgE alphaGAL was 16.8 (0.74-100) kIU / L. 11 had anaphylaxis, 3 had urticaria, and 1 had gastrointestinal symptoms. It took 12 (3-300) months from the first symptoms to the diagnosis. Patients had 6 (1-600) episodes. The problems started 3 (1-14) hours after eating meat. Only 4 patients suspected that the cause of anaphylaxis was meat. 6 patients had episodes that started overnight. In addition to eating red meat, 4 patients needed cofactors (effort, NSAIDs, alcohol) for symptoms. 11 patients follow a strict diet and 10 have no problems, one has less, two patients need to avoid offal, two patients are not strict in the diet.

Conclusion: The diagnosis of anaphylaxis due to allergy to alpha-gal is often missed because, unlike typical anaphylaxis, symptoms appear after several hours, often in the middle of the night. The allergen is quite weak, so patients do not always have problems when eating red meat. This allergy was discovered only a few years ago, so it is still quite unknown among doctors. As a result, these patients are often initially diagnosed with idiopathic anaphylaxis.

Patterns of sensitization and inflammation markers in food allergies in patients from Western Romania

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Background: The goal of this study was to establish a pattern of sensitization in food allergy, as well as to prove that serum eosinophilic cationic protein (ECP) can be used as a clinical marker for chronic inflammation and could assist in diagnosing food allergies.

Methods: The study group consisted of 150 subjects with skin manifestations, which were selected according to specific criteria and were examined clinically (skin prick test, clinical score) and paraclinically (complete blood count, inflammation markers, total serum IgE, specific food IgEs, ECP, diamine oxidase activity, nasal- and pharyngeal samples, anti-Helicobacter pylori IgG, anti-Toxocara IgG, and stool ova). Criteria for exclusion were patients that did not have specific IgE measured, and cases where 2 out of 3 paraclinical blood investigations as for total serum IgE, blood eosinophil count or serum ECP were missing.

Results: 54% of the patients had a final diagnosis of urticaria, 26% atopic dermatitis, 16% angioedema, and 14% dermographism. 38% of the study group also had infections. Regarding the patterns of sensitization in food allergy, the most common allergies in the age group 0-5 years and 5-17 years were due to milk and egg, whereas the most common in >17 years were due to flour, nuts, legumes and fish. With increasing age, food allergy prevalence decreased. 38% of the study group also had infections. We found a strong positive correlation between food allergy and allergy to inhaled allergens. Furthermore, serum ECP does not only reflect chronic inflammation, but also the severity of the ongoing inflammation.

Conclusion: Our findings suggest that the patterns of food allergy change with age and they are also less the cause of urticaria in older children. Serum ECP may be used as a biomarker in skin manifestations showing a possible chronic progression. Thereby, information about the severity of the chronic inflammation can be gathered, which can then be treated accordingly.

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Comparison of CytoBead CeliAK indirect immunofluorescent methods and ALEGRIA ELISA tests in celiac screening

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Objective: The aim of the study was to compare two diagnostic methods, with three ways of detection of anti tTG IgA antibodies, for 45 consecutive samples (analysed in the order they were recived by the laboratory) of adult patients, and to observe what is the correlation of results between these two diagnostic methods.

Introduction: Celiac disease is a serious autoimmune disease that occurs in genetically predisposed people, where the ingestion of gluten leads to inflamatory damage in the small intestine with villous atrophy. The disease occurs in 1 in 100 individuals with symptoms similar to diarrhoea, abdominal pain, and malabsorption, loss of appetite and growth retardation. In the event of delayed diagnosis, it may present with other autoimmune diseases such as neuropathies and multiple sclerosis. The diagnosis is established on a biopsy of the small intestinal mucosa, which is found to be damaged before the patient is put on a gluten free diet, and control biopsy of the regenerated mucosa after the introduction of the strict implemented diet. Determination of anti-DG, anti-tTg IgG and IgA antibodies by ELISA as well as detection of endomysial IgA with immunofluorescence has proven to be the most sensitive serological method in the diagnosis of this disease.

Materials and methods: We analysed serum samples from 45 patients (27 females and 18 males) who we screened for celiac disease. Each serum sample underwent both tests: the CytoBead CeliAK (GA Generic Assays GmbH) multiplex indirect immunofluorescence method and the ALEGRIA (ORGENTEC diagnostika Gmbh) ELISA assay.

After qualitative analysis of each individual sample, the test was determined to be either positive or negative by the indirect immunofluorescence method on monkey oesophageal tissue + bead (purified tTG fixed antigen).The same serum sample was analysed by an ELISA method for anti-tTG IgA quantitative, with a positive or a negative result according to the »CUT OFF« specified by the reagent manufacturer.

Results: We made three types of comparisons:
1.) Bead anti tTG IgA - Endomysium IgA (EmA) and found a 100% test match,
2.) Bead anti tTG IgA - ELISA anti tTG IgA whose test match was 100%,
3.) Endomysium IgA (EmA) - ELISA anti tTG IgA whose test match was 100%,

Conclusion: The compared diagnostic methods for screening of Celiac disease demonstrate a *perfect agreement* between their *respective results*.

The sensitivity and specificity of diagnostic tests to determine food allergy in children with atopic dermatitis

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Background: Food allergies have increased substantially over the past decade. The success of the clinical management is depending on early diagnostic and determining the whole spectrum of sensitization to food allergens.

The scope of the study was to determine the indexes of sensitivity(ISS) and specificity(ISC) of different diagnostic tests to detect food sensitization in children with atopic dermatitis.

Method: There were analyzed the results of the data of the allergic history(AH), of food diary register(FDR), skin test(ST), detection of Ig E specific allergens, oral food challenge(OFC) and reaction of inhibition of leukocyte migration(RIML) at 315 patients aged 1 month up to 18 years suffered with atopic dermatitis. The research results were processed by methods of mathematical statistics the distribution of the frequencies of the variation series depending on the value of the studied feature.

Results: The ISC of AH method was 84.2% and ISS 68%. False positive data were noted in 15.7%, and false negative in 31.3% of patients. AH is most informative for detecting sensitization to most obligate allergens (fish, honey, egg white, citrus) and the least to everyday foods (wheat flour, beef, milk). ST revealed sensitization to the allergen of eggs (32%), egg white (32%), fish (30%), chicken meat (28%), lemon (25%), oranges (23%), tomatoes (23%), milk (22%), grapes (21%).The false negative results ST were most often observed with allergies to milk, eggs, meat, buckwheat, rice, barley, and less often to fish, strawberries, oranges, and raspberries. It was established, that the ISS of the detection of Ig E antibodies has value of 95% with ISC of 86% and respectively the TILM 100% and 90%, DFR 95% and 86%, ST 41% and 71%, OFC 45% and 97%.

Conclusion: In early detection of food sensitivity *in vitro* tests have advantages with higher ISS and ISC in comparison with diagnostic tests *in vivo* with possibility to use them in different age periods, in any period of the disease and also allows to obtain the most complete information for a faster preparation of elimination diets, which underlie the complex therapy of food allergies in children.

Tests for food allergy

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Introduction: Nutrition allergy is an unfavorable immune response to food proteins. The most common food allergens in children are cow's milk proteins, eggs, fish, nuts, peanuts, wheat flour and soy.

The testing begins with the standard, known concentration, nutrition comercial allergens skin prick testing. A more selective test is a skin prick test performed using a fresh food allergen. A skin prick test analyzes the size of wheal diameter, whereas an *in vitro* test measures the value of specific IgE.

So far neither of these tests has had a priority, which means that it is most useful to do both *in vivo* and *in vitro* tests in practice and either confirm or exclude the suspicion of a nutrition allergy. However, gold standard for nutrition allergy diagnosis is a provocation test, but it takes lot of time and there is certain risk for patient.

Objectives: The objective of this study is to determine the concordance between *in vitro* and *in vivo* testing.

Material and methods: This study has involved a group of 571 respondents, 142 out of which are sensitized to cow's milk proteins, 137 to eggs, 98 to peanuts, 76 to soy, 74 to wheat flour and 44 to kiwi. Skin prick testing has been performed using both standard commercial nutrition allergens and fresh food allergens. Specific IgE is measured using UniCAP Pharmacia Upsala method.

Results: This study examines diagnostic procedures and their interrelations for the purpose of proving nutrition allergies. Sensitization and the specificity of the response have been determined for all the three tests, as well as the odds ratio. For **cow's milk protein allergen** SPT sensitization of 0.77 is high, with the lower specificity of 0.21, and the odds ratio of 0.85 with CI (confidence interval) from 0.55 to 1.32. PPT sensitization at 0.92 is high, but the specificity of 0.06 is low, with the odds ratio of 0.67 and CI between 0.34 and 1.34. Specific IgE has the lowest sensitization of 0.62, but it has the highest specificity of 0.41, with the odds ratio of 1.11 and CI of 0.76-1.62. For **egg white allergen** SPT sensitization of 0.93 is high, with the lower specificity of 0.25, and the odds ratio of 4.62 with CI from 2.29 to 9.32. PPT sensitization at 0.99 is high, but the specificity of 0.08 is low and the odds ratio is 11.36 with higher CI – 1.55 - 83.15, which means that we must be very cautious when using only this test to confirm the existence of allergy. Specific IgE sensitization is 0.69, but the specificity is 0.42, and the odds ratio is 1.65 with CI of 1.11- 2.46. For **wheat flour allergen** SPT sensitization is 0.69 and specificity is 0.20, whereas the odds ratio is 0.55 with CI of 0.32-0.93. PPT sensitization at 0.96 is high, but the specificity of 0.07 is low with the odds ratio of 1.68 and CI of 0.51-5.56. Specific IgE sensitization is 0.64 and the specificity is 0.40, with the

odds ratio of 1.18 and CI of 0.72- 1.94. For **peanuts allergen** SPT sensitization is 0.70, and the specificity is 0.20, with the odds ratio of 0.58 and CI from 0.36 to 0.94. PPT sensitization is 0.88, and the specificity of 0.05 is really low, with the lowest odds ratio of 0.41 (compared to other tested allergens) and the lowest CI of 0.20-0.82. Specific IgE sensitization is 0.49, and the specificity has similar value of 0.38, whereas the odds ratio is 0.59 with CI of 0.39-0.91. For **soy allergen** SPT sensitization is 0.70, and the specificity is 0.20, with the odds ratio of 0.57 and CI from 0.34 to 0.97. PPT sensitization is 0.86, with the low specificity of 0.06, and the odds ratio of 0.53 with CI of 0.24-1.18. Specific IgE sensitization is 0.45, and the specificity is 0.38, with the odds ratio of 0.50, which is the lowest odds ratio value for all the tested allergens, and CI of 0.31-0.81. For **kiwi allergen** SPT sensitization of 0.59 was the lowest, whereas the specificity of 0.20 was the same as for other tested allergens, with the lowest odds ratio for positive response 0,20 and CI from 0.19 to 0.67. PPT sensitization of 0.93 was high, with the low specificity of 0.06, and the odds ratio of 0.92 with CI of 0.27-3.11. Specific IgE sensitization was 0.57, and the specificity was 0.40, with the odds ratio of 0.87 and CI of0.47-1.61.

Conclusion: Tests with higher specificity values are more required in the situations when the false positive test results are less desirable than the false negative test results, i.e. with the diseases that are not life threatening. However, a false positive test result could bring about an unnecessary medical intervention. In our study SPT has good sensitization and slightly low specificity; PPT has excellent sensitization, but it has low specificity, whereas specific IgE has the best specificity values with the moderate sensitization. With this study we confirmed that it is often really necessary to do all the three tests and therefore triple-check test results, commercial extract values and test concordance. That way any potentially dangerous oral challenge, performed in order to prove a nutrition allergy, can be avoided.

DRUG ALLERGY AND ANAPHYLAXIS

Unsuccessful desensitization to paclitaxel in patient with high basophil sensitivity

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Introduction: Basophil activation test (BAT) represents a useful tool to detect IgE mediated reactions and predict the severity and threshold of allergic reactions to food and venom allergens, but experiences in drug allergy are limited. Herein we report the first case of positive BAT to paclitaxel.

Case report: A 50-year-old female with estrogen receptor-positive and HER2-positive breast cancer was treated with adjuvant trastuzumab,pertuzumab and paclitaxel. The first two 3-weekly applications of both anti HER-2 drugs were uneventful. During the first 5 minutes of the second infusion of paclitaxel the patient developed a reaction with abdominal cramps, dyspnea, generalized erythema, hypotension (RR 70/40 mmHg) and desaturation (80%). She was treated with methylprednisolone, clemastine, saline, and oxygen. Next day she had again reaction after infusion of 15 ml of paclitaxel with abdominal cramps, dyspnea, heart rate 120/min and was treated with methylprednisolone and clemastine. No tryptase was taken during reactions.

Skin prick test with paclitaxel (1 mg/ml) and IDT (0.001 mg/ml) were negative, but IDT (0.01 mg/ml) was positive. . Basal tryptase was normal (5.1 ug/l). To confirm allergenic activity of paclitaxel sensibilization we performed BAT which was highly positive even at low allergen concentrations. Thus, we showed 80%, 69%, 62%, 67% and 2% of CD63 positive basophils for stimulation with paclitaxel (5 to 0.0005 µg/ml). BAT response to paclitaxel in all three healthy controls was negative (<5%; 5 to 0.0005 µg/ml).

After premedication with antihistamines and steroids a 12 step (3 bags) desensitization protocol was performed. By cumulative dose of 0.022 mg paclitaxel patient had reacted with generalized erythema and pruritus. Shewas treated with adrenaline, clemastine and desensitization was stopped. Next day 16 step protocol was performed and after 0.010 mg paclitaxel generalized urticarial occurred. The infusion was paused, the patient was treated with adrenaline and clemastine. After 30 minutes desensitization was continued but the patent again reacted with generalized urticaria after a cumulative dose of 0.023 mg paclitaxel and treatment was stopped.

Conclusion: High basophil sensitivity at low concentrations of paclitaxel may be associated with the severity of the reaction, a lower threshold of allergic reactions to the allergen could consequently, predict severe side effects during desensitization and even failure to desensitize.

Identification of the potential risk factors for the rate of allergic reaction after bee and vespid sting in adults – a systematic review

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Background: In the past five decades the interest in hypersensitivity reactions caused by stings of Hymenoptera has increased noticablly. Allergic reactions to Hymenoptera stings can be more or less severe. Current criteria to diagnose Hymenoptera venom allergy, can not accurately predict the occurrence or severity of the systemic reaction or even anaphylaxis symptoms, after a sting either with bee or vespid. Our aim was to elucidate some of the possible markers, identified by different researchers, which could play an important role in determining the predictive factor for severe systemic reaction or local reaction in sensitized patients after a bee or vespid sting. The quality of life for the affected persons can be severely dimenished, since many of them are frightened what will happen after being re-stung.

Methods: A systematic literature review was conducted for the period to 31 December 2017 in the bibliographic database PubMed. In the systematic review we included all types of epidemiological studies, most of them were observational prospective and retrospective epidemiological studies, in which researchers identified some possible predictive markers that could be used to identify allergic patients' response to a bee or vespid sting with either local or severe systemic reaction.

Results: In the final analysis of the systematic review 16 original articles were included. The analysis elucidated the prevalence for large local reactions and severe systemic reaction after a bee or vespid sting. We identified the following risk factors that could play an important role to react with severe systemic reaction: the etiology of the Hymenoptera sting, sex, age, history and severity of previous systemic reaction, to be re-stung in the interval of two months, the frequency of the re-stings, atopy, genetic predisposition and mastocytosis.

Conclusions: There are few studies concerning predictive factors for determining the severity of allergic reaction after bee or vespid stings. Also, a verified predictive factor for prognosis still remains unidentified. Further studies in this field are needed. Public health activities could support promotion of awareness for the sensitized patients about proper behavior and eventual treatment with immunotherapy to improve quality of life for the affected.

SKIN ALLERGY

Distribution of different types of chronic urticaria in 233 patients

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Background: Urticaria patients represent a large proportion of referrals to allergy clinics, but the distribution of urticaria types and subtypes is not well known.

Objective: To perform statistical analysis of chronic urticaria (CU) diagnoses assigned to consecutive patients in an outpatient setting of our urticaria center.

Methods: We performed a retrospective study of electronic medical records of CU patients evaluated by the same dermatologist in 12 consecutive months. We searched for urticaria ICD-10 codes. Chronic inducible urticaria (CIndU) was diagnosed by established provocation protocols and instruments. FricTest® was used in all patients and other tests were done only based on patient history.

Results: A total of 233 adult CU patients were found in the records and analyzed (64% female, 36% male; age 43.4 ± 15.0 years). Eighty-two percent had at least one follow up and 18% were seen for the first time only. 55% of patients (127/233) had only chronic spontaneous urticaria (CSU), 42% (99/233) had only CIndU, and 3% (7/233) had both forms. The most common CIndUs were symptomatic dermographism (SD), cold urticaria (ColdU), and cholinergic urticaria (CholU). CIndU was diagnosed in 106 (45%) patients: 38 SD only, 32 ColdU only, 11 CholU only, 7 delayed pressure urticaria (DPU) only, 8 SD-CholU, 3 SD-ColdU, 4 CSU-ColdU, 2 CSU-SD, and one CSU-ColdU-DPU.

Thirty-six patients (64% CSU only, 28% CIndU only, and 8% CSU-CIndU) were not well controlled even with a regular daily fourfold dose of 2nd-generation H1-antihistamines and 3rd line treatment was required.

Conclusion: Our findings demonstrate a heterogeneous clinical picture of CU. There is a need to diagnose and treat all urticaria types in order to achieve disease control.

Features of cold urticaria patients with cold agglutinins

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Background: Cold urticaria (ColdU) phenotypes are not well known. Cold agglutinins (CA) are immunoglobulins that reversibely bind with red blood cells at reduced temperatures causing them to agglutinate. They have been well researched in hematology since they can cause autoimmune hemolytic anemia. They have also been mentioned in publications as factors possibly associated with ColdU, but there are no reports of CA-studies in ColdU and no definitive causative relationships have been determined so far.

Objective: To determine the rate of CA-positive ColdU patients and to analyze clinical characteristics of ColdU patients with and without CA.

Methods: A total of 35 adult patients (66% female, 34% male; age 41.4 ± 13.4 years, disease duration 96.1 ± 103.7 months) with ColdU were prospectively investigated at University Clinic Golnik. Detailed patient history was obtained according to the COLD-CE (comprehensive evaluation of cold urticaria) GA2LEN UCARE project protocol. Blood withdrawal and the CA test with titration at 4˘C was performed at the Blood Transfusion Centre.

Results: CA were found in 30% of patients (14 female, 2 male). CA titer ranged from 1 to 16 (1.4 ± 2.9). The presence of CA was linked to: female gender (*p=0.030*); itch, wheals or angioedema induced by < 20°C ambient air (*p=0.009*); local skin contact with cold liquids (*p=0.018*); < 25°C total body water exposure (*p=0.045*); angioedema induced by cold foods/beverages (*p=0.043*); and disease deteriorations during increased humidity in summer months *(p=0.007*). CA positive patients also had lower disease control based on UCT (Urticaria Control Test) scores (*U=83.5, p=0.023*). The following correlations were found for CA titers: weak negative with UCT scores (r_s=*-0.359, p=0.034*), moderate positive with mean daily temperature of blood withdrawal (r_s=*0.456, p=0.006*), and moderate negative with weight (r_s=*-0.478, p=0.004*).

Conclusion: CA titers in our patients are below the ones clinically significant in hematology and low titers are known to occur in normal beings as well, but our findings demonstrate that CA, in patients with ColdU, may be linked to specific clinical features of ColdU. Further studies will aim to characterize, in more detail, the relevance of CA in ColdU and their potential role in the pathogenesis of ColdU.

Transcriptional differences in patients with chronic spontaneous urticaria treated with omalizumab as potential response predictors

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Background: Chronic spontaneous urticaria [CSU] is characterized by appearance of wheals and/or angioedema. It persists for at least six weeks. Even though the exact underlying pathophysiology remains unknown, release of histamine and other mediators from activated cutaneous mast cells has a key role in the development of clinical signs and symptoms. Omalizumab, a monoclonal antibody that selectively binds to free human IgE, represents a valuable treatment for CSU patients that remain symptomatic despite treatment with high doses of H1 – antihistamines. However, the mechanisms of action that result in reduction of inflammation remain unknown. The aim of our study was to analyse transcriptional differences between responders [CSU-R] and non-responders [CSU-NR] to omalizumab treatment.

Methods: RNAseq based whole transcriptome characterization of total RNA from whole blood samples was performed at different time points in 11 CSU patients - before the omalizumab treatment and after 14 days/3 months of treatment. Eight patients were classified as CSU-R, while three patients as CSU-NR. Characterization of differentially expressed genes [DEGs; cut off was set to FC > 5 and p-value < 0.05] and pathway analysis was made with CLC Genomics Workbench and Ingenuity Pathway Analysis, respectively.

Results: At baseline, before starting omalizumab treatment, 140 genes were differentially expressed between CSU-R and CSU-NR, where cellular movement, chemotaxis and inflammatory response were identified as the most important events that differentiate CSU-R from CSU-NR. Comparison of DEGs before and after treatment in CSU-R contains 18 entities, 17 with lower expression and one (FCER1A) with higher expression after successful treatment. Functional analysis of these genes suggests that omalizumab treatment represses inflammatory response and affects the quantity of cells. No statistically significant differences in gene expression before and after omalizumab treatment were found in the CSU-NR group.

Conclusion: The potential of whole blood transcriptional signature for prediction of response to omalizumab in CSU is shown. These findings further improve our understanding of CSU pathophysiology and mechanism of omalizumab action.

One case of amyloidosis misinterpreted as angioedema

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Amyloidosis is usually a multisystem disease in which abnormal proteins, known as amyloid fibrils, accumulate in a variety of tissues, resulting in a wide spectrum of clinical presentations. We present a case of amyloidosis occurred in 65-year-old woman with massive macroglossia misinterpreted as angioedema. The patient was first examined at the University Hospital Center Emergency Department and was admitted to the Otorhinolaryngology and Maxillofacial Surgery Clinic. Due to suspected angioedema patient was treated with high doses of corticosteroids, antihistamines and C1-esterase inhibitor. Considering that edema of the tongue did not completely regress due to therapy, immunology specialist was consulted and after clinical examination suspicion of amyloidosis, sarcoidosis or myxedema was set. After the extensive laboratory workup and biopsy of the tongue, the diagnosis of primary AL amyloidosis was established.

We present this case of rare and unusual presentation of systemic amyloidosis in order to point up a differential diagnosis of macroglossia.

TUMOUR IMMUNITY

Gene electrotransfer of plasmid DNA encoding proinflammatory chemokines CCL5 and CCL17 to murine tumors alters cytokine expression profile

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The tumor microenvironment represents a primary location in which tumor and immune cells interact. Different subpopulations of immune cells are guided to tumors through interactions between various proinflammatory chemokines secreted by tumor cells and their corresponding receptors of immune cells. The degree of infiltration and activation status of effector immune cells is usually associated with a positive outcome in cancer immunotherapies. Therefore, chemokines in combination with immune activation inducing therapy such as irradiation represent potential immunotherapeutic strategy. To elucidate the effect of overexpression of two proinflammatory chemokines CCL5 and CCL17 on tumor microenvironment we transferred the plasmid DNA encoding each chemokine to tumor cells *in vitro* and *in vivo* by utilizing two delivery methods – lipofection and gene electrotransfer (GET). Two murine breast (4T1 and E0771) and two murine colon (CT26 and MC38) cancer cell lines were transfected *in vitro* with plasmids encoding either CCL5 or CCL17. The viability of 4T1, CT26 and MC38 48 h after lipofection was 90% while the viability of E0771 remained above 80%. Concurrent expression analysis of CCL5, CCL17 and 9 other cytokines 48 h after lipofection showed significantly increased expression of both transfected transgenes, while levels of IL-6 and CXCL10 in the surviving cells were also increased. For *in vivo* study GET after intratumoral injection of plasmids encoding either CCL5 or CCL17 in murine CT26 and 4T1 tumor model (animal license: U34401-1/2015/43) resulted in minor tumor growth delay. Expression analysis at day 3 and day 7 after GET to CT26 tumors showed increased expression of both transgenes. Moreover, concurrent expression analysis of 5 other cytokines revealed increased expression of proinflammatory cytokines IL-6, IL-12 and IFNγ. Overexpression of CCL5 and CCL17 both *in vitro* and *in vivo* resulted in a modified cytokine expression profile associated with inflammation, but did not translate into pronounced antitumor effect. However, GET of plasmids encoding CCL5 or CCL17 followed by irradiation in CT26 and 4T1 tumor model resulted in significant tumor growth delay. Based on the modified tumor microenvironment the scope of future experiments will be focused towards elucidating the type of immune cells present in the tumors after treatment. Furthermore, the optimal time window to combine this therapy with irradiation will be determined.

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Antitumor effect of novel tumor cell-based vaccine varies between immunologically different tumor models

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Background: Tumor cells can be used as the source of tumor-associated antigens to make tumor cell-based vaccines. Our aim was to develop a tumor cell-based vaccine and test its therapeutic and preventative effect in two immunologically different tumor models: less immunogenic B16F10 malignant melanoma and more immunogenic CT26 colorectal carcinoma.

Methods: The vaccine was constructed by mixing cell lysates containing 0.5 or 1 mg of proteins from irradiation killed tumor cells with 50 µg of plasmid DNA encoding interleukin-12 (IL-12). Vaccination was performed by injection of vaccine in the mouse skin, followed by gene electrotransfer of IL-12 using a contact hexagonal multielectrode array (electric pulse parameters were: 170 V/cm, 5.64 Hz, pulse length 150 ms). In the therapeutic setting, the vaccine was applied in the skin distant from the tumor, the tumor was irradiated with 15 Gy concomitantly and tumor growth delay was followed. Histological samples were harvested and stained for the presence of granzyme B positive cells. In the preventative setting, the vaccine was applied in the skin before tumor inoculation and tumor outgrowth and growth delay was followed. All experimental procedures were done in accordance with the national guidelines (U34401–1/2015/16) and EU directive (2010/63/EU).

Results: A synergistic effect between vaccination and tumor irradiation was observed in the B16F10 tumor model, but no contribution of vaccination to tumor irradiation was observed in the CT26 tumor model. In the B16F10 tumor model, the elevated levels of granzyme B positive cells in the skin and tumor samples after the therapy coincided with the higher antitumor efficacy. No such trend was observed in the CT26 tumor model. Interestingly, a preventative vaccination effect was observed in the CT26 tumor model (up to 56% protection), but not in the B16F10 tumor model.

Conclusion: The results suggest a greater contribution of the vaccination to tumor irradiation in the less immunogenic tumor model, while, in a preventative setting, a greater contribution of the vaccination was indicated in the more immunogenic tumor model. In future studies, we will consider these results when investigating the vaccination effects and its mechanism of actions.

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Peritumoral gene electrotransfer of interleukin-12 potentiates the antitumor effect of electrochemotherapy

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Background: The therapeutic effectiveness of electrochemotherapy (ECT) in the clinics is up to 90% of local tumor control; however, a systemic antitumor effect (abscopal effect) has not yet been observed. The aim of the study was to test a new combined therapy including ECT with cisplatin, bleomycin or oxaliplatin and gene electrotransfer (GET) of plasmid encoding interleukin-12 (IL-12) in three immunologically different tumors. We hypothesized that in the combination, IL-12 boosts the *in situ* vaccination effect of ECT by recruiting effector immune cells.

Methods: A malignant melanoma (B16F10), mammary carcinoma (4T1) and colon carcinoma (CT26) were treated. The combined therapy included intratumoral ECT with bleomycin, cisplatin or oxaliplatin (plate electrodes, 8 pulses, 1300 V/cm, 100 µs, 1 Hz) and peritumoral GET of plasmid pORF-mIL-12-ORT encoding murine IL-12 (pin non-invasive multi-electrode array, 12 pulses, 170 V/cm, 150 ms, 2.82 Hz). Growth of primary treated tumors and distant untreated tumors in a dual-flank model mimicking systemic disease was followed. After the therapy, cytometric and immunohistochemical analyses were performed to detect immunologically important biomarkers.

Results: In poorly immunogenic B16F10 melanoma, IL-12 potentiated the antitumor effect of ECT using equally effective low doses of cisplatin, oxaliplatin or bleomycin. However, we observed the most pronounced potentiation after ECT with cisplatin, resulting in 38% of complete responses as well as an abscopal effect. The antitumor effectiveness of this treatment combination could be ascribed to the induction of the local and systemic immune responses. Namely, infiltration of granzyme B positive effector immune cells was observed in both, primary and distant tumors. In comparison to B16F10 melanoma, better responsiveness to ECT was observed in more immunogenic 4T1 and CT26 tumors. In both, the GET of IL-12 did not significantly improve the therapeutic outcome of ECT using either of the chemotherapeutic drugs.

Conclusion: We showed that IL-12 boosts the *in situ* vaccination effect of ECT by recruiting effector immune cells in poorly immunogenic melanoma. Effectiveness of the tested treatment combinations depended on the tumor immune status; ECT was more effective in more immunogenic tumors but the contribution of peritumoral GET was higher in less immunogenic tumors.

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MISCELLANEOUS

NK cell lymphopenia preceding ulcerative colitis for years: a case report

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Background: Etiopathogenesis of ulcerative colitis (UC) has not been fully elucidated. Characteristic changes in the number of circulating immune cells in this disease, which are thought to be due to the disease itself, have been established previously. Here we present the case of a patient with a serious disorder in lymphocyte subpopulations that had been present for three years before the clinical onset of the disease.

Case report: A healthy female respondent, 40 years of age, participated in a clinical trial as a healthy control. Blood analysis with a leukocyte formula and immunophenotyping of peripheral leukocytes were done. She had not suffered from chronic illnesses and had no frequent viral and bacterial infections. Her family history was negative for autoimmune and malignant diseases. There was a mild lymphopenia (1116 cells/μL of blood), CD4 + mild lymphopenia (446 cells/μL), a limit-CD4/CD8 ratio (0.89) and notably reduced number of $CD3^{-}CD16^{+}+56^{+}$ natural killer (NK) cells (45 cells/μL) found in the tests performed. In the further course she had no new complaints nor infections and was feeling well. Three years later, after the stressful event, she first noticed difficulty in controlling intestinal emptying, and soon afterwards, frequent bloody mucoid stools, up to 8 per day. A total colonoscopy with terminal ileoscopy was performed which indicated the existence of chronic ulcerative proctitis with a pronounced degree of activity. Peroral and topical treatment with mesalazine and probiotics resulted in clinical, laboratory and histopathological remissions of the disease. Lymphopenia (1000 cells/μL) persisted during the active phase of the disease. Two years later, during the remission, control immunophenotyping of peripheral leukocytes was performed, which showed the following values: the lymphocyte count was within the reference, but with sustained reduce in a number of CD4+ lymphocytes (464 cells/μL), CD4/CD8 ratio (0.71) and considerable reduce in a number of NK cells (69/μL). B cell lymphocyte count marginally reduced (77 cells/μL).

Conclusion: Changes in lymphocyte subpopulation number not only occur in the active phase of the UC, but may precede the onset of the disease years in advance. Lymphopenia, and in particular NK cell lymphopenia, may participate in the pathogenesis of this disease, and further research on this topic is needed.

A family with X-linked pigmentary disease

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Background: Pigmentary disorder, reticulate, with systemic manifestations, X-linked (PDR) is a X-linked recessive disorder characterized by recurrent infections and sterile inflammation in various organs. Skin hyperpigmentation with a distinctive reticulate pattern is evident by early childhood. This is followed by hypohidrosis, corneal inflammation and scarring, enterocolitis that resembles inflammatory bowel disease, and recurrent urethral strictures.

Case report: We present the first family with PDR diagnosed in Slovenia.

The index case is an 8 years old boy with a history of prolonged coughing, recurrent bronchitis and ear infections. From the age of 2 years, both hypopigmented and hyperpigmented spots on the skin were observed. Born with urgent cesarian section because of preeclampsia and small fetus for gestational age on the 38th week. In the first month, allergic proctocolitis due to milk hipersensitivity, which later resolved. In the first three years he had recurrent lower respiratory infections which required several hospitalisations. Episodes of productive coughing was seen.

HRCT excluded bronchiectasis but tree in bud sign was found. Ophtalmologic evaluation was normal. He has lactose intollerance and is hypersensitive to azitromycine. His imunologic function was thourougly evaluated and didn't revealed specific abnormalities. 50 frequent mutations for cystic fibrosis revealed no mutation. Sweat test was not possible to interprete because of absent sweating. His brother and mother have similar, but less evident skin pigmentations and history of recurrent bronchiolitis, ear infections, obstipation and allergy to nuts and grass pollens. The mother has got oligodontia and had repeated bronchitises during childhood.

Sequencing of the gene *POLA1* (DNA polymerase alpha 1) in the index case and his brother revealed a hemizygous variant c.1375-354A>G in intron 13, which is very likely involved in the splicing process. The variant was described in the literature (Starokadomsky, 2016) in 11 families with X-linked reticulate pigmentary disease. The mother is heterozygous for the same mutation.

Conclusion: according to clinical manifestations and genetic testing performed, we diagnosed a family (mother and two siblings) with X-linked pigmentary disease.

Thus far, a couple of families affected by this rare disorder have been described in the literature. By our knowledge this is the first family described in Slovenia.

GENETICS

Asthma treatment response to inhaled corticosteroids is associated with variant rs2146323 in VEGFA gene

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Background: Asthma is a common chronic disease, characterized by airway inflammation and structural remodelling. Vascular endothelial growth factor (VEGFA) is a major regulator of angiogenesis and vascular permeability and is elevated in asthma patients. Inhaled corticosteroids (ICS) have been shown to decrease VEGF levels and suppress airway inflammation. Since inhibition of *VEGFA* also diminishes asthma symptoms in mice, it is predicted that variants in *VEGFA* gene could be associated with asthma treatment response.

Materials and methods: We genotyped variant rs2146323, in *VEGFA* gene in 208 adult and 40 children asthma patients treated with ICSs. The percentage change in % predicted FEV_1 was analysed after short-term treatment (3 months) and long-term treatment (at least 3 years) in adults, and after 6 and 12 months in children. Changes in Asthma Control Test (ACT) were followed after at least 3 years of treatment in adults and after 12 months in children.

Results: Variant rs2146323 in *VEGFA* was associated with response to ICS treatment. Both, adult and children asthmatics showed improvement in average lung function according to an increase of average FEV_1, % predicted. Children asthmatics with the AA genotype show higher improvement in % predicted FEV_1 after 3 months and after 12 months. While, adult patients with genotypes CC and AC have higher improvement in % predicted FEV_1 and in ACT scores after 3 months and after at least 3 years. In adult asthmatics genotype-dependent differences in treatment response were evident when analysing entire group of patients and in non-atopic patients, suggesting that treatment response was influenced by the atopic status. No association was found between rs2146323 and asthma control after 12 months of ICS therapy in children.

Conclusion: Our study showed that variant rs2146323 in *VEGFA* is associated with treatment response to ICS, assessed as changes in % predicted FEV_1, and ACT scores. In adults the difference in treatment response is highly influenced by atopy and only evident in non-atopic patients. Interestingly, in children asthmatic patients AA genotype is associated with better response, whereas in adults, patients with CC or AC genotypes responded better to ICS treatment.

RARE LUNG DISEASES

A case report of Wegener granulomatosis (WG) presenting epistaxis, hemoptysis and polyarthralgia

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Background: Wegener granulomatosis (WG) is a rare multisystem autoimmune disease characterized by necrotizing granulomatous inflammation, tissue necrosis, and vasculitis in small and medium-sized blood vessels. The classic clinical pattern is a triad involving the upper airways, lungs and kidneys.

Case presentation: A 33-year-old woman was admitted to our hospital with a history of progressively worsening dry cough, shortness of breath, polyarthralgia, fever, epistaxis and hemoptysis. Two months before admission, she had episodes of nasal bleeding, dry cough, fever not more than 38.2°C. Her primary physician did not detect any abnormal findings in the chest radiographs at that time. Two months later, she consulted the doctor again due to the symptoms and because of the chest X-ray with multiple small infiltrates in both lungs, high sedimentation rate she was admitted to our hospital. Lungs were clear to auscultation bilaterally. Laboratory results revealed anemia with Hgb 90g/L, hematocrit 30%, erythrocytes 3600/L, leucocytes 13800/L, CRP 110mg/L, sedimentation rate 70mm/h. Urine sediment – erythrocytes 16-18, proteins +, epithelial cells ++. 24hour proteinuria 0,5g/L (upper limit 0,2). Rheumatoid antibodies: positive c-ANCA 95U/ml, RF 158IU/ml, ASO 88U/ml. ECG with sinus tachycardia of 120 beats/min. Gas analyses in partial respiratory failure with hypoxemia 7,5kPa and hypocapnia 3,6kPa, oxygen saturation 91%. Chest radiography and lung CT showed multiple infiltrates in the bilateral upper lobes. Bronchoscopy finding of intranasal coagulum without changes of nasal mucosa, transoral intubation revealed diffuse erythema and edema of the vulnerable tracheobronchial mucosa without any ulcerous lesions or infiltrative changes. Chest ultrasound with many apical bilateral, subpleural, hypoechogenic changes with zones of central necrosis with maximal diameter 20mm. Ophthalmology examination - punctiform conjunctival bleeding. Transbronchial biopsy was performed and revealed necrotic granulomas with multinucleated giant cells in the bronchial/bronchiolar and parenchymal lesions. Bronchial alveolar lavage (BAL) was performed and showed the small increase of neutrophils (total cell counts: 320/μL, neutrophils: 19.2%, macrophages: 85.0%, lymphocytes: 7.4%, eosinophils: 0.0%) and no growth of bacterial culture. According to the results the diagnosis granulomatosis with polyangiitis, Wegener's granulomatosis. She was successfully treated by rheumatologist with high-dose steroids and cyclophosphamide.

Conclusion: The recognition of multisystem disease involving joints, kidney, eye and lung is critical for diagnosing Wegener's vasculitis.

Predictors of poor outcome in small vessel vasculitis

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Background: Small vessel vasculitis (SVV), according to Chapel Hill Consensus, is vasculitis predominantly affecting small vessels, defined as small intraparenchymal arteries, arterioles, capillaries, and venules, but medium arteries and veins may also be affected. Patients affected with vasculitis have a risk of premature death, especially if the disease is not recognized and treated properly. Poor survival rates are reported in patients with higher BVAS score and the Five Factor Score (FFS).

Methods: Retrospective analysis of clinical records of patients with small vessel vasculitis treated from 2017. – 2019. at the Department of Rheumatology, Clinical Immunology and Allergology, University Hospital Osijek.

Results: 34 patients with small vessel vasculitis (6 EGPA patients, 14 GPA, 7 MPA patients and 7 patients with IgA vasculitis) were included in the study. Age, sex and Birmingham vasculitis activity score (BVAS) were used to asses poor outcome (death in the analyzed period), which was reported in five patients.

Conclusion: Poor outcome was associated in patients with higher BVAS score. There were no differences in survival rate regarding sex, age or type of vasculitis.

Case report of the patient with atypical clinical presentation of eosinophilic granulomatosis with polyangiitis

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Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare small-vessel vasculitis that commonly occurs in patients with bronchial asthma and is characterized by a prodromal, eosinophilic, and vascular phase of the disease. We present a patient who was diagnosed with bronchial asthma and allergic rhinitis at the age of 46, and was treated with inhaled glucocorticoids and a β2 agonist, antihistamines and montelukast. Five months after the introduction of therapy, she becomes febrile, loses weight, has palpable purpura and oligoarthritis. Laboratory analysis showed leukocytosis with eosinophilia, high levels of acute phase reactants and total IgE. Antineutrophil cytoplasmic antibodies (ANCA) were negative, as were other immunological tests. The pathohistological findings of skin bioptates revealed infiltration of eosinophils. On the second day of hospitalization, she develops muscle weakness in the upper and lower extremities and a lesion of the upper and lower motoneurons was confirmed by electromioneurography. Montelukast was omitted from therapy, and pulse doses glucocorticoid (GK) were administered intravenously (i.v.) with clinical improvement and normalization of eosinophils. The finding of cytologic bone marrow puncture raises suspicion of hypereosinophilic syndrome. Infectious analysis excluded other causes of eosinophilia. Given the nephritic syndrome done by the kidney biopsy, the rapid progressive pauci-immune type of glomerulonephritis was confirmed and EGPA was diagnosed. According to the vasculitis protocol, she received cyclophosphamide i.v., with reducing doses of GK. She then developed a pulmonary embolism, which is why she is on anticoagulant therapy. In further controls, a positive finding of perinuclear antibodies (p-ANCA) is coming, and azathioprine is included in therapy with GK, after which the disease went into remission. It is a patient with a markedly progressive course of EGPA, who has predominantly presented with neurogenic damage, with no changes in the lungs characteristic of the vasculitic stage of the disease. In view of the above, it is possible that the eosinophilic phase of EGPA was already at the diagnosis of asthma, and the severity of the clinical picture was further enhanced by the use of montelukast, which has already been described in the available literature.

Acute interstitial pneumonia triggered by strenuous exercise

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Introduction: Acute interstitial pneumonia (AIP) is a rare and severe form of idiopathic interstitial lung disease. The disease is identified by the acute onset of respiratory failure, bilateral lung infiltrates, diffuse alveolar damage on lung histopathology and the absence of an identifiable cause or predisposing condition.

We present a case report of a patient with AIP seemingly triggered by strenuous physical exercise.

Case report: A 48-years-old female without chronic diseases with a documented normal chest radiograph was admitted to the hospital due to acute shortness of breath, respiratory failure and suspected pneumonia. First symptoms included fever, chills and muscle pain that started seven days before admission. Three days before she ran a Ljubljana half-marathon. Initially, she received azithromycin, after which there was no improvement. Moreover, a dry cough appeared. Upon admission, we noted bilateral opacities on chest radiograph, increased CRP (155 mg/L) and a normal level of procalcitonin. Her condition quickly deteriorated. CT showed extensive bilateral infiltrates. Bronchoscopically obtained microbiological samples were negative. The transbronchial biopsy was not attempted. Immuno-serological investigations were negative. After further respiratory deterioration pulses of methylprednisolone (1000 mg for five days) were given, followed by gradual tapering. There was a partial improvement, but respiratory failure persisted. A therapeutic trial with mycophenolatemofetil (MMF) in the initial dose of 500 mg twice daily with an increase to 1000 mg twice daily was started. After that, her clinical and radiological picture started to improve gradually. A follow-up 12 months after the beginning of the disease showed significant regression of infiltrates on chest radiograph and CT. Lung function tests showed normal FVC and FEV_1 (84 % and 89 %, respectively) and mild to moderate impairment of DLco (59 %).

Discussion: We presented a case of a previously healthy patient who was admitted due to rapidly progressive interstitial pulmonary disease after running a half-marathon. A presumptive diagnosis of AIP was made given that lung biopsy was not considered safe. The patient was successfully treated with corticosteroids and MMF. Although we found no previous reports of the use of MMF in AIP, it could be considered as a treatment option.

Extensive pulmonary arteriovenous malformations in Osler-Weber-Rendu syndrome

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Introduction: Osler-Weber-Rendu syndrome or hereditary haemorrhagic telangiectasia (HHT) is an autosomal dominant disorder of vascular development. Its clinical features, that develop with age, are mucocutaneous telangiectasia, arteriovenous malformations, epistaxis and GI bleeding. With the incidence 1 in 5000 it is the main cause of pulmonary arteriovenous malformations (PAVMs), which can lead to haemoptysis, paradoxical embolisms to the central nervous system and brain abscess. PAVMs normally start occurring in puberty and continuously develop in adult life as a result of the pressure the vessels are subjected to over time.

Case Report: A 28-years-old female with diagnosed HHT, sideropenic anaemia and epilepsy after cerebral abscess was admitted to our department from another hospital for further treatment after 3x2x1,5 cm PAVM was discovered in the right superior lobe with CTA of pulmonary arteries. Head MRI showed no signs of AVMs, neither did gastroscopy and colonoscopy that were performed later on. Six years ago, she had embolization of 4 PAVMs. Since then she had occasional haemoptysis that started occurring on daily bases in the last 3 months and caused severe anaemia. She also reported decrease in physical performance especially when walking uphill and being constantly tired. Upon admission she received 3 units of concentrated erythrocytes and tranexamic acid after which bronchoscopy was done but showed no traces of bleeding. Echocardiogram indicated important pulmonary arteriovenous shunt. A repeated CTA of pulmonary arteries showed several additional PAVMs in almost all lobes, the biggest being the one in right superior lobe that we successfully embolized. After the procedure the patient's clinical signs improved. Due to the great extent of the embolization of the largest PAVM, smaller ones were planned to be embolised later. With no recurrent haemoptysis, she was discharged from the hospital with advice to avoid any kind of physical or emotional stress including house chores and pregnancy. In case of further deterioration, lung transplantation could be considered. Consequently, four remaining PAVMs were embolised. In 3 years of follow-up she reported stable condition with no further bleeding. With haemoptysis ceased, satisfactory life quality was achieved and referral for lung transplantation was not needed.

Conclusions: We presented a case of a patient with HHT with several PAVMs on both sides of the lungs with recurring potentially life-threatening haemoptysis and severe anaemia. Her condition was successfully managed by a combination of gradual embolization of PAVMs and non-pharmacological measures including major lifestyle changes. Furthermore, this case illustrates the need for a regular follow-up of patients with HHT with PAVMs in an expert centre as PAVMs may recur and additional intervention may be needed.

Coexistence of Sjogren Syndrome and Sarcoidosis - a case report

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Introduction: Sjogren Syndome (SS) and sarcoidosis are multisystemic autoimmune diseases of unknown etiology which share certain clinical features.

Case report: A 72-year-old woman presented with a several months history of dry mouth, dry eyes and fatigue. She was admitted to the department of immunology where the diagnosis of primary SS was established (based on the existence of xerostomia, xerophthalmia, verified keratoconjunctivitis sicca, low unstimulated salivary flow, abnormal salivary gland scintigraphy, positive antinuclear antibodies). Chest radiograph and computed tomography scan showed bilateral hilar and mediastinal lymphadenopathy with diffuse reticulonodular densities in lungs, so patient continued examination in the department of pulmology. Sedimentation rate, levels of angiotensin converting enzyme and chitotriosidase were elevated. The hemogram and biochemical tests including calcium were normal. Lung function test showed restrictive pattern and carbon monoxide diffusing capacity was lowered. Bronchoscopy with biopsy was performed and histopathologic examination revealed non-caseating granuloma consistent with sarcoidosis. The patient was diagnosed with coexisting SS and sarcoidosis. Treatment for sicca symptoms, hydroxychloroquine and corticosteroids were recommended.

Conclusion: This case shows that possibility of simultaneous presentation of SS and sarcoidosis should not be excluded in clinical practice.

LUNG CANCER

Cardiac Toxicity of Novel Systemic Therapies in Routine Treatment of Advanced Non-Small-Cell Lung Cancer

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Background: Novel systemic therapies in treating non-small-cell lung cancer (NSCLC) enable longer survival of patients (pts) with advanced NSCLC than ever before. With prolonged survival, quality of life, and treatment's side effects are brought more to our attention. Although we have some information about the cardiotoxicity of novel systemic therapies from clinical studies, real-world data on this topic are scarce. This study aimed to monitor the development of cardiac toxicity in pts treated for advanced NSCLC with either immunotherapy or targeted therapy in routine clinical practice.

Methods: This was a prospective, observational study conducted at a single academic center. We followed NSCLC pts treated with either immune checkpoint inhibitor (CPI) or endothelial growth factor receptor tyrosine kinase inhibitor (EGFR TKI) who consented to additional monitoring. During their routine treatment, they had a directed clinical examination, echocardiogram recording, proBNP and troponin T sampling at treatment initiation, months 2 and 4, and then every four months until the end of treatment. Only pts with normal baseline cardiac function were included in the study.

Results: We included 61 pts with advanced NSCLC and a mean age of 63,7±9 years, 34 of them female (56%). 48% of pts (29 pts) were treated with monotherapy with CPI (atezolizumab, nivolumab, or pembrolizumab), while 52% of pts (32 pts) received EGFR TKI (afatinib, gefitinib, erlotinib, or osimertinib). We analyzed recorded data for up to 24 months of treatment; at 4, 12, and 24 months, there were 59, 29, and 15 pts still included, respectively. No pts on either CPI or EGFR TKI developed signs of heart failure during their treatment. In a joint study cohort, left ventricular ejection fraction stayed normal at all time points (p=0.71), the values of troponin T and NTproBNP stayed stable throughout treatment (p=0,45 and p=0,85, respectively).

Conclusion: Our observational study has shown no cardiac toxicity in pts treated for advanced NSCLC with either immunotherapy or targeted therapy in routine clinical practice. Analysis of more sensitive parameters and longer observation times are needed.

LUNG VESSEL DISEASES

Longevity of a patient with chronic thromboembolic pulmonary hypertension

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Background: Pulmonary hypertension (PH) is defined by mean pulmonary arterial pressure (mPAP) equal or greater than 25 mmHg at rest, measured with right heart catheterisation. The diagnosis of pulmonary hypertension is obtained gradually, while simultaneously searching for its etiology. Pulmonary hypertension is classified into five subgroups based on their clinical presentation, pathophysiological findings, haemodynamic characteristics and treatment.

In the last years there has been immense progress in treatment strategies for PH. Therapy is multifaceted and beside the symptomatic treatment it focuses on treatment of the underlying disease. The initial approach consists of several steps; it comprises general measurements (physical therapy and supervised rehabilitation, avoidance and elimination of the risk factors that could exacerbate the disease and provoke it's progression), non-specific supportive therapy (oxygen, diuretics, oral anticoagulant treatment, cardiovascular drugs) and PH-specific treatment (calcium channel blockers, prostanoids, endothelin receptor antagonists, phosphodiesterase type-5 inhibitors.

For chronic thromboembolic pulmonary hypertension, pulmonary endarterectomy is the treatment of choice for operable patients. If no adequate response is achieved the therapy with combination of approved drugs should be implemented and the patient should be evaluated for lung transplantation. Specific pulmonary hypertension treatments and advanced surgical techniques offer a chance to improve not only the quality of patients' life but also increase their survival.

Case presentation: Female patient J.M, born in 1929, non-smoker, a retired professor, admitted to University Clinic Golnik in 2005 for further evaluation of dispnea on exertion, lasting 5 years. In the past month the patient noticed progressive decline in daily physical activities, with her walking distance on a flat surface being reduced to only few steps. Beforehand she was diagnosed with arterial hypertension and hyperlipidemia and was receiving simvastatin (Sinvacor), nicergolin (Adavin) and irbesartan (Aprovel). Physical examination did not reveal any clinically relevant abnormalities. ECG showed sinus rhythm with frequency of 65/min without signs of right heart overload. Laboratory findings were normal, D-dimer negative (109 mcg/l). Arterial blood gasses analysis revealed moderate hypoxemia (pO2 8.0 kPa, SAT 89 %) and no acid-base abnormalities (pH 7.43, pCO2 4.8 kPa, HCO3 23.5 mmol/l). Pulmonary

function tests were normal, (VC 2500 ml (90 %), FEV 1780 ml (96 %), Tiff. 71 %). On transthoracic echocardiography right ventricular pressure was significantly elevated (67 mmHg + CVP). Chest CT showed signs of chronic pulmonary thromboembolism with most of the thrombi partially organised. The patient underwent right heart catheterisation in April 2007, where precapillary pulmonary hypertension was confirmed (right atrium 3 mmHg, right ventricle 55/0 mmHg, pulmonary artery 55/14 mmHg, mPAP 31 mmHg, PCWP 3 mmHg). The patient was classified into group 4 – chronic thromboembolic pulmonary hypertension.

Warfarin therapy with a target INR 2-3 was initiated. The patient was a responder for tested substances and therapy with calcium channel blocker (diltiazem 3x90 mg/day) was implemented after catheterisation. Her previous therapy with Nicergolin (Adavin) and irbesartan (Aprovel) was discontinued. NYHA functional class of the patient improved on therapy from NYHA 3 to NYHA 2. Patient has been followed up closely and in 13 years after the initial diagnosis (od 2007 do 2020) she has remained stable and has not been hospitalised due to pulmonary hypertension. She is now 91 years old and continues to live a fully functional life.

Table 1: Long term follow up of a patient with chronic thromboembolic pulmonary hypertension

6-minute walking test	6.2008	6.2009	6.2012	1.2013	7.2013	7.2014	6.2015
6-minute walking distance	410	406	325	375	340	350	255
SAT%/mean heart rate at begining of test (0')	94%/72	93%/84	93%/87	92%/81	94%/89	93%/98	94%/91
SAT%/mean heart rate at end of test (6')	89%/107	90%/111	89%/109	89%/103	89%/112	86%/119	92%/97
SAT%/mean heart rate after the test (+1')	95%/88	93%/95	92%/95	92%/85	93%/100	89%/105	94%/89

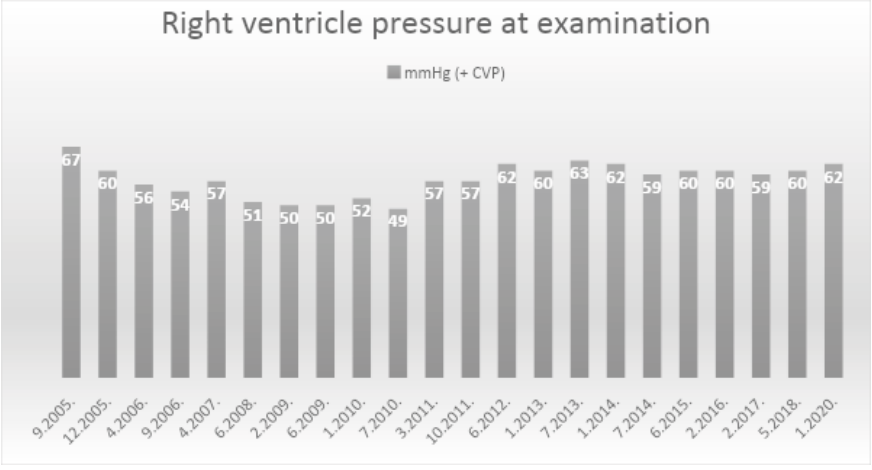

Figure 1: Right ventricle pressure at examination

Discussion: Non-adequately treated pulmonary hypertension is associated with poor prognosis. Until recently treatment consisted of only supportive therapy, but in the last decade immense progress was made in the treatment of individual groups of PH. Before the therapy is introduced a comprehensive diagnostics should be performed to determine the underlying etiology. Based on diagnostic findings, comorbidities, drug tolerance and overall prognosis the most appropriate treatment strategy is implemented. Our case report demonstrates that with adequate diagnostic approach the patient with severe PH can live a quality life without hospitalisations and reach a great age.

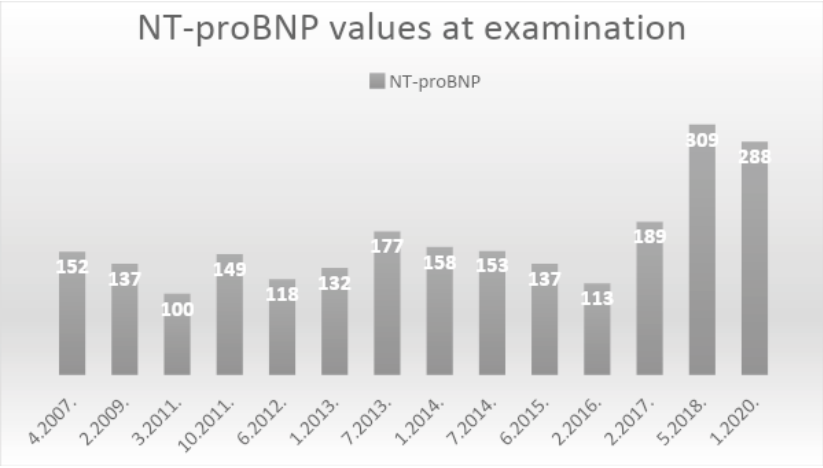

Figure 2: NT-proBNP values at examination

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Successful combined medical therapy (triple combination) and BPA in a patient with severe inoperable CTEPH

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Background: Pulmonary thrombendarterectomy is the primary treatment for patients with chronic thrombembolic pulmonary hypertension. However, if the lesions are too distal to be surgically removed, they can be effectively treated with the balloon pulmonary angioplasty in addition to specific drugs for pulmonary arterial hypertension (1).

Case presentation: We present a 60-year old male with severe, inoperable chronic thromboembolic pulmonary hypertension, who was successfully treated with combination of specific pharmacological therapy (riociguat, macitentan and iloprost) and balloon pulmonary angioplasty (BPA).

This patient presented for the first time in April 2014 with progressive dyspnea, unexplained syncope and a month later with acute pulmonary embolism. Lung ventilation/perfusion scan, CT-A of pulmonary arteries, echocardiography, and right heart catheterization (RHC) in January 2015 confirmed severe, distal chronic thromboembolic pulmonary hypertension (mPAP 48 mmHg, PVR 10.7 WU, PAWP 6 mmHg). We started treatment with riociguat, but pulmonary artery pressures remained severely elevated and RV function continued to worsen. In 2017 we added subcutaneous treprostinil, which was discontinued due to adverse effects. Further disease progression was shown by echocardiography and RHC (PAWP 9 mmHg, mPAP 59 mmHg, PVR 8.2 wu, CI 2.0), repetitive syncopes and worsened 6MWT result. In 2018 patient started with inhalations of iloprost and in January 2019 a treatment with macitentan was added with no significant improvement. In January 2019, the first BPA was performed in AKH Vienna. Until now 10 BPA procedures were performed in total. After only two BPAs syncopes ceased and patient's physical performance improved with every additional BPA. After last BPA invasive measurements showed near normalization of pressures and pulmonary vascular resistance and cardiac index significantly increased (PAWP 8 mmHg, mPAP 29 mmHg, PVR 3.28 wu, CI 3.28, sVO2 72.8). Quality of life has since than practically normalized.

Conclusion: This case report demonstrates drastic improvement of hemodynamic parameters, physical capacity and quality of life in a patient with severe, inoperable chronic thromboembolic pulmonary hypertension. It proves that combination of medical therapy and several repeated BPAs is very effective method of treatment also in patients with severe disease.

Case report: treatment of multiple peripheral pulmonary artery stenoses with balloon pulmonary angioplasty and stent implantation in a young adult

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Background: Peripheral pulmonary artery stenosis (PAS) is a rare disease entity, which can be misdiagnosed as idiopathic pulmonary hypertension or chronic thromboembolic pulmonary hypertension. It is most often seen in children and young adults. Physicians should have PAS in mind in differential diagnosis of all patients with pulmonary arterial hypertension, especially young patients with unexplained dyspnea on exertion - to make the correct diagnosis as early as possible. CT-A of pulmonary arteries and also invasive diagnostic measures (pulmonary angiography) should always be performed for correct diagnosis. The current treatment options for PAS include balloon pulmonary angioplasty (BPA), with a possibility of stenting, which is a novelty, and lung transplantation[1].

Case presentation: A nine year old boy started noticing progressive dyspnea on exertion and diminishing levels of physical fitness. At the age of sixteen, first echocardiogram was performed. It showed signs of mild pulmonary hypertension, no left heart disease and no congenital heart disease. Right heart catheterisation showed no pulmonary hypertension(PH) at rest, but stress echocardiography showed severe PH upon exertion. At the age of 19, he was admitted to our department due to hemoptysis occurred during acute respiratory tract infection. CT-A of the chest showed acute pulmonary embolisms with two pulmonary infarctions. He was treated with antibiotics, but no anticoagulant treatment. Echocardiography showed signs of severe pulmonary hypertension and reduced systolic function of the right ventricle. Prof. Lang from AKH Vienna organized a consultation with Prof. Matsubara from Japan, and we agreed to perform BPA with stent placement at AKH Vienna. Since June 2019 six procedures were performed with 10 drug eluting stents implanted. Dual antiplatelet treatment and riociguat were introduced after the first BPA. The results of the treatment are encouraging: mPAP and PVR dropped to almost normal, desaturation during his six minutes walking test reduced and hemoptysis ceased. The ambition of this modern type of treatment is to postpone lung transplantation as much as possible, but at the same time reduce symptoms and preserve the function of the right heart.

Conclusions: We presented novel treatmet of pulmonary artery stenoses with repetitive balloon pulmonary angioplasties and stenting with encouraging results,

which improved the prognosis, quality of life, and postponed the need for possible lung transplantation.

References:

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Exercise-induced pulmonary hypertension in an adolescent

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Introduction: Pulmonary hypertension is defined by mean pulmonary arterial pressure at rest of 25 mmHg or higher, assessed by right heart catheterization. Clinical presentation is non-specific and may include dyspnoea on exertion, fatigue, chest pain and headaches. Time from symptom onset to definitive diagnosis has not been shortened in the last twenty years, but new specific treatment available calls for changes in the diagnostic procedures and screening.

Case report: A 16-year-old adolescent has been experiencing shortness of breath, poorer physical performance compared to his peers and fatigue for several years; his problems have priorly been diagnosed as exercise-induced asthma although there were no significant changes with inhalers. He has a congenital enamel disorder as well as his brother and father. At the age of seven he was diagnosed with mild aortic isthmus stenosis and arterial hypertension, for which he was receiving amlodipine and enalapril, but he discontinued the therapy.

In June 2016, more extensive diagnostics were performed at our clinic. Examinations of lung functions were within normal values; methacholine testing was negative. Transthoracic echocardiography showed a structurally and functionally normal heart. Ultrasound-assessed systolic pressure in the right ventricle was slightly elevated (40 mmHg + CVP) at rest, while stress echocardiography showed a severe increase in systolic pressure to 110 mmHg + CVP.

Cardiac catheterization was performed and pressures in the right ventricle (30/4 mmHg) and pulmonary artery with normal saturation (30/6-17 mmHg) were measured. Pulmonary angiography revealed several peripheral pulmonary stenoses, slightly more pronounced on the left side. No known genetic disease was detected by diagnostic genetic testing.

Conclusion: Pulmonary arterial hypertension in children and adults often presents similarly as other more common diseases of the lungs and cardiovascular system therefore special attention should be paid to patients with higher risk for pulmonary hypertension. Genetic testing is recommended in all patients with idiopathic pulmonary hypertension, as it can reveal the cause of the disease. Further research is needed to detect yet unrecognized genetic syndromes, among which we could find a common cause of idiopathic pulmonary hypertension, mild narrowing of the aortic isthmus, arterial hypertension detected in childhood and congenital enamel disorder.

Relationship between serum uric acid, mean pulmonary artery pressure and NT-proBNP in patients with pulmonary hypertension

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Introduction: Pulmonary hypertension (PH) is a disease characterized by blood pressure higher than 25 millimeters of mercury (mmHg) in the pulmonary artery measured by right-sided cardiac catheterization (RHC) at rest. The disease itself is multifactorial and associated with a poor prognosis. The course of the disease is influenced by several factors that have not yet been definitively determined. Up to date research has shown that one such a factor might be uric acid (UA). Higher serum values of UA are associated with a more severe course of the disease and higher mortality in patients with pulmonary hypertension (1). The purpose of this analysis of our clinical work is to determine whether there is a relationship between UA, mean pulmonary artery pressure (mPAP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) - a reliable diagnostic marker of cardiac decompensation.

Methods: At our PH Center at the University Clinical Center Ljubljana we performed 49 right heart catheterizations in 2019. Two patients with extremely high NT-proBNP due to advanced chronic renal failure were excluded from analysis. We included in further analysis 28 patients (average age 63.5 years, min 39 max 80 years, 63,6% women) with confirmed PH who also had a measurement of UA besides NT-proBNP in close temporal proximity to the hemodynamic evaluation. The statistical analysis was performed with the IBM SPSS program (version 20). Since values were not distributed normally and due to low number of patients non-parametric methods were used and values were expressed as medians with interquartile ranges.

Results: According to PH classification 8 patients(28.6%) had PH from group I, 8 patients (28.6%) had PH due to left heart diseases, 11 (39.3%) had chronic thromboembolic disease and one patient had PH due to multifactorial reasons (3.6%); mPAP was 44 (34-49) mmHg, NT-proBNP 1345 (397 – 2331) ng/l and UA 411 (313 - 541) µmol/L. We found higher levels of mPAP (45; 42-52 vs. 40; 30-40, p=0,065) and NT-proBNP (1867; 1245-2529 vs. 564; 126-2032, p=0,029) in patients with increased (>430 µmol/L) vs. normal levels of UA. Correlation of UA with mPAP was almost significant (r=0.33, p=0.081) and non-significant with NT-proBNP.

Conclusion: Analysis showed expected positive correlation between UA and mPAP, furthermore both mPAP and NT-proBNP were higher in patients with high UA. Results (although some not statistically strong due to low number of patients and group heterogeneity) are in line with previous studies, which showed that uric acid is a marker of disease severity. In advanced PH UA might be increased directly due to hypoxemia (2) or as a result of several other factors such as use of diuretics, increased oxidative

stress and metabolic syndrome, which are associated with advanced PH. On the other hand, UA might also play a role in the pathogenesis of pulmonary hypertension through impact on endothelial dysfunction (3). Thus, the relationship between PH and high levels of uric acid, confirmed also with our short preliminary analysis, might go in both directions. However, question about the role of UA in pathogenesis of PH remains unsolved. Further studies are needed to provide the answer on this intriguing topic.

Pulmonary Embolism (PE) in patients with Chronic Obstructive Pulmonary Disease (COPD)

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Introduction: Many studies have shown that COPD is a moderate and independent factor for PE. Patients with COPD are at a high risk for PE because of systemic inflammation, limited mobility and co-existing comorbidities: cardiovascular disease, anemia, polycythemia, malnutrition, muscle disorder, osteoporosis, metabolic syndrome, diabetes, gastroesophageal reflux, anxiety, depression, hormonal imbalance, infections, lung cancer, thrombosis.

Methods: Prospective, observational study of 50 hospitalized patients with COPD, diagnosed according to GOLD criteria (stages I-IV), 40-75 years (mean age 65.4±12.3 divided in subgroups (PE-diagnosed/non-PE and with known/undetermined exacerbation etiology). Investigations: clinical risk assessment, laboratory, spirometry, gas-analysis, electrocardiogram, D-dimer (DD), chest X-ray, chest ultrasound. Doppler-ultrasonography of deep-veins of lower-extremities. Patients with high DD and deep vein thrombosis (DVT) or high DD and abnormal chest ultrasound underwent computed-tomography pulmonary-angiography.

Results: PE was diagnosed in 13(26%) of 50 hospitalized COPD patients. Frequencies of PE in PE-diagnosed group according to GOLD-stages I-IV, were 0(0.0%), 1(7.7%), 4(30.8%), 8(61.5%) respectively with positive correlation between airflow limitation and PE. Patients with pleuritic chest-pain, chest ultrasound abnormality, DVT and high DD were more likely to develop PE. DD was significantly higher among patients with PE than those without (2.14±1.4μg/ml vs. 1.5±0.4μg/ml, $P<0.0001$). There was positive correlation between the presence of PE and elevated DD>2.0μg/ml ($P<0.05$). There was no statistically significant difference between patients with PE and without, according to age, gender and comorbidities ($P>0.05$). Immobility and obesity were significantly higher among PE patients, $P<0.05$ and $P<0,0001$ respectively.

Conclusion: Clinical manifestations of PE like pleuritic chest pain, dyspnoea are nonspecific, and easily could be underestimated in COPD patients, which leads to disease worsening, delay of anticoagulant therapy and higher mortality rate.

OBSTRUCTIVE LUNG DISEASES

Inflammatory markers in peripheral blood in patients with asthma

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Asthma is one of the most common chronic diseases all over the world, resulting from a state of persistent sub-acute inflammation of the airways. The main attribute of asthma is inflammation, which leads to airway remodeling, bronchial hyper-reactivity and reversible or partly reversible airway obstruction. Asthma is a chronic inflammatory disorder of the airways in which many cells and inflammatory mediators play a role. (GINA). Many cells and mediators take part in creating the asthmatic inflammatory reaction, but eosinophils play a central role. All of the inflammatory cells and mediators can be detected in the airflow tissue. Some of them can be detected in the asthmatics peripheral blood too.

This study includes 30 patients of the Pulmology and Allergy Clinic, Skopje, with confirmed bronchial asthma, treated with ICS. In all of the patients we followed Eo count, ECP and IL-5 in peripheral blood at the beginning of the study, after 2 and 6 months treatment.

Following the parameters during treatment with ICS we registered changes in all of the tested parameters.

Our conclusion is that the ICS objectively suppress the inflammatory reaction in asthma and the biologic markers (IL-5, Eo and ECP), which we have followed, can measure the accomplished effect. They could be used in every day practice, not only as diagnostic parameters but also as valid therapeutic guides in the treatment of asthma.

Treatment of neutrophilic asthma patients

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Aim of the investigation: to evaluate the effectiveness of basic therapy with ultrafine glucocorticosteroids, tiotropium bromide (Respimat) in standard therapeutic doses and 10% acetylcysteine (via nebulizer) in asthma patients with neutrophilic type of inflammation.

Materials and methods: 30 patients with neutrophilic type of inflammation (blood neutrophils ≥ 4000/μl) were randomized 1:1 to receive fixed combination budesonide/formoterol 320/9 mcg BID (I, control group: male 5, female 10, mean age (53,6 ± 3,8) years, post BD FEV_1 (51,5 ± 4,7) %, FEV_1/FVC (67,2 ± 3,5) or (II, main group: male 9, female 6, mean age (53,6 ± 3,8) years, post BD FEV_1 (51,5 ± 4,7) %, FEV_1/FVC (67,2 ± 3,5) ultrafine beclomethasone 250 mcg, formoterol 12 mcg BID, tiotropium (Respimat) 5 mcg 2 inhalations QD during 3 monthes, additionaly - solution of acetylcysteine 10% 3 ml via nebulaiser during 10 days.

Result: After 3 months of treatment in II group the effectiveness of treatment was 93.3%: statistically significant increased the total score of ACT - from (14.3 ± 1.3) to (20.3 ± 0.8) points ($p < 0.05$), total score of ACQ decreased from (2.3 ± 0.2) to (1.1 ± 0.1) points ($p < 0.05$). Clinically significantly decreased symptom score in SGRQ - from (71.4 ± 5.6) to (51.3 ± 5.0) points, $p < 0.05$. Improvement of clinical symptoms accompanied with increase in MEF50 from (28.9 ± 4.5)% to (41.6 ± 4.2)%, MEF25 from (19.1 ± 2.9)% to (27.6 ± 2.6)% which indicated an improvement in bronchial patency at the level of small bronchi. Studied course of treatment improved the physical tolerability - 6MWT increased from (266.3 ± 16.2) to (312.0 ± 14.4) m, with decrease in shortness of breath (Borg scale) before the test from (2.5 ± 0.3) to (1 , 5 ± 0,1) points and after the test - from (4,1 ± 0,3) to (3,1 ± 0,3) points. Complex therapy was well tolerated by patients and was not accompanied by the development of side effects. In patients of the control group, statistically significant dynamics of the studied indicators were not detected.

Conclusions: In asthma patients with neutrophilic inflammation use in basic therapy ultrafine inhaled glucocorticosteroids + tiotropium bromide (Respimat) in a standard therapeutic dose, formoterol 12 μg BID and inhalations of 10% of QD led to a positive dynamics of clinical symptoms improved the tolerance to physical load, improved quality of life, resulting in 93.3% effectiveness of treatment.

Peripheral blood cell counts as a prognostic biomarker in COPD

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Introduction: This study aimed to determine the association between peripheral blood cell counts and exacerbations of COPD.

Methods: This observational prospective study comprised 97 patients (44 females) with COPD. Their clinical characteristics and a history of exacerbations in the last 12 months were noted. Upon inclusion, all patients had to be in a stable state, at least 4 weeks after the last COPD exacerbation and not receiving systemic corticosteroids. Peripheral blood cell counts were determined upon the first visit. Patients were followed up for 12 months, and the number of moderate and severe exacerbations during this period was recorded.

Results: Patients who had at least one moderate or severe exacerbation during the observational period had lower BMI (24.5 [4.0] vs. 26.4 [4.8], $p = 0.046$), lower age (65 [9] vs. 68 [7] years, $p = 0.037$), worse lung function (FEV_1: 45 [17] vs. 63 [21] %, $p < 0.001$ and FVC: 75 [16] vs. 86 [20] %, $p = 0.005$) and more frequent history of at least one exacerbation in previous 12 months (50.0 vs. 26.2 %, $p = 0.027$), while there was no difference in sex, smoking history or CAT. Peripheral blood cell counts showed higher relative and absolute eosinophil counts in patients with at least one exacerbation as compared to patients without exacerbations (3.01 [2.60] vs. 1.91 [1.27] %, $p = 0.006$ and 225 (190) vs. 154 (99) cells/μL, $p = 0.017$) but there were no significant differences in other parameters. Multivariate analysis using Cox regression model identified lung function (FEV_1) as the only independent predictor of future exacerbations (HR [95% CI]: 0.976 [0.956 - 0.996], $p = 0.019$).

Conclusion: In our cohort of patients with COPD, higher relative and absolute eosinophil counts were seen in patients with at least one observed moderate or severe exacerbation. However, the multivariate analysis confirmed only lung function as an independent predictor of exacerbations.

Efficacy of ultrafine glucocorticosteroide in basic therapy of asthma patients with neutrophilic type of inflammation

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The aim of the investigation: to evaluate the effectiveness of ultrafine glucocorticosteroide in the basic therapy of patients with bronchial asthma (BA) with neutrophilic type of inflammation.

Materials and methods: 30 persistent asthma patients with a predominantly neutrophilic phenotype of inflammation (blood neutrophil count > 4000/μl) and small bronchi and fixed obstruction were divided into 2 groups: I (main group, n=15) - received ultrafine beclomethasone (solution) at a dose of 250 μg and formoterol at a dose of 12 μg 2 BID; II (control group, n=15) continued their previous baseline therapy with fixed combination 320 mcg budesonide and 9 mcg formoterol BID. All patients received salbutamol PRN. The duration of the study course - 3 months.

The work was performed at the expense of the state budget.

Results: The use of ultrafine ICS in basic therapy of asthma patients with neutrophilic inflammation and small bronchi and fixed obstruction allowed to achieve clinical and functional efficacy in 80% of patients: significant reduction in bronchoobstruction at the level of small bronchi - increase in MEF25 from (19.1 ± 2.9)% to (31.9 ± 5.2)%, $p < 0.05$; stabilization of clinical symptoms and increased exercise tolerance - increase of ACT by 3.2 points (from (14.3 ± 1.3) to (17.1 ± 0.3) points), $p < 0.05$, and the number of meters passed by test with a 6-minute walk (6MWT) from (266.3 ± 16.2) m to (283.3 ± 18.8) m, $p < 0.05$. In the control group the studied indicators did not change significantly.

Conclusion: The use of ultrafine glucocorticosteroids in the basic therapy of patients with asthma with neutrophilic inflammation with the presence of small bronchial obstruction, fixed bronchoobstruction allowed to achieve clinical and functional efficacy in 80% of patients. Treatment was well tolerated by patients and was not accompanied by the development of side effects. The method is easy to use and easily accessible to the practitioner.

Airway and systemic inflammatory response to anti–IL-5 therapy in severe asthma patients

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Background: Severe eosinophilic asthma (SEA) is characterized by an increased sputum and/or blood eosinophils, frequent exacerbations and consequent prescribing of an oral corticosteroid (OCS). Anti-IL-5 is therapy of choice for SEA phenotype. Response to anti-IL-5 biologics is not equal in every patient. Some patients are »responders« and reach complete asthma control, on the other hand are »non-responders« who show no improvement or even have clinical worsening. The underlying mechanisms of these different responses are not yet understood.

Aims: To evaluate differences in non-responders and responders to anti–IL-5 treatment.

Methods: We included 17 adult patients with SEA in the Severe Asthma Registry (12 responders and 5 nonresponders). Parameters were assesed at baseline and after 4 months of treatment with mepolizumab 100 mg subcutaneously (in one case benralizumab 30 mg subcutaneously) at University Hospital of Respiratory and Allergic Diseases in Golnik, Slovenia. The following parameters were evaluated: pulmonary function (FEV_1), Asthma Control Test (ACT), OCS dose reduction and number of exacerbations, eosinophil count and IL-5 concentration in induced sputum and eosinophil count in peripheral blood. Statistical analysis was performed by GraphPad Prism 8.0.1.

Results: In responders, anti–IL-5 therapy led to significant increase in FEV_1 (in mililiters $p = 0,002$) and ACT score ($p = 0,001$) and decrease in the exacerbations rate ($p = 0,001$) and OCS dose ($p = 0,0002$). Reduction of blood eosinophil count was observed at follow-up in both groups (non-responders $p = 0,018$; responders $p = 0,0004$) without significantly differing magnitude. A significant drop in sputum eosinophilia in the responders group at follow-up ($p = 0,05$) was demonstrated. Comparing to responders, non-responders had 6 times more sputum eosinophils at follow-up. No differences were showed in IL-5 concentrations at follow-up between the groups in serum ($p = 0,366$) or induced sputum ($p = 0,809$).

Conclusions: Opposed to non-responders, anti–IL-5 therapy in responders significantly improves lung function, number of exacerbations, OCS burden and subjective condition. Sputum eosinophil count has proved to be a significant cellular biomarker of response to anti–IL-5 therapy and better in defining the response to as blood eosinophil count. IL-5 concentration as an alternative biomarker was not demonstrated in neither serum nor induced sputum.

Pulmonary aspergillosis with suspicious sinusal aspergilosis

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Introduction: 28 years old female with CF(Cystic Fibrosis), genotype F508del/1811+1G->C. Stabile condition till two years ago when she started with intermittent temperature , weight loss, dry deep cough, haemoptysis and in the last 4 months pain behind right eye and headache. Temperature as a symptom has multifactorial cause. Finding the cause of the temperature is important for maintaining good lung function and better FEV_1 (forced expiratory volume in the first second) in CF patients.

Methods: We performed many investigations: laboratory (Total IgE=58.0 IU/ml, Specific IgE for Aspergillus fumigatus=0.04 IU/ml), immunological-antinuclear antibodies for all muscular and tissues diseases - negative, Viral markers (Hepatitis/ HIV – negative), microbiological (sputum isolation Staphylococcus aureus -chronic infection and Staphylococcus aureus meticilin resistant-intermittent infection, sputum for Mycobacterium tuberculosis and non typical mycobacterium - negative) and diagnostic imaging (Chest X-Ray, CT chest - bronchiectasis, inflammation zone - tree in bud, solitary cystic bronchiectasis filled with mucus in upper right part of the lungs, Fiber nasal endoscopy with mild hyperemia of the nasal mucosa with poor adhesive secretion, CT head was normal, skin prick test for Aspergillus fumigatus negative), bronchoscopy and in the bronchoalveolar lavage, Aspergillus fumigatus was isolated, which had not been found in any analysis before, Magnetic resonance on head - drainage obstruction of the sphenoidal sinus, filled with dense contents suspected for Aspergillum.

Results: According to the results of the investigations she was threated with Itraconasol for 3 months and the patient became afebrile after. During the patient's treatment, the headache became more intense, so we have consulted a team of ear nose throat (ENT) specialist, ophthalmologist and a neurosurgeon. They concluded that the best option is transnasal access and biopsy of the sphenoidal sinus for completing the diagnosis, but it cannot be done because of the high risk of postoperative complications due to the main disease.

Conclusion: Prolonged fever as a symptom should never be overlooked. On the contrary, it is an alarm for an infection in the body and needs to be thoroughly investigated.

Chronic Obstructive Pulmonary Disease (COPD) as a risk factor for Metabolic Syndrome (MetS)

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Background: MetS represents a cluster of risk factors (abdominal obesity, atherogenic dyslipidemia, hypertension and insulin resistance) that predispose affected patients to systemic inflammation, cardiovascular disease and physical inactivity. COPD is a major health problem worldwide, the fourth leading cause of death with prevalence in increase. There is a limited data about the prevalence of MetS in COPD. The aim of the study is to determine the frequency of coexisting MetS in COPD.

Methods: Case control study of 120 patients with COPD (82 men and 38 women, aged 40-75 years, mean age 64.2±10.4), diagnosed according to Global Initiative for Chronic Obstructive Lung Disease, 30 healthy non-COPD subjects, randomly selected as controls. Anthropometric measurements, fasting blood sugar (FBS), lipid profile, high-sensitivity C-reactive protein (hsCRP), spirometry, CAT (COPD assessment test) and mMRC (Modified Medical Research Council Dyspnea scale) questionnaires, were assessed. COPD subjects were stratified based on combined assessment test (ABCD criteria) and spirometry (stages I - IV).

Results: The presence of MetS was diagnosed in 50(41.67%) of COPD patients vs. 5(16.67%) of controls (p=0.01). The frequencies of the MetS in patients with COPD, GOLD stages I, II, III, and IV, were 50(41,67%), 66(55%), 60(50%), 42(35%) respectively. Frequency of MetS according to combined assessment test (A, B, C, D) was 42(35%), 54(45%), 25(30%), 36(30%) respectively. The presence of MetS was associated with significantly worse cough, sleep and mood ($p<0.01$) and higher total CAT score (p=0.031). Average BMI was 29.18. There was a correlation between the presence of MetS and hs-CRP (p=0.02) and no correlation with the pulmonary function. FBS was higher in COPD than controls (8.5±1.2mmol/L vs 5.4±1.1mmol/L) with statistical significance ($p<0.0001$), but HDL was lower in COPD than controls (42.1±5.4mg/dl vs 53±3.6mg/dl) with statistical significance ($p<0.0001$). Waist circumference and blood pressure were higher in COPD than controls 93.8s±2.4m vs. 92.3±3.1sm, p=0.004, and mean systolic BP 135±10mmHg vs. 113.5±8.1mmHg, $p < 0.0001$.

Conclusion: The high prevalence of MetS in patients with COPD show the urgent need to develop comprehensive strategies for prevention, screening and start of treatment in early stage. Correction of the MetS may have a significant role in prevention of complications related with the COPD.

Bronchial asthma and mental health in children

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Background: The psychological factors are becoming increasingly relevant in children with asthma. Many patients report anxiety and depression, which are psychological conditions that have a negative impact on the therapeutic adherence and in order to maintain control of asthma.

Objective of the study: Capitalizing on the importance of mental health and assessing the impact of psycho-emotional state on the evolution of bronchial asthma in children.

Material and Methods: The descriptive study included 60 children, 10-18 years old, with asthma. All patients completed the specially developed survey, which included clinical data, disease history and life history; Asthma Control Test (ACT), Perceived Stress Scale (SSP) and Questionnaire DASS 21 (which assesses three dimensions: depression, anxiety and stress).

Results: According to ACT, uncontrolled asthma was detected in 8 children (13%), partially controlled in 41 children (68.3%), uncontrolled in 11 children (18.3%). According to SSP, 21 children (35%) had moderate stress levels, all with uncontrolled and partially controlled asthma; level of intense stress, had 4 children (6%), all with uncontrolled asthma. According to DASS 21, moderate level of anxiety had 23 children (38%), moderate level of depression - 18 children (30%), moderate level of stress 7 children (11.6%); all with uncontrolled and partially controlled asthma, but also with a moderate level of stress perception. From the group with controlled asthma, moderate level of anxiety was in 8 children (13.3%). Severe levels were not reported.

Conclusion: Psycho-emotional profile play a significant role on the asthma control level. Understanding the importance of the mental health can lead to elaboration of the interventions in this field that well increase the level of asthma control, and decrease anxiety and stress level.

INFECTION / TUBERCULOSIS

Association of lung tuberculosis and tuberculosis peritonitis - case report

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Introduction: Dissemination of tuberculous bacilli from the primary hearth can occur in persons with poor immune defenses, in poor socio-economic and hygienic conditions, in social shelters…

Case report: Patient male 23 years old, migrant from Pakistan, accommodated at Obrenovac Reception and Transit Center with cough problems with difficulty coughing, shortness of breath, shortness of breath and abdominal pain. Initially examined at the Emergency Center, native radiography done and abdominal ultrasound-finding neat. Chest radiography revealed a spotty inhomogeneous shading in the upper pulmonary fields and the tips of the lungs. Positive inflammatory syndrome, serological analyzes (HIV, HbsAg, HCV) negative. Direct microscopy sputum M negative. Done bronchological examination, endoscopic findings neat, signs of mild inflammation .PCR fiberaspirata-detected Mycobacterium tuberculosis complex. MGIT fibeaspirata-observed acid-alcohol resistant bacilli severe abdominal pain occurs, with several hydroaeric levels observed on native abdominal radiography. Abdominal ultrasound shows distended intestinal curves up to 3.5 cm filled with content of slow peristalsis. Due to ileus emergency surgery performed, pathohistological finding: Inflamacio chr granulomatosa. Continued treatment with antituberculostatics. The patient recovered successfully, K sputum negative.

Conclusion: Tuberculosis is a curable disease. The key to success in treatment is early diagnosis and timely treatment.

Tuberculous pericarditis: Case Report

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Introduction: Tuberculous pericarditis is a serious form of extrapulmonary tuberculosis. The diagnosis can be difficult to establish and is often delayed or missed, resulting in late complications such as constrictive pericarditis and increased mortality.

Case Report: A 53 year old man, with hyperlipidemia present with a 10 days history of shortness of breath, chest pain, palpitation was admitted to hospital. The patient was in good condition, with a temperature of 37,8°C, his blood pressure was 170/100 mmHg, pulse 170 beats/min and oxygen saturation 94%. The findings of chest radiogram showed normal lungs and enlarged heart. The heart rhythm was irregular.

The patient's hemoglobin level was 137g/l, WBC count was $6,5x10^9$/l, CRP was 10 mg/l. The findings of blood chemistry tests, tumor markers, troponin, pBNP were normal.

An ECHO cardiogram revealed a small pericardial effusion without right ventricular collapse.

CT chest scan showed a small pericardial effusion, 13mm calcified lymph node in aortopulmonary window, some subpleural nodules < 5 mm, without pleural effusion.

Multiplex PCR respiratory panel test and microbiological tests of intestinal infections were negative. Serology tests of hepatitis, HIV, Chlamydia, Legionella, Mycoplasma, Borrelia, EBV (IgM), CMV(IgG,IgM) were also negative. Immunoserology tests (ANA, ENA, abti DNA) were negative too. The result of the QuantiFERON-TB test was positive.

The pericardial fluid had a WBC count of $0,9x10^9$/l (97% lymphocytes and 3% neutrophils), proteins 51g/l, glucose 0,4 mmol/l.

Pericardial fluid and 3 sputum specimens were AFB negative.

2 sputum cultures were contaminated and 1 was negative (repeated sputum cultures are in progress).

Culture of pericardial fluid became positive on the 23rd day.

Treatment: Isoniazid, rifampicin, ethambutol and pyrazinamide. The patient is under control by a cardiologist and pulmonologist.

Conclusion: The clinical manifestations of tuberculous pericarditis can be nonspecific. The diagnosis is established by detection of tubercle bacilli in smear or culture of pericardial fluid or by detection of tubercle bacilli or caseating granulomata on histological examination of the pericardium. Options for management of advanced disease are limited.

Prolonged cough, exhaustion without fever

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In this report we described case a 64-year-old non-smoking patient who had cough and exhaustion for 8 years.

Because of these symptoms she was examined as outpatient and bronchoscopy was done, three times in the following period, but investigation did not explain the cause of the disease. The symptoms persisted in varying degrees of intensity, and she was taking symptomatic therapy without doctors controlees. After 8 years existence of symptoms CT thorax showed an excavated change to the right, and the Quantiferon TB GOLD test was positive. Tuberculostatics were started but after one month were discontinued as toxic hepatitis occurred.

Then first time hospital examination performed with detail analyzes. The existence of malignant, systemic disease and pulmonary tuberculosis was excluded. But this time fiberaspirate is documented the existence of respiratory infection caused by non-tuberculous mycobacteriosis (NTM). Identification of mycobacterial culture was done by hybridization reaction (Geno Type Mycobacterium CM-Hain analysis): Mycobacterium abscessus.

Published studies worldwide indicate that the number of people suffering from diseases caused by NTM is on the rise. The greater isolation of pathogens today is also due to the availability of molecular techniques for their identification. The disease can affect the lungs, eye, CNS, skin and soft issues. Therapy is complicated by the causative agent's resistance to antimicrobials.

They are urgently needed quick and inexpensive methods of identification also preventive measures of the spread of infection. It is also necessary to identify more active treatments and perform clinical trials to assess standard effective regimens.

Tuberculous pleural effusion

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Introduction: Tuberculous pleural effusion (TPE) is one of the most common sites of extrapulmonary tuberculosis. Diagnosis is challenging. The gold standard for diagnosis of TPE remains the detection of Mycobacterium tuberculosis in pleural fluid, or pleural biopsy specimens, either by microscopy and/or culture, or the histological demonstration of caseating granulomas in the pleura along with acid fast bacilli (AFB).

The following case illustrates the clinical presentation and diagnostic approach to TPE in a case of a young man who was sent to hospital for a large pleural effusion and suspected empyema.

Case report: A 32-year- old man without chronic illness presented to clinic with a 10 days history of fever up to 38.9° C, right- sided pleuritic chest pain and cough with productive green sputum. An antibiotic amoxicillin was prescribed ten days before hospital admission. After antibiotic therapy he became subfebrile and the chest pain was gone. He additionally complained of loss of appetite and general weakness. He smoked last 7 years and drink alcohol occasionally. He had no known past exposures to tuberculosis. He had not traveled in the past few years. He works as a painter his entire life.

At hospital admission the patient was subfebrile (37.6° C), with normal blood pressure and normal heart rate. The saturation was 94% while breathing room air. Physical examination revealed dullness to percussion and decreased breath sounds throughout his right hemithorax.

Basic laboratory tests were normal with the exception of elevated level of CRP (130 mg/l).

A chest radiograph revealed a large right sided pleural effusion with a gentle small infiltrate in the apex of the right upper lobe.

A CT of the chest revealed parenhymal disease – 2 cm large nodular, partialiy calcined irregular infiltrate in the apex of right upper lobe, right sided pleural effusion with septations, thickened pleura and reactive lymph nodes in the mediastinum.

Thoracentesis removed 1750 ml of straw coloured fluid that had 1000 white blood cells/ µl (91% lymphocytes, 1% mesothelial cells, 2% neutrophils and 6% monohistiocytes). The glucose was 3 mmol/l, total potein 52 g/l, LDH 12,44 µkat/l, pH 7.31. Serum total protein was 76 g/l and serum LDH was 2,01 µkat/l.

Expectorated sputum revealed 3 negative stains for AFB and cultures were also negative for AFB after six weeks of incubation. Sputum and pleural fluid Gram stain and culture were negative.

Two weeks after thoracentesis 3 colonies of Mycobacterium tuberculosis grew in the culture of the pleural fluid, so no further investigations were necessary.

Conclusions: 48-96% of TPE is negative by sputum acid-fast bacilli (AFB) stain and culture. Thoracentesis is the next step to distinguish among malignant, tuberculous, parapneumonic pleural effusion and empyema. Thoracentesis in TPE shows an exudative, lymphocytic pleural effusion in more than 90% of cases, but pleural fluid AFB cultures are positive in less than 20-30% of cases. More invasive diagnostic measures (closed percutaneous needle biopsy or thoracoscopy) are usually required to confirm TPE.

Treatment of non-tuberculous mycobacterial pulmonary disease (NTM-MD) with nebulised amikacin

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Introduction: Treatment of NTM- MD is long-term and relapse may occure. The new BTS guidelines for management of NTM - PD define the regimens and duration of treatment more accurately and take into account the resistance of non-tuberculous mycobacteria and the difficulty of the clinical presentation. Nebulised amikacin may be considered in many cases.

Methods: We occluded patients with NTM-PD, who were treated with nebulised amikacin for the past two years.

Results: 9 people (8 women, 1 man) were treated with nebulised amikacin. The mean age was 62.8 years. Most of them had pre-existing lung disease, the bronchiectasis are being the most commonly reported (77.8%). Most frequently, M.avium was isolated (66.7%), besides this M.abscessus, M. intracellulare, M.kansasii and M.chimaera. 8 patients were treated with rifampicin, ethambutol, clarithromycin and 1 patient with tigecycline and clarithromycin. In addition, all patients received nebulised amikacin, two started with the intravenous amikacin and then continued with the nebulised amikacin, and in one patient switched from the nebulised to the intravenous amikacin. 8 patients (88.9%) reported side effects, 7 patients (77.8%) experienced hoarseness and 1 patient experienced worsening asthma. In 2 patients, nebulised amikacin was previously discontinued due to side effects. 8 patients had a negative outcome of culturing at the end of amikacin treatment, and 1 patient is still positive.

Discussion: According to BTS guidelines, treatment with nebulised amikacin for severe M. avium complex -pulmonary disease (MAC-PD), including M.avium, M.intracellulare and M. chimaera, and for M.abscessus-PD, is recommended. Systemic side effects (ototoxicity) with inhaled amikacin are rare, but respiratory side effects (hoarseness, cough, bronchospasm) are common, as confirmed by our results. The outcome of the cultivation after treatment was negative in 8 patients and for 1 patient we have no negative results so far as he has only been treated for one month.

Conclusion: Treatment of NTM-PD is considered very successful, since all patients are negative after completion with nebulised amikacin. However, follow-up because of possibility of relapse is recommended.

Characterization of concordance between genetic and standard phenotypic DST testing for isoniazid and rifampicin of Mycobacterium tuberculosis isolates in two low-incidence countries

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Background: Slovenia and North Macedonia are low-incidence countries with tuberculosis (TB) incidence rates of 5.3 and 13.0 in 2018, respectively. In both countries, the percentage of drug resistant TB is very low with sporadic cases of MDR-TB. However, global burden of drug-resistant TB continues to increase stimulating the detection of gene variants related with TB drug resistance. Next-generation sequencing (NGS) can provide comprehensive analysis of gene variants linked to drug resistance in *Mycobacterium tuberculosis*. **The aim** of our study was to examine the feasibility of a full-length gene analysis for the drug resistance related genes (*inhA*, *katG*, *rpoB*) using Ion Torrent technology and to compare the NGS results with those obtained from conventional phenotypic drug susceptibility testing (DST) in TB isolates.

Methods: Between 1996 and 2017, we retrospectively selected 56 TB strains from our National mycobacterial culture collection. Of those, 33 TB isolates from Slovenian patients were isolated from various clinical samples and subjected to phenotypic DST in Laboratory for Mycobacteria (University Clinic Golnik, Slovenia). The remaining 23 TB isolates were isolated from Macedonian patients and sent to our laboratory for assistance in phenotypic DST. TB strains included were either mono-, poly- or multidrug resistant. For control purposes, we also randomly selected five TB strains susceptible to first-line anti-TB drugs. To identify gene variants related with drug resistance in genomic DNA extracted from TB isolates, AmpliSeq libraries were generated using the AmpliSeq™ Kit for Chef DL8 and the Ion AmpliSeq TB Research Panel. The sequencing data were analysed manually, comparing the determined variants with published data and data available in the Tuberculosis Drug Resistance Database.

Results: High concordance between genetic (Ion Torrent technology) and standard phenotypic DST testing for isoniazid and rifampicin was observed, with percent of agreement of 77% and 93.4%, sensitivities of 68.2% and 100%, and specificities of 100% and 88.2%, respectively. In TB strains with phenotypic isoniazid resistance (44) the majority of mutations were detected in *katG* codon 315 (20/44; 45,5%), while in TB strains with rifampicin resistance (41) the most prevalent mutation detected was *rpoB* Ser450Leu (17/41; 41,5%).

Conclusion: In conclusion, the genotypic DST using Ion Torrent semiconductor NGS successfully predicted drug resistance with significant shortening of time needed to obtain the resistance profiles from several weeks to just a few days.

A decade of latent tuberculosis monitoring with QuantiFERON TB test in Slovenia

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Background: Without treatment, 5-10 % of people with latent tuberculosis (TB) infection develop active TB at some time in their lives. Patients with compromised immune system, like those with HIV and those receiving anti-TNFα therapy, are especially at risk of developing active TB. It is important to diagnose and treat both active and latent TB with the main goal being the prevention of new outbreaks.

The aim of our study is retrospective analysis of QuantiFERON TB (QFT) results in 12-years period in our country.

Method: From 2005 we have been identifying latent TB infection with the IFN-γ test called QFT TB. It uses collection tubes with specific TB antigens and test controls coated on their inner surface. The QFT method was upgraded over time. At first only two, from 2008 three and from 2015 four blood collection tubes were used. The blood for the test must be collected and transported (at room temperature) to the laboratory in less than 16 hours. After the blood is received, it is incubated for 16-24 h on 37 °C. The following day the amount of released IFN-γ is measured by ELISA method.

Results: Between 2008 and 2019 the Laboratory for Mycobacteria of University Clinic Golnik received 29293 blood samples for latent TB testing. The share of positive QFT results has decreased from 21,0 % in 2008 to 10,7 % in 2019. The number of indeterminate QFT test results has decreased from 11,3 % to 5,9 % in the first year and has since then stayed in the 2,4 % to 6,7 % range. The proportion of rejected blood samples has remained constant with an average of 1,2 %.

Conclusions: Monitoring of QFT test results in the last decade shows that the share of positive latent TB infections is slowly decreasing. This is a consequence of the decrease in the incidence of active TB which has fallen by 46,2 % in the years between 2008 and 2019. In the next few years we may see an increase in the number of active and consequently latent TB cases due to immigration from countries with higher incidence of TB as well as asset re-allocation to battle covid-19 pandemic.

Mycobacterium fortuitum de novo outbreak in surgery practice

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Background: Skin and soft tissue infections caused by nontuberculous mycobacteria (NTM), especially the rapid growing mycobacteria (RGM), apper to be increasing in incidence. *Mycobacterium fortuitum* complex have been isolated from soil and various water-related sources, rarely cause infections. These opportunistic pathogens most commonly cause localized skin and soft tissue infections, especially common after breast surgery.

Case presentations: In the department of surgery post-operative wound infection of four previously healthy women were detected. In three breast implants were inserted and abdominal operation was performed in the fourth patient. All four patients were operated by the same team in the same operating theatre. The clinical picture was characterized by only localized inflammation of the wounds and the lack of systemic signs of inflammation.

Epidemiological investigations: Unfiltered water was sampled from hand-wash tap water in the operating room area, the tap water, the staff shower.

Results: *M. senegalense*, which belongs to *M. fortuitum* complex was isolated from four patients and from the nozzle of the washbasin in the staff bathroom.

Conclusion: This report describes the second laboratory-confirmed cases of *M. fortuitum* complex breast infections related to the hospital water supply. In most reported cases of RGM infection, the source of contamination is difficult to identify. *M. fortuitum* complex is resistant to chlorination and is capable of biofilm formation. Colonization of the hospital water supply with pathogens that are relatively resistant to common disinfection protocols is a concern, and eradication of NTMs is difficult.

Promising Approaches for the Treatment of Critically Ill Patients with covid-19

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Covid-19 is an infectious disease caused by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) and can present a wide range of symptoms, ranging from mild to severe respiratory symptoms and even death. 4-12% of all covid-19 patients develop a severe form of the disease, thus it is vital to find new treatments. A literature review was performed and it identified studies indexed in the bibliographic database MEDLINE, published up to the 13th September of 2020. Data from 17 articles was employed.

Out of all the treatments, convalescent plasma therapy (CPT) and dexamethasone are possibly the best additional therapies for critically ill patients.

CTP is a form of passive immunisation using the blood of recovered patients. Almost all the patients treated with CTP experienced a decrease in symptom severity, including resolution of ARDS, absorption of lung lesions and normalisation of body temperature. CTP may shorten the duration of disease and reduce mortality of critically ill patients. So far, there have been no reports of adverse drug reactions. Risks regarding CTP are mostly associated with transfusion of blood-borne diseases and reactions to serum components. This risk of transfusion-related acute lung injury and antibody-dependent enhancement should be taken into consideration when deciding whether to use CTP, however unlikely these complications are.

Dexamethasone is a synthetic corticosteroid, that has been shown to possess anti-inflammatory and immunosuppressive properties. Administration of dexamethasone has been shown to shorten the duration of hospitalisation, when compared to the control group. Additionally, it reduced the mortality of patients receiving invasive mechanical ventilation by 12,1 % and of patients receiving oxygen support without invasive mechanical ventilation by 2,9%. Dexamethasone did not prove to be useful for treating patients without oxygen therapy. Patients reported no serious adverse drug reactions.

SARS-CoV-2 pandemic poses new challenges for the treatment of the critically ill, due to the severity of the disease it causes and the sheer number of patients. New approaches will hopefully decrease the fatality of covid-19 and help sustain the operating state of healthcare systems.

Uporaba gojenih alogenskih mezenhimskih matičnih/ stromalnih celic (MSC) za zdravljenje Akutnega respiratornega distresnega sindroma (ARDS) ter brazgotinjenja pljuč zaradi virusa SARS-Cov 2

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MSC v zadnjem času dobivajo vse več pozornosti zaradi njihove močne sposobnosti uravnavanja imunskega sistema in protivnetnega delovanja, kar je bilo dokazano na različnih medicinskih indikacijah. Imunomodulacija, ki jo povzročijo MSC, ni odvisna od poglavitnega histokompatibilnega kompleksa (MHC), ni odvisna od specifičnega antigena in vključuje vse imunske celice. Kar dodatno govori v prid zdravljenju z MSC sta dejstvi, da se MSC iz krvi primarno prefiltrirajo skozi pljuča (cca v 48h so vsi MSC v pljučih) ter dejstvo, da MSC uravnavajo vnetje preko širokega spektra citokinov in rastnih faktorjev (kar ni zanemarljivo predvsem zaradi tega, ker tudi virus vnetje stimulira preko široke palete citokinov). Poleg imunomodulacije mezenhimske matične/stromalne celice tudi zmanjšujejo nastanek fibroze, kar je prav tako velika težava pri hudih oblikah COVID-19, tudi pri prebolevnikih.

Spodbudni rezultati o zdravljenju hudih oblik COVID-19 z MSC so prišli kmalu po začetku epidemije iz Kitajske. V preliminarni klinični študiji intravenske aplikacije alogenskih MSC ($1x10^6$ MSC/kg pacientove teže) je bilo vključenih 7 pacientov (45 – 75 let). Pljučna funkcija in bolezenski simptomi so se močno izboljšali v 2 dneh po administraciji MSC. Večina MSC se akumulirajo v pljučih, kar izboljša pljučno mikrookolje, ustavlja pretiran imunski odziv, ščitijo epitelne celice pljučnih mešičkov spodbujajo popravilo tkiv, zmanjšujejo pljučno fibrozo in izboljšujejo pljučno funkcijo. Infuzija MSC je pri pacientih sistemsko močno zmanjšalo vnetje. Koncentracije pro-inflamatornih citokinov v serumu so se močno zmanjšale.

Za zdravljenje COVID-19 se testira mnogo pristopov, MSC pa kažejo veliko uporabnost za zdravljenje COVID-19. V septembru 2020 je bilo na platformi ClinicalTrials.gov registriranih 42 kliničnih študij, ki raziskujejo potencial MSC za zdravljenje COVID-19. Poleg tega tudi večja podjetja, aktivna na področju celičnih terapij, objavljajo začetke študij in pozitivne rezultate (Athersys Inc., Mesoblast Ltd., Pluristem Therapeutics Inc., itd.)

MISCELLANEOUS

Foreign body airway aspiration in adults: twenty years of experience and therapeutic approach

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Background: Tracheobronchial foreign body (FB) aspiration in adults is an uncommon but potentially life-threatening event. It usually presents as choking, followed by cough and dyspnoea. However, these findings are inconsistent and may mimic chronic lung diseases, atelectasis or pneumonia. Bronchoscopy remains the gold standard for diagnosis and management of FB aspiration. We present our experience of dealing with various types of FB aspiration in airways of adult patients with focus on bronchoscopic techniques and potential complications of FB extraction and late consequences on the tracheobronchial tree.

Methods: Analysis of patients between 2000 and 2020 admitted to our department for FB removal from airways was performed. Patients underwent local or general anaesthesia. Flexible bronchoscopy with forceps, snares, basket or flexible cryoprobe was used.

Results: 39 patients were admitted with an average age 59.8 year. Nine patients had a clinical picture of acute FB aspiration, while others had signs and symptoms such as atelectasis, pneumonia, chronic cough. One third of patients had general anesthesia while the rest had local anaesthesia with flexible bronchoscope.

Discovered FBs were hazelnuts, grape seed, speaking apparatus, bone, tumour, teeth, cherry pawn, stone, peanut, garlic, stent fibres, petiole, corn, coagulated aspirated blood, mucus aspiration and pills. Two had lobar atelectasis after intubation. Two had massive hemoptysis with acute respiratory insufficiency. Massive blood coagula were successfully removed with cryoprobe. Mortality rate due to FB aspiration and intervention itself was zero.

Conclusion: FB aspiration still accounts for about 1 in 400 bronchoscopic procedures. This makes it difficult for an individual to develop adequate experiences for successful FB extraction. An experienced team including bronchoscopist, bronchoscopy assistants, nurse, and anesthesiologist are required for successful extraction of airway FB. The vast majority of FBs can be extracted safely with flexible bronchoscopy and the use of forceps, baskets and cryoprobe.

Pulmonary rehabilitation and exercise training in severe chronic obstructive pulmonary disease - individualized approach

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Background: It is well documented that pulmonary rehabilitation program (PRP) including physical activity improves physical abilities and fitness to all patients.

Exercise training of patients with severe chronic obstructive pulmonary disease (COPD) should be individualized with regard to their limitations. The benefits of such rehabilitation are greater control, prolonged monitoring and better outcome of treatment.

Methods: Two patients with a similar stage of the disease, but very different in terms of body composition and abilities were included into individualized PRP with respiratory physiotherapy and exercise program for improving strength, flexibility and cardiovascular endurance (compiled by the master of kinesiology).

Patient 1: 66 old man with COPD D on long-term oxygen therapy (LTOT) was normally nourished. The patient's limitation were breathlessness and poor cardiovascular endurance.

Patient 2: 65 old man with COPD D on LTOT, with a first degree obesity. The patient's limitation was severe COPD disease and obesity, which consequently limits activities of daily living and health enhancing physical activity.

Once per week strength exercises were repeated under supervision and perform an endurance (cardiovascular) training.

Physical fitness and cardiovascular endurance were tested at the beginning of rehabilitation and after two months: Grip strength test, 30 s sit to stand test and 30 s biceps curl test.

Results:

	Case 1	**Case 2**
	T1	
Grip strength (dynamometer)	24 kg	35 kg
Sit to stand test 30s	6	8 (stopped at 24s)
Biceps curl 30 s	5	14
	T2 (two months later)	
Grip strength test (dynamometer)	27 kg	36 kg
Sit to stand test 30s	5	9
Biceps curl 30 s	7	16

Conclusion: Pulmonary rehabilitation program in patients with severe COPD on long-term oxygen therapy has to be individualized, under careful control and continuous monitoring.

Lung transplantation programme in Slovenia: initial results

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Introduction: Lung transplantation is a highly complex method of treatment for selected patients with terminal lung disease. With the increase of the number of eligible candidates and the standardization of the method, it was possible to set up a transplantation centre in University Medical Centre (UMC) Ljubljana in 2018. We report our initial experience.

Methods: Analysis of internal registry of patients with lung transplantation was done. Patient's characteristics were compared to the previous group that was referred to AKH Vienna for lung transplantation.

Results: From 15.9.2018 to 15.3.2020 there were 13 lung transplantations (4 females) done in UMC Ljubljana. Indications were COPD (n = 6 [46.2 %]), cystic fibrosis (n = 3 [23.1 %]), idiopathic pulmonary fibrosis (n = 2 [15.4 %]), bronchiectasis (n = 1 [7.7 %]) and lymphangioleiomyomatosis (n = 1 [7.7 %]). Compared to previous cohort referred for transplantation to AKH Vienna (71 patients, 35 females), there was a tendency towards higher proportion of patients with COPD (p = 0.080) and the patients were older (median [Q1 - Q3], 58 [33 - 60] vs. 42 [23 - 58] years, p = 0.052). Only one patient died during the first 90 days post-transplantation, yielding 92.3 % 90-days survival, which is similar to survival of the cohort referred to AKH Vienna (94.4 % 90-days survival).

Conclusions: Initial results show comparable early lung transplantation success rate as noted in a previous cohort of patients referred to AKH.

Reasons for the abandonment of CPAP treatment of sleep apnoea

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Treatment with positive pressure (CPAP) is the most effective way to treat sleep apnoea. It successfully eliminates breathing pauses, hypoxia and night unrest. It diminishes cardiovascular risk and proneness to work-related and traffic injuries. Even so, it was noted that a quarter of patients do not use their PAP treatment regularly, long enough or at all.

Aim: to determine why there is a low compliance to CPAP treatment.

We contacted all patients who did not use at all or properly their CPAP and considered the reasons for abandoning therapy. We analyzed 208 patients (195 male, 37 female) independently of AHI/ODI, 65 abandoned treatment, 52 male, 13 female. According to daytime sleepiness and naps during work or driving, they were divided in:

a. Symptomatic, 18 abandoned (16 men 2 women)
b. Asymptomatic, 47 abandoned, (36 men, 11 women)

1. **immediate abandonment**, did not even agree to CPAP, (6a+15b)
   These feared suffocation, had claustrophobia, uncomfortable mask, convicted there was an easier way (internet), wish to be operated on, and poor understanding from the patient or surroundings.
2. **early abandonment** after the first control, 2 to 3 months of treatment, (4a+10b). They were convinced there was an easier way (internet) dry and swollen nose mucosa, conjunctivitis, ill-fitting masks.
3. **late abandonment** a year or more after beginning therapy, (5a+14b)
   Aesthetic reasons, believing there was an easier way (internet), dry, swollen nose mucosa, conjunctivitis, ill-fitting masks, desire for surgery
4. **irregular usage** of more than 70% of the night, less than 4 hours of continuous use during the night,(2a+9b).The reasons were work in shifts or outdoors, uncomfortable mask, belief that all night PAP is useless.

Conclusion: the reasons for rejecting and abandonment of CPAP treatment are bad mask choice, claustrophobia, belief that there is no problem, aesthetics, partner's bad co-operation, work in shifts or outdoors, bad internet information or desire for surgery. The percentage of women abandoning treatment in every category is higher than for men. Abandonment of CPAP treatment during sleep is connected to a subjective feeling of drowsiness during daytime.

Suggestion: 2 masks to be issued at the same time, as by patients' choice. Alternate use would increase compliance.

Influence of air pollution on exacerbation of bronchial asthma

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Introduction: Air pollution is the largest health risk in the world. Today, 92% of the world's population inhales polluted air. More than 7 million people (WHO) die annually from the effects of polluted air in the world. Air pollution is primarily responsible for increasing the prevalence of respiratory and cardiovascular diseases. Of particular importance are gases: Ozone, Carbon monoxide, Nitrogen dioxide, Sulfur dioxide and particulate matter PM 2.5, PM 10. Studies by the European Health Risk Agency and WHO are consistent and confirm that air pollution has a significant negative impact on health and development asthma.

Research objective: To evaluate the impact of harmful gases and dust particles on the increase of acute exacerbations of asthma.

Material and Methods: The following parameters of the measurement stations of the Ministry of Physical Planning and Environment were used: PM 2,5, SO2, NO2, CO2 and O3. All hospitalized patientes with asthma exacerbations during one year.

Results: An increased percentage of acute asthma exacerbations and hospitalizations were observed in months when concentrations of particulate matter and gas were increased beyond the allowable values.

Conclusion: The concentration of pollutant pollutants and exposure lengths have a significant effect on asthma exacerbations and an increased percentage of hospitalizations.

Influence of breathing on posture and influence of posture on breathing

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Introduction: Respiration is a natural process, a function controlled by the central nervous system. Breathing movements influence not only the basic metabolic processes, but also our posture or the mobility of the spine itself. Correct breathing is also a prerequisite for the physiological stabilization of the spine and vice versa. Depending on our lifestyle, we begin to influence and restrict these breathing movements through our inappropriate motor habits. As our posture deteriorates, we also change our breathing.

Methods: By reviewing the literature, we aim to highlight both directional causality and the relationship between the biomechanics of breathing and the biomechanics of posture, and to emphasize the techniques of their evaluation.

Results: Poor posture affects the breathing, which is limited, shallow and natural can cause many other problems with breathing, such as chest stiffness and chest inspiration, congestion of each area of the spine (from neck to sacrum, most thoracic transition), Problems in the abdominal cavity, insufficient involvement of muscles and muscle imbalance, disorders of fixation of the upper and lower chest, improper use or a high diaphragm, impaired functioning of internal organs and glands, etc ...

Discussion and conclusion: Respiration is usually analyzed in terms of respiratory measurements and vital functions, and too little attention is paid to postural function. Both respiratory and motor diagnostics and therapy must include both components - the influence of breathing on posture and the influence of posture on breathing. The latter can be achieved by combining respiratory therapy, manual therapy and kinesiotherapy.

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Z ZDRAVILOM FASENRA DO NIČLE

Fasenra 30 mg raztopina za injiciranje v napolnjenem injekcijskem peresniku

NA VOLJO OD 10. 6. 2020

NA VOLJO OD 10. 6. 2020

NIČ POSLABŠANJ pri 74 % bolnikov v 2. letu zdravljenja v 56-tedenski raziskavi varnosti ob podaljšanem zdravljenju[1]*

NIČ OGK pri 52 % ustreznih bolnikov v primerjavi z 19 % bolnikov ob placebu[2]**

NIČ EOZINOFILCEV v krvi (mediana) po 1. dnevu[3]

*BORA: Bolniki iz predhodnih raziskav (SIROCCO in CALIMA), ki so med 56-tedenskim ocenjevalnim obdobjem še naprej prejemali zdravilo na vsakih 8 tednov. Ob izhodišču so imeli bolniki število eozinofilcev v krvi ≥ 300 celic/µl

**ZONDA: Bolniki z izhodiščnim odmerkom OGK ≤ 12,5 mg so opustili uporabo teh zdravil (p = 0,002). Ob izhodišču so imeli bolniki število eozinofilcev v krvi ≥ 150 celic/µl

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

▼Za to zdravilo se izvaja dodatno spremljanje varnosti. Tako bodo hitreje na voljo nove informacije o njegovi varnosti. Zdravstvene delavce naprošamo, da poročajo o katerem koli domnevnem neželenem učinku zdravila.

Fasenra 30 mg raztopina za injiciranje v napolnjeni injekcijski brizgi
Fasenra 30 mg raztopina za injiciranje v napolnjenem injekcijskem peresniku

SESTAVA: Ena napolnjena injekcijska brizga vsebuje 30 mg benralizumaba v 1 ml. En napolnjen injekcijski peresnik vsebuje 30 mg benralizumaba v 1 ml. Benralizumab je humanizirano monoklonsko protitelo, pridobljeno v celicah jajčnika kitajskega hrčka s tehnologijo rekombinantne DNA. **INDIKACIJE:** Zdravilo Fasenra je indicirano kot dodatno vzdrževalno zdravljenje za odrasle bolnike s hudo eozinofilno astmo, ki ni ustrezno urejena kljub velikim odmerkom inhalacijskih kortikosteroidov in dolgodelujočih agonistov β. **ODMERJANJE IN NAČIN UPORABE:** Zdravljenje z zdravilom Fasenra mora uvesti zdravnik, ki ima izkušnje z diagnosticiranjem in zdravljenjem hude astme. Samoinjiciranje pride v poštev le pri bolnikih, ki že imajo izkušnje z zdravljenjem z zdravilom Fasenra. Priporočeni odmerek je 30 mg v subkutani injekciji na 4 tedne prve 3 odmerke, pozneje pa na 8 tednov. Starejšim bolnikom, bolnikom z okvaro ledvic ali jeter odmerka ni treba prilagoditi. Varnost in učinkovitost zdravila Fasenra pri otrocih, starih od 6 do 18 let, nista bili dokazani. Zdravilo Fasenra se uporablja kot subkutana injekcija. Zdravilo je treba injicirati v stegno ali trebuh. Če da injekcijo zdravnik ali skrbnik, lahko uporabi tudi nadlaket. **KONTRAINDIKACIJE:** Preobčutljivost za zdravilno učinkovino ali katerokoli pomožno snov. **POSEBNA OPOZORILA IN PREVIDNOSTNI UKREPI:** Zdravila Fasenra se ne sme uporabljati za zdravljenje akutnih poslabšanj astme. Če je primerno zmanjšanje odmerkov kortikosteroida, mora biti zmanjšanje postopno in mora potekati pod nadzorom zdravnika. *Preobčutljivostne reakcije:* po uporabi benralizumaba so se pojavile akutne sistemske reakcije, vključno z anafilaktičnimi reakcijami in preobčutljivostnimi reakcijami (npr. urtikarija, papularna urtikarija, izpuščaj). Te reakcije se lahko pojavijo v nekaj urah po uporabi, a v nekaterih primerih se pojavijo v nekaj dneh. Anamneza anafilaksije, nepovezane z benralizumabom, je lahko dejavnik tveganja za anafilaksijo po uporabi zdravila Fasenra. V skladu s klinično prakso je treba bolnike po uporabi zdravila Fasenra ustrezen čas spremljati. V primeru preobčutljivostne reakcije je treba zdravilo Fasenra trajno prenehati uporabljati in uvesti ustrezno zdravljenje. *Parazitske okužbe (okužbe s helminti):* Eozinofilci so lahko vpleteni v imunski odziv na nekatere okužbe s helminti. Bolniki, ki so imeli znano okužbo s helminti, niso bili vključeni v klinična preskušanja. Bolnike z obstoječimi okužbami s helminti je treba zdraviti pred uvedbo zdravljenja z zdravilom Fasenra. Če se bolnik okuži med zdravljenjem z zdravilom Fasenra in se ne odzove na zdravljenje z antihelmintiki, je treba zdravljenje z zdravilom Fasenra prekiniti, dokler okužba ne mine. **MEDSEBOJNO DELOVANJE Z DRUGIMI ZDRAVILI:** Randomizirana, dvojno slepa študija vzporednih skupin, ki je zajela 103 bolnike s hudo astmo, stare od 12 do 21 let, ni pokazala, da bi zdravljenje z benralizumabom neugodno vplivalo na odzive humoralnih protiteles, ki jih povzroči cepljenje proti sezonskim virusom influence. Vpliva benralizumaba na farmakokinetiko sočasno uporabljenih zdravil ni pričakovati. Encimi citokroma P450, mehanizmi iztočne črpalke in mehanizmi vezave na beljakovine niso vključeni v očistek benralizumaba. O izraženosti IL-5Rα na jetrnih celicah ni dokazov. Izguba eozinofilcev ne povzroči kroničnih sistemskih sprememb vnetnih citokinov. **NEŽELENI UČINKI:** Najpogosteje opisana neželena učinka med zdravljenjem sta glavobol (8 %) in faringitis (3 %). Poročali so o anafilaktičnih reakcijah. V kliničnih študijah je benralizumab v obdobju od 48 do 56 tednov prejemalo skupno 2514 bolnikov, od katerih jih je 1663 imelo hudo, neurejeno eozinofilno astmo. Pogosti neželeni učinki: faringitis (opredeljen z naslednjimi združenimi prednostnimi izrazi: faringitis, bakterijski faringitis, virusni faringitis in streptokokni faringitis), preobčutljivostne reakcije (opredeljene z naslednjimi združenimi prednostnimi izrazi: urtikarija, papularna urtikarija in izpuščaj), glavobol, zvišana telesna temperatura in reakcija na mestu injiciranja. Anafilaktične reakcije so poročane z neznano pogostnostjo. V podaljšanem preskušanju bolnikov z astmo o dolgoročni varnosti zdravila Fasenra je bil poročan profil neželenih učinkov podoben kot v predhodnih preskušanjih. **POSEBNA NAVODILA ZA SHRANJEVANJE:** Shranjujte v hladilniku (2 °C do 8 °C). Zdravilo Fasenra je lahko shranjeno na sobni temperaturi do 25 °C največ 14 dni. Ko zdravilo Fasenra vzamete iz hladilnika, ga je treba uporabiti v 14 dneh ali ga zavreči. Napolnjeno injekcijsko brizgo/napolnjen injekcijski peresnik (Fasenra Pen) shranjujte v originalni ovojnini za zagotovitev zaščite pred svetlobo. Ne zamrzujte. Ne pretresajte. Ne izpostavljajte vročini. **VRSTA IN VSEBINA OVOJNINE:** Napolnjena injekcijska brizga: En mililiter raztopine v napolnjeni injekcijski brizgi za enkratno uporabo iz stekla tipa I, z nameščeno 1/2-colsko iglo debeline 29 G iz nerjavnega jekla, s togim ščitnikom igle in s Fluorotecom prekritim čepom bata v pasivni varnostni napravi. Pakiranje vsebuje 1 napolnjeno injekcijsko brizgo za enkratno uporabo. Napolnjen injekcijski peresnik (Fasenra Pen): En mililiter raztopine v sterilnem napolnjenem injekcijskem peresniku za enkratno uporabo iz stekla tipa I, z nameščeno 1/2-colsko iglo debeline 29 G iz nerjavnega jekla, s togim ščitnikom igle in s Fluorotecom prekritim čepom bata v napolnjenem injekcijskem peresniku. Pakiranje vsebuje 1 napolnjen injekcijski peresnik za enkratno uporabo (Fasenra Pen). **NAČIN IZDAJANJA ZDRAVILA:** Rp/Spec - Predpisovanje in izdaja zdravila je le na recept zdravnika specialista ustreznega področja medicine ali od njega pooblaščenega zdravnika. **DATUM REVIZIJE BESEDILA:** junij 2019 (SI-0682). **IMETNIK DOVOLJENJA ZA PROMET:** AstraZeneca AB, S-151 85, Sodertalje, Švedska. **Pred predpisovanjem, prosimo, preberite celoten povzetek glavnih značilnosti zdravila.** Dodatne informacije so na voljo pri družbi AstraZeneca UK Limited, Podružnica v Sloveniji, Verovškova 55, Ljubljana.

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1. Busse WW, et al. *Lancet Respir Med.* 2019;7(1):46-59. doi: 10.1016/S2213-2600(18)30406-5.9. **2.** Nair P, et al. *N Engl J Med.* 2017; 376:2448-58. doi:10.1056/NEJMoa1703501. **3.** Laviolette M, et al. *J Allergy Clin Immunol.* 2013;132:1086-1096. doi:10.1016/j.jaci.2013.05.020.

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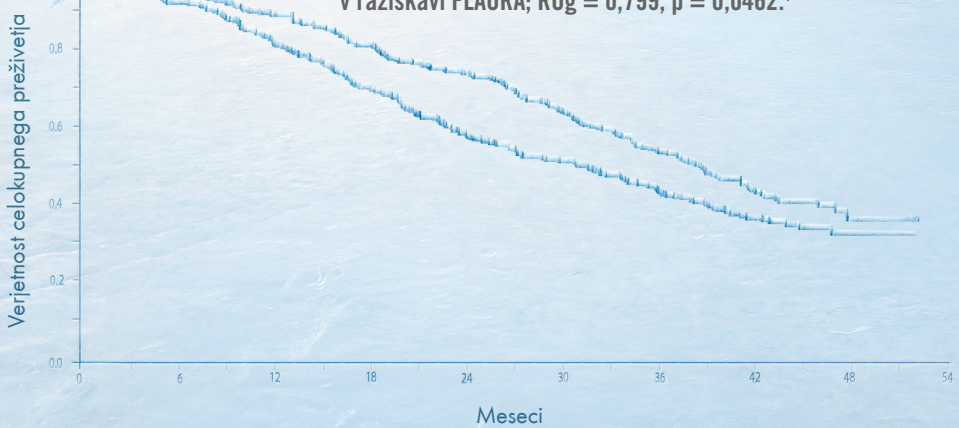
REZULTATI CELOKUPNEGA PREŽIVETJA V RAZISKAVI FLAURA POTRJUJEJO, DA JE ZDRAVILO TAGRISSO STANDARD V PRVI LINJI ZDRAVLJENJA ODRASLIH BOLNIKOV Z LOKALNO NAPREDOVALIM ALI METASTATSKIM NSCLC Z EGFR MUTACIJAMI

TAGRISSO™ osimertinib

TAGRISSO
PRELOMNICA V ZDRAVLJENJU
Mediana OS
38,6 m V PRIMERJAVI Z 31,8 m

Zdravilo Tagrisso v primerjavi z gefitinibom/erlotinibom v raziskavi FLAURA; ROg = 0,799, p = 0,0462.[1]



OS...celokupno preživetje; EGFR... receptor za epidermalni rastni faktor; NSCLC...nedrobnocelični rak pljuč; m...meseci; ROg...razmerje ogroženosti

Skrajšan povzetek glavnih značilnosti zdravila

▼ Za to zdravilo se izvaja dodatno spremljanje varnosti. Tako bodo hitreje na voljo nove informacije o njegovi varnosti. Zdravstvene delavce naprošamo, da poročajo o katerem koli domnevnem neželenem učinku zdravila.

TAGRISSO 40 mg filmsko obložene tablete / TAGRISSO 80 mg filmsko obložene tablete

SESTAVA: Ena filmsko obložena tableta vsebuje 40 ali 80 mg osimertiniba. **INDIKACIJE:** Zdravilo Tagrisso je kot monoterapija indicirano za prvo linijo zdravljenja odraslih bolnikov z lokalno napredovalim ali metastatskim nedrobnoceličnim rakom pljuč, katerega receptor za epidermalni rastni faktor ima aktivirajoče mutacije in za zdravljenje odraslih bolnikov z lokalno napredovalim ali metastatskim NSCLC, pozitivnim za mutacijo T790M EGFR. **ODMERJANJE IN NAČIN UPORABE:** Zdravljenje z zdravilom Tagrisso mora uvesti zdravnik, ki ima izkušnje z zdravili za zdravljenje raka. Pri odločanju o uporabi zdravila Tagrisso je treba določiti stanje mutacije EGFR v vzorcih tumorja ali plazme z uporabo validirane testne metode. Priporočeni odmerek je 80 mg osimertiniba enkrat na dan do napredovanja bolezni ali nesprejemljivih toksičnih učinkov. Zdravilo Tagrisso je mogoče vzeti s hrano ali brez nje, vsak dan ob istem času. Glede na varnost in prenašanje pri posameznem bolniku je lahko potrebna prekinitev odmerjanja in/ali zmanjšanje odmerka. V primeru potrebe po zmanjšanju odmerka je treba odmerek zmanjšati na 40 mg enkrat na dan. Bolnikom, ki po zmanjšanju odmerka zdravila ne prenesejo, je treba osimertinib ukiniti in razmisliti o drugačni terapiji. Bolnikom z blago ali zmerno okvaro jeter odmerka ni treba prilagoditi, vendar je treba zdravilo Tagrisso pri teh bolnikih uporabljati previdno. Na podlagi kliničnih študij in populacijske farmakokinetične analize prilagajanje odmerka ni potrebno pri bolnikih z blago ali z zmerno okvaro jeter. Varnost in učinkovitost zdravila nista ugotovljeni pri bolnikih s hudo okvaro jeter. Na podlagi kliničnih študij in populacijske farmakokinetične analize bolnikom z blago, zmerno ali hudo okvaro ledvic odmerka ni treba prilagoditi. Varnost in učinkovitost tega zdravila nista ugotovljeni pri bolnikih s končno odpovedjo ledvic (očistek kreatinina manj kot 15 ml/min, izračunan po Cockroft-Gaultovi enačbi) in pri bolnikih na dializi. Pri zdravljenju bolnikov s hudo okvaro ledvic in končno odpovedjo ledvic je potrebna previdnost. **KONTRAINDIKACIJE:** Preobčutljivost za zdravilno učinkovino ali katerokoli pomožno snov. Šentjanževke se ne sme uporabljati skupaj z zdravilom Tagrisso. **OPOZORILA IN PREVIDNOSTNI UKREPI:** Pri odločanju o uporabi zdravila Tagrisso za zdravljenje lokalno napredovalega ali metastatskega NSCLC je pomembno določiti stanje mutacije T790M EGFR. Opraviti je treba validirano preiskavo tumorske DNK, dobljene iz vzorca tkiva, ali tumorske DNK v obtoku (ctDNA – circulating tumor DNA), dobljene iz vzorca plazme. Določitev prisotne mutacije T790M v vzorcu tkiva ali plazme pomeni, da je bolnik primeren za zdravljenje z zdravilom Tagrisso. O intersticijski bolezni pljuč (IBP) ali neželenih učinkih, podobnih IBP (npr. o pnevmonitisu), so poročali pri 3,9 % od 1142 bolnikov, ki so v študijah FLAURA in AURA prejemali zdravilo Tagrisso; opažali so hude, življenjsko ogrožajoče in včasih smrtne primere intersticijske bolezni pljuč (IBP) ali neželenih učinkov, podobnih IBP (npr. pnevmonitisa). Večina primerov se je po prenehanju zdravljenja izboljšala ali je izginila. Bolniki z anamnezo IBP, z zdravili izzvane IBP, radiacijskega pnevmonitisa, ki je zahteval zdravljenje s steroidi, ali kakršnimi koli znaki klinično aktivne IBP niso bili vključeni v klinične študije. Vse bolnike z akutnim nastankom in/ali nepojasnjenim poslabšanjem pljučnih simptomov je treba skrbno pregledati, da bi izključili IBP. V času preiskovanja teh simptomov je treba zdravljenje s tem zdravilom prekiniti. Če je diagnosticirana IBP, je treba ukiniti zdravljenje z zdravilom Tagrisso in uvesti ustrezno zdravljenje, kot je potrebno. Ponovna uvedba zdravila TAGRISSO pride v poštev le po skrbnem pretehtanju koristi in tveganj pri posameznem bolniku. Stevens-Johnsonov sindrom: V povezavi z zdravljenjem z zdravilom TAGRISSO so poročali o redkih primerih Stevens Johnsonovega sindroma (SJS). Pred uvedbo zdravljenja je treba bolnike seznaniti z znaki in simptomi SJS. Če se pojavijo znaki ali simptomi, ki nakazujejo SJS, je treba zdravljenje z zdravilom TAGRISSO nemudoma prekiniti ali končati. Podaljšanje intervala QTc: Bolnikom, zdravljenim z zdravilom Tagrisso, se pojavi podaljšanje intervala QTc. Takšno podaljšanje lahko poveča tveganje za ventrikularne tahiaritmije (npr. torsade de pointes) ali nenadno smrt. Uporabi osimertiniba se je treba pri bolnikih s prirojenim sindromom dolgega intervala QT izogniti, če je le mogoče. O rednih kontrolah elektrokardiograma (EKG) in elektrolitov je treba razmisliti pri bolnikih s kongestivnim srčnim popuščanjem, elektrolitskimi motnjami in prejemnikih zdravil, za katera je znano, da podaljšajo interval QTc. Prekinite uporabo pri bolnikih, ki se jim interval QTc podaljša preko 500 msec na vsaj 2 ločenih posnetkih EKG, in ga ne uporabljajte, dokler ni interval QTc manj kot 481 msec oziroma do njegove vrnitve na izhodiščno vrednost, če je izhodiščni interval QTc 481 msec ali več. Potem začnite zdravilo Tagrisso znova uporabljati v manjšem odmerku. Trajno ukinite zdravljenje z osimertinibom, če se bolniku pojavi podaljšanje intervala QTc v kombinaciji s čimer koli od naslednjega: torsade de pointes, polimorfna ventrikularna tahikardija, znaki/simptomi resne motnje srčnega ritma. Spremembe v krčljivosti srca: Pri bolnikih s srčnimi dejavniki tveganja in bolnikih s stanji, ki prizadenejo LVEF, je treba razmisliti o nadziranju delovanja srca, vključno z ocenjevanjem LVEF izhodiščno in med zdravljenjem. Pri bolnikih, ki se jim med zdravljenjem pojavijo pomembni srčni znaki ali simptomi, je treba razmisliti o nadziranju delovanja srca, vključno z ocenjevanjem LVEF. Keratitis: O keratitisu so poročali pri 0,7 % bolnikov, zdravljenih z zdravilom Tagrisso v študijah FLAURA in AURA. Bolnike z znaki in simptomi, ki nakazujejo keratitis (na primer vnetje očesa, solzenje, občutljivost na svetlobo, zamegljen vid, bolečine v očesu in/ali pordelost očesa), je treba nemudoma napotiti k specialistu oftalmologu. Starost in telesna masa: Pri bolnikih starih nad 65 let ali bolnikih z telesno maso pod 50 kg je lahko prisotno povečano tveganje za pojav neželenih učinkov 3. ali višje stopnje. Pri teh bolnikih je priporočeno skrbno spremljanje. **MEDSEBOJNO DELOVANJE Z DRUGIMI ZDRAVILI:** Močni induktorji CYP3A lahko zmanjšajo izpostavljenost osimertinibu. Osimertinib lahko poveča izpostavljenost substratom BCRP in P-glikoproteina (P-gp). Študije in vitro so pokazale, da poteka presnova I. faze osimertiniba pretežno s CYP3A4 in CYP3A5. Podatki iz klinične farmakokinetične študije so pokazali, da ni verjetno, da bi zaviralci CYP3A4 vplivali na izpostavljenost osimertinibu. Dodatnih katalizacijskih encimov niso odkrili. Podatki klinične farmakokinetične študije o sočasno uporabi z rifampicinom kažejo, da se je sočasni uporabi močnih induktorjev CYP3A (npr. fenitoina, rifampicina, karbamazepina) in zdravila Tagrisso priporočljivo izogniti. Izpostavljenost osimertinibu lahko zmanjšajo tudi zmerni induktorji CYP3A4 (npr. bosentan, efavirenz, etravirin, modafinil), zato jih je treba uporabljati previdno oziroma se jim je treba izogniti, če je mogoče. Kliničnih podatkov, ki bi omogočali priporočila za prilagoditev odmerka zdravila Tagrisso, ni na voljo. Sočasna uporaba šentjanževke je kontraindicirana. Glede na podatke klinične farmakokinetične študije je pri sočasni uporabi zdravila Tagrisso in rosuvastatina ter ostalih zdravil, katerih odstranjevanje je odvisno od BCRP in imajo ozek terapevtski indeks, treba bolnike skrbno spremljati glede znakov spremenjenega prenašanja zaradi večje izpostavljenosti sočasnemu zdravilu med prejemanjem zdravila Tagrisso. Tveganja za manjšo izpostavljenost hormonskim kontraceptivom ni mogoče izključiti. Bolnike, ki sočasno jemljejo zdravila, katerih odstranjevanje je odvisno od P-gp in imajo ozek terapevtski indeks (npr. digoksin, dabigatran, in aliskiren), je treba skrbno spremljati glede znakov spremenjenega prenašanja zaradi večje izpostavljenosti sočasnemu zdravilu v času prejemanja zdravila Tagrisso. **NEŽELENI UČINKI:** Podatki iz dveh randomiziranih študijah III. faze (FLAURA – prva linija in AURA3 – le druga linija) in iz dveh študij z eno samo skupino (AURAex in AURA2 – druga linija ali več) in eni študiji I. faze (AURA1 – prva linija ali več) povzemajo izpostavljenost zdravilu Tagrisso pri 1142 bolnikih z nedrobnoceličnim rakom pljuč in pozitivno mutacijo EGFR. Večina neželenih učinkov je bila glede na resnost 1. ali 2. stopnje. Najpogostejša neželena učinka zdravila sta bila driska (49 %) in izpuščaj (47 %). V obeh študijah skupaj je bilo neželenih učinkov 3. stopnje 9,7 % in 4. stopnje 0,9 %. Med bolniki, ki so prejemali zdravilo Tagrisso 80 mg enkrat na dan, so zaradi neželenih učinkov odmerek zmanjšali 2,1 % bolnikom. Ukinitev uporabe zdravila zaradi neželenih učinkov je bilo 4,3 %. Zelo pogosti neželeni učinki: driska, stomatitis, izpuščaj, suha koža, paronihija, srbenje ter zmanjšano število trombocitov, levkocitov, limfocitov in nevtrofilcev. Pogosti neželeni učinki: intersticijska bolezen pljuč. **VRSTA IN VSEBINA OVOJNINE:** Al/Al perforirani pretisni omoti za enkratni odmerek. Škatle z 28 x 1 tableto (4 pretisni omoti). **NAČIN IZDAJANJA ZDRAVILA:** samo na recept **DATUM REVIZIJE BESEDILA:** julij 2020 (SI-0991) **IMETNIK DOVOLJENJA ZA PROMET:** AstraZeneca AB, S-151 85, Sodertalje, Švedska

Pred predpisovanjem, prosimo, preberite celoten povzetek glavnih značilnosti zdravila.
Dodatne informacije so na voljo pri družbi AstraZeneca UK Limited, Podružnica v Sloveniji, Verovškova 55, Ljubljana.

1. Ramalingam SS. Osimertinib vs comparator EGFR-TKI as first-line treatment for EGFRm advanced NSCLC (FLAURA): Final overall survival analysis [oral presentation]. Predstavljeno na: European Society of Medical Oncology; September 27-October 1, 2019; Barcelona, Spain. Abstract LBA5.

SI-1003

SYMBICORT®

OLAJŠEVALEC PO POTREBI OB VZDRŽEVALNEM ZDRAVLJENJU

SPREMINJA ŽIVLJENJA[1]

SYMBICORT® ZDAJ OLAJŠEVALEC PRVE IZBIRE

za bolnike z zmerno do težko astmo, izkorišča njihovo naravno vedenje, da iščejo olajšanje, in tako zmanjša število poslabšanj.[2]

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

Symbicort Turbuhaler 80 µg/4,5 µg na odmerek, prašek za inhaliranje / Symbicort Turbuhaler 160 µg/4,5 µg na odmerek, prašek za inhaliranje / Symbicort Turbuhaler 320 µg/9 µg na odmerek, prašek za inhaliranje

SESTAVA: Vsak inhalator Symbicort Turbuhaler 80 µg/4,5 µg na odmerek vsebuje 120 odmerkov, pri čemer vsak oddani odmerek (tisti, ki pride iz ustnika) vsebuje učinkovini budezonid (80 µg na vdih) in formoterolijev fumarat dihidrat (4,5 µg na vdih). Vsak inhalator Symbicort Turbuhaler 160 µg/4,5 µg na odmerek vsebuje 120 odmerkov, pri čemer vsak oddani odmerek vsebuje učinkovini budezonid (160 µg na vdih) in formoterolijev fumarat dihidrat (4,5 µg na vdih). Vsak inhalator Symbicort Turbuhaler 320 µg/9 µg na odmerek vsebuje 60 odmerkov, pri čemer vsak oddani odmerek vsebuje učinkovini budezonid (320 µg na vdih) in formoterolijev fumarat dihidrat (9 µg na vdih). **INDIKACIJE: ASTMA:** Zdravilo Symbicort Turbuhaler je indicirano za redno zdravljenje astme, kadar je primerna uporaba kombinacije (vdihanega kortikosteroida in dolgodelujočega agonista adrenergičnih receptorjev β_2). Zdravilo Symbicort Turbuhaler 80 µg/4,5 µg je indicirano pri odraslih, mladostnikih in otrocih, starih 6 let ali več. Zdravili Symbicort Turbuhaler 160 µg/4,5 µg in Symbicort Turbuhaler 320 µg/9 µg sta indicirani pri odraslih in mladostnikih, starih 12 let in starejših. Opomba: Zdravilo Symbicort Turbuhaler 80 µg/4,5 µg ni primerno za bolnike s hudo astmo. **KOPB:** Zdravili Symbicort Turbuhaler 160 µg/4,5 µg in Symbicort Turbuhaler 320 µg/9 µg sta indicirani pri odraslih, starih 18 let ali več, za simptomatsko zdravljenje bolnikov s KOPB s forsiranim ekspiracijskim volumnom v 1 sekundi (FEV1) < 70 % predvidenega normalnega (post-bronhodilatatorno) in anamnezo poslabšanj kljub rednemu bronhodilatatornemu zdravljenju. **ODMERJANJE**: Bolnika je treba opozoriti, da mora natančno prebrati navodila za uporabo.

ASTMA: Zdravilo Symbicort Turbuhaler ni namenjeno za začetno zdravljenje astme. Odmerek je treba titrirati o najmanjšega odmerka, ki še učinkovito nadzoruje simptome bolezni. Če najmanjši priporočeni odmerek dolgoročno obvladuje simptome, lahko naslednji korak obsega poskus zdravljenja z IGK samim. Z zdravilom Symbicort Turbuhaler sta možna dva načina zdravljenja astme: **A. Vzdrževalno zdravljenje z zdravilom Symbicort Turbuhaler:** Bolnik za redno vzdrževalno zdravljenje uporablja zdravilo Symbicort Turbuhaler, kot olajševalec pa ločeno uporablja hitrodelujoč bronhodilatator. Bolnikom je treba naročiti, naj imajo vedno na razpolago ločen hitrodelujoč bronhodilatator za rešilno uporabo. ***Priporočeni odmerki: Odrasli (stari 18 let ali več):*** Symbicort Turbuhaler 80 µg/4,5 µg in Symbicort Turbuhaler 160 µg/4,5 µg 1–2 vdiha dvakrat na dan, nekateri bolniki lahko potrebujejo do največ 4 vdihe dvakrat na dan. Symbicort Turbuhaler 320 µg/9 µg 1 vdih dvakrat na dan, nekateri bolniki lahko potrebujejo do največ dva vdiha dvakrat na dan. ***Mladostniki (12 do 17 let):*** Symbicort Turbuhaler 80 µg/4,5 µg in Symbicort Turbuhaler 160 µg/4,5 µg 1–2 vdiha dvakrat na dan. Symbicort Turbuhaler 320 µg/9 µg 1 vdih dvakrat na dan. ***Otroci (stari 6 –12 let):*** 2 vdiha dvakrat na dan (samo Symbicort Turbuhaler 80 µg/4,5 µg). Ko je v običajni praksi dosežen nadzor simptomov z uporabo inhalatorja dvakrat na dan, lahko titracija do najmanjšega učinkovitega odmerka vključuje zdravilo Symbicort Turbuhaler enkrat na dan. ***Otroci, mlajši od 6 let:*** Ker je na voljo le malo podatkov, zdravilo Symbicort Turbuhaler ni priporočljivo za otroke, mlajše od 6 let. **B. Vzdrževalno in olajševalno zdravljenje z zdravilom Symbicort (samo z zdravili *Symbicort Turbuhaler 80 µg/4,5 µg in Symbicort Turbuhaler 160 µg/4,5*):** Bolniki uporabljajo dnevni vzdrževalni odmerek zdravila Symbicort, dodatno pa ga uporabijo po potrebi, če se pojavijo simptomi. Bolnikom je treba naročiti, naj imajo zdravilo Symbicort kot olajševalec vedno pri sebi. Če bolnik uporablja zdravilo Symbicort Turbuhaler kot olajševalec za preprečevanje bronhokonstrikcije, izzvane z alergeni ali telesno obremenitvijo, se morata zdravnik in bolnik pogovoriti o takšni uporabi; priporočila za uporabo mora upoštevati pogostnost bolnikove potrebe po zdravilu. V primeru pogoste potrebe po bronhodilataciji brez hkratne potrebe po večjem odmerku inhalacijskih kortikosteroidov je treba uporabiti nek drug olajševalec. ***Priporočeni odmerki: Odrasli in mladostniki (stari 12 let in starejši):*** Priporočeni vzdrževalni odmerek sta 2 vdiha na dan, bodisi kot 1 vdih zjutraj in 1 vdih zvečer bodisi kot 2 vdiha zjutraj ali zvečer. Za nekatere bolnike, ki prejemajo Symbicort Turbuhaler 160 µg/4,5 µg je lahko primeren vzdrževalni odmerek 2 vdiha dvakrat na dan. Če se pojavijo simptomi, mora bolnik narediti še 1 dodaten vdih. Če so simptomi po nekaj minutah še prisotni, mora uporabiti 1 dodatno inhalacijo. Naenkrat ne sme uporabiti več kot 6 inhalacij. Celotni dnevni odmerek večji od 8 vdihov v normalnih okoliščinah ni potreben, a za krajše obdobje se lahko uporablja celotni dnevni odmerek do 12 vdihov. Bolniki, ki jemljejo več kot 8 vdihov na dan, se morajo vsekakor posvetovati z zdravnikom. Zdravnik mora ponovno oceniti njihovo stanje in pretehtati njihovo vzdrževalno zdravljenje. ***Otroci do 12. leta:*** Vzdrževalno in olajševalno zdravljenje z zdravilom Symbicort Turbuhaler za otroke ni priporočljivo.

KOPB: ***Priporočeni odmerki za odrasle:*** Symbicort Turbuhaler 160 µg/4,5 µg 2 vdiha dvakrat na dan in Symbicort Turbuhaler 320 µg/9 µg 1 vdih dvakrat na dan. **KONTRAINDIKACIJE:** Preobčutljivost za budezonid, formoterol ali inhalirano laktozo. **POSEBNA OPOZORILA IN PREVIDNOSTNI UKREPI:** V primeru prenehanja zdravljenja se z uporabo zdravila ne sme prekiniti nenadoma, ampak je treba odmerek zmanjševati postopoma. O popolni opustitvi inhalacijskih kortikosteroidov se ne sme razmišljati, razen če je potrebna začasno za potrditev diagnoze astme. Če bolnik ugotovi, da je zdravljenje neučinkovito ali če preseže največji priporočeni odmerek zdravila Symbicort Turbuhaler, mora poiskati zdravniško pomoč. Bolnike je treba opozoriti, naj uporabljajo vzdrževalne odmerke zdravila Symbicort Turbuhaler, kot jih je predpisal zdravnik, tudi če nimajo simptomov. Ko so simptomi astme pod nadzorom, pride v poštev postopno zmanjševanje odmerka zdravila Symbicort Turbuhaler. Med zmanjševanjem odmerka je potrebno bolnike redno spremljati. Uporabljati je treba najmanjši učinkoviti odmerek. Bolnikom zdravila Symbicort Turbuhaler ne smemo uvesti med poslabšanjem astme ali kadar se jim simptomi astme bistveno ali akutno poslabšajo. Če se bolniku pojavi paradoksalni bronhospazem, je treba uporabo zdravila Symbicort Turbuhaler takoj prekiniti; bolnika je treba pregledati in uvesti drugo zdravljenje, če je treba. Možne učinke na mineralno gostoto kosti je treba še zlasti upoštevati pri bolnikih, ki dolga obdobja dobivajo velike odmerke in imajo sočasne dejavnike tveganja za osteoporozo. Če obstaja razlog za sum o motenem delovanju nadledvičnih žlez zaradi predhodnega sistemskega zdravljenja s steroidi, je pri prehodu na zdravilo Symbicort Turbuhaler potrebna previdnost. Tudi dolgotrajno zdravljenje z velikimi odmerki IGK, zlasti v odmerkih, večjih od priporočenih, lahko klinično pomembno zavre delovanje nadledvičnih žlez. Zato pride med obdobji stresa, npr. v primeru hudih okužb ali elektivne operacije, v poštev dodatna zaščita s sistemskimi kortikosteroidi. Da bi čim bolj zmanjšali tveganje orofaringealne kandidoze, je treba bolniku naročiti, da si mora po inhaliranju vzdrževalnega odmerka usta sprati z vodo. Če se pojavi orofaringealna kandidoza, si mora bolnik usta sprati tudi po vsaki inhalaciji po potrebi. Zdravilo Symbicort Turbuhaler predpisujte previdno pri bolnikih s tirotoksikozo, feokromocitomom, sladkorno boleznijo, nezdravljeno hipokaliemijo, hipertrofično obstruktivno kardiomiopatijo, idiopatsko subvalvularno aortno stenozo, hudo hipertenzijo, anevrizmo ali drugimi hudimi srčno-žilnimi boleznimi. Previdnost je potrebna pri zdravljenju bolnikov s podaljšanim intervalom QTc. Tudi formoterol sam lahko povzroči podaljšanje interval QTc. Pri sistemski in topični uporabi kortikosteroidov lahko poročajo o motnjah vida. Pediatrična populacija: priporočljivo je redno spremljanje telesne višine otrok, ki dolgotrajno dobivajo IGK. Za preostala opozorila in previdnostne ukrepe glejte celoten povzetek. **INTERAKCIJE:** Z močnimi zaviralci CYP3A4 (ketokonazol, klaritromicin, nefazodon, zaviralci proteaz HIV...) je verjetno izrazito povečanje koncentracije budezonida v plazmi, zato se je sočasni uporabi treba izogniti. Zdravila Symbicort Turbuhaler se zato ne sme dajati skupaj z inhibitorji adrenergičnih receptorjev beta (vključno s kapljicami za oko), če za to ne obstajajo tehtni razlogi. Sočasno zdravljenje s kinidinom, dizopiramidom, prokainamidom, fenotiazini, antihistaminiki (terfenadin) in tricikličnimi antidepresivi lahko podaljša interval QTc in poveča tveganje ventrikularnih aritmij. Poleg tega lahko L-dopa, L-tiroksin, oksitocin in alkohol poslabšajo toleranco srca za simpatikomimetike β_2. Sočasno zdravljenje z zaviralci monoaminooksidaze, vključno z zdravili, ki imajo podobne lastnosti kot furazolidon in prokarbazin, lahko sproži hipertenzivne reakcije. Bolniki, ki sočasno dobijo anestezijo s halogeniranimi ogljikovodiki, imajo večje tveganje za pojav aritmij. Sočasna uporaba drugih beta-adrenergičnih ali antiholinergičnih zdravil ima lahko aditiven bronhodilatatoren učinek. Pri bolnikih, ki prejemajo glikozide digitalisa, lahko hipokaliemija poveča nagnjenost k aritmijam. Hipokaliemija je lahko posledica zdravljenja z β_2 agonisti in se lahko okrepi ob sočasnem zdravljenju z derivati ksantina, kortikosteroidi in diuretiki. Medsebojnega delovanja budezonida in formoterola z drugimi zdravili za zdravljenje astme niso opazili. Študije medsebojnega delovanja so izvedli le pri odraslih. **NOSEČNOST IN DOJENJE:** Med nosečnostjo je treba zdravilo Symbicort Turbuhaler uporabiti le, če koristi odtehtajo morebitna tveganja. Uporabljati je treba najmanjši učinkoviti odmerek budezonida, potreben za vzdrževanje ustreznega obvladanja astme. Uporaba zdravila Symbicort Turbuhaler pri doječi ženski pride v poštev le, če je pričakovana korist za mater večja od morebitnega tveganja za otroka. **GLAVNI NEŽELENI UČINKI:** Pogosti: okužbe orofarinksa s kandido, pljučnica (pri bolnikih s KOPB), glavobol, tremor, palpitacije, blago draženje žrela, kašelj, hripavost. Občasni: agresija, psihomotorična hiperaktivnost, anksioznost, motnje spanja, omotica, zamegljen vid, tahikardija, mišični krči, navzea, podplutbe. Redki: zgodnje in zapoznele preobčutljivostne reakcije, npr. eksantem, urtikarija, srbenje, dermatitis, angioedem in anafilaktična reakcija, hipokaliemija, bronhospazem, motnje srčnega ritma, npr. atrijska fibrilacija, supraventrikularna tahikardija, ekstrasistole. **REŽIM IZDAJE ZDRAVILA:** Zdravilo se izdaja le na recept. **IMETNIK DOVOLJENJA ZA PROMET:** AstraZeneca AB, Kvarnbergagatan, SE-151 85 Södertälje, Švedska **ZADNJA REVIZIJA BESEDILA:** julij 2019 (SI-0721) **Pred predpisovanjem, prosimo, preberite celoten povzetek glavnih značilnosti zdravila.** Dodatne informacije so na voljo pri družbi AstraZeneca UK Limited, Podružnica v Sloveniji, Verovškova 55, Ljubljana.

REFERENCE: 1. Povzetek glevnih značilnosti zdravila Symbicort Turbohaler 160 µg/4,5 µgna odmerek prašek za inhaliranje, julij 2019 **2.** Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2020. Dostopano na http://www.ginasthma.org/, maj 2020

BERLIN-CHEMIE MENARINI

RELVAR ELLIPTA

flutikazonfuroat/vilanterol

Stalna 24-urna učinkovitost z eno samo inhalacijo na dan*[1]

*Pomembno povečanje od izhodišča do 12. tedna v povprečnem zaporednem (0-24 ur) uteženem FEV1 s kombinacijo flutikazonfuroat/vilanterol (FF/VI v nadaljevanju) 100/25 µg enkrat dnevno v primerjavi s FF (p < 0.001, primarni cilj); ni bilo pomembne razlike med FF/VI 100 ali 200/25 µg enkrat dnevno (le opisna primerjava).[1] Prospektivna, aktivno kontrolirana, randomizirana, dvojno slepa, stratificirana, multicentrična raziskava vzporednih skupin, faze III, izpeljana v več državah, ki je primerjala učinkovitost FF/VI 100 ali 200/25 µg, enkrat dnevno, v Ellipta vdihovalniku (n = 346 za vsako skupino) s FF 100 µg enkrat dnevno (n = 347) pri bolnikih z zmerno do hudo perzistentno astmo, starosti ≥ 12 let (n = 1.039, randomizacija 1:1:1), v trajanju 12 tednov. Primarni cilj raziskave je bila sprememba od izhodišča do 12. tedna v povprečnem zaporednem (0-24 ur) uteženem FEV1 s FF/VI 100/25 µg enkrat dnevno v primerjavi s FF 100 µg enkrat dnevno.[1]

IGK, inhalacijski glukokortikoid; LABA, dolgodelujoči agonist receptorjev beta2; FEV1, forsirani ekspiracijski volumen v 1. sekundi

1. Bernstein DI et al. J Asthma 2015;52(10):1073–83. 2. **Relvar Ellipta** *povzetek glavnih značilnosti zdravila, datum rev. 12/18.*

Terapevtske indikacije[2]: Astma. Zdravilo **Relvar Ellipta** je indicirano za redno zdravljenje astme pri odraslih in mladostnikih, starih 12 let ali več, za katere je primerna uporaba kombiniranega zdravila (dolgodelujočega agonista adrenergičnih receptorjev beta2 in inhalacijskega kortikosteroida): bolniki, ki bolezni nimajo ustrezno urejene ob uporabi inhalacijskih kortikosteroidov in inhalacijskih kratkodelujočih agonistov adrenergičnih receptorjev beta$_2$ "po potrebi"; bolniki, ki imajo bolezen ustrezno urejeno ob uporabi inhalacijskih kortikosteroidov in dolgodelujočih agonistov adrenergičnih receptorjev beta2. *KOPB* (kronična obstruktivna pljučna bolezen). Zdravilo Relvar Ellipta je indicirano za simptomatsko zdravljenje odraslih s KOPB, ki imajo FEV1 < 70 % predvidenega normalnega (po bronhodilatatorju), z anamnezo poslabšanj kljub rednemu zdravljenju z bronhodilatatorjem.

Relvar Ellipta 92 mikrogramov/22 mikrogramov prašek za inhaliranje, odmerjeni
Relvar Ellipta 184 mikrogramov/22 mikrogramov prašek za inhaliranje, odmerjeni

Sestava: Ena inhalacija zagotavlja oddani odmerek (odmerek, ki pride iz ustnika inhalatorja) 92 µg oziroma 184 µg flutikazonfuroata in 22 µg vilanterola (v obliki trifenatata). To ustreza odmerjenemu odmerku 100 µg oziroma 200 µg flutikazonfuroata, kar ustreza 25 µg vilanterola (v obliki trifenatata). Pomožne snovi: laktoza monohidrat.

Terapevtske indikacije: Astma: Zdravilo Relvar Ellipta je indicirano za redno zdravljenje astme pri odraslih in mladostnikih, starih 12 let ali več, za katere je primerna uporaba kombiniranega zdravila (dolgodelujočega agonista adrenergičnih receptorjev beta, in inhalacijskega kortikosteroida): bolniki, ki bolezni nimajo ustrezno urejene ob uporabi IKS in inhalacijskih kratkodelujočih agonistov adrenergičnih receptorjev beta$_2$ "po potrebi" in bolniki, ki imajo bolezen ustrezno urejeno ob uporabi IKS in dolgodelujočih agonistov adrenergičnih receptorjev beta$_2$. KOPB: Zdravilo Relvar Ellipta je indicirano za simptomatsko zdravljenje odraslih s KOPB, ki imajo FEV$_1$ < 70 % predvidenega normalnega (po bronhodilatatorju), z anamnezo poslabšanj kljub rednemu zdravljenju z bronhodilatatorjem. **Odmerjanje in način uporabe:** Bolniki z astmo morajo dobiti tisto jakost zdravila Relvar Ellipta, ki vsebuje odmerek flutikazonfuroata (FF), ustrezen izrazitosti njihove bolezni. Zdravniki, ki predpisujejo to zdravilo, morajo vedeti, da je pri bolnikih z astmo odmerek 100 µg flutikazonfuroata (FF) enkrat na dan približno enakovreden odmerku 250 µg flutikazonpropionata (FP) dvakrat na dan, odmerek 200 µg FF enkrat na dan pa je približno enakovreden odmerku 500 µg FP dvakrat na dan. ASTMA *Odrasli in mladostniki, stari 12 let ali več:* Za odrasle in mladostnike v starosti 12 let ali več, ki potrebujejo nizek do srednji odmerek IKS v kombinaciji z dolgodelujočim agonistom adrenergičnih receptorjev beta$_2$, pride v poštev začetni odmerek ene inhalacije zdravila Relvar Ellipta 92/22 µg enkrat dnevno. Če bolniki z zdravilom Relvar Ellipta 92/22 µg bolezni nimajo ustrezno urejene, pride v poštev zvišanje odmerka na 184/22 µg; to lahko prinese dodatno izboljšanje urejenosti astme. Zdravnik mora bolnike redno kontrolirati, da ostane jakost uporabljane kombinacije flutikazonfuroat/vilanterol optimalna in se spremeni le po nasvetu zdravnika. Odmerek je treba titrirati do najnižjega odmerka, ki učinkovito obvladuje simptome. Za odrasle bolnike in mladostnike, stare 12 let ali več, ki potrebujejo višji odmerek IKS v kombinaciji z dolgodelujočim agonistom adrenergičnih receptorjev beta$_2$, pride v poštev zdravilo Relvar Ellipta 184/22 µg. Bolnikom se pljučna funkcija po navadi izboljša v 15 minutah po inhaliranju zdravila Relvar Ellipta. Vendar je treba bolnikom povedati, da je za vzdrževanje nadzora nad simptomi astme potrebna redna vsakodnevna uporaba in da morajo zdravilo uporabljati tudi, ko nimajo simptomov. Če se simptomi pojavijo v obdobju med odmerki, mora bolnik za takojšnje olajšanje uporabiti inhalirani kratkodelujoči agonist adrenergičnih receptorjev beta$_2$. *Otroci, mlajši od 12 let:* Varnost in učinkovitost zdravila Relvar Ellipta pri otrocih, mlajših od 12 let, za indikacijo astme še nista ugotovljeni. KOPB *Odrasli, stari 18 let ali več:* Ena inhalacija zdravila Relvar Ellipta 92/22 µg enkrat na dan. Zdravilo Relvar Ellipta 184/22 µg ni indicirano pri bolnikih s KOPB. Ta odmerek v primerjavi z odmerkom 92/22 µg nima dodatnih koristi, obstaja pa lahko večje tveganje za pljučnico in sistemske neželene učinke, povezane s kortikosteroidi.Bolnikom se pljučna funkcija po navadi izboljša v 16 do 17 minutah po inhaliranju zdravila Relvar Ellipta. Zdravilo Relvar Ellipta ni primerno za uporabo v pediatrični populaciji za indikacijo KOPB. *Starejši ljudje (> 65 let), bolniki z okvaro ledvic:* Prilagoditev odmerka v tej populaciji ni potrebna. *Bolniki z okvaro jeter:* Uporaba pri bolnikih z okvaro jeter zahteva previdnost. Bolniki z okvaro jeter imajo lahko večje tveganje za sistemske neželene učinke kortikosteroidov. Za bolnike z zmerno ali hudo okvaro jeter je najvišji odmerek 92/22 µg Za inhalacijsko uporabo. Zdravilo je treba uporabljati vsak dan ob istem času. Dokončna odločitev o uporabi zvečer ali zjutraj mora biti prepuščena presoji zdravnika. Če je zdravilo shranjeno v hladilniku, je treba inhalator vsaj eno uro pred uporabo pustiti zunaj, da se ogreje na sobno temperaturo. **Bolnike je treba poučiti o tem, kako pravilno vzamejo zdravilo.**

Kontraindikacije: Preobčutljivost na učinkovini ali katero koli pomožno snov. **Posebna opozorila in previdnostni ukrepi:** Flutikazonfuroat/vilanterol se ne sme uporabljati za zdravljenje simptomov akutne astme ali akutnega poslabšanja KOPB; za to je potreben kratkodelujoč bronhodilatator. Če bolnikova uporaba kratkodelujočih bronhodilatatorjev za olajšanje narašča, to kaže na slabšanje urejenosti bolezni in bolnikovo stanje je treba znova oceniti. Bolniki zdravljenja astme ali KOPB s flutikazonfuroatom/vilanterolom ne smejo končati brez zdravniškega nadzora, ker se lahko simptomi po prenehanju ponovijo.Med zdravljenjem s flutikazonfuroatom/vilanterolom se lahko pojavijo z astmo povezani neželeni učinki in poslabšanja. Bolnikom je treba naročiti, naj v primeru, da simptomi astme po uvedbi zdravila Relvar Ellipta niso obvladani ali se poslabšajo, zdravljenje nadaljujejo, a naj se hkrati posvetujejo z zdravnikom. Pojavi se lahko paradoksni bronhospazem s takojšnjim pojačanjem piskajočega dihanja po uporabi zdravila. Takšno stanje je treba nemudoma zdraviti s hitrodelujočim inhalacijskim bronhodilatatorjem. Uporabo zdravila Relvar Ellipta je treba takoj prekiniti, bolnika pregledati in uvesti drugo zdravljenje, če je potrebno. Med uporabo simpatikomimetičnih zdravil, vključno z zdravilom Relvar Ellipta, se lahko pojavijo kardiovaskularni učinki, npr. motnje srčnega ritma, kakršne so supraventrikularna tahikardija in ekstrasistole. Bolniki s hudo kardiovaskularno boleznijo ali motnjami srčnega ritma, hipertiroidizmom, nekorigirano hipokaliemijo ali pri bolnikih, ki so nagnjeni k nizkim vrednostim kalija v serumu, flutikazonfuroat /vilanterol uporabljati previdno. Pri bolnikih z zmerno do hudo okvaro jeter je treba uporabiti odmerek 92/22 µg in bolnike je treba kontrolirati glede sistemskih neželenih učinkov, povezanih s kortikosteroidi. Med uporabo vseh IKS se lahko pojavijo sistemski učinki, zlasti med dolgotrajno uporabo velikih odmerkov. Ti učinki so veliko manj verjetni kot med uporabo peroralnih kortikosteroidov. Med možnimi sistemskimi učinki so Cushingov sindrom, Cushingoidne značilnosti, supresija nadledvičnih žlez, zmanjšanje mineralne gostote kosti, upočasnitev rasti pri otrocih in mladostnikih, katarakta in glavkom ter, redkeje, različni psihološki ali vedenjski učinki, med njimi psihomotorična hiperaktivnost, motnje spanja, anksioznost, depresija ali agresivnost (zlasti pri otrocih). Flutikazonfuroat/vilanterol je treba uporabljati previdno pri bolnikih s pljučno tuberkulozo in bolnikih s kroničnimi ali nezdravljenimi okužbami.Pri sistemski in topični uporabi kortikosteroidov lahko poročajo o motnjah vida. Če se pri bolniku pojavijo simptomi, kot so zamegljen vid ali druge motnje vida, ga je potrebno upoštevati za napotitev k oftalmologu zaradi ovrednotenja možnih vzrokov, ki lahko vključujejo katarakto, glavkom ali redke bolezni, kot je centralna serozna horioretinopatija, o katerih so poročali po sistemski in topični uporabi kortikosteroidov. Opisani so primeri zvišane koncentracije glukoze v krvi pri sladkornih bolnikih; to morate upoštevati, če zdravilo predpišete bolnikom z anamnezo sladkorne bolezni. Pri bolnikih s KOPB, ki so prejemali IKS, so opažali večjo pojavnost pljučnice, tudi pljučnice, ki je zahtevala sprejem v bolnišnico. Obstaja- jo določeni dokazi, da se tveganje za pljučnico povečuje s povečevanjem odmerka steroida, vendar to ni bilo dokončno dokazano v vseh študijah. Ni dokončnih kliničnih dokazov, da se stopnja tveganja za pljučnico znotraj skupine IKS zdravil razlikuje. Zdravniki morajo biti pri bolnikih s KOPB pozorni na morebiten pojav pljučnice, kajti klinične značilnosti takšne okužbe se prekrivajo s simptomi poslabšanj KOPB. Med dejavniki tveganja za pljučnico pri bolnikih s KOPB so trenutno kajenje, višja starost, nizek indeks telesne mase (ITM) in huda KOPB. Z višjim odmerkom je bila incidenca pljučnice pri bolnikih z astmo pogosta. Incidenca pljučnice je bila številsko večja pri bolnikih z astmo, ki so jemali flutikazonfuroat/vilanterol 184/22 µg, kot pri tistih, ki so jemali flutikazonfuroat / vilanterol 92/22 µg ali placebo. Bolniki z redko dedno intoleranco za galaktozo, laponsko obliko zmanjšane aktivnosti laktaze ali malabsorpcijo glukoze/galaktoze ne smejo jemati tega zdravila. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Klinično pomembna medsebojna delovanja z zdravili zaradi flutikazonfuroata/vilanterola v kliničnih odmerkih niso verjetna, ker je koncentracija v plazmi po inhaliranju nizka.Antagonisti adrenergičnih receptorjev beta$_2$ lahko oslabijo ali antagonizirajo učinek agonistov adrenergičnih receptorjev beta$_2$. Sočasni uporabi z antagonisti adrenergičnih receptorjev beta$_2$ (tako neselektivnih kot selektivnih) se je treba izogibati, razen če ostajajo nujni razlogi za njihovo uporabo.Flutikazonfuroat in vilanterol se oba hitro očistita z obsežno presnovo prvega prehoda z jetrnim encimom CYP3A4. Previdnost je potrebna med sočasno uporabo z močnimi zaviralci CYP3A4 (npr. ketokonazol, ritonavir, zdravila, ki vsebujejo kobicistat), ker obstaja možnost večje sistemske izpostavljenosti flutikazonfuroatu in vilanterolu. Sočasni uporabi se je treba izogniti, razen če koristodtehta povečano tveganje za pojav sistemskih neželenih učinkov kortikosteroidov; v tem primeru je treba bolnike nadzorovati glede sistemskih neželenih učinkov kortikosteroidov. Flutikazonfuroat in vilanterol sta oba substrata P-gp. Sočasna uporaba drugih simpatikomimetičnih zdravil (samih ali kot sestavin kombiniranega zdravljenja) lahko stopnjuje neželene učinke flutikazonfuroata/vilanterola. Zdravila Relvar Ellipta se ne sme uporabljati skupaj z drugimi dolgodelujočimi agonisti adrenergičnih receptorjev beta$_2$ ali z zdravili, ki vsebujejo dolgodelujoče agoniste adrenergičnih receptorjev beta$_2$. **Nosečnost:** Uporaba flutikazonfuroata /vilantérola pri nosečnicah pride v poštev le, če je pričakovana korist za mater večja od možnega tveganja za plod. **Dojenje:** Odločiti se je treba bodisi za prenehanje dojenja bodisi za prenehanje zdravljenja s flutikazonfuroat/vilanterolom, upoštevaje koristi dojenja za otroka in koristi zdravljenja za žensko. **Plodnost:** Podatkov o plodnosti pri človeku ni. Študije na živalih niso pokazale, da bi flutikazonfuroat/vilanterol vplival na plodnost. **Vpliv na sposobnost vožnje in upravljanja s stroji:** Flutikazonfuroat in vilanterol nimata vpliva ali imata zanemarljiv vpliv na sposobnost vožnje in upravljanja strojev. **Neželeni učinki:** Zelo pogosti: glavobol, nazofaringitis. Pogosti: pljučnica, okužba zgornjih dihal, bronhitis, gripa, kandidoza ust in žrela, orofaringealne bolečine, sinuzitis, vnetje žrela, rinitis, kašelj, disfonija, bolečine v trebuhu, artralgija, bolečine v hrbtu, zlomi, mišični krči, pireksija. Občasni: hiperglikemija, zamegljen vid, ekstrasistole. Ostali neželeni učinki so navedeni v Povzetku glavnih značilnosti zdravila. **Vrsta in vsebina ovojnine:** Škatla, ki vsebuje 1 inhalator s 30 odmerki. Uporabite v 6 tednih od odprtja vrečke. **Imetnik dovoljenja za promet:** GlaxoSmithKline (Ireland) Limited, Irska **Način in režim izdaje:** Predpisovanje in izdaja zdravila je le na recept. **Datum zadnje revizije besedila:** 12/2018 **Dodatne informacije so na voljo pri:**

BERLIN-CHEMIE / A. Menarini Distribution Ljubljana d.o.o., Dolenjska cesta 242c, 1000 Ljubljana, telefon 01 300 2160, faks 01 300 2169; e-mail: slovenia@berlin-chemie.com

Datum priprave informacije junij 2019. Te informacije o zdravilu na recept so namenjene izključno strokovni javnosti. Pred predpisovanjem, prosimo, preberite celoten povzetek glavnih značilnosti imetnika dovoljenja za promet z zdravilom. Berlin-Chemie/A. Menarini Distribution Ljubljana d.o.o. ne priporoča uporabe tega zdravila drugače kot je navedeno v povzetku glavnih značilnosti zdravila.

MOČ DVEH

2 bronhodilatatorja[1]

2 krat dnevno[1]

2 koraka za inhalacijo[1]

Brimica® Genuair® je indicirana za vzdrževalno bronhodilatacijsko zdravljenje za lajšanje simptomov pri odraslih bolnikih s kronično obstruktivno pljučno boleznijo (KOPB).[1]

SI-BRI-04-2019_ad one sided, datum priprave: oktober 2019, datum veljavnosti: oktober 2021

Literatura: 1 Brimica® Genuair® Povzetek glavnih značilnosti zdravila, 08/2019

Samo za strokovno javnost.

▼Za to zdravilo se izvaja dodatno spremljanje varnosti. Tako bodo hitreje na voljo nove informacije o njegovi varnosti. Zdravstvene delavce naprošamo, da poročajo o katerem koli domnevnem neželenem učinku zdravila. Glejte poglavje 4.8, kako poročati o neželenih učinkih.

Brimica Genuair 340 mikrogramov/12 mikrogramov, prašek za inhaliranje

Sestava: En dostavljen odmerek (odmerek, ki pride iz ustnika) vsebuje 396 mikrogramov aklidinijevega bromida (kar ustreza 340 mikrogramom aklidinija) in 11,8 mikrogramov formoterolijevega fumarat dihidrata. To ustreza izmerjenemu odmerku 400 mikrogramov aklidinijevega bromida (kar ustreza 343 mikrogramov aklidinija) in izmerjenemu odmerku 12 mikrogramov formoterolijevega fumarat dihidrata. En dostavljen odmerek vsebuje približno 11 mg laktoze (v obliki monohidrata). **Terapevtske indikacije:** Zdravilo Brimica Genuair je indicirano za vzdrževalno bronhodilatacijsko zdravljenje za lajšanje simptomov pri odraslih bolnikih s kronično obstruktivno pljučno boleznijo (KOPB). **Odmerjanje in način uporabe:** Priporočen odmerek je en vdih dvakrat na dan. Za starejše bolnike, za bolnike z okvaro ledvic ali jeter ni potrebno prilagajanje odmerka. Pediatrična populacija: Ni primerno za uporabo pri otrocih in mladostnikih za indikacijo KOPB. Za inhaliranje. Bolnike je treba poučiti o tem, kako pravilno vzamejo zdravilo, ker lahko inhalator Genuair deluje drugače od inhalatorjev, ki so jih bolniki že prej uporabljali. Pomembno je bolnike poučiti, da natančno preberejo navodila za uporabo v Navodilu za uporabo. Pred prvo uporabo je treba zapečateno vrečko pretrgati in jo tako odpreti ter iz nje vzeti inhalator. Vrečko in sušilno sredstvo je treba zavreči. **Kontraindikacije:** Preobčutljivost na učinkovini ali katero koli pomožno snov. **Posebna opozorila in previdnostni ukrepi:** Astma: Zdravilo ni namenjeno uporabi pri astmi; klinične študije z zdravilom Brimica Genuair pri astmi niso bile izvedene. Paradoksni bronhospazem: V kliničnih študijah z zdravilom Brimica Genuair v priporočenem odmerku niso opazili paradoksnega bronhospazma. Paradoksni bronhospazem pa so opazili pri drugih vrstah inhalacijskih terapij. Če pride do tega, je treba zdravljenje z zdravilom prekiniti in razmisliti o drugačnem zdravljenju. Zdravilo ni indicirano za zdravljenje akutnih epizod bronhospazma. Kardiovaskularni učinki: Zdravilo morate pri bolnikih, ki so imeli v zadnjih 6 mesecih miokardialni infarkt, nestabilno angino pektoris, na novo diagnosticirano aritmijo v zadnjih 3 mesecih, interval QTc (metoda po Bazettu) nad 470 ms ali so bili v zadnjih 12 mesecih hospitalizirani zaradi odpovedi srca funkcijskega razreda III in IV po razvrstitvi NYHA, uporabljati previdno. Agonisti β_2-adrenergičnih receptorjev lahko pri nekaterih bolnikih zvišajo srčni utrip in krvni tlak, povzročijo spremembe v elektrokardiogramu (EKG). Agoniste β_2-adrenergičnih receptorjev z dolgotrajnim delovanjem je treba uporabljati previdno pri bolnikih z ahamnezo podaljšanja intervala QTc ali znanim podaljšanjem tega intervala in pri bolnikih, ki se zdravijo z zdravili, ki vplivajo na interval QTc. Sistemski učinki: Zdravilo je treba pri bolnikih s hudimi srčnožilnimi boleznimi, konvulzivnimi motnjami, tirotoksikozo in feokromocitomom uporabljati previdno. Pri visokih odmerkih agonistov β_2-adrenergičnih receptorjev se lahko pojavijo presnovni učinki hiperglikemije in hipokaliemije. Antiholinergični učinek: Suha usta, učinek, ki opažajo pri zdravljenju z antiholinergiki, so lahko dolgoročno povezana z zobnim kariesom. Zaradi njegovega antiholinergičnega delovanja je treba zdravilo Brimica Genuair uporabljati previdno pri bolnikih s simptomatično hiperplazijo prostate, zastajanjem urina ali glavkomom zaprtega zakotja. Vsebnost laktoze: bolniki z redko dedno intoleranco na galaktozo, odsotnostjo encima laktaze ali malabsorpcijo glukoze/galaktoze, ne smejo jemati tega zdravila. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Sočasno dajanje zdravila Brimica Genuair z drugimi zdravili, ki vsebujejo antiholinergike in/ali dolgo delujoče agoniste β_2-adrenergičnih receptorjev, ni bilo raziskano, zato ni priporočeno. Hipokaliemično zdravljenje: Sočasno hipokaliemično zdravljenje z metilksantinskimi derivati, steroidi ali diuretiki, ki ne ohranjajo kalija, lahko stopnjuje možni hipokaliemični učinek agonistov β_2-adrenergičnih receptorjev, zato je pri sočasni uporabi potrebna previdnost. Zaviralci ß-adrenergičnih receptorjev: Zdravila, ki vsebujejo zaviralce ß-adrenergičnih receptorjev, lahko oslabijo ali antagonizirajo učinek agonistov β_2-adrenergičnih receptorjev. Druga zdravila: Zdravilo Brimica Genuair je treba pri bolnikih, ki prejemajo zdravila, ki dokazano podaljšujejo interval QTc, kot so zaviralci MAO, tricikličnimi antidepresivi, antihistaminiki ali makrolidi, uporabljati previdno zaradi njihove možne okrepitve delovanja formoterola. **Nosečnost:** Podatkov o uporabi zdravila Brimica Genuair pri nosečnicah ni. Zdravilo Brimica Genuair se lahko uporablja med nosečnostjo samo, če se pričakuje, da koristi odtehtajo morebitna tveganja. Dojenje: Ni znano, ali se aklidinij (in/ali njegovi presnovki) ali formoterol izloča v materino mleko. Študije na podganah so pokazale izločanje majhne količine aklidinija (in/ali presnovkov) in formoterola v materino mleko, zato je treba o nadaljevanju zdravljenja z zdravilom Brimica Genuair pri doječih materah razmišljati samo, če se pričakuje, da koristi za mater odtehtajo morebitna tveganja za novorojenca. Plodnost: Ni verjetno, da bi dajanje priporočenih odmerkov Brimica vplivalo na plodnost pri ljudeh. **Vpliv na sposobnost vožnje in upravljanja s stroji:** Zdravilo Brimica Genuair nima vpliva ali ima zanemarljiv vpliv na sposobnost vožnje in upravljanja s stroji. Pojav zamegljenega vida ali omotice lahko vpliva na sposobnost vožnje ali upravljanja s stroji. **Neželeni učinki:** Pogosti: nazofaringitis, okužba sečil, sinusitis, zobni absces, nespečnost, tesnoba, glavobol, omotica, tresavica, kašelj, diareja, navzea, suha usta, mialgija, mišični krči, zvišana vrednost kreatin fosfokinaze v krvi. Ostali neželeni učinki so navedeni v Povzetku glavnih značilnosti zdravila. **Vrsta in vsebina ovojnine:** Škatla, ki vsebuje 1 inhalator s 60 odmerki. Uporabite v 60 dneh od odprtja vrečke. **Imetnik dovoljenja za promet:** AstraZeneca AB, SE-151 85 Södertälje, Švedska **Način in režim izdaje:** Predpisovanje in izdaja zdravila je le na recept. **Datum zadnje revizije besedila:** 08/2019

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MANJ INHALACIJ. ZA VEČ VDIHA.[1*]

Edina KOPB trojna terapija v eni sami inhalaciji dvnono.[2**,†]

Zdravilo Trelegy Ellipta je indicirano za vzdrževalno zdravljenje odraslih bolnikov z zmerno do hudo kronično obstruktivno pljučno boleznijo (KOPB), ki niso zadostno zdravljeni s kombinacijo inhalacijskega kortikosteroida in dolgodelujočega agonista adrenergičnih receptorjev ß2 ali s kombinacijo dolgodelujočega agonista adrenergičnih receptorjev ß2 in dolgodelujočega antagonista muskarinskih receptorjev.[2,†]

TRELEGY ELLIPTA

flutikazonfuroat/umeklidinij/vilanterol

*Manj inhalacij: Enkrat dnevno odmerjanje zdravila *Trelegy Ellipta* (UMEK/VIL/FF 74.1/ 25/ 100 µg) v primerjavi z dvakrat dnevnim odmerjanjem kombinacije FOR/BUD 12/400 µg.[1] Za več vdiha: Pomembno povečanje od izhodišča do 24. tedna v najmanjšem FEV_1 z zdravilom *Trelegy Ellipta* enkrat dnevno v primerjavi s kombinacijo FOR/BUD 12/400 µg dvakrat dnevno.[1]

Prospektivna, aktivno nadzorovana, randomizirana, dvojno slepa, z dvojnim placebom, multicentrična klinična raziskava vzporednih skupin, faze III, ki je primerjala učinkovitost in varnost zdravila *Trelegy Ellipta* enkrat dnevno plus placebo dvakrat dnevno preko vdihovalnika Turbuhaler (n = 911) s kombinacijo FOR/BUD 12/400 µg dvakrat dnevno preko vdihovalnika Turbuhaler plus placebo enkrat dnevno preko vdihovalnika Ellipta (n = 899), pri bolnikih s KOPB, starosti ≥ 40 let, rezultatom testa COPD Assessment Test (CAT) ≥ 10 in FEV_1 <50% ali FEV_1 ≥50% do <80% plus ≥2 zmerni poslabšanji KOPB v preteklem letu ali ≥1 hudo poslabšanje KOPB v preteklem letu, v trajanju 24 tednov (n = 1,810). Podskupina prvih 430 bolnikov vključenih v raziskavo, ki so se strinjali s podaljšanim zdravljenjem (n = 430) je bila zdravljenja z UMEK/VIL/FF 74.2/25/100 µg enkrat dnevno preko vdihovalnika Ellipta plus placebo dvakrat dnevno preko vdihovalnika Turbuhaler (n = 210) ali s kombinacijo FOR/BUD 12/400 µg dvakrat dnevno preko vdihovalnika Turbuhaler plus placebo enkrat dnevno preko vdihovalnika Ellipta (n = 220), v trajanju 52 tednov. Ko-primarna cilja raziskave sta bila sprememba od izhodišča do 24. tedna v najmanjšem FEV_1 in skupni rezultat vprašalnika SGRQ.[1]

** Ena inhalacija zagotavlja oddani odmerek (odmerek, ki zapusti ustnik) 92 mikrogramov flutikazonfuroata, 65 mikrogramov umeklidinijevega bromida (to ustreza 55 mikrogramom umeklidinija) in 22 mikrogramov vilanterola (kot trifenatata). To ustreza odmerjenemu odmerku 100 mikrogramov flutikazonfuroata, 74,2 mikrograma umeklidinijevega bromida, kar je enakovredno 62,5 mikrograma umeklidinija in 25 mikrogramov vilanterola (kot trifenatata).[2]

†*Trelegy Ellipta* je kombinacija inhalacijskega glukokortikoida, dolgodelujočega agonista adrenergičnih receptorjev beta2 in dolgodelujočega antagonista muskarinskih receptorjev (IGK/LABA/LAMA). Priporočeni in največji odmerek je ena inhalacija zdravila *Trelegy Ellipta* enkrat na dan.[2]

FEV_1, forsirani ekpiracijski volumen v 1 sekundi; UMEK, umeklidinijev bromid; VIL, vilanterol trifenatat; FF, flutikazonfuroat; BUD, budezonid; FOR, formoterol; SGRQ, vprašalnik St. George's Respiratory Questionnaire.

1. Lipson DA et al. Am J Respir Crit Care Med.2017;196:438-446.
2. Povzetek glavnih značilnosti zdravila *Trelegy Ellipta*, datum rev. besedila 09/2020.

Te informacije o zdravilu na recept so namenjene izključno strokovni javnosti. Pred predpisovanjem, prosimo, preberite celoten povzetek glavnih značilnosti imetnika dovoljenja za promet z zdravilom. Berlin Chemie /A. Menarini Distribution Ljubljana d.o.o. ne priporoča uporabe tega zdravila drugače kot je navedeno v povzetku glavnih značilnosti zdravila.

Datum priprave informacije oktober 2020.

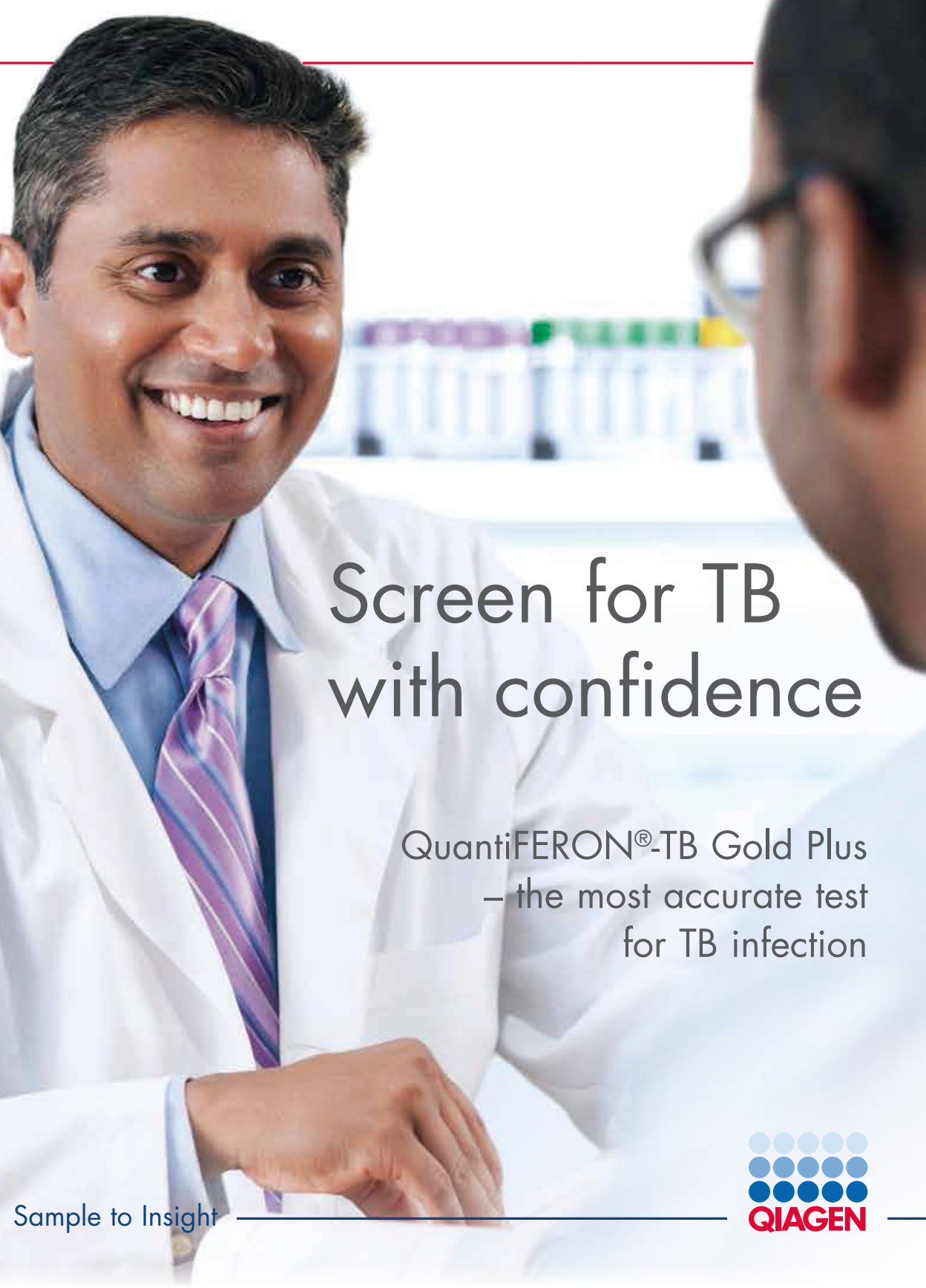
SI-TRE-08-2020_digital

▼Za to zdravilo se izvaja dodatno spremljanje varnosti. Tako bodo hitreje na voljo nove informacije o njegovi varnosti. Zdravstvene delavce naprošamo, da poročajo o katerem koli domnevnem neželenem učinku zdravila. Glejte poglavje 4.8, kako poročati o neželenih učinkih.

Trelegy Ellipta 92 mikrogramov/ 55 mikrogramov/22 mikrogramov prašek za inhaliranje, odmerjeni **Sestava:** Ena inhalacija zagotavlja oddani odmerek (odmerek, ki zapusti ustnik) 92 mikrogramov flutikazonfuroata, 65 mikrogramov umeklidinijevega bromida (to ustreza 55 mikrogramom umeklidinija) in 22 mikrogramov vilanterola (kot trifenatata). To ustreza odmerjenemu odmerku 100 mikrogramov flutikazonfuroata, 74,2 mikrograma umeklidinijevega bromida, kar je enakovredno 62,5 mikrograma umeklidinija in 25 mikrogramov vilanterola (kot trifenatata). Vsak dostavljen odmerek vsebuje približno 25 mg laktoze. **Terapevtske indikacije:** Zdravilo Trelegy Ellipta je indicirano za vzdrževalno zdravljenje odraslih bolnikov z zmerno do hudo KOPB, ki niso zadostno zdravljeni s kombinacijo inhalacijskega kortikosteroida in dolgodelujočega agonista adrenergičnih receptorjev ß2 ali s kombinacijo dolgodelujočega agonista adrenergičnih receptorjev beta2 in dolgodelujočega antagonista muskarinskih receptorjev. **Odmerjanje in način uporabe:** Priporočeni in največji odmerek je ena inhalacija zdravila Trelegy Ellipta 92/55/22 mikrogramov enkrat na dan, vsak dan ob istem času. Bolnikom, starejšim od 65 let, bolnikom z okvaro ledvic odmerka ni treba prilagoditi. Bolnikom z blago, zmerno ali hudo okvaro jeter odmerka ni treba prilagoditi. Pri bolnikih z zmerno do hudo okvaro jeter je treba zdravilo Trelegy Ellipta uporabljati previdno. V pediatrični populaciji (mlajši od 18 let) zdravilo Trelegy Ellipta nima relevantne uporabe za indikacijo KOPB. Za inhalacijsko uporabo. Po inhalaciji morajo bolniki splakniti usta z vodo, vode ne smejo pogoltniti. Bolnike je treba poučiti o tem, kako pravilno vzamejo zdravilo. **Kontraindikacije:** Preobčutljivost na učinkovini ali katero koli pomožno snov v zdravilu. **Posebna opozorila in previdnostni ukrepi:** Zdravila Trelegy Ellipta se ne sme uporabljati pri bolnikih z astmo, ker v tej populaciji bolnikov ni raziskano. Ni kliničnih podatkov, ki bi potrjevali uporabo zdravila Trelegy Ellipta za zdravljenje akutnega bronhospazma ali akutnega poslabšanja KOPB (tj, za rešilno zdravljenje). Naračanje uporabe kratkodelujočih bronhodilatatorjev za obajšanje simptomov je lahko znak, da se urejenost bolezni slabša. Če se KOPB med zdravljenjem z zdravilom Trelegy Ellipta poslabša, je treba znova oceniti tako bolnika kot shemo zdravljenja KOPB, Bolniki ne smejo končati zdravljenja z zdravilom Trelegy Ellipta brez zdravniškega nadzora, ker se lahko simptomi po prenehanju zdravljenja ponovijo. Uporaba flutikazonfuroata/umeklidinija/vilanterola (FLU/UME/VIL) lahko povzroči paradoksni bronhospazem – pojav piskajočega dihanja in kratke sape takoj po uporabi zdravila – ki je lahko smrtno nevaren. Če se pojavi paradoksni bronhospazem, je treba zdravljenje z zdravilom Trelegy Ellipta nemudoma prenehati. Bolnika je treba oceniti in uvesti drugo zdravljenje, če je potrebno. Po uporabi antagonistov muskarinskih receptorjev in simpatikomimetikov, vključno z UME in VIL, se lahko pojavijo KVSI učinki, npr. motnje srčnega ritma, kot sta atrijska fibrilacija in tahikardija. Zato je treba zdravilo Trelegy Ellipta previdno uporabljati pri bolnikih, ki imajo kakšno nestabilno ali življenjsko ogrožujočo kardiovaskularno bolezen. Bolnike z zmerno do hudo okvaro jeter, ki prejemajo zdravilo Trelegy Ellipta, je treba nadzorovati glede sistemskih neželenih učinkov, povezanih s kortikosteroidi. Med uporabo vseh inhalacijskih kortikosteroidov se lahko pojavijo sistemski učinki, zlasti med dolgotrajno uporabo velikih odmerkov. Ti učinki so veliko manj verjetni kot med uporabo peroralnih kortikosteroidov. Pri sistemski in topični uporabi kortikosteroidov lahko poročajo o motnjah vida. Če se pri bolniku pojavijo simptomi, kot so zamegljen vid ali druge motnje vida, ga je potrebno upoštevati za napotitev k oftalmologu zaradi ovrednotenja možnih vzrokov, ki lahko vključujejo katarakto, glavkom ali redke bolezni, kot je centralna serozna horioretinopatija, o katerih so poročali po sistemski in topični uporabi kortikosteroidov, Zdravilo Trelegy Ellipta je treba uporabljati previdno pri bolnikih s konvulzivnimi motnjami ali tirotoksikozo in pri bolnikih, ki so nenavadno odzivni na agoniste adrenergičnih receptorjev beta2. Zdravilo Trelegy Ellipta je treba uporabljati previdno pri bolnikih s pljučno tuberkulozo in pri bolnikih s kroničnimi ali nezdravljenimi okužbami. Zdravilo Trelegy Ellipta je treba uporabljati previdno pri bolnikih z glavkomom z ozkim zakotjem ali retenco urina. Bolnike je treba seznaniti z znaki in simptomi akutnega glavkoma z ozkim zakotjem; naročiti jim je treba, da morajo v primeru takšnih znakov ali simptomov nemudoma prenehati uporabljati zdravilo Trelegy Ellipta in se posvetovati z zdravnikom. Pri bolnikih s KOPB, ki so prejemali inhalacijske kortikosteroide, so opažali večjo pojavnost pljučnice, tudi pljučnice, ki je zahtevala sprejem v bolnišnico. Obstajajo določeni dokazi, da se tveganje za pljučnico povečuje s povečevanjem odmerka steroida, vendar to ni bilo dokončno dokazano v vseh študijah. Zdravniki morajo biti pri bolnikih s KOPB pozorni na morebiten pojav pljučnice, kajti klinične značilnosti takšne okužbe se prekrivajo s simptomi poslabšanj KOPB. Med dejavniki tveganja za pljučnico pri bolnikih s KOPB so trenutno kajenje, višja starost, nizek indeks telesne mase (ITM) in huda KOPB, Agonisti adrenergičnih receptorjev beta2 lahko nekaterim bolnikom povzročijo pomembno hipokaliemijo s posledičnimi neželenimi KVS učinki, Zničanje kalija v serumu je po navadi prehodno in ne zahteva dodajanja, Previdnost je potrebna, če se zdravilo Trelegy Ellipta uporablja z drugimi zdravili, ki lahko prav tako povzročijo hipokaliemijo, Agonisti adrenergičnih receptorjev beta2 lahko nekaterim bolnikom povzročijo prehodno hiperglikemijo. Po uvedbi zdravljenja z zdravilom Trelegy Ellipta je treba sladkornim bolnikom natančneje kontrolirati glukozo v plazmi, Zdravilo vsebuje laktozo, Bolniki z redko dedno intoleranco za galaktozo, laponsko obliko zmanjšane aktivnosti laktaze ali malabsorpcijo glukoze/galaktoze ne smejo jemati tega zdravila. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Klinično pomembna medsebojna delovanja z zdravili zaradi FLU/UME/VIL v kliničnih odmerkih niso verjetna, ker je koncentracija v plazmi po inhaliranju nizka. Antagonisti adrenergičnih receptorjev beta2 lahko oslabijo ali antagonizirajo učinek agonistov adrenergičnih receptorjev beta2, kakršen je VIL. Če obstaja potreba po uporabi antagonistov beta, je treba razmisliti o uporabi kardioselektivnih antagonistih beta, vendar pa je med sočasno uporabo potrebna previdnost; to velja tako za selektivne kot za kardioselektivne antagoniste beta. Previdnost je potrebna med sočasno uporabo z močnimi zaviralci CYP3A4 (npr. ketokonazol, ritonavir, zdravila, ki vsebujejo kobicistat), ker obstaja možnost večje sistemske izpostavljenosti flutikazonfuroatu in vilanterolu, to pa lahko poveča možnost neželenih učinkov. Sočasni uporabi se je treba izogniti, razen če korist odtehta povečano tveganje za pojav sistemskih neželenih učinkov kortikosteroidov; v tem primeru je treba bolnike nadzorovati glede sistemskih neželenih učinkov kortikosteroidov. Sočasna uporaba zdravila Trelegy Ellipta z drugimi dolgodelujočimi muskarinskimi antagonisti ali dolgodelujočimi agonisti adrenergičnih receptorjev beta2 ni raziskana in ni priporočljiva, ker lahko poveča neželene učinke. Sočasno hipokaliemično zdravljenje z metiksantinskimi derivati, steroidi ali diuretiki, ki ne ohranjajo kalija, lahko stopnjuje možni hipokaliemični učinek agonistov adrenergičnih receptorjev ß2, zato je potrebna previdnost. **Nosečnost:** Uporaba zdravila Trelegy Ellipta pri nosečnicah pride v poštev le, če pričakovana korist za mater upravičuje morebitno tveganje za plod. **Dojenje:** Odločiti se je treba bodisi za prenehanje dojenja bodisi za prenehanje zdravljenja z zdravilom Trelegy Ellipta, upoštevaje koristi dojenja za otroka in koristi zdravljenja za žensko. **Plodnost:** Podatkov o vplivu kombinacije flutikazonfuroat/umeklidinij/vilanterol na plodnost pri človeku ni. **Vpliv na sposobnost vožnje in upravljanja s stroji:** Kombinacija flutikazonfuroat/umeklidinij/vilanterol nima vpliva ali ima zanemarljiv vpliv na sposobnost vožnje in upravljanja s stroji. **Neželeni učinki:** Pogosti: pljučnica, okužba zgornjih dihal, bronhitis, faringitis, rinitis, sinuzitis, gripa, nazofaringitis, kandidoza ust in žrela, okužba sečil, glavobol, kašelj, orofaringealna bolečina, zaprtost, artralgija, bolečina v hrbtu. Občasni: virusna okužba dihal, supraventrikularna tahikardija, tahikardija, atrijska fibrilacija, disfonija, suha usta, zlomi. Ostali neželeni učinki so navedeni v Povzetku glavnih značilnosti zdravila. **Vrsta in vsebina ovojnine:** Škatla, ki vsebuje 1 inhalator s 30 odmerki. Uporabite v 6 tednih od odprtja vrečke. **Imetnik dovoljenja za promet:** GlaxoSmithKline Trading Services Limited. **Irska Način in režim izdaje:** Predpisovanje in izdaja zdravila je le na recept, Datum zadnje revizije besedila: 09/2020. Dodatne informacije so na voljo pri:

BERLIN-CHEMIE / A. Menarini Distribution Ljubljana d.o.o., Dolenjska cesta 242c, 1000 Ljubljana, telefon 01 300 2160, faks 01 300 2169; e-mail: slovenia@berlin-chemie.com

BERLIN-CHEMIE MENARINI



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QIAGEN

Čas je ključnega pomena pri diagnozi IPF-a*[1-3]

HITREJE POSTAVITE DIAGNOZO, VEČJI DOBROBIT BO OPAZIL VAŠ BOLNIK.[2-4]

IPF je neusmiljeno napredujoča in izčrpavajoča bolezen, ki jemlje bolnikom njihov dih in s tem njihovo neodvisnost.[3,5-8]

Diagnoza je kompleksen proces in njena upočasnitev lahko bolniku skrajša življenje.[1-3]

Da bi dobili zgodnjo in natančno diagnozo, smernice podpirajo proaktiven in sodelovalni pristop s strani specialistov multidisciplinarnega tima.[3,8-11]

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* IPF= idiopatska pljučna fibroza

PC-SL-100162 Samo za strokovno javnost. Datum priprave informacije: januar 2020

V kolikor imate medicinsko vprašanje v povezavi z zdravilom podjetja Boehringer Ingelheim, Podružnica Ljubljana, Vas prosimo da pokličete na telefonsko številko 01/5864-000 ali pošljete vaše vprašanje na elektronski naslov: medinfo@boehringer-ingelheim.com.

UKREPAJMO

IPF NE ČAKA

Boehringer Ingelheim

Boehringer Ingelheim RCV,
Podružnica Ljubljana, Šlandrova 4b, 1231 Ljubljana Črnuče

Pljučni bolnik in koronavirus
Na kaj posebej paziti?

Bolniki s pljučnimi boleznimi sodite v bolj tvegano skupino za resnejše zaplete, zato še bolj dosledno upoštevajte vse nasvete NIJZ.

Samoizolacija in dobra higiena rok sta zato za vas izredno pomembni.

Izogibajte se vsem nenujnim stikom z drugimi ljudmi. Dobro razmislite tudi o nujnosti stikov z bližnjimi, predvsem najmlajšimi, saj majhni otroci še niso sposobni upoštevanja zaščitnih ukrepov in so lahko prenašalci virusa.

Redno zračite prostore!

Poskrbite za raznovrstno prehrano z dovolj sadja in zelenjave.

Pijte dovolj toplih napitkov. To vam vlaži dihalne poti in redči sluz, kar zmanjša možnost okužb.

Za obisk trgovine ali lekarne prosite svoje bližnje, ki so mlajši in zdravi. Naredite spisek stvari, ki vam zadostujejo vsaj za nekaj dni.

Sprehod v naravi je zelo priporočljiv. (Seveda pa upoštevajte trenutne nasvete vlade in NIJZ.) Izogibajte se le močno obljudenih poti. Ohranite razdaljo nekaj metrov do vseh, ki jih srečate.

Poskrbite, da ohranite telesno kondicijo!
Tudi doma se lahko dobro razgibate. Nekaj predlogov:

- **Uporabite sobno kolo.**
- **Med sedenjem nekajkrat vstanite in sedite nazaj.**
- **Izvajajate dihalne in raztezne vaje.**
- **Za ohranjanje mišične mase rok, dvigujte uteži, ki jih lahko zamenjate s polnimi pločevinkami ali plastenkami.**

Če kadite, je zdaj morda pravi čas, da zmanjšate porabo cigaret ali popolnoma prenehate s kajenjem.

Redno jemljite inhalacijska zdravila.

Prepričajte se, da vdihovalnik pravilno uporabljate.
V pomoč so vam lahko tudi spletne strani:
www.vdihovalniki.si
www.klinika-golnik.si/bolniki-obiskovalci/izobrazevalni-center-za-bolnike

V primeru poslabšanja simptomov, ravnajte v skladu z navodili vašega zdravnika (povečajte odmerke inhalacijskih zdravil). Za nasvet pokličite po telefonu ali pošljite elektronsko pošto. Pred obiskom zdravnika ga pokličite po telefonu.

Ne ostanite brez stikov. Po telefonu pokličite prijatelje in bližnje. Če vam je domača tehnologija in računalnik, se povežite preko Skype, Viber, Whatsup, Facebooka,..

In..ostanite pozitivni! Kljub resni situaciji je vedno čas za smeh in hvaležnost

Ostanite zdravi!

Viri: www.nijz.si; www.copdfoundation.org; https://www.blf.org.uk/support-for-you/coronavirus/people-living-with-lung-condition; www.ginaasthma.org; www.goldcopd.org Dostop do vseh virov: marec 2020

Boehringer Ingelheim

Boehringer Ingelheim RCV,
Podružnica Ljubljana,
Šlandrova 4b, 1231 Ljubljana - Črnuče

MPR-SL-100036
Datum priprave informacije: marec 2020
Informacijsko gradivo za javnost

BISTVENI PODATKI IZ POVZETKA GLAVNIH ZNAČILNOSTI ZDRAVILA
Trimbow® 87 mikrogramov/5 mikrogramov/9 mikrogramov inhalacijska raztopina pod tlakom

Kakovostna in količinska sestava: En dostavljen odmerek (odmerek, ki zapusti ustnik) vsebuje 87 mikrogramov beklometazondipropionata, 5 mikrogramov formoterolijevega fumarata dihidrata in 9 mikrogramov glikopironija (v obliki 11 mikrogramov glikopironijevega bromida). **Indikacije:** Vzdrževalno zdravljenje pri odraslih bolnikih z zmerno do hudo obliko kronične obstruktivne pljučne bolezni (KOPB), ki ni ustrezno zdravljena s kombinacijo inhalacijskega kortikosteroida in dolgodelujočega agonista adrenergičnih receptorjev beta$_2$ ali s kombinacijo dolgodelujočega agonista adrenergičnih receptorjev beta$_2$ in dolgodelujočega antagonista muskarinskih receptorjev. **Odmerjanje:** Priporočeni odmerek sta dve inhalaciji zdravila dvakrat na dan. Največji odmerek sta dve inhalaciji dvakrat na dan. Pri starejših bolnikih odmerka ni treba prilagajati. Zdravilo se lahko uporablja v priporočenem odmerku pri bolnikih z blago do zmerno okvaro ledvic. Uporaba zdravila pri bolnikih s hudo okvaro ledvic ali s končno ledvično odpovedjo, ki zahteva dializno zdravljenje, zlasti v povezavi s pomembnim zmanjšanjem telesne mase, je možna le, če so pričakovane koristi večje od možnih tveganj. Relevantnih podatkov o uporabi zdravila pri bolnikih s hudo okvaro jeter ni, zato je treba zdravilo pri teh bolnikih uporabljati previdno. Zdravilo ni namenjeno za uporabo pri pediatrični populaciji. **Način uporabe:** Za inhaliranje. Za zagotovitev pravilne uporabe zdravila mora zdravnik ali drug zdravstveni delavec bolniku pokazati, kako se inhalator pravilno uporablja, nato pa redno preverjati ustreznost bolnikove tehnike inhaliranja. Bolniku je treba svetovati, da natančno prebere Navodilo za uporabo in sledi napotkom v navodilu. **Kontraindikacije:** Preobčutljivost na beklometazondipropionat, formoterolijev fumarat dihidrat, glikopironij ali katero koli pomožno snov. **Posebna opozorila in previdnostni ukrepi:** Zdravilo ni indicirano za zdravljenje akutnih epizod bronhospazmov ali za zdravljenje akutnega poslabšanja KOPB (tj. kot rešilno zdravljenje). Po jemanju zdravila so poročali o takojšnjih preobčutljivostnih reakcijah. Če se pojavijo znaki, ki kažejo na alergijsko reakcijo, zlasti angioedem, urtikarijo ali kožni izpuščaj, je treba uporabo zdravila takoj prekiniti in uvesti drugo zdravljenje. Lahko se pojavi paradoksni bronhospazem. Zdravilo je treba uporabljati previdno pri bolnikih s srčnimi aritmijami, zlasti z atrioventrikularnim blokom tretje stopnje in tahiaritmijami, idiopatsko subvalvularno aortno stenozo, hipertrofično obstruktivno kardiomiopatijo, hudo boleznijo srca, okluzivnimi boleznimi žilja, arterijsko hipertenzijo in anevrizmo. Previdnost je potrebna tudi pri zdravljenju bolnikov z znanim podaljšanjem intervala QTc ali sumom nanj. Če je načrtovana anestezija s halogeniranimi anestetiki, je treba zagotoviti, da se zdravilo ne uporabi vsaj 12 ur pred začetkom anestezije, saj obstaja tveganje srčnih aritmij. Previdnost je potrebna tudi pri bolnikih s tirotoksikozo, sladkorno boleznijo, feokromocitomom in nezdravljeno hipokaliemijo. Pri bolnikih s KOPB, ki so prejemali inhalacijske kortikosteroide, so opažali večjo pojavnost pljučnice, tudi pljučnice, ki je zahtevala sprejem v bolnišnico. Pri vseh inhalacijskih kortikosteroidih se lahko pojavijo sistemski učinki, zlasti ob visokih odmerkih, ki se jih jemlje dolgo časa. Dnevni odmerek zdravila Trimbow ustreza srednjemu odmerku inhalacijskega kortikosteroida. Ti učinki so bistveno manj verjetni med uporabo inhaliranih kortikosteroidov kot med uporabo peroralnih kortikosteroidov. Zdravilo je treba uporabljati previdno pri bolnikih z aktivno ali mirujočo pljučno tuberkulozo ter glivično in virusno okužbo dihal. Zdravljenje z agonistom adrenergičnih receptorjev beta$_2$ lahko povzroči potencialno resno hipokaliemijo. Posebna pozornost se svetuje pri hudi obliki KOPB, ker lahko hipoksija stopnjuje ta učinek. Hipokaliemijo lahko okrepi tudi sočasno zdravljenje z drugimi zdravili, ki lahko inducirajo hipokaliemijo, kot so derivati ksantina, steroidi in diuretiki. Inhaliranje formoterola lahko povzroči povišanje ravni glukoze v krvi. Glikopironij je treba pri bolnikih z glavkomom z zaprtim zakotjem, prostatično hiperplazijo ali zastajanjem urina uporabljati previdno, bolnike pa obvestiti o znakih in simptomih akutnega glavkoma z zaprtim zakotjem in jim naročiti, naj prenehajo uporabljati zdravilo in se takoj posvetujejo z zdravnikom, če se pojavijo ti znaki ali simptomi. Zaradi antiholinergičnega učinka glikopironija se ne priporoča dolgotrajnega sočasnega dajanja zdravila Trimbow z drugimi zdravili, ki vsebujejo antiholinergike. Pri bolnikih s hudo okvaro ledvic in pri bolnikih s hudo okvaro jeter, se lahko zdravilo uporablja le, če so pričakovane koristi večje od možnih tveganj. Z namenom zmanjšanja orofaringealnih okužb s kandido je treba bolnikom svetovati, da si usta izperejo z vodo ali jo grgrajo, a naj je ne pogoltnejo, ali da si po inhaliranju predpisanega odmerka umijejo zobe. Pri sistemski in topični uporabi kortikosteroidov lahko poročajo o motnjah vida. Če se pri bolniku pojavijo simptomi, kot so zamegljen vid ali druge motnje vida, ga je potrebno opuščevati za napotitev k oftalmologu zaradi ovrednotenja možnih vzrokov, ki lahko vključujejo katarakto, glavkom ali redke bolezni, kot je centralna serozna horioretinopatija. **Interakcije:** Cimetidin, zaviralci CYP3A (npr. ritonavir, kobicistat), nekardioselektivni zaviralci beta adrenergičnih receptorjev (vključno s kapljicami za oko), druga beta-adrenergična zdravila, kinidin, dizopiramid, prokainamid, antihistaminiki, zaviralci MAO, triciklični antidepresivi, fenotiazini, L-dopa, L-tiroksin, oksitocin, alkohol, zdravila, ki imajo podobne lastnosti kot furazolidon in prokarbazin, anestetiki iz skupine halogeniranih ogljikovodikov, derivati ksantina, steroidi, diuretiki, digitalisovi glikozidi, disulfiram in metronidazol. Ne priporoča se dolgotrajnega sočasnega dajanja zdravila Trimbow z drugimi zdravili, ki vsebujejo antiholinergike. **Neželeni učinki:** *Pogosti:* pljučnica (pri bolnikih s KOPB), faringitis, oralna kandidiaza, okužba sečil, nazofaringitis, glavobol, disfonija. *Občasni:* gripa, oralna glivična okužba, orofaringealna kandidiaza, ezofagealna kandidiaza, sinusitis, rinitis, gastroenteritis, vulvovaginalna kandidiaza, granulocitopenija, alergijski dermatitis, hipokaliemija, hiperglikemija, nemir, tremor, omotica, disgevzija, hipoestezija, otosalpingitis, atrijska fibrilacija, podaljšanje intervala QT na elektrokardiogramu, tahikardija, tahiaritmija, palpitacije, hiperemija, vročinski oblivi, hipertenzija, kašelj, produktivni kašelj, draženje žrela, epistaksa, driska, suha usta, disfagija, navzea, dispepsija, skeleč občutek na ustnicah, zobni karies, (aftozni) stomatitis, izpuščaj, urtikarija, pruritus, hiperhidroza, mišični spazem, mialgija, bolečine v okončinah, mišično - skeletna bolečina v prsnem košu, utrujenost, zvečanje ravni C-reaktivnega proteina, povečano število trombocitov, zvečanje vrednosti prostih maščobnih kislin, zvečanje ravni insulina v krvi, zvečanje vrednosti ketonskih teles v krvi, zmanjšanje ravni kortizola. **Način in režim izdaje:** Predpisovanje in izdaja zdravila je le na recept. **Imetnik dovoljenja za promet:** Chiesi Farmaceutici S.p.A., Via Palermo 26/A, 43122 Parma, Italija. **Datum zadnje revizije besedila:** 23.01.2019. **Pred predpisovanjem se seznanite s celotnim povzetkom glavnih značilnosti zdravila.**

Datum priprave informacije: december 2020 . Podrobnejše informacije so na voljo pri predstavniku imetnika dovoljenja za promet z zdravilom v Sloveniji: **CHIESI SLOVENIJA, d.o.o.**, Šmartinska cesta 53, Ljubljana
SAMO ZA STROKOVNO JAVNOST TR 8/20
[1]Trimbow SmPC

Chiesi
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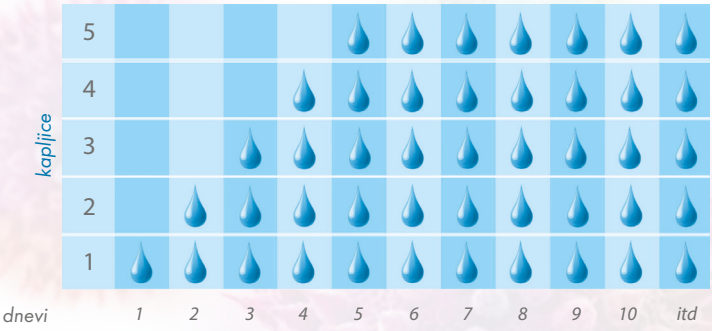
Podjezična Imunoterapija

Priporočeno odmerjanje

Začetno zdravljenje



Dnevno do porabe viale

Terapijo je potrebno izvajati 3 do 5 let

- 1 viala vsebuje 24 ml
- Zadostuje za približno 3 mesece
- V petih dneh do vzdrževalnega odmerka
- Enostavna uporaba
- Prilagodljiv odmerek kapljic

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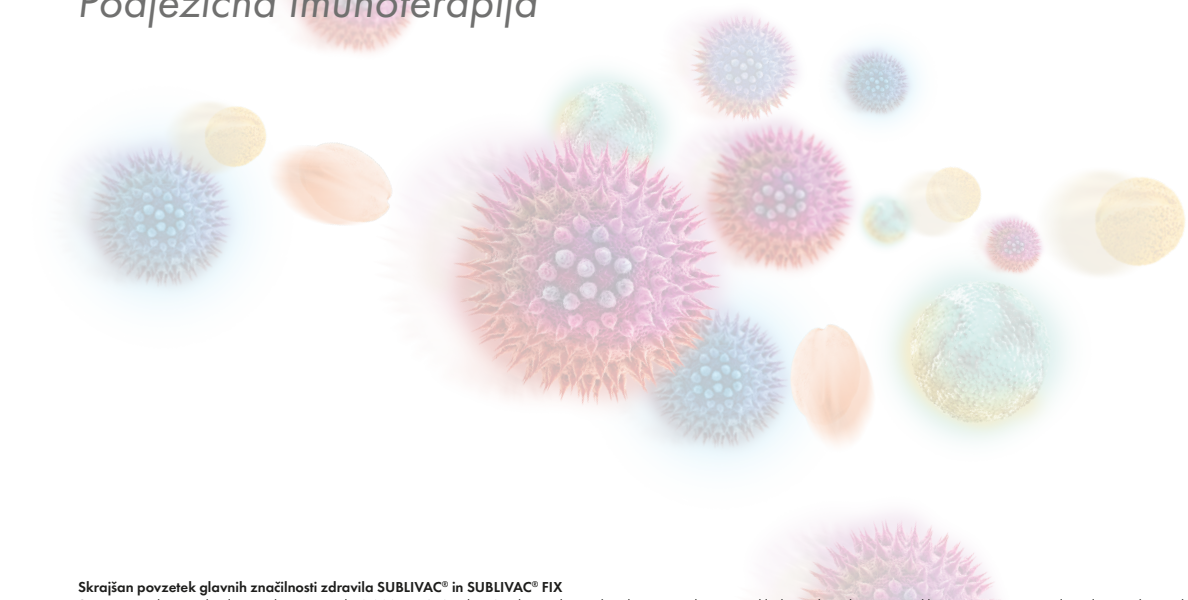
Podjezična Imunoterapija



Skrajšan povzetek glavnih značilnosti zdravila SUBLIVAC® in SUBLIVAC® FIX
Sestava: podjezične kapljice vsebujejo na ml 10.000 au, AUN ali PUN alergenskega ekstrakta, pripravljenega v skladu z zdravnikovim navodilom. Pomožne snovi: glicerol, aminokaprojska kislina, dinatrijev fosfat hidrat, natrijev dihidrogen, fosfat dihidrat, olje iz poprove mete, prečiščena voda. **Terapevtske indikacije:** zdravljenje alergijskih reakcij takojšnje preobčutljivosti(IgE posredovanih), kot so alergijski rinitis, alergijski konjunktivitis in alergijska bronhialna astma, induciranih z alergeni. **Odmerjanje in uporaba:** prvi dan začetnega zdravljenja se začne z eno kapljico. Ta odmerek se povečuje vsak dan za eno kapljico, dokler se ne doseže najvišjega dnevnega odmerka petih kapljic. Zdravljenje se nadaljuje s petimi kapljicami. Kapljice se aplicira pod jezik vsaj 1 minuto (optimalno 2-3 minute) pred požiranjem. Za odmerjanje in aplikacijo kapljic se lahko uporablja žlica. Priporočamo, da se po uporabi kapalka očisti, na primer z mokro krpo. Zdravljenje je potrebno nadaljevati od 3 do 5 let. **Kontraindikacije:** nekontrolirana bronhialna astma s FEV_1 pod 70%, hude avtoimunske bolezni, imunska pomanjkljivost in imunosupresija, neoplastične bolezni s prisotnimi simptomi, uvedba zdravljenja med nosečnostjo, hudo vnetje ustne sluznice, preobčutljivost na katerokoli pomožno snov. **Neželeni učinki:** lokalne reakcije v ustih in žrelu, otekanje ustnic ali jezika. Pojav specifičnih alergijskih simptomov kot so blage sistemske reakcije (srbenje oči, kihanje, kašljanje, atopični ekcem). V redkih primerih se lahko pojavijo intenzivne sistemske reakcije npr. kratka sapa, generalizirana urtikarija ali Quinckejev edem. Po zaužitju se lahko pojavi driska in bolečine v trebuhu. Ti simptomi se običajno pojavijo v 30 minutah po zaužitju zdravila, lahko se pojavijo tudi po nekaj urah. V posameznih primerih so poročali o anafilaktičnem šoku. **Način in režim izdajanja:** SUBLIVAC® in SUBLIVAC® FIX sta na voljo na recept, neposredno predpisan pacientu. **Za vse dodatne informacije se lahko obrnete na zastopnika zdravila:** Iris, Mednarodna trgovina d.o.o., Cesta v Gorice 8, 1000 Ljubljana. **Imetnik dovoljenja za promet:** HAL Allergy BV, P.O. Box 1204, 2302 BE Leiden, The Netherlands. **Datum zadnje revizije besedila:** 02/2020.

Zastopa in prodaja:.
Iris, Mednarodna trgovina d.o.o.
Cesta v Gorice 8, 1000 Ljubljana
Tel: 01/200-66-46
narocilo@iris.si

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Širok razpon visoko kvalitetnih alergenskih izvlečkov

Izjemna prilagodljivost

Samostojno odmerjanje v domačem okolju

Dokazano učinkovito zdravljenje pri otrocih in odraslih

Staloral

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

IME ZDRAVILA: Staloral 10 IR/ml + 100 IR/ml ali 10 IC/ml + 100 IC/ml podjezično pršilo, raztopina; Staloral 10 IR/ml + 300 IR/ml podjezično pršilo, raztopina; Staloral 100 IR/ml ali 100 IC/ml podjezično pršilo, raztopina; Staloral 300 IR/ml podjezično pršilo, raztopina. **KAKOVOSTNA IN KOLIČINSKA SESTAVA:** ena viala vsebuje 10 ml raztopine z 10, 100 ali 300 IR/ml (standardizirani alergenski ekstrakti) ali 10 ali 100 IC/ml (nestandardizirani alergenski ekstrakti) enega ali mešanice več alergenskih ekstraktov. **KLINIČNI PODATKI Terapevtske indikacije:** Alergije tipa I (klasifikacija po Gellu in Coombsu) zajemajo predvsem rinitis, konjunktivitis, rinokonjunktivitis ali astmo (blago do zmerno) in so lahko sezonske ali celoletne. Cilj specifične imunoterapije je preprečiti klinične posledice stika senzbilizirane osebe z alergenom, če so etiološki dejavniki jasno ugotovljeni. **Odmerjanje in način uporabe:** Specifično imunoterapijo je treba uvesti takoj, ko je postavljena diagnoza. Prej ko se začne zdravljenje, večja bo učinkovitost zdravila. Pri otrocih lahko začnete z zdravljenjem pri starosti od 3 do 4 let, najbolje pa je začeti okoli 5. leta starosti. Pri otrocih ali mlajših odraslih uvedete to zdravljenje kot terapijo prve izbire takoj, ko bo to glede na jakost simptomov potrebno. Pri sezonskih alergijah je priporočljivo začeti zdravljenje pred sezono cvetenja. Odmerek pred začetkom sezone cvetenja najprej povečate na največji odmerek, ki ga bolnik še dobro prenaša. Bolnik nadaljuje z jemanjem največjega odmerka, ki ga še dobro prenaša, do konca sezone cvetenja. Odmerjanje zdravila ni odvisno od starosti, ampak mora biti prilagojeno jakosti odzivanja posameznega bolnika. Terapija zajema 2 fazi: začetna faza zdravljenja s postopnim povečevanjem odmerka in vzdrževalna faza zdravljenja s stalnimi odmerki. Pred jemanjem zdravila je treba preveriti oz. zagotoviti, da uporabljeni ekstrakt res ustreza predpisanemu ekstraktu in preveriti tudi rok uporabnosti. **1. Začetno zdravljenje: povečevanje odmerka** Zdravilo se jemlje dnevno, v naraščajočih odmerkih, dokler ni dosežen vzdrževalni odmerek. **2. Vzdrževalno zdravljenje: stalni odmerek** Ko bolnik enkrat doseže največji odmerek, naj ga jemlje bodisi vsak dan ali trikrat na teden. Priporočeno odmerjanje je najmanj 8 pritiskov 3-krat na teden ali 4 pritiski na dan z uporabo koncentracije 300 IR/ml. V kliničnih raziskavah so bolniki dobro prenašali odmerjanje v količinah, ki so ustrezale 10 pritiskom na dan v koncentraciji 300 IR/ml. **Dolžina zdravljenja** Splošno pravilo je, da je treba specifično imunoterapijo izvajati od 3 do 5 let. Pri sezonskih alergijah lahko traja zdravljenje tudi več sezon. **Način uporabe** Zdravilo se jemlje zjutraj na tešče. Odmerek ekstrakta si da bolnik tako, da pritisne na odmerno črpalko (1 pritisk odmeri 0,1 ml), ki jo usmeri naravnost pod jezik in ekstrakt zadrži pod jezikom še 2 minuti, nato ga pogoltne. Uporabo zdravila pri otrocih morajo nadzirati odrasli. **KONTRAINDIKACIJE:** Preobčutljivost za katerokoli pomožno snov (glejte seznam pomožnih snovi), težja imunska pomanjkljivost, maligne bolezni, nestabilna astma, avtoimunske bolezni, trajno zdravljenje z zaviralci receptorjev beta. **POSEBNA OPOZORILA IN PREVIDNOSTNI UKREPI:** Po potrebi pred terapijo nadzirajte simptome s primernim zdravljenjem. Bolniki, ki jim predpišete podjezično uporabo alergenov, morajo imeti na voljo tudi standardno simptomatsko zdravljenje (kortikosteroidi, agonisti beta-2 receptorjev, antagonisti histaminskih receptorjev H1). Zdravilo ni primerno za zdravljenje otrok, ki so mlajši od 3 let. To zdravilo vsebuje 1 mmol natrija na ml (ali 1 mmol natrija na maksimalni dnevni odmerek 10 pritiskov alergenskega ekstrakta s koncentracijo 10 IR/ml). To je treba upoštevati pri bolnikih, ki so na dieti z nadzorovanim vnosom natrija. **MEDSEBOJNO DELOVANJE Z DRUGIMI ZDRAVILI IN DRUGE OBLIKE INTERAKCIJ:** Ni poročil o medsebojnem delovanju tega zdravila z drugimi zdravili. **PLODNOST, NOSEČNOST IN DOJENJE:** Bolnice, ki zanosijo v teku ciklusa specifične imunoterapije v vzdrževalnem odmerku (t.j. stalnem odmerku), lahko zdravljenje nadaljujejo. Če pa bolnica zanosi v fazi začetnega zdravljenja (postopno povečevanje odmerka), je bolje, da s terapijo preneha. **SPOSOBNOST VOŽNJE IN UPRAVLJANJA S STROJI:** Zdravilo Staloral nima vpliva ali ima zanemarljiv vpliv na sposobnost vožnje in upravljanja s stroji. **NEŽELENI UČINKI:** Desenzitizacija je alergensko zdravljenje, ki lahko sproži neželene alergijske učinke, ki so lahko lokalni in/ali sistemski. Ni nujno, da bolnik prejeti odmerek dobro prenaša. To se lahko skozi čas spreminja v funkciji specifične reaktivnosti posameznika in okolja. V primeru pojava neželenih učinkov je treba način odmerjanja znova oceniti. Pogosti neželeni učinki: oralni pruritus, edem, orofaringealno neugodje, navzea, bolečina v trebuhu, bruhanje, diareja. Občasni neželeni učinki: konjunktivitis, rinitis, astma, urtikarija. Neznana pogostnost: angioedem, anafilaktični šok, laringealni edem, kašelj, orofaringealni edem. Večino časa so pogosti neželeni učinki blagi do zmerni in ni potrebno spreminjati režima odmerjanja. Sistemski učinki, kot so rinitis, konjunktivitis, urtikarija ali astma, so občasni in je lahko potrebno simptomatsko zdravljenje z antagonisti histaminskih receptorjev H1, beta-2 mimetiki ali morda peroralnimi kortikosteroidi. V vsakem primeru mora zdravnik, ki predpiše zdravilo, ponovno oceniti shemo odmerjanja ali koristi nadaljnje specifične imunoterapije. V vsakem primeru mora bolnik obvestiti zdravnika o pojavu neželenega učinka med prejemanjem specifične imunoterapije. Pri zmernih sindromskih reakcijah (urtikarija, rinitis, astma) je lahko potrebno simptomatsko zdravljenje z antagonisti histaminskih receptorjev H1, beta-2 mimetiki ali morda celo peroralnimi kortikosteroidi. **IMETNIK DOVOLJENJA ZA PROMET:** STALLERGENES, 6 rue Alexis de Tocqueville, 92160 ANTONY, Francija. **DATUM ZADNJE REVIZIJE BESEDILA:** 29.8.2018 **REŽIM IZDAJE:** Rp/Spec LISTA: V* SAMO ZA STROKOVNO JAVNOST! Celoten Povzetek glavnih značilnosti zdravila dobite pri naših strokovnih sodelavcih ali na sedežu družbe! V Sloveniji zastopa: Ewopharma d.o.o., Cesta 24. junija 23, 1231 Lj - Črnuče.
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Datum priprave: 12/2020; SI.20.STALORAL.05

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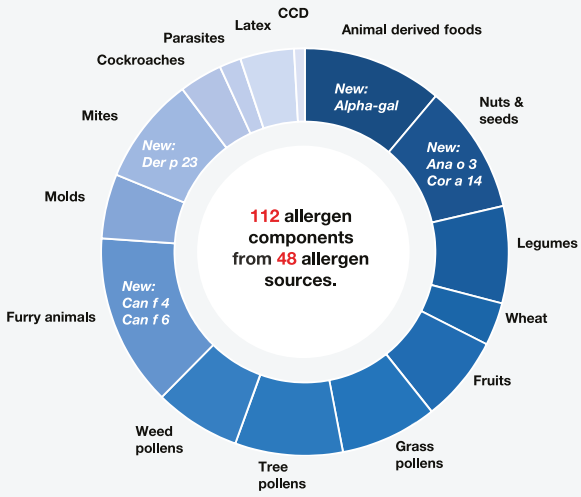

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Opsumit®
macitentan

Zdravilo Opsumit je kot samostojno zdravilo ali v kombinaciji indicirano za dolgotrajno zdravljenje pljučne arterijske hipertenzije (PAH) pri odraslih bolnikih s funkcionalnim razredom (FR) II do III po SZO.

Učinkovitost je bila ugotovljena v populaciji s PAH, vključno z idiopatično in dedno PAH, PAH, povezano z boleznimi vezivnega tkiva, in PAH, povezano z zdravljeno preprosto prirojeno boleznijo srca[1].

Referenca: 1. SmPC Opsumit 10 mg filmsko obložene tablete. Datum zadnje revizije besedila: 17. april 2020

Pred predpisovanjem zdravila Opsumit natančno preberite celoten Povzetek glavnih značilnosti zdravila, ki je na voljo na sedežu podjetja Medis, d.o.o. ali na spletni strani Evropske agencije za zdravila http://www.ema.europa.eu.

Imetnik dovoljenja za promet z zdravilom: Janssen-Cilag International NV; Turnhoutseweg 30; B-2340 Beerse Belgija.

SAMO ZA STROKOVNO JAVNOST

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MEDIS

SI-OPS-1120-001

Skrajšan povzetek glavnih značilnosti zdravila Opsumit / macitentan

Ime zdravila: Opsumit 10 mg filmsko obložene tablete. **Sestava zdravila:** Ena filmsko obložena tableta vsebuje 10 mg macitentana. *Pomožne snovi z znanim učinkom:* Ena filmsko obložena tableta vsebuje približno 37 mg laktoze (v obliki monohidrata) in približno 0,06 mg sojinega lecitina (E322). **Terapevtske indikacije:** Zdravilo Opsumit je kot samostojno zdravilo ali v kombinaciji indicirano za dolgotrajno zdravljenje pljučne arterijske hipertenzije (PAH) pri odraslih bolnikih s funkcionalnim razredom (FR) II do III po SZO. Učinkovitost je bila ugotovljena v populaciji s PAH, vključno z idiopatično in dedno PAH, PAH, povezano z boleznimi vezivnega tkiva, in PAH, povezano z zdravljeno preprosto prirojeno boleznijo srca. **Odmerjanje in način uporabe:** Zdravljenje mora uvesti in nadzirati zdravnik z izkušnjami v zdravljenju PAH. Odmerjanje: Priporočeni odmerek je 10 mg enkrat na dan. *Starejši:* Prilagajanje odmerka pri bolnikih, starih več kot 65 let, ni potrebno. Kliničnih izkušenj pri bolnikih, starejših od 75 let, je malo. Zato je treba zdravilo Opsumit v tej populaciji uporabljati previdno. *Jetrna okvara:* Na podlagi farmakokinetičnih (FK) podatkov odmerka pri bolnikih z blago, zmerno ali hudo jetrno okvaro ni treba prilagajati. Vendar pa kliničnih izkušenj z uporabo macitentana pri bolnikih s PAH z zmerno ali hudo jetrno okvaro ni. Zdravila Opsumit se ne sme uvesti pri bolnikih s hudo jetrno okvaro ali s klinično pomembno zvišanimi jetrnimi aminotransferazami (več kot trikratna zgornja normalna meja (> 3 × ULN (Upper Limit of Normal)). *Ledvična okvara:* Na podlagi FK podatkov prilagoditev odmerka pri bolnikih z ledvično okvaro ni potrebna. Kliničnih izkušenj z uporabo macitentana pri bolnikih s PAH s hudo ledvično okvaro ni. Uporaba zdravila Opsumit se ne priporoča pri bolnikih, ki se zdravijo z dializo. *Pediatrična populacija:* Varnost in učinkovitost macitentana pri otrocih in mladostnikih, starih manj kot 18 let še nista bili dokazani. *Način uporabe*: Filmsko obloženih tablet ni mogoče prelomiti in jih je treba cele pogoltniti z vodo. Jemati jih je možno s hrano ali brez nje. Zdravilo Opsumit je treba jemati vsak dan ob istem času. Če bolnik izpusti odmerek zdravila Opsumit, je treba bolniku povedati, da ga vzame čim prej, nato pa z naslednjim odmerkom nadaljuje ob načrtovanem času. Bolniku je treba povedati, da naj ne vzame dveh odmerkov hkrati, če je kateri odmerek izpustil. **Kontraindikacije:** preobčutljivost na učinkovino, sojo ali katero koli pomožno snov; nosečnost; ženske v rodni dobi, ki ne uporabljajo učinkovite kontracepcije; dojenje; bolniki s hudo jetrno okvaro; izhodiščne vrednosti jetrnih aminotransferaz (aspartat aminotransferaze (AST) in/ali alanin aminotransferaz (ALT) > 3 × ULN). **Posebna opozorila in previdnostni ukrepi:** Razmerja med koristmi in tveganje macitentana pri bolnikih s funkcionalnim razredom pljučne arterijske hipertenzije I po SZO niso ugotavljali. Delovanje jeter: S PAH in z antagonisti receptorjev endotelina (ERA, endothelin receptor antagonists) je povezano zvišanje jetrnih aminotransferaz (AST, ALT). Zdravila Opsumit se ne sme uvesti pri bolnikih s hudo jetrno okvaro ali zvišanimi aminotransferazami (> 3-kratna ULN) in se ne priporoča pri bolnikih z zmerno jetrno okvaro. Pred uvedbo zdravila Opsumit je treba pridobiti rezultate preiskav jetrnih encimov. Bolnike je treba spremljati za pojav znakov poškodbe jeter, priporoča pa se tudi mesečno spremljanje vrednosti ALT in AST. Če se pojavijo trdovratna, nepojasnjena, klinično pomembna zvišanja aminotransferaz, ali če zvišanja spremlja zvišanje bilirubina > 2 × ULN ali klinični simptomi poškodbe jeter (npr. zlatenica), je treba zdravljenje z zdravilom Opsumit prekiniti. O ponovni uvedbi zdravila Opsumit lahko razmislimo, ko se ravni jetrnih encimov pri bolnikih, ki niso imeli kliničnih simptomov poškodbe jeter, vrnejo v normalni razpon. Priporoča se pridobitev nasveta hepatologa. Koncentracije hemoglobina: Zdravljenje z antagonisti receptorja endotelina, vključno z macitentanom, je povezano z zmanjšanjem koncentracij hemoglobina. V s placebom kontroliranih študijah z macitentanom povezano zmanjšanje koncentracij hemoglobina ni bilo progresivno in se je po prvih 4-12 tednih zdravljenja stabiliziralo, nato pa je ostalo med kroničnim zdravljenjem stabilno. Z macitentanom in drugimi ERA so poročali o primerih anemije, zaradi katere je bilo potrebno zdravljenje s transfuzijo krvnih celic. Uvedba zdravila Opsumit se ne priporoča pri bolnikih s hudo anemijo. Priporočljivo je, da pred uvedbo zdravljenja izmerite koncentracije hemoglobina, nato pa preiskave med zdravljenjem ponavljate, kot je klinično indicirano. Pljučna vensko-okluzivna bolezen: Pri uporabi vazodilatatorjev (v glavnem prostaciklinov) pri bolnikih s pljučno vensko-okluzivno boleznijo so poročali o primerih pljučnega edema. Posledično je treba pomisliti na možnost pljučne vensko-okluzivne bolezni, če se pojavijo znaki pljučnega edema pri bolnikih s PAH, ki dobivajo macitentan. Uporaba pri ženskah v rodni dobi: Zdravljenje z zdravilom Opsumit se sme pri ženskah v rodni dobi uvesti samo, če je bila odsotnost nosečnosti potrjena, če je bilo ženski ustrezno svetovano glede uporabe kontracepcije in če uporablja učinkovito kontracepcijo. Ženske še 1 mesec po prekinitvi uporabe zdravila Opsumit ne smejo zanositi. V času zdravljenja z zdravilom Opsumit se priporočajo mesečni testi nosečnosti za zgodnje prepoznavanje morebitne nosečnosti. Sočasna uporaba z močnimi induktorji CYP3A4: V prisotnosti močnih induktorjev CYP3A4 se lahko učinkovitost macitentana zmanjša. Kombinaciji macitentana z močnimi induktorji CYP3A4 (npr. rifampicin, šentjanževka, karbamazepin in fenitoin) se je treba izogniti. Sočasna uporaba z močnimi zaviralci CYP3A4: Previdnost je potrebna, ko se macitentan daje sočasno z močnimi zaviralci CYP3A4 (npr. itrakonazol, ketokonazol, vorikonazol, klaritromicin, telitromicin, nefazodon, ritonavir in sakvinavir). Ledvična okvara: Bolniki z ledvično okvaro so morda med zdravljenjem z macitentanom bolj izpostavljeni tveganju hipotenzije in anemije. Zato se priporoča spremljanje krvnega tlaka in hemoglobina. Kliničnih izkušenj z uporabo macitentana pri bolnikih s PAH in hudo ledvično okvaro ni. Pri tej populaciji se priporoča previdnost. Z uporabo zdravila Opsumit pri bolnikih na dializi ni izkušenj, zato se macitentan v tej populaciji ne priporoča. Starejši: Izkušenj z macitentanom je pri bolnikih, starih več kot 75 let, malo, zato je treba zdravilo Opsumit pri tej populaciji uporabljati previdno. Pomožne snovi: Zdravilo Opsumit vsebuje laktozo. Bolniki z redko dedno intoleranco za galaktozo, popolnim pomanjkanjem laktaze ali malabsorpcijo glukoze/galaktoze ne smejo jemati tega zdravila. Tablete zdravila Opsumit vsebujejo sojin lecitin. Bolniki, preobčutljivi na sojo, zdravila Opsumit ne smejo uporabljati. **Interakcije:** Študije *in vitro*: V presnovi macitentana in nastajanju njegovih presnovkov sodelujejo encimi citokroma P450, CYP3A4, CYP2C8, CYP2C9 in CYP2C19. Macitentan in njegovi aktivni presnovki nimajo klinično pomembnega zaviralnega ali indukcijskega učinka na encime citokroma P450. Macitentan in njegov aktivni presnovek v klinično pomembnih koncentracijah nista zaviralca jetrnih ali ledvičnih privzemnih prenašalcev, vključno z organskimi anionskimi prenašalskimi polipeptidi (OATP1B1 in OATP1B3). Macitentan in njegov aktivni presnovek nista pomembna substrata za OATP1B1 in OATP1B3, vendar vstopata v jetra s pasivno difuzijo. Macitentan in njegov aktivni presnovek v klinično pomembnih koncentracijah nista zaviralca jetrne ali ledvične iztočne črpalke, vključno s proteinom odpornosti na več zdravil (P-gp, MDR-1), prenašalci več zdravil in prenašalci toksinske ekstruzije (MATE1 in MATE2-K). Macitentan ni substrat za P-gp/MDR-1. Macitentan in njegov aktivni presnovek v klinično koncentracijah ne delujejo medsebojno z beljakovinami, ki sodelujejo pri jetrnem prenosu žolčne soli, tj. z eksportno črpalko žolčne soli (BSEP, bile salt export pump) in polipeptidom, ki je soprenašalec od natrija odvisnega tavroholata (NTCP, sodium-dependent taurocholate co-transporting polypeptide). Študije *in vivo*: *Močni induktorji CYP3A4:* Sočasno zdravljenje z rifampicinom 600 mg na dan, močnim induktorjem CYP3A4, je zmanjšalo izpostavljenost macitentanu v stanju dinamičnega ravnovesja za 79 %, vendar pa ni vplivalo na izpostavljenost aktivnemu presnovku. Upoštevati je treba zmanjšano učinkovitost macitentana v prisotnosti močnih induktorjev CYP3A4, kot je rifampicin. Zato se je treba sočasni uporabi macitentana z močnimi induktorji CYP3A4 izogniti. *Ketokonazol:* V prisotnosti ketokonazola 400 mg enkrat na dan, močnim zaviralcem CYP3A4, se je izpostavljenost macitentanu zvišala za približno 2-krat. Predvideno zvišanje je bilo približno 3-kratno v prisotnosti ketokonazola 200 mg dvakrat na dan z uporabo fiziološkega modela farmakokinetičnega modeliranja (PBPK). Upoštevati je treba negotovosti tega modeliranja. Izpostavljenost aktivnemu presnovku macitentana se je zmanjšala za 26 %. Previdnost je potrebna pri sočasni uporabi macitentana z močnimi zaviralci CYP3A4. *Varfarin:* Dajanje macitentana v več odmerkih po 10 mg enkrat na dan ni vplivalo na izpostavljenost S-varfarinu (substrat CYP2C9) ali R-varfarinu (substrat CYP3A4) po enem odmerku 25 mg varfarina. Macitentan ni vplival na farmakodinamični učinek varfarina na mednarodno normalizirano razmerje (INR, International Normalized Ratio). Varfarin ni vplival na farmakokinetiko macitentana in njegovega aktivnega presnovka. *Sildenafil:* V stanju dinamičnega ravnovesja se je izpostavljenost sildenafilu 20 mg trikrat na dan zvečala za 15 % med sočasno uporabo macitentana 10 mg enkrat na dan. Sildenafil, ki je substrat CYP3A4, ni vplival na farmakokinetiko macitentana, medtem ko se je izpostavljenost aktivnemu presnovku macitentana zmanjšala za 15 %. Te spremembe niso klinično pomembne. Učinkovitost in varnost macitentana v kombinaciji s sildenafilom pri bolnikih s PAH so dokazali v s placebom kontroliranem preskušanju. *Ciklosporin A:* Sočasno zdravljenje s ciklosporinom A 100 mg dvakrat na dan, kombiniranim zaviralcem CYP3A4 in OATP, v stanju dinamičnega ravnovesja ni spremenila izpostavljenosti macitentanu in njegovemu aktivnemu presnovku v klinično pomembnem obsegu. *Hormonski kontraceptivi:* Macitentan 10 mg enkrat na dan ni vplival na farmakokinetiko peroralnega kontraceptiva (noretisteron 1 mg in etinilestradiol 35 µg). *Zdravila, ki so substrati proteina odpornosti na raka dojke (BCRP-Breast cancer resistance protein):* Macitentan v odmerku 10 mg enkrat na dan ni vplival na farmakokinetiko substrata BCRP (1 mg rociguata; 10 mg rosuvastatina). **Plodnost, nosečnost in dojenje:** Nosečnost: Podatkov o uporabi macitentana pri nosečnicah ni. Študije na živalih so pokazale vpliv na sposobnost razmnoževanja. Možno tveganje za ljudi še ni znano. Zdravilo Opsumit je kontraindicirano med nosečnostjo in pri ženskah v rodni dobi, ki ne uporabljajo učinkovite kontracepcije. Uporaba pri ženskah v rodni dobi/kontracepcija pri moških in ženskah: Zdravljenje z zdravilom Opsumit se sme pri ženskah v rodni dobi uvesti samo, če je bila odsotnost nosečnosti potrjena, če je bilo ženski ustrezno svetovano glede uporabe kontracepcije in če uporablja učinkovito kontracepcijo. Ženske še 1 mesec po prekinitvi uporabe zdravila Opsumit ne smejo zanositi. V času zdravljenja z zdravilom Opsumit se priporočajo mesečni testi nosečnosti za zgodnje prepoznavanje morebitne nosečnosti. Dojenje: Ni znano, ali se macitentan izloča v materino mleko. Pri podganah se macitentan in njegovi presnovki med dojenjem izločajo v mleko. Tveganja za dojenega otroka ne moremo izključiti. Zdravilo Opsumit je kontraindicirano med dojenjem. Plodnost pri moških: Po zdravljenju z macitentanom so pri samcih živali opazili razvoj testikularne tubularne atrofije. Pomen tega izsledka za ljudi ni znan, vendar poslabšanja spermatogeneze ni mogoče izključiti. **Povzetek neželenih učinkov:** Zelo pogosti: nazofaringitis, bronhitis, anemija, zmanjšana raven hemoglobina, glavobol, edem, zastajanje tekočine. Pogosti: faringitis, gripa, okužba sečil, levkopenija, trombocitopenija, zvišane ravni aminotransferaze, hipotenzija, kongestija nosu. **Način in režim predpisovanja in izdaje zdravila:** Predpisovanje in izdaja zdravila je le na recept, zdravilo pa se uporablja samo v bolnišnicah. Izjemoma se lahko uporablja pri nadaljevanju zdravljenja na domu ob odpustu iz bolnišnice in nadaljnjem zdravljenju. **Imetnik dovoljenja za promet:** Janssen-Cilag International NV, Turnhoutseweg 30, B-2340 Beerse, Belgija. **Pred predpisovanjem, prosimo, preberite povzetek glavnih značilnosti zdravila. Datum revizije besedila**: 04/2020

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Imetnik dovoljenja za promet z zdravilom: Ferrer Internacional S.A., Gran Via Carlos III, 94, 08028 - Barcelona, Španija.
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Skrajšan povzetek glavnih značilnosti zdravila REMODULIN / treprostinil

Ime zdravila in sestava: REMODULIN 1 mg/ml raztopina za infundiranje. En mililiter vsebuje 1 mg treprostinila v obliki natrijevega treprostinilata. Ena 20 ml viala z raztopino vsebuje 20 mg treprostinila v obliki natrijevega treprostinilata (natrijeva sol nastane in situ med proizvodnjo končnega zdravila). REMODULIN 2,5 mg/ml raztopina za infundiranje. En mililiter vsebuje 2,5 mg treprostinila v obliki natrijevega treprostinilata. Ena 20 ml viala z raztopino vsebuje 50 mg treprostinila v obliki natrijevega treprostinilata (natrijeva sol nastane in situ med proizvodnjo končnega zdravila). REMODULIN 5 mg/ml raztopina za infundiranje. En mililiter vsebuje 5 mg treprostinila v obliki natrijevega treprostinilata. Ena 20 ml viala z raztopino vsebuje 100 mg treprostinila v obliki natrijevega treprostinilata (natrijeva sol nastane in situ med proizvodnjo končnega zdravila). REMODULIN 10 mg/ml raztopina za infundiranje. En mililiter vsebuje 10 mg treprostinila v obliki natrijevega treprostinilata. Ena 20 ml viala z raztopino vsebuje 200 mg treprostinila v obliki natrijevega treprostinilata (natrijeva sol nastane in situ med proizvodnjo končnega zdravila). **Terapevtske indikacije:** Zdravljenje idiopatske ali dedne pljučne arterijske hipertenzije (PAH) za izboljšanje tolerance za telesno aktivnost in simptomov pri bolnikih, razvrščenih v 3. razred po razvrstitvi New York Heart Association (NYHA). **Odmerjanje in način uporabe:** Zdravilo Remodulin se daje v obliki neprekinjene subkutane ali intravenske infuzije. Zaradi tveganj, povezanih s kronično vstavljenimi centralnimi venskimi katetri, vključno z resnimi okužbami krvi, je subkutano infundiranje (nerazredčeno) prednostni način dajanja, neprekinjeno intravensko infundiranje pa je pridržano za bolnike, ki so stabilizirani s subkutanim infundiranjem treprostinila vendar subkutane poti več ne prenašajo in pri katerih se to tveganje smatra za sprejemljivo. Zdravljenje lahko začnejo in nadzorujejo le zdravniki, izkušeni v zdravljenju pljučne hipertenzije. Odmerjanje: Odrasli: *Začetek zdravljenja pri bolnikih, ki predhodno še niso prejemali prostaciklinov:* Zdravljenje je treba začeti pod skrbnim zdravniškim nadzorom v enoti, kjer je mogoče zagotoviti intenzivno nego. Priporočena začetna hitrost infundiranja je 1,25 ng/kg/min. Če bolniki začetni odmerek slabo prenašajo, je treba hitrost infundiranja zmanjšati na 0,625 ng/kg/min. *Prilagoditve odmerka:* V prvih štirih tednih zdravljenja je treba hitrost infundiranja povečevati pod zdravniškim nadzorom postopno po 1,25 ng/kg/min tedensko, nato pa po 2,5 ng/kg/min tedensko. Da bi dosegli vzdrževalni odmerek, pri katerem se simptomi izboljšajo in ki ga bolniki prenašajo, je treba odmerek prilagoditi individualno in pod zdravniškim nadzorom. Med 12-tedenskim preskušanjem je bila učinkovitost ohranjena samo, če je bil odmerek v povprečju povečan 3-krat do 4-krat mesečno. Namen stalne prilagoditve odmerka je določiti odmerek, pri katerem se izboljšajo simptomi PAH in hkrati minimalizirajo prekomerni farmakološki učinki zdravila Remodulin. Neželeni učinki, kot so vročinski oblivi, glavobol, hipotenzija, slabost, bruhanje in driska, so v splošnem odvisni od uporabljenega odmerka treprostinila. V nadaljevanju zdravljenja lahko izginejo, če pa vztrajajo ali jih bolniki ne morejo več prenašati, je treba hitrost infuzije zmanjšati, da se zmanjša njihova intenziteta. V fazi spremljanja kliničnih preskušanj so bili povprečni odmerki, doseženi po 12 mesecih, 24 mesecih in 48 mesecih, 26 ng/kg/min, 36 ng/kg/min in 42 ng/kg/min. Pri bolnikih s čezmerno telesno maso (≥ 30 % nad idealno telesno maso) je začetni odmerek in povečanje odmerkov potrebno določiti glede na idealno telesno maso. Nenadna ukinitev ali nenadno znatno zmanjšanje odmerka zdravila Remodulin lahko povzroči povratni učinek pljučne arterijske hipertenzije. Zato se priporoča izogibanje prekinitvi zdravljenja z zdravilom Remodulin in ponovno uvedbo zdravila takoj po nenadnem nenamernem zmanjšanju odmerka ali prekinitvi. Usposobljeno zdravniško osebje določi optimalno strategijo za ponovno uvedbo infundiranja zdravila Remodulin za vsak posamezni primer posebej. V večini primerov se lahko infundiranje zdravila Remodulin po nekajurni prekinitvi uvede z enako stopnjo odmerka; pri prekinitvah, ki trajajo dalj časa, pa je treba odmerek zdravila Remodulin ponovno titrirati. Starejši: Na splošno je treba odmerek pri starejših izbrati previdno, ob upoštevanju zmanjšanega delovanja jeter, ledvic in srca, sočasnih bolezni ali drugih zdravil, ki jih bolnik jemlje. Otroci in mladostniki: Podatki za bolnike pod 18. letom starosti so omejeni. Na osnovi kliničnih preskušanj, ki so na voljo, ni mogoče oceniti ali učinkovitost in varnost priporočene sheme odmerjanja za odrasle lahko ekstrapoliramo na otroke in mladostnike. Skupine bolnikov z večjim tveganjem: Bolniki z jetrno okvaro: Pri bolnikih z okvaro jeter je potrebna previdnost zaradi tveganja za povečano sistemsko izpostavljenost, ki lahko zmanjša toleranco in poveča od odmerka odvisne neželene učinke. Začetni odmerek zdravila Remodulin je treba zmanjšati na 0,625 ng/kg/min, nato pa ga previdno postopoma povečevati. Bolniki z ledvično okvaro: Ker se treprostinil in njegovi presnovki izločajo večinoma z urinom, je treba bolnike z ledvično okvaro zdraviti previdno, da bi preprečili škodljive posledice zaradi morebitnega povečanja sistemske izpostavljenosti. Način prehoda na intravensko zdravljenje z epoprostenolom: Kadar je potreben prehod na intravensko dajanje epoprostenola, je treba prehodno fazo opraviti pod strogim zdravniškim nadzorom. Pri tem se lahko uporabi naslednja priporočena shema prehoda. Infuzije treprostinila je treba najprej počasi zmanjšati na 2,5 ng/kg/min. Po najmanj eni uri novega doseženega odmerka treprostinila se lahko začne zdravljenje z največjim odmerkom epoprostenola, 2 ng/kg/min. Odmerek treprostinila je treba nato zmanjševati v zaporednih presledkih po najmanj dve uri in sočasno, po vzdrževanju začetnega odmerka najmanj eno uro, večati odmerek epoprostenola. Za **način uporabe** glejte celoten Povzetek glavnih značilnosti zdravila za posamezno jakost. **Kontraindikacije:** Znana preobčutljivost za treprostinil ali katerokoli pomožno snov; pljučna arterijska hipertenzija, povezana z vensko okluzivno boleznijo; kongestivna srčna odpoved zaradi hude okvare delovanja levega prekata; hudo okvarjeno delovanje jeter (Child-Pughov razred C).; aktiven čir na želodcu, intrakranialna krvavitev, poškodba ali drugo stanje s krvavitvijo; prirojene ali pridobljene okvare zaklopk s klinično pomembno disfunkcijo srčne mišice, ki ni povezana s pljučno hipertenzijo; huda koronarna srčna bolezen ali nestabilna angina pektoris; miokardni infarkt v preteklih šestih mesecih; dekompenzirana srčna odpoved, ki ni pod skrbnim zdravniškim nadzorom; hude aritmije; cerebrovaskularni dogodki (na primer tranzitorna ishemična ataka, kap) v preteklih treh mesecih. **Posebna opozorila in previdnostni ukrepi:** Pri odločitvi o začetku zdravljenja z zdravilom Remodulin morate upoštevati veliko verjetnost, da bo neprekinjeno infundiranje trajalo dalj časa. Zato je treba pretehtati bolnikovo pripravljenost in odgovornost za sprejetje vstavljenega katetra in naprave za infundiranje. Treprostinil je močan pljučni in sistemski vazodilatator. Pri osebah, pri katerih je sistemski arterijski tlak nizek, lahko zdravljenje s treprostinilom poveča tveganje za sistemsko hipotenzijo. Zdravljenje ni priporočeno pri bolnikih s sistoličnim arterijskim tlakom, nižjim od 85 mmHg. Priporočljivo je, da se ob spremembi odmerka spremlja sistemski krvni tlak in srčni utrip, infundiranje pa je treba prekineti, če se razvijejo simptomi hipotenzije oziroma, če sistolični krvni tlak pade pod 85 mmHg. Nenadna odtegnitev ali hitro znatno zmanjšanje odmerka zdravila Remodulin lahko povzroči ponovni pojav pljučne arterijske hipertenzije. Če bolnik med zdravljenjem z zdravilom Remodulin dobi pljučni edem, je treba upoštevati možnost, da je s tem povezana pljučna venska okluzivna bolezen. Zdravljenje morate prekiniti. Pri bolnikih s čezmerno telesno maso (ITM večji od 30 kg/m2) je očistek treprostinila počasnejši. Korist subkutanega zdravljenja z zdravilom Remodulin pri bolnikih s hujšo pljučno arterijsko hipertenzijo (4. razred po razvrstitvi NYHA) ni bila ugotovljena. Razmerja učinkovitosti in varnosti zdravila Remodulin pri pljučni arterijski hipertenziji, povezani z levo-desnim srčnim spojem, portalno hipertenzijo ali okužbo z virusom HIV, niso raziskovali. Bolnikom z jetrno in ledvično okvaro je treba zdravilo odmerjati previdno. Ker se treprostinil in njegovi presnovki izločajo večinoma z urinom, je treba bolnike z okvarjenim delovanjem ledvic zdraviti previdno, da bi preprečili škodljive posledice zaradi morebitnega povečanja sistemske izpostavljenosti. Bodite previdni v primerih, pri katerih lahko treprostinil z zaviranjem agregacije trombocitov poveča nevarnost krvavitve. Sočasna uporaba zaviralca encima citokroma P450 (CYP) 2C8 (npr. gemfibrozila) lahko poveča izpostavljenost (tako Cmax kot tudi AUC) treprostinilu. Povečana izpostavljenost pa povečuje verjetnost neželenih učinkov, povezanih z uporabo treprostinila. Zato je treba razmisliti o zmanjšanju odmerka treprostinila. Sočasna uporaba spodbujevalca encima CYP2C8 (npr. rifampicina) lahko zmanjša izpostavljenost treprostinilu. Manjša izpostavljenost pa verjetno zmanjša klinično učinkovitost. Zato je treba razmisliti o povečanju odmerka treprostinila. Neželeni učinki, pripisani intravenskemu sistemu dovajanja zdravila: Pri bolnikih, ki so prejemali zdravilo Remodulin v obliki intravenske infuzije, so poročali o okužbah krvi in sepsi, povezanih s centralnim venskim katetrom. Ta tveganja se pripisujejo sistemu dovajanja zdravila. Retrospektivna ocena sedmih centrov v Združenih državah Amerike, kjer so za zdravljenje PAH zdravilo Remodulin uporabljali intravensko, je pokazala stopnjo incidence za okužbe krvi, povezane s katetrom, 1,10 dogodka na 1.000 katetrskih dni. Zdravniki morajo poznati niz možnih po Gramu negativnih in po Gramu pozitivnih organizmov, s katerimi se lahko bolnik pri centralnem venskem katetrom dolgoročno okuži, zato je neprekinjeno subkutano infundiranje nerazredčenega zdravila Remodulin prednostni način dajanja. Klinična ekipa, odgovorna za zdravljenje, mora zagotoviti, da je bolnik povsem usposobljen in zmožen za uporabo izbrane infundirne naprave. **Interakcije:** Upoštevati je treba interakcije z diuretiki, antihipertenzivi ali drugimi vazodilatatorji, zaviralci agregacije trombocitov, vključno z nesteroidnimi protivnetnimi in protirevmatičnimi zdravili in antikoagulanti, furosemidom, spodbujevalci/zaviralci encima citokroma P450 (CYP) 2C8, bosentanom, sildenafilom. **Plodnost, nosečnost in dojenje:** Ženskam v rodni dobi se med zdravljenjem z zdravilom Remodulin priporoča uporaba kontracepcije. Uporaba zdravila Remodulin med nosečnostjo je dovoljena samo, če potencialna korist za nosečnico upravičuje potencialno tveganje za zarodek. Ženskam, ki jemljejo Remodulin, je treba svetovati, da prenehajo z dojenjem. **Povzetek neželenih učinkov:** Za popoln seznam neželenih učinkov glejte celoten Povzetek glavnih značilnosti zdravila, te informacije vključujejo zelo pogoste in pogoste neželene učinke. *Zelo pogosti (≥ 1/10)*: glavobol, vazodilatacija, zardevanje, driska, siljenje na bruhanje, izpuščaj, bolečine v čeljustih, bolečine na mestu infundiranja, reakcija na mestu infundiranja, krvavitev ali hematom. *Pogosti (≥ 1/100 do < 1/10)*: omotica, hipotenzija, krvavitve, bruhanje, pruritus, mialgija, artralgija, bolečina v okončini, edem. **Način in režim predpisovanja in izdaje zdravila:** Predpisovanje in izdaja zdravila je le na recept, zdravilo pa se uporablja samo v bolnišnicah. Izjemoma se lahko uporablja pri nadaljevanju zdravljenja na domu ob odpustu iz bolnišnice in nadaljnjem zdravljenju. **Imetnik dovoljenja za promet:** FERRER INTERNACIONAL, S.A., Gran Vía Carlos III, 94, 08028 – Barcelona, Španija. **Pred predpisovanjem, prosimo, preberite povzetek glavnih značilnosti zdravila. Datum revizije besedila**: 10/2018.

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ALVESCO. **DIHAJTE GLOBOKO.**

Pomagajte svojim bolnikom lažje dihati z zdravilom Alvesco[1]

Zdravilo Alvesco je na voljo v dveh jakostih[1]: 80 mikrogramov in 160 mikrogramov.

- **Drobni delci zdravila Alvesco dosežejo do velikih in malih dihalnih poti[2]**
- **Odlična učinkovitost pri nadzoru vnetja in zmanjšanju simptomov astme[1, 3-4]**
- **Visoka pljučna depozicija in distribucija[1, 3-4]**
- **Majhna sistemska izpostavljenost[1, 3-4]**
- **Titriranje odmerka (korak naprej in korak nazaj) brez ogrožanja varnosti[1, 5-6]**
- **Majhna pojavnost neželenih učinkov[1]**
- **Učinkovitost pri odmerjanju enkrat na dan[1, 3]**
- **Hiter začetek delovanja (znotraj 2,5 ur)[7]**

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA ALVESCO / CIKLEZONID

Ime zdravila in sestava: Alvesco 80 mikrogramov/odmerek inhalacijska raztopina pod tlakom. En vpih (odmerek iz ustnika) vsebuje 80 mikrogramov ciklezonida. Alvesco 160 mikrogramov/odmerek inhalacijska raztopina pod tlakom. En vpih (odmerek iz ustnika) vsebuje 160 mikrogramov ciklezonida. **Terapevtske indikacije:** Zdravljenje za nadzor kronične astme pri odraslih in mladostnikih (starejših od 12 let). **Odmerjanje in način uporabe:** Zdravilo se uporablja samo za inhaliranje. Odmerjanje: Priporočeni odmerki za odrasle in mladostnike: 160 mikrogramov enkrat na dan, kar pri večini bolnikov vodi do obvladovanja astme. Pri nekaterih bolnikih s hudo obliko astme se lahko ob jemanju manjšega odmerka ali prenehanju peroralnega jemanja kortikosteroidov uporabijo večji odmerki do 640 mikrogramov na dan (odmerjen dvakrat na dan po 320 mikrogramov). Bolnikom je treba dati inhalacijski odmerek ciklezonida glede na resnost njihove bolezni. Simptomi se začnejo izboljševati v roku 24 ur po zdravljenju z zdravilom Alvesco. Ko je nadzor astme dosežen, je treba odmerek zdravila Alvesco individualno prilagoditi in titrirati do najmanjšega odmerka, potrebnega za vzdrževanje ustreznega nadzora astme. Zmanjšanje odmerka na 80 mikrogramov enkrat na dan je za nekatere bolnike lahko učinkovit vzdrževalni odmerek. Alvesco inhalacijska raztopina pod tlakom naj bi se uporabljala zvečer, čeprav je dokazano, da je tudi jutranje odmerjanje Alvesco inhalacijske raztopine pod tlakom učinkovito. Končna odločitev o jutranjem ali večernem odmerjanju je prepuščena zdravniku. Bolniki s hudo astmo so izpostavljeni tveganju akutnih napadov, zato je potrebno redno ocenjevati nadzor astme, vključno s preiskavami pljučne funkcije. Pogostejša uporaba bronhodilatatorjev s kratkotrajnim delovanjem za lajšanje simptomov astme kaže na poslabšanje nadzora astme. Če bolnik ugotovi, da se je učinkovitost lajšanja simptomov z bronhodilatatorjem s kratkotrajnim delovanjem zmanjšala, ali da potrebuje več inhalacij kot običajno, mora poiskati zdravniško pomoč. V takem primeru je potrebno znova oceniti stanje bolnika in presoditi o potrebi po intenzivnejšem protivnetnem zdravljenju (npr. višji odmerki Alvesco inhalacijske raztopine pod tlakom za kratko obdobje ali zdravljenje s peroralnimi kortikosteroidi). Huda poslabšanja astme je treba zdraviti na običajen način. Da bi se zadovoljile posebne potrebe bolnika, kot so težave pri sprožitvi inhalatorja in hkratnem vdihu, se Alvesco inhalacijska raztopina pod tlakom lahko uporablja z nastavkom AeroChamber Plus. *Starejši bolniki in bolniki z okvaro ledvic ali jeter:* Pri starejših bolnikih in bolnikih z okvaro jeter ali ledvic odmerka ni treba prilagajati. *Pediatrična populacija:* Zaenkrat ni na voljo dovolj podatkov o zdravljenju s ciklezonidom pri otrocih do 12 let starosti. Način uporabe: Bolnika je treba poučiti o pravilni uporabi inhalatorja. **Kontraindikacije:** Preobčutljivost na ciklezonid ali katerokoli pomožno snov. **Posebna opozorila in previdnostni ukrepi:** Kot velja za vse inhalacijske kortikosteroide, je potrebno uporabljati Alvesco inhalacijsko raztopino pod tlakom previdno pri bolnikih z aktivno ali mirujočo pljučno tuberkulozo, glivičnimi, virusnimi ali bakterijskimi okužbami in to le, če so ti bolniki ustrezno zdravljeni. Kot velja za vse inhalacijske kortikosteroide, Alvesco inhalacijska raztopina pod tlakom ni indicirana za zdravljenje astmatičnega statusa ali drugih akutnih epizod astme, ki zahtevajo intenzivne ukrepe. Alvesco inhalacijska raztopina pod tlakom ni namenjena lajšanju akutnih simptomov astme, pri katerih je potrebna uporaba inhalacijskega bronhodilatatorja s kratkotrajnim delovanjem. Bolnikom je treba svetovati, naj imajo tak olajševalec na razpolago. Pojavijo se lahko sistemski učinki inhalacijskih kortikosteroidov, še posebno pri velikih odmerkih, predpisanih za daljše obdobje. Ti učinki so manj verjetni kot pri uporabi peroralnih kortikosteroidov. Možni sistemski učinki so supresija delovanja nadledvične žleze, upočasnjena rast pri otrocih in mladostnikih, zmanjšanje mineralne gostote kosti, siva mrena in glavkom, redkeje pa spekter psiholoških ali vedenjskih učinkov, vključno s psihomotorično hiperaktivnostjo, motnjami spanja, tesnobo, depresijo ali agresijo (zlasti pri otrocih). Pri otrocih in mladostnikih, ki se dolgotrajno zdravijo z inhalacijskimi kortikosteroidi, je priporočljivo redno nadziranje telesne višine. Pri bolnikih s hudo okvaro jeter se pričakuje večja izpostavljenost, zato je takšne bolnike treba nadzirati glede možnega pojava sistemskih učinkov. Zaradi ugodnega učinka inhalacijskega ciklezonida bi se morala potreba po peroralnih steroidih zmanjšati. Bolniki, ki preidejo s peroralnih steroidov na inhalacijski ciklezonid, so še dolgo časa po prehodu izpostavljeni tveganju okvare nadledvične žleze. Možnost pojava posameznih simptomov lahko traja še nekaj časa. Za podrobne informacije glejte celoten povzetek glavnih značilnosti zdravila. **Interakcije:** Sočasnemu dajanju močnih zaviralcev CYP3A4 (npr. ketokonazol, itrakonazol in ritonavir ali nelfinavir) se je torej treba izogibati, razen če pričakovana korist odtehta povečano tveganje za sistemske neželene učinke kortikosteroidov. **Nosečnost in dojenje:** Kot druge glukokortikoide se tudi ciklezonid med nosečnostjo lahko uporablja le, če je morebitna korist za mater večja od morebitnega tveganja za plod. Uporabiti je treba najnižji učinkoviti odmerek ciklezonida, potreben za vzdrževanje ustreznega nadzora astme. **Neželeni učinki:** *Občasni:* navzea, bruhanje, neprijeten okus v ustih, reakcije na mestu uporabe, suha sluznica na mestu uporabe, glivične infekcije v ustih, glavobol, hripavost, kašelj po inhaliranju, paradoksni bronhospazem, ekcem in izpuščaj. *Redki:* palpitacije, bolečine v trebuhu, dispepsija, angioedem, preobčutljivost, hipertenzija. *Neznana pogostnost:* psihomotorična hiperaktivnost, motnje spanja, tesnoba, depresija, agresija, vedenjske spremembe (pretežno pri otrocih). **Način in režim predpisovanja in izdaje zdravila:** Predpisovanje in izdaja zdravila je le na recept. **Imetnik dovoljenja za promet:** Covis Pharma Europe B.V., Gustav Mahlerplein 2, 1082MA Amsterdam, Nizozemska. **Pred predpisovanjem, prosimo, preberite povzetek glavnih značilnosti zdravila. Datum revizije besedila:** 08/2020.

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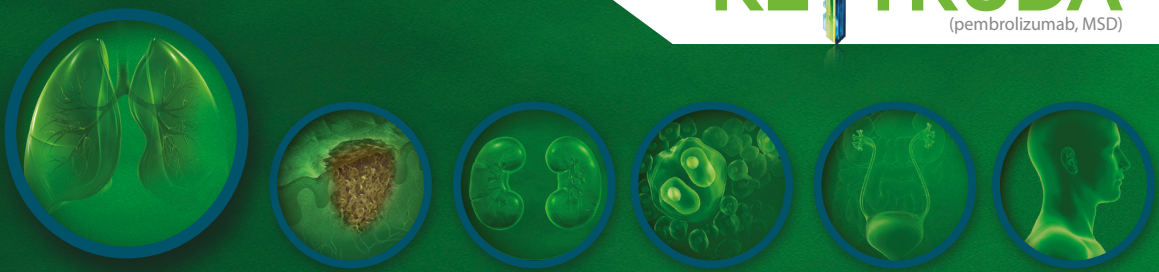

Nedrobnocelični pljučni rak[1] | Melanom[1] | Rak ledvičnih celic[1] | Hodgkinov limfom[1] | Urotelijski karcinom[1] | Ploščatocelični karcinom glave in vratu[1]

References: 1. Keytruda EU SmPC

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

Pred predpisovanjem, prosimo, preberite celoten Povzetek glavnih značilnosti zdravila!

Ime zdravila: KEYTRUDA 25 mg/ml koncentrat za raztopino za infundiranje vsebuje pembrolizumab.

Terapevtske indikacije: Zdravilo KEYTRUDA je kot samostojno zdravljenje indicirano za zdravljenje: napredovalega (neoperabilnega ali metastatskega) melanoma pri odraslih; za adjuvantno zdravljenje odraslih z melanomom v stadiju III, ki se je razširil na bezgavke, po popolni kirurški odstranitvi; metastatskega nedrobnoceličnega pljučnega raka (NSCLC) v prvi liniji zdravljenja pri odraslih, ki imajo tumorje z ≥ 50 % izraženostjo PD-L1 (TPS) in brez pozitivnih tumorskih mutacij EGFR ali ALK; lokalno napredovalega ali metastatskega NSCLC pri odraslih, ki imajo tumorje z ≥ 1 % izraženostjo PD-L1 (TPS) in so bili predhodno zdravljeni z vsaj eno shemo kemoterapije, bolniki s pozitivnimi tumorskimi mutacijami EGFR ali ALK so pred prejemom zdravila KEYTRUDA morali prejeti tudi tarčno zdravljenje; odraslih bolnikov s ponovljenim ali neodzivnim klasičnim Hodgkinovim limfomom (cHL), pri katerih avtologna presaditev matičnih celic (ASCT) in zdravljenje z brentuksimabom vedotinom (BV) nista bila uspešna, in odraslih bolnikov, ki za presaditev niso primerni, zdravljenje z BV pa pri njih ni bilo uspešno; lokalno napredovalega ali metastatskega urotelijskega raka pri odraslih, predhodno zdravljenih s kemoterapijo, ki je vključevala platino; lokalno napredovalega ali metastatskega urotelijskega raka pri odraslih, ki niso primerni za zdravljenje s kemoterapijo, ki vsebuje cisplatin in imajo tumorje z izraženostjo PD-L1 ≥ 10, ocenjeno s kombinirano pozitivno oceno (CPS); ponovljenega ali metastatskega ploščatoceličnega raka glave in vratu (HNSCC) pri odraslih, ki imajo tumorje z ≥ 50 % izraženostjo PD-L1 (TPS), in pri katerih je bolezen napredovala med zdravljenjem ali po zdravljenju s kemoterapijo, ki je vključevala platino. Zdravilo KEYTRUDA je kot samostojno zdravljenje ali v kombinaciji s kemoterapijo s platino in 5-fluorouracilom (5-FU) indicirano za prvo linijo zdravljenja metastatskega ali neoperabilnega ponovljenega ploščatoceličnega raka glave in vratu pri odraslih, ki imajo tumorje z izraženostjo PD-L1 s CPS ≥ 1. Zdravilo KEYTRUDA je v kombinaciji s pemetreksedom in kemoterapijo na osnovi platine indicirano za prvo linijo zdravljenja metastatskega neploščatoceličnega NSCLC pri odraslih, pri katerih tumorji nimajo pozitivnih mutacij EGFR ali ALK; v kombinaciji s karboplatinom in bodisi paklitakselom bodisi nab-paklitakselom je indicirano za prvo linijo zdravljenja metastatskega ploščatoceličnega NSCLC pri odraslih; v kombinaciji z aksitinibom je indicirano za prvo linijo zdravljenja napredovalega raka ledvičnih celic (RCC) pri odraslih. **Odmerjanje in način uporabe**: Testiranje PD-L1 pri bolnikih z NSCLC, urotelijskim rakom ali HNSCC: Za samostojno zdravljenje z zdravilom KEYTRUDA je priporočljivo opraviti testiranje izraženosti PD-L1 tumorja z validirano preiskavo, da izberemo bolnike z NSCLC ali predhodno nezdravljenim urotelijskim rakom. Bolnike s HNSCC je treba za samostojno zdravljenje z zdravilom KEYTRUDA ali v kombinaciji s kemoterapijo s platino in 5-fluorouracilom (5-FU) izbrati na podlagi izraženosti PD-L1, potrjene z validirano preiskavo. Odmerjanje: Priporočeni odmerek zdravila KEYTRUDA za samostojno zdravljenje je bodisi 200 mg na 3 tedne ali 400 mg na 6 tednov, apliciran z intravensko infuzijo v 30 minutah. Priporočeni odmerek za kombinirano zdravljenje je 200 mg na 3 tedne, apliciran z intravensko infuzijo v 30 minutah. Za uporabo v kombinaciji glejte povzetke glavnih značilnosti sočasno uporabljenih zdravil. Če se uporablja kot del kombiniranega zdravljenja skupaj z intravensko kemoterapijo, je treba zdravilo KEYTRUDA aplicirati prvo. Bolnike je treba zdraviti do napredovanja bolezni ali nesprejemljivih toksičnih učinkov. Pri adjuvantnem zdravljenju melanoma je treba zdravilo uporabljati do ponovitve bolezni, pojava nesprejemljivih toksičnih učinkov oziroma mora zdravljenje trajati do enega leta. Če je aksitinib uporabljen v kombinaciji s pembrolizumabom, se lahko razmisli o povečanju odmerka aksitiniba nad začetnih 5 mg v presledkih šest tednov ali več. Pri bolnikih starih ≥ 65 let, bolnikih z blago do zmerno okvaro ledvic, bolnikih z blago okvaro jeter prilagoditev odmerka ni potrebna. Odlo:itev odmerka ali ukinitev zdravljenja: Zmanjšanje odmerka zdravila KEYTRUDA ni priporočljivo. Za obvladovanje neželenih učinkov je treba uporabo zdravila KEYTRUDA zadržati ali ukiniti, prosimo, glejte celoten Povzetek glavnih značilnosti zdravila. **Kontraindikacije**: Preobčutljivost na učinkovino ali katero koli pomožno snov. **Povzetek posebnih opozoril, previdnostnih ukrepov, interakcij in neželenih učinkov**: Imunsko pogojeni neželeni učinki (pnevmonitis, kolitis, hepatitis, nefritis, endokrinopatije, neželeni učinki na kožo in drugi): Pri bolnikih, ki so prejemali pembrolizumab, so se pojavili imunsko pogojeni neželeni učinki, vključno s hudimi in smrtnimi primeri. Večina imunsko pogojenih neželenih učinkov, ki so se pojavili med zdravljenjem s pembrolizumabom, je bila reverzibilnih in so jih obvladali s prekinitvami uporabe pembrolizumaba, uporabo kortikosteroidov in/ali podporno oskrbo. Pojavijo se lahko tudi po zadnjem odmerku pembrolizumaba in hkrati prizadanejo več organskih sistemov. V primeru suma na imunsko pogojene neželene učinke je treba poskrbeti za ustrezno oceno za potrditev etiologije oziroma izključitev drugih vzrokov. Glede na izrazitost neželenega učinka je treba zadržati uporabo pembrolizumaba in uporabiti kortikosteroide – za natančna navodila, prosimo, glejte Povzetek glavnih značilnosti zdravila Keytruda. Zdravljenje s pembrolizumabom lahko poveča tveganje za zavrnitev pri prejemnikih presadkov čvrstih organov. Pri bolnikih, ki so prejemali pembrolizumab, so poročali o hudih z infuzijo povezanih reakcijah, vključno s preobčutljivostjo in anafilaksijo. Pembrolizumab se iz obtoka odstrani s katabolizmom, zato presnovnih medsebojnih delovanj zdravil ni pričakovati. Uporabi sistemskih kortikosteroidov ali imunosupresivov pred uvedbo pembrolizumaba se je treba izogibati, ker lahko vplivajo na farmakodinamično aktivnost in učinkovitost pembrolizumaba. Vendar pa je kortikosteroide ali druge imunosupresivne mogoče uporabiti za zdravljenje imunsko pogojenih neželenih učinkov. Kortikosteroide je mogoče uporabiti tudi kot premedikacijo, če je pembrolizumab uporabljen v kombinaciji s kemoterapijo, kot antiemetično profilakso in/ali za ublažitev neželenih učinkov, povezanih s kemoterapijo. Ženske v rodni dobi morajo med zdravljenjem s pembrolizumabom in vsaj še 4 mesece po zadnjem odmerku pembrolizumaba uporabljati učinkovito kontracepcijo, med nosečnostjo in dojenjem se ga ne sme uporabljati.

Varnost pembrolizumaba pri samostojnem zdravljenju so v kliničnih študijah ocenili pri 5.884 bolnikih z napredovalim melanomom, kirurško odstranjenim melanomom v stadiju III (adjuvantno zdravljenje), NSCLC, cHL, urotelijskim rakom ali HNSCC s štirimi odmerki (2 mg/kg na 3 tedne, 200 mg na 3 tedne in 10 mg/kg na 2 ali 3 tedne). V tej populaciji bolnikov je mediani čas opazovanja znašal 7,3 mesece (v razponu od 1 dneva do 31 mesecev), najpogostejši neželeni učinki zdravljenja s pembrolizumabom so bili utrujenost (32 %), navzea (20 %) in diareja (20 %). Večina poročanih neželenih učinkov pri samostojnem zdravljenju je bila po izrazitosti 1. ali 2. stopnje. Najresnejši neželeni učinki so bili imunsko pogojeni neželeni učinki in hude z infuzijo povezane reakcije. Varnost pembrolizumaba pri kombiniranem zdravljenju s kemoterapijo so ocenili pri 1.067 bolnikih NSCLC ali HNSCC, ki so v kliničnih študijah prejemali pembrolizumab v odmerkih 200 mg, 2 mg/kg ali 10 mg/kg na vsake 3 tedne. V tej populaciji bolnikov so bili najpogostejši neželeni učinki naslednji: anemija (50 %), navzea (50 %), utrujenost (37 %), zaprtost (35%), diareja (30 %), nevtropenija (30 %), zmanjšanje apetita (28 %) in bruhanje (25 %). Pri kombiniranem zdravljenju s pembrolizumabom je pri bolnikih z NSCLC pojavnost neželenih učinkov 3. do 5. stopnje znašala 67 %, pri zdravljenju samo s kemoterapijo pa 66 %, pri kombiniranem zdravljenju s pembrolizumabom pri bolnikih s HNSCC 85 % in pri zdravljenju s kemoterapijo v kombinaciji s cetuksimabom 84 %. Varnost pembrolizumaba v kombinaciji z aksitinibom so ocenili v klinični študiji pri 429 bolnikih z napredovalim rakom ledvičnih celic, ki so prejemali 200 mg pembrolizumaba na 3 tedne in 5 mg aksitiniba dvakrat na dan. V tej populaciji bolnikov so bili najpogostejši neželeni učinki diareja (54 %), hipertenzija (45 %), utrujenost (38 %), hipotiroidizem (35 %), zmanjšan apetit (30 %), sindrom palmarno-plantarne eritrodisestezije (28 %), navzea (28 %), zvišanje vrednosti ALT (27 %), zvišanje vrednosti AST (26 %), disfonija (25 %), kašelj (21 %) in zaprtost (21 %). Pojavnost neželenih učinkov 3. do 5. stopnje je bila med kombiniranim zdravljenjem s pembrolizumabom 76 % in pri zdravljenju s sunitinibom samim 71 %. Za celoten seznam neželenih učinkov, prosimo, glejte celoten Povzetek glavnih značilnosti zdravila

Način in režim izdaje zdravila: H – Predpisovanje in izdaja zdravila je le na recept, zdravilo se uporablja samo v bolnišnicah.

Imetnik dovoljenja za promet z zdravilom: Merck Sharp & Dohme B.V. , Waarderweg 39, 2031 BN Haarlem, Nizozemska.

MSD

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Šmartinska cesta 140, 1000 Ljubljana, tel: +386 1/ 520 42 01, fax: +386 1/ 520 43 50

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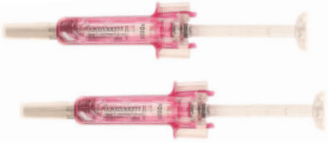
Samo za strokovno javnost.

H - Predpisovanje in izdaja zdravila je le na recept, zdravilo pa se uporablja samo v bolnišnicah. Pred predpisovanjem, prosimo, preberite celoten Povzetek glavnih značilnosti zdravila Keytruda, ki je na voljo pri naših strokovnih sodelavcih ali na lokalnem sedežu družbe.

KRONIČNA SPONTANA URTIKARIJA



Odobren odmerek je **300 mg** (2 x 150 mg) vsake štiri tedne s subkutano injekcijo.[1]

Skrajšan povzetek glavnih značilnosti zdravila Xolair

Ime zdravila: Xolair 150 mg raztopina za injiciranje v napolnjeni injekcijski brizgi. **Sestava:** Vsaka napolnjena injekcijska brizga z 1 ml raztopine vsebuje 150 mg omalizumaba. Omalizumab je humanizirano monoklonsko protitelo, ki ga izdelujejo s tehnologijo rekombinantne DNA v liniji sesalskih celic ovarija kitajskega hrčka (CHO- Chinese hamster ovary). **Terapevtske indikacije:** Kronična spontana urtikarija: Zdravilo Xolair je indicirano kot dodatno zdravilo za zdravljenje odraslih in mladostnikov (starih 12 let ali več), ki imajo kronično spontano urtikarijo, njihov odziv na zdravljenje z zaviralci histaminskih receptorjev H1 pa ni zadosten. Alergijska astma: Zdravilo Xolair je indicirano tudi za zdravljeneje alergijske astme pri odraslih, mladostnikih in otrocih (starih 6 do <12 let). Za podrobnejše informacije glede terapevtske indikacije alergijska astma prosimo preberite celoten povzetek glavnih značilnosti zdravila. **Odmerjanje:** Kronična spontana urtikarija: Priporočeni odmerek je 300 mg s subkutano injekcijo vsake štiri tedne. Alergijska astma: Ustrezni odmerek in pogostnost zdravila Xolair se določata z izhodiščnim IgE (i.e./ml), izmerjenim pred začetkom zdravljenja, in s telesno maso (maks. 150 kg). Največji priporočeni odmerek je 600 mg omalizumaba enkrat na dva tedna. Zdravilo Xolair je namenjeno dolgotrajnemu zdravljenju. Za podrobnejše informacije glede odmerjanja pri terapevtski indikaciji alergijska astma prosimo preberite celoten povzetek glavnih značilnosti zdravila. Posebne skupine bolnikov: O uporabi zdravila Xolair pri bolnikih, starejših od 65 let, in pri bolnikih z okvaro jeter ali ledvic, so na voljo le omejeni podatki. Posebno prilagajanje odmerkov ni priporočeno. Za uporabo pri alergijski astmi varnost in učinkovitost zdravila Xolair pri pediatričnih bolnikih starih manj kot 6 let nista bili dokazani. Za uporabo pri kronični spontani urtikariji varnost in učinkovitost zdravila Xolair pri pediatričnih bolnikih, starih manj kot 12 let, nista bili dokazani. Način uporabe: Zdravilo je namenjeno samo za subkutano uporabo. Zdravila Xolair se ne sme dajati intravensko ali intramuskularno. Odmerke, ki presegajo 150 mg, je treba razdeliti in aplicirati na dveh ali več mestih injiciranja. Bolniki brez anamneze anafilaksije si lahko od 4. odmerka dalje sami injicirajo zdravilo Xolair oziroma jim ga lahko injicira njihov negovalec, če zdravnik presodi, da je to primerno. Bolnika oziroma negovalca je treba pred tem naučiti ustrezne tehnike injiciranja in prepoznavanja zgodnjih znakov in simptomov resne alergijske reakcije. Bolnikom oziroma njihovim negovalcem je treba naročiti, naj injicirajo celotno količino zdravila Xolair po navodilih v Navodilu za uporabo. **Kontraindikacije:** preobčutljivost na učinkovino ali katerokoli pomožno snov. **Posebna opozorila in previdnostni ukrepi:** Splošno: Zdravilo Xolair ni indicirano za zdravljenje akutnih eksacerbacij astme, akutnega bronhospazma ali astmatičnega statusa. Zdravilo Xolair ni indicirano za zdravljenje bolnikov s sindromom hiperimunoglobulina E ali alergijske bronhopulmonalne aspergiloze ali za preprečevanje anafilaktičnih reakcij, vključno s tistimi, ki jih izzove alergija na hrano, atopijski dermatitis ali alergijski rinitis. Zdravljenja z zdravilom Xolair niso proučevali pri bolnikih z avtoimunskimi boleznimi, s stanji, v katere je vpleten imunski kompleks, ali z že obstoječimi okvarami ledvic ali jeter. Nenadne ukinitve sistemskih kortikosteroidov ali kortikosteroidov za inhalacijo po uvedbi zdravljenja z zdravilom Xolair ne priporočajo. Bolezni imunskega sistema: *Alergijske reakcije tipa I:* Pri uporabi omalizumaba se lahko pojavijo lokalne ali sistemske alergijske reakcije tipa I, vključno z anafilaksijo in anafilaktičnim šokom. Lahko se zgodi, da se pojavijo šele po dolgotrajnem zdravljenju, vendar je večina teh reakcij je nastopila v prvih 2 urah po prvem in po enem od nadaljnih injiciranj zdravila Xolair, nekatere pa so nastopile tudi po več kot 2 urah in celo več kot 24 urah po injiciranju. Do večine anafilaktičnih reakcij je prišlo v okviru prvih treh odmerjanj zdravila Xolair, zato mora prve tri odmerke zdravila aplicirati ali njihovo apliciranje nadzorovati zdravstveni delavec. Anafilaksija brez povezave z omalizumabom v anamnezi lahko predstavlja dejavnik tveganja za pojav anafilaksije po odmerjanju zdravila Xolair. Zato mora bolnikom z ugotovljeno anamnezo anafilaksije zdravilo Xolair aplicirati zdravstveni delavec, ki mora imeti ob aplikaciji zdravila Xolair vedno na voljo zdravila za zdravljenje anafilaktičnih reakcij, pripravljena za takojšnjo uporabo. Če pride do anafilaktične ali druge resne alergijske reakcije, je treba odmerjanje zdravila Xolair takoj prekiniti in uvesti ustrezno zdravljenje. Bolnikom moramo povedati, da so takšne reakcije možne, ob pojavu alergijskih reakcij pa morajo poiskati takojšnjo zdravniško pomoč. *Serumska bolezen:* Pri bolnikih, zdravljenih s humaniziranimi monoklonskimi protitelesi, med katera sodi tudi omalizumab, so opažali serumsko bolezen in njej podobne reakcije, ki so zapoznele alergijske reakcije tipa III. *Churg-Straussov sindrom in hipereozinofilni sindrom:* Pri bolnikih s hudo astmo se v redkih primerih izrazi sistemski hipereozinofilni sindrom ali alergijski eozinofilni granulomatozni vaskulitis (Churg-Straussov sindrom). Pri bolnikih, ki uporabljajo zdravila za zdravljenje astme, vključno z omalizumabom, se v redkih primerih izrazita oziroma razvijeta sistemska eozinofilija in vaskulitis. Pri teh bolnikih je treba biti pozoren glede pojavljanja izrazite eozinofilije, izpuščaja v povezavi z vaskulitisom, slabšanja pljučnih simptomov, bolezenskih sprememb v obnosnih votlinah, zapletov na srcu in/ali nevropatije. Pri vseh hudih primerih navedenih bolezni imunskega sistema je treba pretehtati možnost prekinitve zdravljenja z omalizumabom. Infestacije s paraziti (helminti) IgE utegne biti vpleten v imunski odziv na nekatere infestacije s helminti. Sistemski eritematozni lupus V kliničnih študijah in obdobju trženja zdravila so poročali o primerih sistemskega eritematoznega lupusa (SLE) pri bolnikih z zmerno do hudo astmo in tistih s kronično spontano urtikarijo. Patogeneza SLE ni dobro pojasnjena. Osebe s preobčutljivostjo na lateks Snemljiv pokrovček igle pri tej napolnjeni injekcijski brizgi vsebuje derivat naravnega lateksa. zato obstaja določeno tveganje za preobčutljivostne reakcije, ki ga ni mogoče povsem izključiti. Nosečnosti in dojenje: Zdravila Xolair se ne sme uporabljati med nosečnostjo, razen če je nujno potrebno. Ženske v času dojenja ne smejo prejemati omalizumaba. **Medsebojno delovanje z drugimi zdravili:** IgE utegne biti vpleten v imunski odziv na nekatere infestacije s helminti. Če se bolniki ne odzovejo na priporočeno zdravljenje infestacije s helminti, je treba pretehtati možnost ukinitve zdravila Xolair. Encimi citokroma P450, iztočne črpalke in mehanizmi vezave beljakovin nimajo vpliva na očistek omalizumaba, zato obstajajo za interakcije med zdravili le manjše možnosti. Ni farmakološkega razloga za pričakovanje, da bi pogosto predpisovana zdravila, ki se uporabljajo pri zdravljenju astme in kroničnе spontane urtikarije, medsebojno delovala z omalizumabom. **Neželeni učinki:** **Kronična spontana urtikarija** (pri uporabi 300 mg omalizumaba) ***Pogosti:*** sinusitis, glavobol, artralgija, reakcije na mestu injiciranja, okužba zgornjih dihal. **Alergijska astma Zelo pogosti:** zvišana telesna temperatura (pri otrocih, starih 6 do <12 let). ***Pogosti:*** glavobol (zelo pogosti pri otrocih, starih 6 do <12 let), bolečine v zgornjem delu trebuha (pri otrocih, starih 6 do <12 let), reakcije na mestu injiciranja, na primer oteklina, eritem, bolečina, pruritus. ***Občasni:*** faringitis, sinkopa, parestezije, zaspanost, vrtoglavost, ortostatska hipotenzija, navali rdečice, alergijski bronhospazem, kašelj, znaki in simptomi dispepsije, driska, navzea, preobčutljivost za svetlobo, urtikarija, izpuščaj, pruritus, gripi podobna bolezen, otekanje zgornjih udov, zvečanje telesne mase, utrujenost. ***Redki:*** infestacija s parazitom, anafilaktična reakcija, druga resna alergijska stanja, razvoj protiteles proti omalizumabu, edem larinksa, angioedem, sistemski eritematozni lupus. ***Pogostnost neznana:*** idiopatična trombocitopenija, vključno s hudimi primeri, serumska bolezen, lahko vključuje zvišano telesno temperaturo in limfadenopatijo, alergijski granulomatozni vaskulitis (oziroma Churg-Straussov sindrom), alopecija, artralgija, mialgija, otekanje sklepov. Opis izbranih neželenih učinkov povezanih z obema indikacijama V kliničnih preskušanjih so bile anafilaktične reakcije redke. V kontroliranih kliničnih preskušanjih in pri vmesni analizi podatkov iz observacijske študije, so opažali številčno neravnovesje arterijskih trombemboličnih dogodkov (le-ti so vključevali možgansko kap, tranzitorno ishemično atako, miokardni infarkt, nestabilno angino pektoris, kardiovaskularno smrt (vključno s smrtjo iz neznanega vzroka)). Le redki bolniki so imeli koncentracije trombocitov pod spodnjo mejo okvira normalnih vrednosti laboratorija. **Način in režim izdajanja:** H/Rp. **Imetnik dovoljenja za promet:** Novartis Europharm Limited, Vista Building, Elm Park, Merrion Road, Dublin 4, Irska. **Dodatne informacije in literatura:** Novartis Pharma Services Inc., Verovškova ulica 57, 1000 Ljubljana, Slovenija. **Pred predpisovanjem natančno preberite zadnji odobreni povzetek glavnih značilnosti zdravila. Datum zadnje revizije skrajšanega povzetka glavnih značilnosti zdravila: januar 2019.**

Literatura: 1. Povzetek glavnih značilnosti zdravila Xolair 75 mg/150 mg raztopina za injiciranje v napolnjeni injekcijski brizgi, datum zadnje revizije besedila januar 2019.

Samo za strokovno javnost | Datum priprave materiala: januar 2019 | SI-2019-XOL-014

NOVARTIS Novartis Pharma Services Inc., Podružnica v Sloveniji
Verovškova 57, 1000 Ljubljana, telefon: 01 3007550

Xolair® omalizumab

Prvo in edino konjugirano cepivo proti pnevmokokom, odobreno za uporabo pri dojenčkih, otrocih, mladostnikih in odraslih bolnikih.[1,2]

En sam odmerek pri starejših od 2 let.[1*]

Nedavna okužba z virusom gripe lahko poveča možnosti za okužbo s pljučnico za kar 100-krat.[3]

Cepivo Prevenar 13 je mogoče dati sočasno s sezonskim štirivalentnim inaktiviranim cepivom proti gripi.[1]

BISTVENI PODATKI IZ POVZETKA GLAVNIH ZNAČILNOSTI ZDRAVILA

PREVENAR 13 suspenzija za injiciranje, cepivo proti pnevmokokom, polisaharidno, konjugirano (13-valentno, adsorbirano)
Sestava in oblika zdravila: En odmerek (0,5 ml) vsebuje pnevmokokne polisaharide serotipa 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F in 23F, ki so konjugirani na nosilno beljakovino CRM_{197}, adsorbirani na aluminijev fosfat. **Indikacije:** Aktivna imunizacija za preprečevanje invazivnih bolezni, pljučnice in akutnega vnetja srednjega ušesa, ki jih povzroča *Streptococcus pneumoniae* pri dojenčkih, otrocih in mladostnikih, starih od 6 tednov do 17 let. Aktivna imunizacija za preprečevanje invazivnih bolezni in pljučnice, ki jih povzroča *S. pneumoniae* pri odraslih, starih 18 let in več, ter starejših. **Odmerjanje in način uporabe:** Sheme cepljenja s cepivom Prevenar 13 morajo temeljiti na uradnih priporočilih. Dojenčki in otroci, stari od 6 tednov do 5 let: Priporočljivo je, da se cepljenje pri dojenčkih, ki so prejeli prvi odmerek cepiva Prevenar 13, dokonča s cepivom Prevenar 13. Dojenčki, stari od 6 tednov do 6 mesecev: V osnovni shemi s tremi odmerki priporočeno cepljenje sestavljajo štirje odmerki po 0,5 ml. Shemo osnovnega cepljenja sestavljajo trije odmerki, cepljenje s prvim odmerkom pa se običajno opravi pri starosti 2 mesecev. Med dvema odmerkoma mora miniti vsaj 1 mesec. Cepljenje s prvim odmerkom se lahko opravi že pri starosti šestih tednov. Cepljenje s četrtim (obnovitvenim) odmerkom je priporočljivo opraviti v starosti od 11. do 15. meseca. Nedonošenčki (< 37 tednov nosečnosti): Priporočeno shemo sestavljajo štirje odmerki po 0,5 ml. Shemo osnovnega cepljenja za dojenčke sestavljajo trije odmerki. Cepljenje s prvim odmerkom se običajno opravi pri starosti 2 mesecev. Med dvema odmerkoma mora miniti vsaj 1 mesec. Cepljenje s prvim odmerkom se lahko opravi že pri starosti šestih tednov. Cepljenje s četrtim (obnovitvenim) odmerkom je priporočljivo opraviti v starosti od 11. do 15. meseca. Predhodno necepljeni dojenčki in otroci, stari 7 mesecev ali več: Dojenčki, stari od 7 do 11 mesecev, prejmejo 2 odmerka, vsak po 0,5 ml. Med obema odmerkoma mora miniti vsaj 1 mesec. Cepljenje s tretjim odmerkom je priporočljivo v drugem letu življenja. Otroci, stari od 12 do 23 mesecev, prejmejo 2 odmerka, vsak po 0,5 ml. Med obema odmerkoma morata miniti vsaj 2 meseca. Otroci in mladostniki, stari od 2 do 17 let, prejmejo 1 odmerek po 0,5 ml. Shema cepljenja s cepivom Prevenar 13 za dojenčke in otroke, ki so bili predhodno cepljeni s cepivom Prevenar (7-valentno) (serotipi *S. pneumoniae* 4, 6B, 9V, 14, 18C, 19F in 23F): Prevenar 13 vsebuje istih 7 serotipov kot Prevenar na isti nosilni beljakovini CRM_{197}. Pri dojenčkih in otrocih, pri katerih se je cepljenje začelo s cepivom Prevenar, se lahko preide na Prevenar 13 kadarkoli med shemo. Majhni otroci (12-59 mesecev), ki so popolnoma imunizirani s cepivom Prevenar (7-valentnim), morajo prejeti en 0,5 ml odmerek cepiva Prevenar 13 za sprožitev imunskih odgovorov na 6 dodatnih serotipov. Tak odmerek cepiva Prevenar 13 je treba dati najmanj 8 tednov po zadnjem odmerku cepiva Prevenar (7-valentnega). Otroci in mladostniki (5 do 17 let) lahko prejmejo enkratni odmerek cepiva Prevenar 13, če so bili predhodno cepljeni z enim ali več odmerki cepiva Prevenar. Tak odmerek cepiva Prevenar 13 je treba dati najmanj 8 tednov po zadnjem odmerku cepiva Prevenar (7-valentnega). Odrasli, stari 18 let in več, ter starejši: En sam odmerek. Potreba po ponovnem cepljenju z naslednjim odmerkom cepiva Prevenar 13 ni bila dokazana. Ne glede na to, ali je bil bolnik predhodno že cepljen proti pnevmokokom, je v primeru priporočljive uporabe 23-valentnega pnevmokoknega polisaharidnega cepiva najprej treba dati Prevenar 13. Posebne populacije: Posamezniki, ki so zaradi osnovnih bolezni lahko nagnjeni k invazivni pnevmokokni bolezni (kot je srpastocelična anemija ali okužba s HIV), vključno z osebami, ki so bile predhodno cepljene z enim ali več odmerki 23-valentnega pnevmokoknega polisaharidnega cepiva, lahko prejmejo vsaj en odmerek cepiva Prevenar 13. Posamezniki s presadkom hematopoetskih matičnih celic (HSCT): priporočeno shemo sestavljajo štirje odmerki po 0,5 ml. Osnovno shemo sestavljajo 3 odmerki; cepljenje s prvim odmerkom se običajno opravi 3 do 6 mesecev po HSCT. Med dvema odmerkoma mora miniti vsaj 1 mesec. Cepljenje s četrtim (obnovitvenim) odmerkom je priporočljivo opraviti 6 mesecev po tretjem odmerku. Način uporabe: Cepivo je treba injicirati intramuskularno. Pri dojenčkih je najprimernejše mesto injiciranja anterolateralni predel stegna (mišica *vastus lateralis*), pri otrocih in odraslih pa deltoidna mišica nadlakti. **Kontraindikacije:** Preobčutljivost na učinkovine, katerokoli pomožno snov ali davični toksoid. Kot pri drugih cepivih je treba cepljenje odložiti pri osebah, ki imajo hudo akutno vročinsko bolezen. Blaža okužba, na primer prehlad, ni razlog za odložitev cepljenja. **Posebna opozorila in previdnostni ukrepi:** Cepiva Prevenar 13 se ne sme aplicirati intravaskularno. Dajanju cepiva lahko v redkih primerih sledi anafilaktična reakcija. Pri cepljenju je, tako kot pri vseh cepivih, ki se injicirajo, treba zagotoviti ustrezno obliko zdravljenja in zdravniškega nadzora, ki mora biti v takšnem primeru nemudoma na voljo. S tem cepivom v obliki intramuskularne injekcije ne smemo cepiti posameznikov s trombocitopenijo ali kako drugo motnjo strjevanja krvi, pri kateri je intramuskularno dajanje kontraindicirano. Cepivo se sme dati subkutano, če je korist cepljenja znatno večja od možnega tveganja. Kot velja tudi za druga cepiva, je možno, da Prevenar 13 pred pnevmokoknimi boleznimi ne bo zaščitil vseh cepljenih oseb. Pri posameznikih z oslabljeno imunsko odzivnostjo je imunski odziv na aktivno imunizacijo lahko zmanjšan. Podatki o varnosti in imunogenosti za posamezníke s srpastocelično anemijo, okužbo s HIV ali HSCT so omejeni; pri posameznikih iz drugih specifičnih skupin imunsko oslabljenih posameznikov pa niso na voljo, zato je treba potrebo po cepljenju pretehtati individualno. To cepivo vsebuje manj kot 1 mmol natrija (23 mg) na odmerek, kar v bistvu pomeni 'brez natrija'. Dojenčki in otroci, stari od 6 tednov do 5 let: Uporaba konjugiranega cepiva proti pnevmokokom ne nadomesti uporabe 23-valentnega pnevmokoknega polisaharidnega cepiva pri otrocih, starih ≥ 2 leti, s stanji, zaradi katerih obstaja večje tveganje za invazivno bolezen, ki jo povzroča bakterija *S. pneumoniae*. Pri osnovnem cepljenju veliko prezgodaj rojenih nedonošenčkov (rojenih pred ali v 28. tednu nosečnosti), še posebej tistih z respiratorno nezrelostjo v anamnezi, je treba upoštevati možnost pojava apneje in potrebo po 48-urnem do 72-urnem spremljanju pljučne funkcije. Ker je korist cepljenja v tej skupini dojenčkov velika, se cepljenja ne sme izpustiti ali odložiti. Za serotipe, ki jih vsebuje cepivo, pričakujemo, da bo zaščita pred vnetjem srednjega ušesa manjša kot zaščita pred invazivnimi boleznimi. Pri sočasni uporabi cepiva Prevenar 13 s cepivom Infanrix hexa (DTPa-HBV-IPV/Hib) je stopnja vročinskih reakcij podobna kot pri sočasni uporabi cepiva Prevenar (7-valentnega) in cepiva Infanrix hexa. Pri sočasni uporabi so opazili tudi zvečano stopnjo poročanja konvulzij (z vročino ali brez nje) ter epizod hipotonije in zmanjšane odzivnosti. Pri otrocih z napadi krčev ali anamnezo vročinskih krčev in tistih, ki prejmejo Prevenar 13 skupaj s cepivom proti oslovskemu kašlju s celimi celicami, je treba uvesti zdravljenje vročine. **Medsebojno delovanje z drugimi zdravili:** Dojenčki in otroci, stari od 6 tednov do 5 let: Prevenar 13 se lahko uporablja skupaj s katerimkoli od naslednjih antigenov, bodisi v obliki monovalentnih ali kombiniranih cepiv: s cepivom proti davici, tetanusu, z acelularnim cepivom proti oslovskemu kašlju ali s cepivom proti oslovskemu kašlju s celimi celicami, s cepivom proti *Haemophilus influenzate* tipa b, z inaktiviranim cepivom proti poliomielitisu, s cepivom proti hepatitisu B, s cepivom proti meningokokom serološke skupine C, s cepivom proti ošpicam, mumpsu, rdečkam, noricam in rotavirusom. Otrokom, ki so prejeli ustrezno osnovno cepljenje s cepivom Prevenar 13 (skladno z lokalnimi priporočili), lahko med 12. in 23. mesecem Prevenar 13 dajemo tudi sočasno s polisaharidnim cepivom proti meningokokom seroloških skupin A, C, W in Y, konjugiranim na tetanusni toksoid. Podatki iz klinične študije o vplivu profilaktične uporabe ibuprofena in paracetamola na imunski odziv na Prevenar 13 kažejo, da lahko uporaba paracetamola sočasno ali v istem dnevu kot cepljenje zmanjša imunski odziv na Prevenar 13 pri cepljenju dojenčkov. Odziv na obnovitveni odmerek, dan pri 12 mesecih starosti, so bili nespremenjeni. Otroci in mladostniki, stari od 6 do 17 let, ter odrasli, stari od 18 do 49 let: Podatki o sočasni uporabi z drugimi cepivi niso na voljo. Odrasli, stari 50 let in več: Prevenar 13 lahko dajemo sočasno s sezonskim trivalentnim ali štirivalentnim inaktiviranim cepivom proti gripi. Sočasne uporabe z drugimi cepivi niso raziskali. Različna cepiva za injiciranje je treba vedno injicirati na različna mesta. Sočasnega dajanja cepiva Prevenar 13 in 23-valentnega pnevmokoknega polisaharidnega cepiva niso raziskali. **Plodnost, nosečnost in dojenje:** Podatkov o uporabi pri nosečnicah ni, zato se je treba uporabi med nosečnostjo izogibati. Ni znano, ali se 13-valentno pnevmokoko konjugirano cepivo pri človeku izloča v mleko. Študije na živalih ne kažejo neposrednega ali posrednega škodljivega vpliva na sposobnost razmnoževanja. **Vpliv na sposobnost vožnje in upravljanja strojev:** Nima vpliva ali ima zanemarljiv vpliv, vendar lahko nekateri neželeni učinki začasno vplivajo na sposobnost vožnje in upravljanja strojev. **Neželeni učinki:** Dojenčki in otroci, stari od 6 tednov do 5 let: Zelo pogosti neželeni učinki (≥ 1/10) so zmanjšan apetit, pireksija, razdražljivost; rdečina, zatrdlina/oteklina, bolečina/občutljivost na mestu cepljenja; somnolenca, motnje spanja; rdečina ali zatrdlina/oteklina na mestu cepljenja 2,5 cm-7,0 cm v premeru. Otroci in mladostniki, stari od 6 do 17 let: Zelo pogosti neželeni učinki so zmanjšan apetit, razdražljivost; rdečina, zatrdlina/oteklina, bolečina/občutljivost na mestu cepljenja; somnolenca, motnje spanja, občutljivost na mestu cepljenja (vključno z motnjami gibanja). Odrasli, stari 18 let in več, ter starejši: Zelo pogosti neželeni učinki so zmanjšan apetit, glavoboli, diareja, bruhanje, izpuščaj, mrzlica, utrujenost; rdečina, zatrdlina/oteklina, bolečina/občutljivost na mestu cepljenja; omejena sposobnost gibanja roke, pireksija, artralgija, mialgija. **Način izdajanja:** Predpisovanje in izdaja zdravila je le na recept, zdravilo pa se uporablja samo v javnih zdravstvenih zavodih ter pri pravnih in fizičnih osebah, ki opravljajo zdravstveno dejavnost. **Imetnik dovoljenja za promet:** Pfizer Europe MA EEIG, Boulevard de la Plaine 17, 1050 Bruxelles, Belgija. **Datum zadnje revizije besedila:** 14.11.2019
Pred predpisovanjem se seznanite s celotnim povzetkom glavnih značilnosti zdravila.

Literatura: 1. Povzetek glavnih značilnosti zdravila Prevenar 13, 14.11.2019. **2.** Povzetek glavnih značilnosti zdravila Synflorix, 22.11.2018. **3.** Shrestha S, Foxman B, Berus J, et al. The role of influenza in the epidemiology of pneumonia. *Sci Rep*. 2015;5:15314.

* Potreba po ponovnem cepljenju z dodatnim odmerkom cepiva Prevenar 13 ni bila dokazana. Pri posameznikih s presadkom hematopoetskih matičnih celic priporočeno shemo cepljenja sestavljajo 4 odmerki cepiva Prevenar 13 po 0,5 ml. Osnovno shemo sestavljajo trije odmerki. Cepljenje s prvim odmerkom se običajno opravi 3 do 6 mesecev po presadku hematopoetskih matičnih celic. Med dvema odmerkoma mora miniti vsaj 1 mesec. Cepljenje s četrtim (obnovitvenim) odmerkom je priporočljivo opraviti 6 mesecev po tretjem odmerku.[1]

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Prevenar 13®
cepivo proti pnevmokokom, polisaharidno, konjugirano (13-valentno, adsorbirano)

PRE-08-20 **"Samo za strokovno javnost"**

LORVIQUA®▼
LORLATINIB

NASLEDNJA LINIJA JE JASNA

Zdravilo Lorviqua v monoterapiji je indicirano za zdravljenje odraslih bolnikov z napredovalim nedrobnoceličnim rakom pljuč (NSCLC), ki je ALK (anaplastična limfomska kinaza) pozitiven, pri katerih je bolezen napredovala po:[1]

- **zdravljenju z alektinibom ali ceritinibom kot prvim ALK zaviralcem tirozin kinaze (TKI); ali**
- **zdravljenju s krizotinibom in vsaj še 1 drugim ALK TKI.**

Zdravila Lorviqua Zavod za zdravstveno zavarovanje Slovenije še ni razvrstil na listo zdravil.[2]

NSCLC = (Non-Small Cell Lung Cancer) nedrobnocelični rak pljuč, **ALK** = anaplastična limfomska kinaza, **TKI** = (Tyrosine Kinase Inhibitor) zaviralec tirozin kinaze.

BISTVENI PODATKI IZ POVZETKA GLAVNIH ZNAČILNOSTI ZDRAVILA

Lorviqua 25 mg, 100 mg filmsko obložene tablete
▼Za to zdravilo se izvaja dodatno spremljanje varnosti. Tako bodo hitreje na voljo nove informacije o njegovi varnosti. Zdravstvene delavce naprošamo, da poročajo o kateremkoli domnevnem neželenem učinku zdravila. Glejte poglavje 4.8 povzetka glavnih značilnosti zdravila, kako poročati o neželenih učinkih. **Sestava in oblika zdravila:** Ena filmsko obložena tableta vsebuje 25 mg ali 100 mg lorlatiniba in 1,58 mg oz. 4,20 mg laktoze monohidrata. **Indikacije:** Zdravljenje odraslih bolnikov z napredovalim nedrobnoceličnim rakom pljuč (NSCLC – *Non-Small Cell Lung Cancer*), ki je ALK (anaplastična limfomska kinaza) pozitiven, pri katerih je bolezen napredovala po: zdravljenju z alektinibom ali ceritinibom kot prvim ALK zaviralcem tirozin kinaze (TKI – *Tyrosine Kinase Inhibitor*) ali zdravljenju s krizotinibom in vsaj še 1 drugim ALK TKI. **Odmerjanje in način uporabe:** Zdravljenje mora uvesti in nadzorovati zdravnik, ki ima izkušnje z uporabo zdravil za zdravljenje rakavih bolezni. Priporočeni odmerek je 100 mg peroralno enkrat na dan. Zdravljenje je priporočeno, dokler bolniku prinaša klinično korist brez nesprejemljive toksičnosti. Če bolnik izpusti odmerek ga mora vzeti takoj, ko se spomni, razen če do naslednjega odmerka manjka manj kot 4 ure. Bolniki ne smejo vzeti 2 odmerkov hkrati, da bi nadomestili izpuščeni odmerek. Prilagajanje odmerkov: Ravni zmanjšanja odmerka: *prvo zmanjšanje odmerka*: 75 mg peroralno enkrat na dan; *drugo zmanjšanje odmerka*: 50 mg peroralno enkrat na dan. Zdravljenje je treba trajno prekiniti, če bolnik ne prenaša odmerka 50 mg peroralno enkrat na dan. Za prilagajanje odmerkov zaradi neželenih učinkov glejte preglednico 1 v SmPC-ju. Posebne populacije: *Starejši bolniki (≥ 65 let):* Zaradi omejenih podatkov priporočil o odmerjanju ni mogoče dati. *Okvara ledvic*: Prilagajanje odmerkov pri bolnikih z normalnim delovanjem in blago ali zmerno (CL$_{cr}$: ≥ 30 ml/min) okvaro ni potrebno. Podatki o uporabi pri bolnikih s hudo okvaro (CL$_{cr}$: < 30 ml/min) so zelo omejeni, zato uporaba ni priporočljiva. *Okvara jeter:* Pri bolnikih z blago okvaro ni potrebno prilagajanje odmerkov. Podatkov o uporabi pri zmerni ali hudi okvari ni, zato uporaba ni priporočljiva. *Pediatrična populacija*: Varnost in učinkovitost pri otrocih in mladostnikih, starih < 18 let, nista bili dokazani. Način uporabe: Peroralna uporaba, vsak dan ob približno istem času, s hrano ali brez nje. Tablete je treba pogoltniti cele. **Kontraindikacije:** Preobčutljivost na učinkovino ali katerokoli pomožno snov. Uporaba močnih induktorjev CYP3A4/5. **Posebna opozorila in previdnostni ukrepi:** Hiperlipidemija: Uporaba je povezana z zvečanji vrednosti holesterola in trigliceridov v serumu – morda bo treba uvesti ali povečati odmerek zdravil za zniževanje ravni lipidov. Učinki na osrednje živčevje: Opazili so učinke na osrednje živčevje, vključno s spremembami v kognitivni funkciji, razpoloženju ali govoru – morda bo treba prilagoditi odmerek ali prekiniti zdravljenje. Atrioventrikularni blok: Pri bolnikih, ki so prejemali lorlatinib, so poročali o podaljšanju intervala PR in AV-bloku. Potrebno je spremljanje EKG in morda bo treba prilagoditi odmerek. Zmanjšanje iztisnega deleža levega prekata: Pri bolnikih, ki so prejemali lorlatinib in pri katerih so opravili izhodiščno in še vsaj eno nadaljnjo oceno iztisnega deleža levega prekata (LVEF – Left Ventricular Ejection Fraction), so poročali o zmanjšanju LVEF. Če imajo bolniki dejavnike tveganja za srce ali stanja, ki vplivajo na LVEF, ali se jim med zdravljenjem pojavijo pomembni srčni znaki/simptomi, je treba razmisliti o spremljanju srca, vključno z oceno LVEF. Zvečanje vrednosti lipaze in amilaze: Pri bolnikih, ki so prejemali lorlatinib, se je pojavilo zvečanje vrednosti lipaze in/ali amilaze. Zaradi sočasne hipertrigliceridemije in/ali morebitnega intrinzičnega mehanizma je treba upoštevati tveganje za pankreatitis. Intersticijska bolezen pljuč (ILD – *Interstitial Lung Disease*)/pnevmonitis: Pri uporabi lorlatiniba so se pojavili hudi ali življenjsko ogrožajoči pljučni neželeni učinki, skladni z ILD/pnevmonitisom. Vse bolnike, pri katerih pride do poslabšanja respiratornih simptomov, ki kažejo na ILD/pnevmonitis, je treba takoj pregledati glede ILD/pnevmonitisa. Laktoza: Vsebuje laktozo. Bolniki z redko dedno intoleranco za galaktozo, odsotnostjo encima laktaze ali malabsorpcijo glukoze/galaktoze ne smejo jemati tega zdravila. Natrij: Bolnike na dieti z nadzorovanim vnosom natrija je treba obvestiti, da je to zdravilo v bistvu 'brez natrija'. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Učinek zdravil na lorlatinib: *Induktorji CYP3A4/5:* Sočasna uporaba močnih induktorjev CYP3A4/5 (npr. rifampicin, karbamazepin, enzalutamid, mitotan, fenitoin in šentjanževka) je kontraindicirana. Sočasni uporabi zmernih induktorjev CYP3A4/5 se je treba izogibati, saj lahko pride do zmanjšanja koncentracij lorlatiniba v plazmi. *Zaviralci CYP3A4/5:* Sočasni uporabi močnih zaviralcev CYP3A4/5 (npr. boceprevir, kobicistat, itrakonazol, ketokonazol, posakonazol, troleandomicin, vorikonazol, ritonavir, paritaprevir v kombinaciji z ritonavirom in ombitasvirom in/ali dasabuvirom ter ritonavir v kombinaciji z elvitegravirom, indinavirom, lopinavirom ali tipranavirom in grenivka ali grenivkin sok), se je treba izogibati, saj lahko pride do zvečanja koncentracij lorlatiniba v plazmi (če je sočasna uporaba nujna, je treba zmanjšati odmerek lorlatiniba). Učinek lorlatiniba na druga zdravila: *Substrati CYP3A4/5:* Izogibati se je treba sočasnemu dajanju lorlatiniba in substratov CYP3A4/5 z ozkimi terapevtskimi indeksi (npr. alfentanil, ciklosporin, dihidroergotamin, ergotamin, fentanil, hormonski kontraceptivi, pimozid, kinidin, sirolimus in takrolimus), saj lahko lorlatinib zmanjša koncentracije teh zdravil. *Substrati P-glikoproteina:* Substrate P-gp, ki imajo ozke terapevtske indekse (npr. digoksin, dabigatraneteksilat), je treba v kombinaciji z lorlatinibom uporabljati previdno, saj obstaja verjetnost, da se koncentracija teh substratov v plazmi zmanjša. *Študije in vitro s prenašalci zdravil, ki niso P-gp:* Lorlatinib je treba v kombinaciji s substrati BCRP, OATP1B1, OATP1B3, OCT1, MATE1 in OAT3 uporabljati previdno, saj klinično pomembnih sprememb v plazemski izpostavljenosti teh substratov ni mogoče izključiti. **Plodnost, nosečnost in dojenje:** Ženskam v rodni dobi je treba svetovati, naj se med zdravljenjem z lorlatinibom izogibajo zanositvi in naj med zdravljenjem uporabljajo visoko učinkovito nehormonsko metodo kontracepcije, saj lahko lorlatinib povzroči, da hormonski kontraceptivi postanejo neučinkoviti. Učinkovito kontracepcijo je treba uporabljati še vsaj 35 dni po zaključku zdravljenja. Med zdravljenjem in še vsaj 14 tednov po zadnjem odmerku morajo bolniki, ki imajo partnerice v rodni dobi, uporabljati učinkovito kontracepcijo. Nosečnost: Študije na živalih so pokazale embriofetalno toksičnost, zato uporaba med nosečnostjo ali pri ženskah v rodni dobi, ki ne uporabljajo kontracepcije, ni priporočljiva. Dojenje: Med zdravljenjem in še 7 dni po zadnjem odmerku je treba prenehati z dojenjem. Plodnost: Zdravljenje lahko ogrozi plodnost pri moških. **Vpliv na sposobnost vožnje in upravljanja strojev:** Ima zmeren vpliv na sposobnost vožnje in upravljanja strojev. Potrebna je previdnost, saj se pri bolnikih lahko pojavijo učinki na osrednje živčevje. **Neželeni učinki:** Zelo pogosti: anemija, hiperholesterolemija, hipertrigliceridemija, učinki na razpoloženje, učinki na kognitivne funkcije, periferna nevropatija, glavobol, motnja vida, diareja, navzea, zaprtje, izpuščaj, artralgija, mialgija, edem, utrujenost, zvečanje telesne mase, zvečanje vrednosti lipaze, zvečanje vrednosti amilaze. **Način in režim izdaje:** Rp/Spec. - Predpisovanje in izdaja zdravila je le na recept zdravnika specialista ustreznega področja medicine ali od njega pooblaščenega zdravnika. **Imetnik dovoljenja za promet:** Pfizer Europe MA EEIG, Boulevard de la Plaine 17, 1050 Bruxelles, Belgija. **Datum zadnje revizije besedila:** 02.04.2020

Pred predpisovanjem se seznanite s celotnim povzetkom glavnih značilnosti zdravila.

Literatura: 1. Povzetek glavnih značilnosti zdravila Lorviqua, 2.4.2020. **2.** Centralna baza zdravil. Dostopno na: http://www.cbz.si/cbz/bazazdr2.nsf/Search?SearchView&Query=(%5BTXIMELAS1%5D=_lorviqua*)&SearchOrder=4&SearchMax=301. Dostopano: oktober, 2020.

Pfizer Luxembourg SARL, GRAND DUCHY OF LUXEMBOURG, 51, Avenue J.F. Kennedy, L – 1855,
Pfizer, podružnica Ljubljana, Letališka cesta 29a, 1000 Ljubljana

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Zdravilo Alunbrig se uporablja kot monoterapija za zdravljenje odraslih bolnikov z napredovalim nedrobnoceličnim pljučnim rakom (NSCLC – non small cell lung cancer), pozitivnim na anaplastično limfomsko kinazo (ALK), ki še niso bili zdravljeni z inhibitorjem ALK. [1]

SKRAJŠANI POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

▼ Za to zdravilo se izvaja dodatno spremljanje varnosti. Tako bodo hitreje na voljo nove informacije o njegovi varnosti. Zdravstvene delavce naprošamo, da poročajo o katerem koli domnevnem neželenem učinku zdravila. Pred predpisovanjem preberite celoten povzetek glavnih značilnosti zdravila (SmPC).

Ime zdravila: ALUNBRIG 30 mg filmsko obložene tablete; ALUNBRIG 90 mg filmsko obložene tablete; ALUNBRIG 180 mg filmsko obložene tablete

Kakovostna in količinska sestava: ALUNBRIG 30 mg filmsko obložene tablete. Ena filmsko obložena tableta vsebuje 30 mg brigatiniba. ALUNBRIG 90 mg filmsko obložene tablete. Ena filmsko obložena tableta vsebuje 30 mg brigatiniba. ALUNBRIG 180 mg filmsko obložene tablete. Ena filmsko obložena tableta vsebuje 30 mg brigatiniba.Indikacije: Zdravilo Alunbrig se uporablja kot monoterapija za zdravljenje odraslih bolnikov z napredovalim nedrobnoceličnim pljučnim rakom (NSCLC – non small cell lung cancer), pozitivnim na anaplastično limfomsko kinazo (ALK), ki še niso bili zdravljeni z inhibitorjem ALK. Zdravilo Alunbrig se uporablja kot monoterapija za zdravljenje odraslih bolnikov z napredovalim NSCLC pozitivnim na ALK, ki so bili predhodno zdravljeni z zdravilom krizotinib. Odmerjanje/način uporabe: Priporočeni začetni odmerek je 90 mg enkrat na dan prvih 7 dni, nato pa 180 mg enkrat na dan. Če se jemanje zdravila Alunbrig prekine za 14 dni ali dlje iz drugega razloga kot so neželeni učinki, je treba zdravljenje nadaljevati z odmerkom 90 mg enkrat na dan za obdobje 7 dni, preden se odmerek poveča na predhodno toleriran odmerek. Če odmerek ni bil zaužit ali se je po zaužitju pojavilo bruhanje, se dodatnega odmerka ne sme zaužiti in je potrebno naslednji odmerek zaužiti ob predhodno načrtovanem času. Prilagoditve odmerka: Huda okvara jeter: priporočljiv zmanjšan začetni odmerek 60 mg enkrat na dan v prvih 7 dneh, ter nato 120 mg enkrat na dan. Huda okvara ledvic: priporočljiv zmanjšan začetni odmerek 60 mg enkrat na dan v prvih 7 dneh, ter nato 90 mg enkrat na dan. Starejši: odmerka ni treba prilagajati. Kontraindikacije: Preobčutljivost na učinkovino ali katero koli pomožno snov. Posebna opozorila in previdnostni ukrepi (pri uporabi brigatiniba): Neželeni učinki na pljuča Pri bolnikih lahko pride do hudih, življenjsko nevarnih in smrtnih neželenih učinkov na pljučih, vključno z značilnostmi, ki so enake kot pri IPB/pnevmonitisu. Večina neželenih učinkov na pljuča je bila opažena v prvih 7 dneh zdravljenja. Neželeni učinki na pljuča stopnje 1-2 so bili odpravljeni s prekinitvijo zdravljenja ali spremembo odmerka. Višja starost in kratek interval (manj kot 7 dni) med zadnjim odmerkom krizotiniba in prvim odmerkom zdravila Alunbrig sta bila neodvisno povezana s povečano stopnjo teh neželenih učinkov na pljuča. Nekateri bolniki so zaradi pnevmonitisa zboleli kasneje med zdravljenjem z zdravilom Alunbrig. Bolnike je zlasti v prvem tednu zdravljenja treba skrbno spremljati zaradi novih ali poslabšanih simptomov dihal (npr. dispneja, kašelj itd.). Bolnike, pri katerih so se pojavili znaki pnevmonitisa s poslabšanimi simptomi bolezni dihal, je treba nemudoma pregledati. Če sumite na pnevmonitis, je treba odmerjanje zdravila Alunbrig začasno prekiniti, bolnika pa oceniti glede morebitnih drugih vzrokov simptomov (npr. pljučna embolija, napredovanje tumorja, infekcijska pljučnica). Odmerek je treba ustrezno spremeniti. Hipertenzija: treba je redno nadzorovati krvni tlak. Bradikardija: Redno je treba spremljati srčni utrip in krvni tlak. Motnje vida: Bolnikom je treba svetovati, naj poročajo o kakršnih koli simptomih motenj vida. Zvišanje kreatin fosfokinaze (CPK): Bolnikom je treba svetovati, naj poročajo o kakršnih koli nepojasnjenih bolečinah v mišicah, občutljivosti ali šibkosti mišic. Zvišanje encimov trebušne slinavke: treba je redno nadzorovati koncentracijo amilaze in lipaze. Hepatotoksičnost: pojavilo se je zvišanja jetrnih encimov (aspartat-aminotransferaza, alanin-aminotransferaza) in bilirubin. Glede na resnost laboratorijsko odkritih nepravilnosti je treba zdravljenje začasno prekiniti in ustrezno spremeniti odmerek. Medsebojno delovanje zdravil: Izogibati se je treba sočasni uporabi zdravila Alunbrig z močnimi zaviralci CYP3A. Če se sočasni uporabi močnih zaviralcev CYP3A ni mogoče izogniti, je treba odmerek zdravila Alunbrig zmanjšati s 180 mg na 90 mg ali z 90 mg na 60 mg. Po prekinitvi uporabe močnega zaviralca CYP3A je treba zdravljenje z zdravilom Alunbrig nadaljevati z odmerkom, ki ga je bolnik prenašal pred začetkom uporabe močnega zaviralca CYP3A. Izogibati se je treba sočasni uporabi zdravila Alunbrig z močnimi in zmernimi induktorji CYP3A. Plodnost: Ženskam v rodni dobi je treba svetovati, naj med zdravljenjem in vsaj 4 mesece po zadnjem odmerku uporabljajo učinkovito nehormonsko kontracepcijo. Moškim s partnericami v rodni dobi je treba svetovati, naj uporabijo učinkovito kontracepcijo med zdravljenjem in vsaj 3 mesece po zadnjem odmerku zdravila Alunbrig. Laktoza Zdravilo Alunbrig vsebuje laktozo monohidrat. Bolniki z redko dedno intoleranco za galaktozo, odsotnostjo encima laktaze ali malabsorpcijo glukoze/galaktoze ne smejo jemati tega zdravila.

Medsebojno delovanje z drugimi zdravili in druge oblike interakcij: Učinkovine, ki lahko zvišajo koncentracijo brigatiniba v plazmi: Zaviralci CYP3A brigatinib je substrat CYP3A4/5. Sočasna uporaba večkratnih odmerkov itrakonazola, ki je močan zaviralec CYP3A, je povečala koncentracijo brigatiniba v krvi.Sočasni uporabi močnih zaviralcev CYP3A z zdravilom Alunbrig, vključno z nekaterimi protivirusnimi zdravili (npr. indinavirjem, nelfinavirjem, ritonavirjem, sakvinavirjem), makrolidnimi antibiotiki (npr. klaritromicinom, telitromicinom, troleandomicinom), antimikotiki (npr. ketokonazolom, vorikonazolom), mibefradilom in nefazodonom, se je treba izogibati. Zmerni zaviralci CYP3A (npr. diltiazem in verapamil) lahko povečajo AUC brigatiniba za približno 40%. Pri kombinaciji z zmernimi zaviralci CYP3A prilagajanje odmerka ni potrebno. Grenivka ali sok grenivke lahko prav tako zviša koncentracije brigatiniba v plazmi in se ji je treba izogibati. Zaviralci CYP2C8: brigatinib je substrat CYP2C8. Sočasna uporaba večkratnih odmerkov gemfibrozila, ki je močan zaviralec CYP2C8, je zmanjšala koncentracijo brigatiniba v krvi. Pri sočasnem odmerjanju močnih zaviralcev CYP2C8 prilagajanje odmerka ni potrebno.Zaviralci P-gp in BCRP: Pri sočasni uporabi z zaviralci P-gp in BCRP prilagajanje odmerka zdravila Alunbrig ni potrebno. Učinkovine, ki lahko znižajo koncentracijo brigatiniba v plazmi: Induktorji CYP3.. sočasna uporaba večkratnih odmerkov rifampicina, je zmanjšala koncentracijo brigatiniba v krvi. Treba se je izogibati sočasni uporabi močnih induktorjev CYP3A z zdravilom Alunbrig, vključno z rifampicinom, karbamazepinom, fenitoinom, rifabutinom, fenobarbitalom in šentjanževko. Zmerni induktorji CYP3A lahko zmanjšajo AUC brigatiniba za približno 50%. Izogibati se je treba sočasni uporabi zmernih induktorjev CYP3A z zdravilom Alunbrig, vključno z, vendar ne omejeno na efavirenz, modafinil, bosentan, etravirin in nafcilin. Učinkovine, katerim lahko brigatinib spremeni koncentracijo v plazmi: Substrati CYP3A: brigatinib je induktor CYP3A4. Zmanjša lahko koncentracije v plazmi pri sočasno uporabljenih zdravilih, ki se v glavnem presnavljajo s CYP3A. Zato je treba pri sočasni uporabi zdravila Alunbrig s substrati CYP3A z ozkim terapevtskim indeksom (npr. alfentanilom, fentanilom, kinidinom, ciklosporinom, sirolimusom, takrolimusom) izogibati, ker se lahko zmanjša njihova učinkovitost. Zdravilo Alunbrig lahko inducira tudi druge encime in transporte (npr. CYP2C, P-gp) preko enakih mehanizmov, ki so odgovorni za indukcijo CYP3A (npr. aktivacija pregnanskega X receptorja). Transportni substrati: Sočasna uporaba brigatiniba s substrati P-gp (npr. digoksin, dabigatran, kolhicin, pravastatin), BCRP (npr. metotreksat, rosuvastatin, sulfasalazin), organskim kationskim prenašalcem 1 (OCT1), proteini za ekstruzijo več zdravil in toksinov 1 (Mate1), in 2K (MATE2K) lahko poveča njihovo koncentracijo v plazmi. Bolnike je treba skrbno spremljati, ko je zdravilo Alunbrig sočasno uporabljeno s substrati teh transporterjev z ozkim terapevtskim indeksom (npr. digoksin, dabigatran, metotreksat). Plodnost, nosečnost in dojenje: Ženske v rodni dobi/Kontracepcija za moške in ženske Ženskam v rodni dobi je treba svetovati, naj ne zanosijo in vsaj 4 mesece po zadnjem odmerku uporabijo učinkovito nehormonsko kontracepcijo in moškim, naj med zdravljenjem ne zaplodijo otroka. Moškim s partnericami v rodni dobi je treba svetovati, naj uporabijo učinkovito kontracepcijo med zdravljenjem in vsaj 3 mesece po zadnjem odmerku zdravila Alunbrig. Nosečnost: V primeru jemanja zdravila Alunbrig med nosečnostjo, lahko to povzroči okvaro ploda. Če se zdravilo Alunbrig uporablja med nosečnostjo ali če bolnica zanosi med jemanjem tega zdravila, je treba bolnico seznaniti s potencialno nevarnostjo za plod. Dojenje: Ni znano, ali se zdravilo Alunbrig izloča v materino mleko.Plodnost: Na voljo ni nobenih podatkov o vplivu zdravila Alunbrig na plodnost. Neželeni učinki: Najpogostejši neželeni učinki (≥25%), o katerih so poročali pri bolnikih, ki so se zdravili z zdravilom Alunbrig pri priporočenem režimu odmerjanja, so zvišana AST, hiperglikemija, hiperinsulinemija, anemija, zvišana CPK, navzea, povečana lipaza, zmanjšano število limfocitov, povečana ALT, diareja, povečana amilaza, utrujenost, kašelj, glavobol, povečana alkalna fosfataza, hipofosfatemija, zvišana vrednost APTT, izpuščaj, bruhanje, dispneja, hipertenzija, zmanjšano število belih krvnih celic, mialgija in periferna nevropatija. Najpogostejši resni neželeni učinki (≥2%), o katerih so poročali pri bolnikih, zdravljenih z zdravilom Alunbrig pri priporočenem režimu odmerjanja, razen pri učinkih, povezanih z napredovanjem neoplazme, so bili pnevmonitis, pljučnica in dispneja. Za podroben profil neželenih učinkov zdravila Alunbrig in medsebojno delovanje z drugimi zdravili glejte celoten povzetek glavnih značilnosti zdravila. O katerem koli domnevnem neželenem učinku zdravila morate poročati na Javno agencijo Republike Slovenije za zdravila in medicinske pripomočke, Sektor za farmakovigilanco, Nacionalni center za farmakovigilanco, Slovenčeva ulica 22, SI-1000 Ljubljana, Tel: +386 (0)8 2000 500, Faks: +386 (0)8 2000 510, e-pošta: h-farmakovigilanca@jazmp.si, spletna stran: www.jazmp.si. Posebna navodila za shranjevanje: Za shranjevanje zdravila niso potrebna posebna navodila. Imetnik dovoljenja za promet z zdravilom: Takeda Pharma A/S, Dybendal Alle 10. 2630 Taastrup, Danska. Datum zadnje revizije besedila: 01. apr. 2020. Datum priprave informacije: april 2020. Režim izdaje zdravila: Rp/Spec. Dodatne informacije so na voljo pri: Takeda GmbH, Podružnica Slovenija, Bleiweisova cesta 30, Ljubljana, tel: 059 082 480.

1. Povzetek glavnih značilnosti zdravila ALUNBRIG, www.europa.ema.eu, Datum revizije besedila: 07. sep. 2020.

SAMO ZA STROKOVNO JAVNOST
C-APROM/SI/BRI/0005 Datum priprave: oktober 2020

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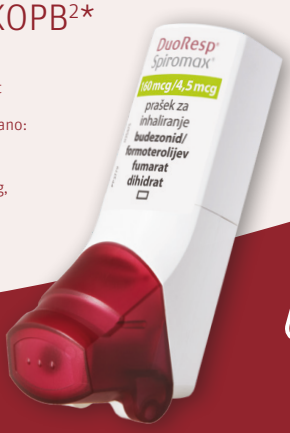
Intuitivno oblikovan za nedvoumno uporabo.

- Nagrajeno oblikovanje[1]
- Nared za uporabo zgolj z dvigom pokrovčka
- Za uporabo pri astmi in KOPB[2]*



1. MDEA 2015. Dodatne informacije o nagradi za odličnost pri oblikovanju v medicini so na voljo na: http://www.canontradeshows.com/expo/awards/awards. Dostopano: september 2017.
2. SmPC DuoResp Spiromax 160 mcg/4,5 mcg, 120 odmerkov & DuoResp Spiromax 320 mcg/9 mcg, 60 odmerkov

* Uporaba zdravila DuoResp Spiromax® je dovoljena zgolj pri bolnikih, starih 18 let ali več.

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KOPB: Simptomatsko zdravljenje bolnikov s hudo obliko KOPB (FEV $_1$ < 50 % predvidenega normalnega FEV $_1$) in s ponavljajočimi se poslabšanji v anamnezi, pri katerih se kljub zdravljenju z dolgodelujočimi bronhodilatatorji pojavljajo znatni simptomi. **Povzetek odmerjanja in načina uporabe** Zdravilo DuoResp Spiromax ni indicirano za uporabo pri otrocih, starih 12 let ali manj, ali mladostnikih, starih od 13 do 17 let. Astma: Zdravilo DuoResp Spiromax ni primerno za začetno zdravljenje astme. Zdravljenje z zdravilom ni ustrezno pri odraslih bolnikih z blago obliko astme, ki ni ustrezno nadzorovana z inhalacijskim kortikosteroidi in inhalacijskimi kratkodelujočimi agonisti adrenoreceptorjev β_2, ki se uporabljajo po potrebi. Odmerek je treba titrirati do najmanjšega odmerka, pri katerem je še ohranjen učinkovit nadzor nad simptomi. Ko v običajni praksi dosežemo ustrezen nadzor simptomov z odmerjanjem nižje jakosti zdravila dvakrat na dan, lahko titracijo do manjšega še učinkovitega odmerka opravimo tudi z zmanjšanjem pogostnosti odmerjanja na enkrat na dan. DuoResp Spiromax 160 mcg/4,5 mcg: Zdravilo DuoResp Spiromax za vzdrževalno zdravljenje Bolnikom je treba svetovati, da naj imajo svoj ločeni inhalator s hitrodelujočim bronhodilatatorjem kot olajševalcem vedno na razpolago za hitro obvladanje simptomov. Odrasli (18 let in več): 1–2 vdiha dvakrat na dan. Pri nekaterih bolnikih bodo morda potrebni največ 4 vdihi dvakrat na dan. Zdravilo DuoResp Spiromax za vzdrževalno in olajševalno zdravljenje Bolniki redno jemljejo dnevni vzdrževalni odmerek zdravila DuoResp Spiromax, ob pojavu simptomov pa po potrebi dodatne odmerke zdravila DuoResp Spiromax. Vzdrževalno in olajševalno zdravljenje z zdravilom DuoResp Spiromax je primerno predvsem za bolnike: -z neustrezno nadzorovano astmo, ki pogosto potrebujejo inhalator z olajševalcem; -s poslabšanjem astme v preteklosti, pri katerem je bila potrebna medicinska intervencija. Priporočeni odmerki: Odrasli (18 let in več): priporočen vzdrževalni odmerek je 2 vdiha na dan, bodisi 1 vdih zjutraj in 1 vdih zvečer ali pa 2 vdiha zjutraj oziroma 2 vdiha zvečer. Za nekatere bolnike je primeren vzdrževalni odmerek 2 vdiha dvakrat dnevno. Ob pojavu simptomov naj bolniki po potrebi naredijo še 1 dodaten vdih. Če so simptomi po nekaj minutah še vedno prisotni, naj naredijo še 1 vdih. Naenkrat ne smejo narediti več kot 6 vdihov. Celotni dnevni odmerek, večji od 8 vdihov, v običajnih okoliščinah ni potreben. Kljub temu je lahko v določenih omejenih časovnih obdobjih celotni dnevni odmerek 12 vdihov. Bolniki, ki uporabljajo več kot 8 vdihov dnevno, morajo obiskati zdravnika. Zdravnik jih bo ponovno pregledal in ocenil njihovo vzdrževalno zdravljenje. KOPB: Odrasli (18 let in več): 2 vdiha dvakrat na dan. DuoResp Spiromax 320 mcg/9mcg: Astma: Treba uporabljati le kot vzdrževalno zdravljenje. Odrasli (18 let in več): 1 vdih dvakrat na dan. KOPB: Odrasli (18 let in več): 1 vdih dvakrat na dan. Starejši bolniki (≥ 65 let): Ni posebnih zahtev za odmerjanje. Bolniki z okvaro ledvic ali jeter: Podatkov ni na voljo. **Povzetek kontraindikacij** Preobčutljivost na zdravilni učinkovini ali katero koli pomožno snov. **Povzetek posebnih opozoril in previdnostnih ukrepov** Če bolnik ugotavlja, da je zdravljenje neučinkovito, ali če preseže največji priporočeni odmerek zdravila DuoResp Spiromax, mora poiskati zdravniško pomoč. Nenadno in progresivno poslabšanje nadzora simptomov astme ali KOPB je lahko za bolnika življenjsko nevarno, zato je potreben nujen zdravniški pregled. Bolnikom svetujte, naj imajo inhalator z olajševalcem vedno pri roki.Bolnike je treba opozoriti, naj uporabljajo vzdrževalni odmerek zdravila DuoResp Spiromax skladno z navodili zdravnika, tudi če nimajo simptomov. Profilaktična uporaba zdravila DuoResp Spiromax, na primer pred telesnim naporom, ni bila preučena. Zdravilo DuoResp Spiromax kot olajševalec se uporablja v primerih, ko se pojavijo simptomi, ne pa redno v profilaktične namene, na primer pred telesnim naporom. V takih primerih je treba razmisliti o uporabi hitrodelujočega bronhodilatatorja. Simptomi astme Bolnikom se ne sme uvesti zdravila med poslabšanjem astme ali v obdobju pomembnega oziroma akutnega poslabšanja simptomov astme. Med zdravljenjem z zdravilom se lahko pojavijo resni neželeni učinki, povezani z astmo, in poslabšanje bolezni. Če po uvedbi zdravila simptomi astme niso nadzorovani ali se poslabšajo, naj bolniki nadaljujejo z zdravljenjem in poiščejo zdravniško pomoč. Med zdravljenjem se lahko pojavi paradoksni bronhospazem, ki ga prepoznamo po okrepitvi piskanja v pljučih in težkega dihanja,takoj po vdihu zdravila. V tem primeru je treba zdravljenje z zdravilom takoj prekiniti. Paradoksni bronhospazem se odziva na hitrodelujoči inhalacijski bronhodilatator in ga moramo zdraviti takoj. Sistemski učinki Pri uporabi vseh inhalacijskih kortikosteroidov se lahko pojavijo sistemski učinki, še posebno, če so bili predpisani veliki odmerki za dlje časa. Med možnimi sistemskimi učinki so Cushingov sindrom, Cushingoidne značilnosti, supresija nadledvične žleze, zmanjšanje kostne mineralne gostote, kataraktа in glavkom ter redkeje vrsta psiholoških in vedenjskih učinkov, vključno s psihomotorno hiperaktivnostjo, motnjami spanja, anksioznostjo, depresijo ali agresijo. Učinki na kostno gostoto Treba je razmisliti o možnih učinkih na kostno gostoto, še posebej pri bolnikih, ki prejemajo večje odmerke za dalјša obdobja in imajo sočasne dejavnike tveganja za osteoporozo. Delovanje nadledvične žleze Če obstaja kakršen koli razlog za sum na motnjo delovanja nadledvične žleze zaradi prejšnje sistemskega zdravljenja s steroidi, je pri prehodu na zdravljenje s fiksno kombinacijo budezonida/formoterolijevega fumarata potrebna previdnost. Kortikosteroidi v visokih odmerkih Klinično pomembna adrenalna supresija se lahko pojavi tudi pri bolnikih, ki so imeli podaljšano zdravljenje z visokimi odmerki inhalacijskih kortikosteroidov, še posebej v odmerkih, višjih od priporočenih. Zato je treba razmisliti o dodatni uporabi sistemskih kortikosteroidov v obdobjih stresa, kot so npr. hude okužbe ali pred neurgentnimi kirurškimi posegi. Hitro zmanjšanje odmerka steroidov lahko povzroči akutno adrenalno krizo. Simptomi in znaki, ki se lahko pojavijo pri akutni adrenalni krizi, so včasih nejasni, lahko pa vključujejo anoreksijo, bolečine v trebuhu, izgubo telesne teže, utrujenost, glavobol, navzeo, bruhanje, motnje zavesti, konvulzije, hipotenzijo in hipoglikemijo. Zdravljenja z dopolnilnimi sistemskimi steroidi ali inhalacijskim budezonidom ne smemo nenadno prekiniti. Prehod s peroralnega zdravljenja Med prehodom s peroralnega zdravljenja na zdravljenje s fiksno kombinacijo budezonida/formoterolijevega fumarata se občajno pojavi splošno manjše delovanje sistemskih steroidov, kar lahko povzroči pojav alergijskih ali artritičnih simptomov, kot so npr. rinitis, ekcem in bolečine v mišicah in sklepih. Za te težave je treba uvesti posebno zdravljenje. Peroralne okužbe Da bi lahko na najmanjšo možno mero zmanjšali tveganje za orofaringealno okužbo s kandido, bolniku naročite, naj si po vsakem vzdrževalnem odmerku spere usta z vodo. Ob pojavu orofaringealne kandidoze si morajo bolniki sprati usta tudi po vsaki inhalaciji po potrebi. Pljučnica pri bolnikih z KOPB Pri bolnikih s KOPB, ki so prejemali inhalacijske kortikosteroide, so opažali večjo pojavnost pljučnice, tudi pljučnice, ki je zahtevala sprejem v bolnišnico. Obstajajo določeni dokazi, da se tveganje za pljučnico povečuje s povečevanjem odmerka steroida, vendar to ni bilo dokončno dokazano v vseh študijah. Ni dokončnih kliničnih dokazov, da se stopnja tveganja za pljučnico znotraj skupine inhalacijskih kortikosteroidnih zdravil razlikuje. Zdravniki morajo biti pri bolnikih s KOPB pozorni na morebiten pojav pljučnice, kajti klinične značilnosti takšne okužbe se prekrivajo s simptomi poslabšanj KOPB. Med dejavniki tveganja za pljučnico pri bolnikih s KOPB so trenutno kajenje, višja starost, nizek indeks telesne mase (ITM) in huda KOPB. Medsebojno delovanje z drugimi zdravili Sočasnemu zdravljenju z itrakonazolom in ritonavirjem ali drugim močnim zaviralcem CYP3A4 se je treba. Če to ni mogoče, pazite, da bo časovni razmik med njuno uporabo kolikor je mogoče dolg. Pri bolnikih, ki jemljejo močne zaviralce CYP3A4, zdravljenje s fiksno kombinacijo budezonida/formoterolijevega fumarata ni priporočeno. Previdnost pri posebnih boleznih Kombinacijo budezonida in formoterolijevega fumarat dihidrata v fiksnih odmerkih predpisujte previdno pri bolnikih s tirotoksikozo, feokromocitomom, sladkorno boleznijo, nezdravljeno hipokaliemijo, hipertrofično obstruktivno kardiomiopatijo, idiopatsko subvalvularno aortno stenozo, hudo hipertenzijo, anevrizmo ali drugimi hudimi kardiovaskularnimi boleznimi, kot so na primer ishemična srčna bolezen, tahiaritmije ali hudo srčno popuščanje. Pomožne snovi To zdravilo vsebuje laktozo. Bolniki z redko dedno intoleranco za galaktozo, laponsko obliko zmanjšane aktivnosti laktaze ali malabsorpcijo glukoze/galaktoze, ne smejo jemati tega zdravila. Pomožna snov laktoza vsebuje majhne količine mlečnih beljakovin, ki lahko povzročijo alergijske reakcije. **Povzetek medsebojnega delovanja z drugimi zdravili in drugih oblik interakcij** Močni zaviralci CYP3A4 (npr. ketokonazol, itrakonazol, vorikonazol, posakonazol, klaritromicin, telitromicin, nefazodon in zaviralci proteaze HIV) bodo zelo verjetno povečali plazemsko koncentracijo budezonida, zato se je treba izogibati sočasni uporabi. Če to ni mogoče, pazite, da bo časovni razmik med uporabo zaviralca in budezonida kolikor je mogoče dolg. Pri bolnikih, ki jemljejo močne zaviralce CYP3A4, kombinacija budezonida in formoterolijevega fumarata dihidrata v fiksnih odmerkih kot vzdrževalno in olajševalno zdravljenje ni priporočeno. Antagonisti receptorjev receptorjev β lahko oslabijo ali zavrejo delovanje formotrola. **Povzetek neželenih učinkov** Najpogostejši neželeni učinki so farmakološko pričakovani neželeni učinki zdravljenja z agonisti adrenergičnih receptorjev β_2, kot so tremor in palpitacije. Pogosti: Okužbe s kandido v ustih in žrelu, pljučnica (pri bolnikih s KOPB), glavobol, tremor, palpitacije, blago draženje grla, kašljanje in hripavost. **Imetnik dovoljenja za promet z zdravilom** Teva Pharma B.V., Swensweg 5, 2031 GA Haarlem, Nizozemska **Način in režim izdaje zdravila Rp** - Predpisovanje in izdaja zdravila je le na recept **Datum zadnje revizije besedila** marec 2020

Samo za strokovno javnost. Datum priprave informacije: november 2020

Za podrobnejše informacije o zdravilu, prosimo, preberite celoten Povzetek glavnih značilnosti zdravila, ki je objavljen na spletni strani Evropske agencije za zdravila (www.ema.europa.eu) ali se obrnite na zastopnika imetnika dovoljenja za promet z zdravilom v Sloveniji, Pliva Ljubljana d.o.o., Pot k sejmišču 35, 1231 Ljubljana-Črnuče, tel: 01 58 90 390, e-mail: info@tevasi.si.

DUOR-SI-00002

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

Spiolto® Respimat® 2,5 mikrograma/2,5 mikrograma raztopina za inhaliranje
Kakovostna in količinska sestava: prejeti odmerek vsebuje 2,5 mikrograma tiotropija (v obliki bromida monohidrata) in 2,5 mikrograma olodaterola (v obliki klorida) na vpih. Prejeti odmerek je količina, ki jo bolnik prejme po prehodu zdravila skozi ustnik. Pomožna snov z znanim učinkom: to zdravilo vsebuje 0,0011 mg benzalkonijevega klorida ob vsaki sprožitvi (vpihu). Za celoten seznam pomožnih snovi glejte poglavje 6.1. **Terapevtske indikacije:** zdravilo Spiolto Respimat je indicirano za vzdrževalno bronhodilatacijsko zdravljenje, ki zmanjša simptome pri odraslih bolnikih s kronično obstruktivno pljučno boleznijo (KOPB). **Odmerjanje in način uporabe:** zdravilo je namenjeno samo za inhaliranje. Vložek je možno vstaviti samo v inhalator Respimat in ga z njim uporabljati. Dva vpiha z inhalatorjem Respimat predstavljata en odmerek zdravila. Priporočeni odmerek je 5 mikrogramov tiotropija in 5 mikrogramov olodaterola, vnesenih z dvema vpihoma z inhalatorjem Respimat enkrat na dan, vsak dan ob istem času. Bolnik priporočenega odmerka ne sme preseči. *Okvara jeter:* o uporabi olodaterola pri bolnikih s hudo okvaro jeter ni podatkov. *Okvara ledvic:* pri bolnikih s hudo okvaro ledvic je malo izkušenj z uporabo olodaterola. *Pediatrična populacija:* zdravilo Spiolto Respimat ni namenjeno za uporabo pri pediatrični populaciji (mlajši od 18 let). **Kontraindikacije:** preobčutljivost na učinkovini ali katero koli pomožno snov. Preobčutljivost za atropin ali njegove derivate, npr. ipratropij ali oksitropij, v anamnezi. **Posebna opozorila in previdnostni ukrepi:** astma (zdravila Spiolto Respimat ne smejo uporabljati bolniki z astmo), ni primeren za akutne epizode, paradoksni bronhospazem (lahko povzroči paradoksni bronhospazem), previdno ga je treba uporabljati pri glavkomu z ozkim zakotjem, hiperplaziji prostate in zapori vratu sečnega mehurja, očesni simptomi (bolnike je treba opozoriti, naj pazijo, da razpršeno zdravilo ne bi zašlo v oči), zobni karies (zaradi suhih ust, se lahko v daljšem obdobju razvije zobni karies), okvara ledvic (pri bolnikih z zmerno do hudo okvaro ledvic smemo uporabljati zdravilo Spiolto Respimat samo, če je pričakovana korist zdravljenja večja od možnega tveganja. Pri bolnikih s hudo okvaro ledvic ni na voljo izkušenj z dolgotrajno uporabo). Učinki na srce in ožilje; pri bolnikih, ki so v preteklem letu utrpeli srčni infarkt, bolnikih z nestabilno ali življenjsko nevarno srčno aritmijo, bolnikih, ki so se v preteklem letu zdravili v bolnišnici zaradi srčnega popuščanja ali so imeli diagnozo paroksizmalne tahikardije je treba zdravilo uporabljati previdno. Olodaterol ima lahko pri nekaterih bolnikih klinično pomembne učinke na srce in ožilje, ki se kažejo kot pospešen pulz, zvišan krvni tlak in/ali simptomi. Zdravilo lahko povzroči tudi spremembe na EKG, npr. sploščenost vala T in depresijo segmenta ST. Previdnost je potrebna pri bolnikih s srčnožilnimi boleznimi, zlasti z ishemično boleznijo srca, hudo srčno dekompenzacijo, srčnimi aritmijami, hipertrofično obstrukcijsko kardiomiopatijo, hipertenzijo in anevrizmo, konvulzivnimi motnjami ali tirotoksikozo, znanim ali domnevnim podaljšanjem intervala QT in bolnikih, ki so neobičajno odzivni na simpatikomimetične amine). Lahko povzroči hipokaliemijo, hiperglikemijo (lahko zviša raven glukoze v plazmi). Previdnost je potrebna pri anesteziji (potrebna je previdnost pri načrtovanih operacijah s halogeniranimi ogljikovodikovimi anestetiki). Zdravila Spiolto Respimat ne smemo uporabljati hkrati z zdravili, ki vsebujejo dolgodelujoče agoniste adrenergičnih receptorjev beta,. Zdravila Spiolto Respimat bolniki ne smejo uporabiti pogosteje kot enkrat na dan. Po uporabi zdravila Spiolto Respimat se lahko pojavijo takojšnje preobčutljivostne reakcije. Benzalkonijev klorid lahko povzroči sopenje ali težave z dihanjem. Pri bolnikih z astmo je tveganje za tovrstne neželene učinke povečano. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** antiholinergična zdravila, druge adrenergične učinkovine, derivati ksantina, steroidi ali diuretiki; agonisti adrenergičnih receptorjev beta, zaviralci MAO in triciklični antidepresivi, zdravila, ki podaljšajo QTc; flukonazol in ketokonazol. Iz previdnostnih razlogov se je med nosečnostjo bolje izogibati uporabi zdravila Spiolto Resimat. Tako kot drugi agonisti adrenergičnih receptorjev beta2 lahko tudi olodaterol zaradi sproščajočega učinka na gladke materinične mišice zavre porod. Med dojenjem je uporaba kontraindicirana. Pri vožnji avtomobila in upravljanju s stroji je potrebna previdnost. Če se pojavita omotica ali zamegljen vid, naj se bolniki izogibajo dejavnostim, ki so lahko nevarne, npr. vožnji in upravljanju s stroji. **Neželeni učinki:** *pogosti:* suha usta. *Občasni:* omotica, nespečnost, glavobol, atrijska fibrilacija, palpitacije, tahikardija, hipertenzija, kašelj, disfonija in zaprtje. *Redki:* nazofaringitis, zamegljen vid, supraventrikularna tahikardija, epistaksa, laringitis, faringitis, gingivitis, navzea, orofaringealna kandidoza, angioedem, urtikarija, preobčutljivost, pruritus, bolečina v hrbtu, artralgija, retencija urina, okužba sečil in dizurija. *Neznana pogostnost:* dehidracija, glavkom, povišan očesni tlak, bronhospazem, sinusitis, črevesna zapora, paralitični ileus, zobni karies, disfagija, gastroezofagealna refluksna bolezen, glositis, stomatitis, anafilaktična reakcija, izpuščaj, suha koža, kožne okužbe in razjede ter oteklost sklepov. **Način in režim izdaje:** Rp. **Imetnik dovoljenja za promet:** Boehringer Ingelheim International GmbH, Binger Strasse 173, D-55216 Ingelheim am Rhein, Nemčija. **Za podrobnejše informacije glejte** Povzetek glavnih značilnosti zdravila z dne 20.03.2020.

Literatura: 1. Dhand R s sod. Int J COPD 2019. DOI 10.2147.COPD.S190639 **2.** SPIOLTO® RESPIMAT® Povzetek glavnih značilnosti zdravila. Marec 2020. **3.** Buhl R s sod. ERJ. 2015;45:969-79. 4. Singh D s sod. Respir Med. 2015; 109(10):1312-9.

**V kolikor imate medicinsko vprašanje v povezavi z zdravilom podjetja Boehringer Ingelheim, Podružnica Ljubljana,
Vas prosimo, da pokličete na telefonsko številko 01/5864-000 ali pošljete vaše vprašanje na elektronski naslov: medinfo@boehringer-ingelheim.com.**

Boehringer Ingelheim

Boehringer Ingelheim RCV,
Podružnica Ljubljana, Šlandrova 4b, Ljubljana

Samo za strokovno javnost.
Datum priprave informacije: oktober 2020
PC-SL-100326

Združenje pnevmologov Slovenije
Slovenian Respiratory Society