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ROLE AND CLINICAL SIGNIFICANCE OF IL-33 IN PATIENTS WITH ASTHMA

УЛОГАТА И КЛИНИЧКОТО ЗНАЧЕЊЕ НА IL-33 КАЈ ПАЦИЕНТИ СО АСТМА

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Abstract

Introduction. Asthma is a chronic inflammatory disease of the airways in which many cells play a role with secreting a variety of mediators responsible for the clinical manifestation of asthma. It is assumed that IL-33 is one of the earliest-released mediators and can orchestrate the immune cascade of the disease.
The aimof this study was to examine the role and clinical significance of IL-33 as a new and insufficiently explored mediator of inflammation in patients with uncontrolled moderate asthma.
Methods. The study included 87 patients with asthma. Serum IL-33 was measured in all patients by ELISA method. The obtained data were statistically analyzedusing the Kolmogorov-Smirnov and Shapiro-Wilk's test. Qualitative data were presented in absolute and relative numbers, and quantitative data were presented with measures of descriptive statistics. Statistically significant values were considered forp <0.05.
Results. Majority of included patients were female (75.86%). The average age of patientswas 42.3±15.9 years. The results of IL-33 in all patients were significantly increased compared to the reference value of IL-33 which is 0pg/ml. The average values of IL-33 ranged from 6.47±29.3 and they were insignificantly higher in the group with female patients compared to males (p=0.27), and insignificantly correlated with age (p=0.26).
Conclusion. Even though a limited number of studies haveexplored the IL-33, results have shown higher serum level of IL-33 in asthma patients compared to healthy people, emphasizing the factthat IL-33 is an attrac tive candidate for targeted therapy and prognosis inasthma patients.

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Keywords: asthma; IL-33; ST2; IL-1 family

Апстракт

Вовед. Астмата е хронично инфламаторно заболување на дишните патишта во кое учествуваат многубројни клетки, кои излачуваат мноштво медијатори одговорни за клиничката слика на болеста. Се претпоставува дека IL-33 е еден од првите медијатори, кои се излачуваат на самиот почетокот и ја оркестира целата имунолошка каскада на болеста.
Целтана трудот е дефинирањенаулогата и на клиничкото значењето на медијаторот на инфламацијата IL-33, како нов и недоволно истражен медијатор кај пациенти со неконтролирана средна астма.
Методи. Во студијата се вклучени 87 пациенти со астма и кај сите е измеренсерумски IL-33 со ELISA метод. Добиените податоци беа статистички обработени со Kolmogorov-Smirnov и Shapiro-Wilk'stест. Квалитативните податоци беа презентирани со апсолутни и со релативни броеви, квантитативните податоци беа прикажани со мерките на дескриптивна статистика. За статистички сигнификантни беа земени вредностите на p<0.05.
Резултати. Во истражувањето, во поголем број беа вклучени испитаниciод женски пол (75.86%). Испитаниците беа на просечна возраст од 42.3±15.9 години. Добиените резултати за IL-33 кај сите пациенти беа сигнификатно зголемени, во однос на референтната вредност за IL-33, која изнесува 0 pg/ml, додека просечните вредности на IL-33 се движеа од 6.47±29.3 и покажаа дека се несигнификантно повисоки во групата на женски испитаници, споредено со машките (p=0.27), и дека несигнификантно корелираат со возраста на испитаниците (p=0.26).
Заклучок. И покрај лимитираноста на бројот на студии кои го истражуваат IL-33, сепак, резултатите укажуваат дека е зголемно нивото на серумскиот IL-33 кај астматичарите, во однос на здравите

лица, истакнувајќи дека IL-33 е атрактивен кандидат за таргетирана терапија и прогноза на астмата.

Клучни зборови: астма, IL-33, ST2; IL-1 фамилија

Introduction

Asthma is a worldwide problem and is one of the most common chronic diseases which affect more than 334 million people worldwide [1-3]. It is estimated that the number of people with asthma will grow by more than 100 million by 2025. Women were more likely than men and boys more likely than girls to have asthma [4-6]. Approximately 500,000 annual hospitalizations are due to asthma, and 250 000 deaths annually [3,7,8]. In the Republic of Macedonia 100,000 or 5% of the population suffer from asthma [9,10].

Asthma is a chronic inflammatory disease of the airways in which many cells and cellular elements play a role (mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and dendritic cells). The chronic inflammation is associated with airway hyperrsponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment [11].

Chronic inflammation of the asthmatic airway leads to epithelial desquamation, infiltration of the airway wall with T cells especially dominated Th2 helper-CD4+ lymphocytes, **smooth muscle** hypertrophy and hyperplasia, vascular congestion, edema due to plasma leakage and mucus plugging [12-17]. All these changes could lead to thickening of the airway walls due to subepithelial fibrosis and reduction of their lumen [18,19].

In this chronic inflammation are involved more than 100 mediators and the cytokines take central place in this inflammation (they are proteins with low molecular weight produced by almost all eukaryotic cells and act through specific receptor "cell surface"). Cytokines are often produced in cascades, as one cytokine stimulates its target cells to produce additional cytokines. Different cell types may secrete the same cytokine, or for a single cytokine may act on several different cell types. Cytokines can also act synergistically with two or more cytokines acting together or antagonistically with cytokines causing opposing activities. Cells that produce cytokines are B cells, T cells, dendritic cells, NK, Tc, Th, Th1, Th2, endothelial cells, mast cells, plasma cells, progenitor, bone marrow, thymus and tumor cells together with fibroblasts, leukocytes, monocytes and macrophages [20-21].

The interleukins are cytokines that stimulate the proliferation and differentiation of immune cells. IL-1 activates T cells, IL-2 stimulates the proliferation of antigen-activated T and B cells; IL-4, IL-5 and IL-6 stimulated proliferation and differentiation of B cells; interferon-gamma (IFNγ) activates macrophages while IL-3, IL-7, and (GM-CSF) stimulate hematopoiesis [22,23].

T cells play a key role in coordinating the immune response in asthma. The key to the functioning of T cells is a molecule that binds to the antigen: T cells receptor. Generally the T cells which have the CD4+ act as helper cells (Th2-Ly), and CD8+ act as cytotoxic cells (Tc-Ly). CD4+ helper cells, differentiate into subpopulations of T cells in Th1, Th2, Th9, Th17, Th22 and T follicular effectors cell. Th2 cellsproduce, IL-4, IL-5, IL-9, IL-13, GM-CSF andIL-25, IL-31, IL-33 that are responsible for chronic eosinophilic inflammation, inflammation in allergic diseases, including asthma [22-27].

Interleukin-33 (IL-33) is a novel cytokine which was found in 2005. It belongs to the IL-1 family consisting of 11 members, high proinflammatory cytokines which play a key role in the early asthmatic responses. IL-33 is a potent type 2-inducing cytokine. It can bind to receptors ST2, which is highlyexpressed on some cells, including mast cellsand Th2 cells. It is found in various cells including fibroblasts, bronchial and epithelialcells, endothelial cells, and some immune cells, as well asma crophages and dendritic cells [28-31].

It is assumed that IL-33 is one of the earliest-released mediators and can orchestrate the immune cascade of asthma and stands out as an attractive candidate for discovering various therapeutic modalities, especially a new targeted therapy (Figure 1).

The limited numbers of studies which have investigated IL-33 with their results have shown an increased level of serum IL-33 in asthmatics compared to healthy subjects and pointed out that IL-33 is an important cytokine for correct diagnosis, evolution, treatment and prognosis of asthma.

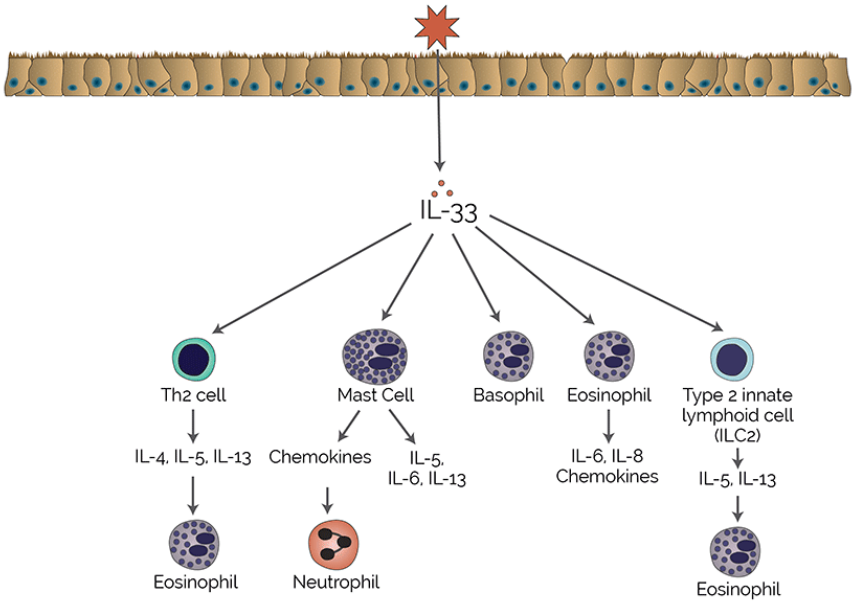

Fig. 1. IL-33 is an upstream cytokine that functions as a central mediator in asthma

The aim of this study was to examine the role and clinical significance of IL-33, as a new and insufficiently explored mediator of inflammation in patients with uncontrolled moderate asthma.

Materials and methods

The study included 87 patients with diagnosis of uncontrolled moderate persistent asthma treated at the Clinic of Pulmonology and Allergology in Skopje. Serum IL-33 levels were measured in all patients by ELISA method at the Institute of Immunobiology and Human Genetics, Faculty of Medicine, Ss Cyril and Methodius University of Skopje. The reference values for IL-33 were 0 pg/ml.

Inclusion criteria: patients who were diagnosed and classified in uncontrolled moderate persistent asthma at PHI University Clinic of Pulmonology and Allergology according to the actual version of the GINA guidelines (Global Initiative for Asthma) [11] and Guidelines for the Diagnosis and Management of Asthma (EPR-3) of National Asthma Education Prevention Program (NAEPP) [32].

Uncontrolled asthma defined as at least one of the following [33]:

1) Poor symptom control: ACQ consistently >1.5, or ACT <20 (or "not well controlled" by NAEPP/ GINA guidelines over 3 months of evaluation.
2) Frequent severe exacerbations: two or more bursts of systemic CS (3 days each) in the previous year.
3) Serious exacerbations: at least one hospitalization, ICU stay or mechanical ventilation in the previous year.
4) Airflow limitation: after appropriate bronchodilator withhold FEV1 <80% predicted (in the face of reduced FEV1/FVC defined as less than the lower limit of normal).

All patients had allergic stable asthma because there was no increase in symptoms or need for additional medication for at least 4 weeks. Eosinophils in peripheral blood in all patients were counted at the University Clinic of Clinical Biochemistry. Some of the patients had arterial hypertension, but had no other comorbidities that could increase IL-33 level. The age of the patients was 20-71 years.

Exclusion criteria: pregnancy, severe diseases of the immune, endocrine, haematological cardiac, renal, gastrointestinal, neurologicalsystem, psychiatricdisorders, and neoplastic diseases**.**

Statistical analysis

The results were statistically analyzed by the statistical program SPSS for Windows 17.0. For testing the normal distribution of data Kolmogorov - Smirnov and Shapiro-Wilk's test and Spearman Rank Order Correlations-test were used. The qualitative data were presented in absolute and relative numbers, and the quantitative data were presented with the measures of descriptive statistics (mean ±SD, median with IQR). Statistical significance was defined as a P value<0.05.

Results

The study included 87 patients with uncontrolled moderate persistent asthma; the majority were females-66 women (75.86%), and 21 were men (24.14%). The average age of patients was 42.3±15.9 years (Table 1).

The results of IL-33 (average values 6.47±29.3 pg/ml) in all asthma patients were significantly increased com-

pared to healthy people which results were in range of reference value of IL-33 (0 pg/ml).
The average values of IL-33 ranged from 6.47±29.3 and were insignificantly higher in women compared to men (p=0.27) (Table 2).
The obtained values of IL-33 showed an insignificant correlation with the age of patients (p = 0.26) (Figure 2).

Table 1. Characteristics of patients with average age of patients

Characteristics of patients		
Sex		**n (%)**
Women		66 (75.86)
Man		21 (24.14)
Age		
mean±SD	(42.3±15.9)	Min-max (20-71)

Table 2. Descriptive statistics of IL-33

Normal level IL-33=0pg/ml IL-33	**mean±SD**	**Median**	**Q25 - Q75**	**p-level**
Women	7.91±33.5	1.83	1.68-2.05	
Men	1.95±0.9	1.76	1.68-1.87	p=0.27
Total	6.47±29.3	1.79	1.68-1.98	

p (Mann-Whitney test)

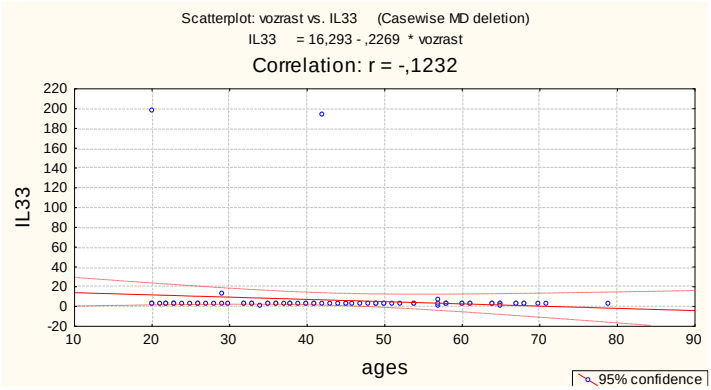

Fig. 2. Correlation between IL-33 and age in asthma patients (r =-.1232, p=0.26)

The value of eosinophils in peripheral blood was significantly increased in all asthma patients compared to healthy people, and the analyzed correlation between values of IL-33 and eosinophils showed a statistically insignificant correlation (IL-33/Eo: r<0.05, R=0.0563). It means that patients who have an increased level of IL-33 have increased concentrations of eosinophils in peripheral blood, but statistically insignificant; perhaps there were patients with neutrophilic asthma among other patients.

Discussion

IL-33 is generally released from damaged immune cells and signals through its receptor ST2 and plays important roles in type-2 innate immunity, and functions as an "alarmin" or a danger signal for cellular damage or cellular stress [34]. The role of IL-33 in lung injury was first identified mainly in lung inflammation and allergic diseases such as asthma [35,36].
In mouse models, transgenic over-expression or administration of IL-33 generates airway eosinophilia, up-regulated Type 2 cytokine expression, elevated serum IgE, AHR and mucus hypersecretion. Conversely, neutralization of IL-33 leads to reduction of airway inflammation, IgE levels, Type 2 cytokine expression, goblet cell hyperplasia, and AHR [37-38].
A recent study by Kaur D et al. showed that bronchial epithelium, airway smooth muscle (ASM), and mast cells expressed IL-33 and correlated with airway hyper responsiveness (AHR) in latter asthma [34,39].
More recent researches have implicated additional roles of IL-33 in asthma, but unfortunately, thereare a limited number of studies which have investigated IL-33. Their results showed an increased level of serum IL-33 in asthmatics compared to healthy subjects as demonstrated in our study, too. The results of meta-analysis which included four studies and evaluated 222 patients with asthma revealed that serum level of IL 33 was higher in asthma patients compared to that in healthy people [34, 37,40-44].
IL-33 have been shown to exert their effects on progenitor cells, mast cells, granulocytes, lymphocytes and dendritic cells. In human studies of allergic asthma, IL-33 and ST2 expression in serum, lung tissue and BALF have found to be higher in asthmatics compared to healthy controls and correlated with asthma severity [37,45-47].
Studies which analyzed correlation between serum levels of IL-33 and asthma severity found an increased serum level of IL-33 in all three forms of asthma (severe, moderate and mild asthma) [34,37,40,44-51].

However, the results of meta analysis which analyzed level of IL-33 in sputum, showed that the sputum IL-33 were increased in severe asthma, but not higher in moderate asthma patients than that in healthy people [44,49,51] Hamzaoui A. *et al*. revealed that IL-33 and ST2 were increased in young and adult asthmatic patients, emphasizing the fact that there were a series of factors influencing the IL-33 and ST2 expression level in asthma patients, including year, sex, races, severity of the disease [51]. But, our study showed no significant differrence between women and men with higher value of serum IL-33, and an insignificant correlation with the age of patients. Endobronchial biopsies from Préfontaine D. et al. proved increased levels of IL-33 in endothelial and epithelial cells in patients with asthmatic lungs, but they were absent in control samples; positive correlation with severity of asthma was also shown [44,46,47].

Bartosz Stolarski *et al*. in their study demonstrated that the IL-33/ST2 signaling pathway activates airway eosinophils that exacerbate airway inflammation in an autocrine and paracrine manner. However, in our study this correlation between IL-33 and eosinophils has proved to be insignificant [52]. Eosinophils are significant effector cells involved into the late and chronic stage of the allergic inflammatory response, and the explanation could be that eosinophils and IL-5 are cytokines which are detected during the late phase response and it is not detectable in early response to antigen provocation like IL-33, which are high proinflammatory cytokines with a key role in the early asthmatic responses [53,54].

Conclusion

IL-33 is new and insufficiently explored mediator of inflammation with assumption that is one of the earliest-releasedsignaling mediators secreted at the beginning in the allergic and non-allergic asthma and can orchestrate a whole immunologic cascade in asthma.

IL-33 stimulates immune activity especially Th2 immune response, and stands out as an attractive candidate for detection of other therapeutic modalities such as the new targeted therapy which would suppress IL-33, and is significantly increased in patients with asthma. By acting on the immune response by reducing the excretion of markers of inflammation could help us to make correct diagnosis, therapy, evaluation and prognosis of asthma.

Conflict of interest statement. None declared.

References

1. Masoli M, Fabian D, Holt S, Beasley R. The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy* 2004; 59(5): 469-478.
2. Beasley R. The Global Burden of Asthma Report, Global Initiative for Asthma (GINA). Available from http://www.ginasthma.org 2004.
3. World Health Organization. Global surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach, 2007.
4. Eder W, Ege MJ, Von Mutius E. The asthma epidemic. New England Journal of Medicine 2006; 355: 2226-2235.
5. Centers for Disease Control and Prevention, Vital Signs, May 2011.
6. Centers for Disease Control. National Surveillance for Asthma-United States, 1980-2004. *MMWR* 2007; 56(SS08); 1-14; 18-54.
7. American Lung Association. Epidemiology & Statistics Unit, Research and Program Services. Trends in Asthma Morbidity and Mortality, November 2007.
8. Akinbami, L. Asthma prevalence, health care use and mortality: United States 2003-05, CDC National Center for Health Statistics, 2006.
9. Gjorcev A. Makedonski nacionalen plan i program za dijagnostika i lekuvanje na bronhilajnata asthma-realnost i vizija, 1996.
10. Vladimir Cvetanov. *Alergiskite bolesti vo R. Makedonija* 2006; 151-174.
11. Global Initiative for Asthma (GINA), GINA Report 2016, Global Strategy for Asthma Management and Prevention, updated 2016; http://www.ginasthma.org.
12. Holgate ST. Genetic and environmental interaction in Allergy and asthma. *J Allergy Clin Immunol* 1999; 104(6): 1139-1146.
13. Burke W, Fesinmeyer M, Reed K, *et al*. Family history as a predictor of asthma risk. *Am J Prev Med* 2003; 24: 160-169.
14. Thomas MJ, Kemeny DM. Novel CD4 and CDS T-cell subsets. *Allergy* 1998; 53: 1122-1132.
15. Heard BE, Hossain S. Hyperplasia of bronchial muscle in asthma. *J Pathol* 1973; 110: 319-331.
16. Shiels IA, Bowler SD, Taylor SM. Airway smooth muscle proliferation in asthma: the potential of vascular leakage to contribute to pathogenesis. *Med Hypotheses* 1995; 45: 37-40.
17. Brewster CE, *et al*. Myofibroblasts and subepithelial fibrosis in bronchial asthma. *Am J Respir Cell Mol Biol* 1990; 3: 507-511.
18. Dirkje S Postma, Wim Timens. Remodeling in Asthma and Chronic Obstructive Pulmonary Disease. *American Thoracic Society* 2006; 3(5): 434-439.
19. Christopher L, *et al*. Effect of bronchoconstriction on Airway Remodeling in Asthma. *N Engl J Med* 2011; 364: 2006-2015.
20. Barnes PJ. Pathophysiologu of asthma. *Eur Respir Mon* 2003; 23: 84-113.
21. Kuipers H, Lambrecht BN. The interplay of dendritic cells, Th2 cells and regulatory T cells in asthma. *Curr OpinImmunol* 2004; 16(6): 702-708.
22. Abbas AK, Lichtman Ah, Pober JS. *Cellular and Molecular Immunology*, 4nd ed. 2000; 235-69.
23. Roitt IM, and Delves PJ. *Essential Immunology*, 10th ed. 2001; 177-199.
24. Park SJ, Lee YC. Interleukin-17 regulation: an attractive therapeutic approach for asthma. *Respir Res* 2010; 11: 78.
25. Larche M, Robinson DS, Kay AB. The role of T lymphocytes in the pathogenesis of asthma. *J Allergy Clin Immunol* 2003; 111: 450-463.
26. Miyahara N, Swanson BJ, Takeda K, *et al*. Effector CD8(+) T cells mediate inflammation and airway hyper responsiveness. *Nat Med* 2004; 10: 865-869.
27. Zhu J, Hidehiro Y, William EP. Differentiation of effector CD4 T cell populations. *Annu Rev Immunol* 2010; 28: 445-489.

28. Borish L, Steinke JW. Interleukin-33 in asthma:how big of a role does it play? *Curr Allergy Asthma Rep* 2011; 11: 7-11.
29. Schmitz J, *et al*. IL-33, an interleukin-1-like cytokinethat signals via the IL-1 receptor-relatedprotein ST2 and induces Thelper type 2-associatedcytokines. *Immunity* 2005; 23: 479-490.
30. Kakkar R and Lee RT. The IL-33/ST2 pathway: therapeutic target and novel biomarker. *Nat Rev Drug Discov* 2008; 7: 827-840.
31. Miller AM. Role of IL-33 in inflammation and disease. *J Inflamm* 2011; 8: 22.
32. National Institutes of Health. National Asthma Education and Prevention Program Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Accessed: January 1, 2009.
33. Kian Fan Chung, *et al*. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *European Respiratory Journal*, April, 2014.
34. Jing Chang, *et al*. IL-33 Signaling in Lung Injury. *Transl Perioper Pain Med* 2016; 1(2): 24-32.
35. Lloyd CM. IL-33 family members and asthma - bridging innate and adaptive immune responses. *Current opinion in immunology* 2010; 22(6): 800-806.
36. Miller AM. Role of IL-33 in inflammation and disease. *Journal of inflammation* 2011; 8(1): 22.
37. Brittany M. Salter, *et al*. IL-25 and IL-33 induce Type 2 inflammation in basophils from subjects with allergic asthma. *Respiratory Research* 2016; 17: 5.
38. Lee HY, *et al*. Blockade of IL-33/ST2 ameliorates airway inflammation in a murine model of allergic asthma. *Exp Lung Res* 2014; 40(2): 66-76.
39. Kaur D, *et al*. IL-33 drives airway hyper-responsiveness through IL-13-mediated mast cell: airway smooth muscle crosstalk. *Allergy* 2015; 70(5): 556-567.
40. Ma XY, Luo YL, Lai WY. IL-33 levels in peripheral blood plasma and sputum of patients with bronchial asthma and their correlation with symptoms of patients, pulmonary function, and eosinophil numbers. *J Third Mil Med Univ* 2011; 33: 1526-1529.
41. Zhang HQ, Wu LF, Sun ZL. Serum levels of IL33 and IL5 in patients with allergic rhinitis and bronchial asthma. *Journal of Zhejiang Medicine* 2013; 35: 1755-1756.
42. Li QY, Huang XX, Zhang HY. Significance of changes of serum interleuin in patient with acute attack of bronchial asthma. *China Medicine* 2013; 8: 1556-1557.
43. Gluck J, Rymarczyk B, Rogala B. Serum IL-33 but not ST2 level is elevated in intermittent allergic rhinitis and is a marker of the disease severity. *Inflamm Res* 2012; 61: 547-550.
44. Rui Li, *et al*. Interleukin-33 and receptor ST2 as indicators in patients with asthma: a meta-analysis. *Int J Clin Exp Med* 2015; 8(9): 14935-14943.
45. Azazi EA, *et al*. Serum levels of Interleukin-33 and its soluble receptor ST2 in asthmatic patients. *Egyptian Journal of Chest Diseases and Tuberculosis* 2013.
46. Prefontaine D, *et al*. Increased expression of IL-33 in severe asthma: evidence of expression by airway smooth muscle cells. *J Immunol* 2009; 183: 5094-5103.
47. Prefontaine D, *et al*. Increased IL-33 expression by epithelial cells in bronchial asthma. *J Allergy Clin Immunol* 2010; 125: 752-754.
48. Li YM, Cheng XM. Clinical significance of IL-18and IL-33 levels changes in the treatmentof bronchial asthma with acute attack stageby glucocorticoids. *Practical Pharmacy and Clinical Remedies* 2013; 16: 897-899.
49. Liu SP, Ma R, Li XA. The relationship between interleukin 33 promotes and lung inflammationin asthmatic children. *Chin J Diffic and Compl* Cas 2013; 12: 422-424.
50. Liao XM. Changes of plasma interleukin 33 inasthmatic patients and its clinical significance. *Journal of Clinical Pulmonary Medicine* 2014; 19: 33-35.
51. Hamzaoui A, *et al*. Induced sputum levels of IL-33 and soluble ST2 in young asthmatic children. *J Asthma* 2013; 50: 803-809.
52. Bartosz Stolarski, *et al*. IL-33 Exacerbates Eosinophil-Mediated Airway Inflammation. *J Immunol* 2010; 185(6): 3472-3480.
53. Pecaric-Petkovic T, *et al*. Human basophils and eosinophils are the direct target leukocytes of the novel IL-1 family member IL-33. *Blood* 2009; 113(7): 1526-1534.
54. Keisuke Oboki, *et al*. IL-33 and Airway Inflammation Allergy. *Asthma Immunol Res* 2011; 3(2): 81-88.