Satisfaction Level of Rheumatoid Arthritis Patients Enrolled in the Treatment with Subcutaneous Tocilizumab

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Abstract: *Background*: The introduction of biological-Disease Modifying Agents (bDMARDs) has allowed serious improvement in the treatment of patients with rheumatoid arthritis (RA) by providing a better quality of life (QoL). Such improvements have been shown in patients using subcutaneous form of Tocilizumab SC (TCZ-SC), a humanized monoclonal antibody against IL-6 receptor.

Objective: To assess the subcutaneous treatment satisfaction level and to evaluate the epidemiological profile of RA patients treated with TCZ-SC in North Macedonian Patients with RA.

Methods: An observational study was conducted at the University Rheumatology Clinic in Skopje between October 1st and December 15th 2018, including 48 patients who have received TCZ-SC. In order to obtain patient's satisfaction level and to evaluate the epidemiological characteristics of the patients, a standardized questionnaire was developed.

Results: The mean age of the patient's cohort was 50.9 years and 88.5% of the patients were females. More than half of the patients (58%) had high disease activity with mean disease duration of 5.35 years. Eighty three percent of the patients were entitled to receive subcutaneous TCZ because of the insufficient efficacy of previous treatment, All patients enrolled in the treatment with TCZ-SC, reported to be satisfied or very satisfied with the subcutaneous application of TCZ. They were also very satisfied with the previous education and the opportunity to receive the treatment at home.

Conclusions: Tocilizumab as an efficient and well tolerated bDMARD is becoming a standard of care in the treatment of patients suffering from RA, offering unprecedented benefits for QoL improvement and satisfying the patients' needs for modern and effective treatment.

Keywords: Rheumatoid arthritis, Tocilizumab-subcutaneous, Tocilizumab intravenous, treatment satisfaction level, patient's preferences, epidemiological characteristics.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune systemic inflammatory disease characterized by joint pain, stiffness, swelling and destruction due to the synovial inflammation [1]. It affects approximately 0.5% to 1% of the population in the industrialised world causing significant morbidity and early mortality [2,3]. Some of the available treatment options relieve the symptoms of the disease, others are used to slow down and eventually stop the evolving course of the disease and inhibit structural damage [4,5].

Significant advances in the treatment of RA have been made over the past 20 years with the introduction of biologic therapies i.e biological Disease Modifying Agents (b-DMARDs), [6]. With these medications, many RA patients have seen rapid and sustained improvements, allowing for less disability and better QoL [7].

Tocilizumab is a humanized mAb against the IL-6 receptor which blocks IL-6 signalling by binding to both soluble and membrane-bound IL-6R. TCZ is available in two different forms of administration, an intravenous (TCZ-IV) and a subcutaneous form (TCZ-SC).

The intravenous TCZ (TCZ-IV) formulation has been approved in Europe in 2009 for the management of patients with refractory RA, previously treated with conventional DMARDs and tumour necrosis factor inhibitors (TNF-i), which was followed by the approval of the subcutaneous (TCZ-SC) formulation in 2014 [8]. The efficacy and safety of TCZ-SC have been studied and proved in many clinical trials.

In the study BREVACTA, TCZ-SC was compared with placebo and had significantly greater efficacy using the American College of Rheumatology (ACR) response rates, as well as joint damage scores [9]. The ADACTA study compared tocilizumab with the long-time blockbuster drug adalimumab and showed that tocilizumab is superior versus adalimumab in terms of efficacy, with a favourable safety profile [10].

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In the MUSASHI clinical trial, 348 patients were randomized to receive either TCZ-SC or TCZ-IV, in a double-blind design. The results showed that TCZ-SC was not inferior, compared to TCZ-IV, in terms of efficacy and adverse events [9].

In SUMMACTA study, TCZ-SC was compared with TCZ-IV in 1262 patients with a 1:1 randomisation [11]. At week 97, the proportion of patients achieving ACR 20/50/70 responses and Disease Activity Score 28 (DAS28) remission were comparable in both treatment arms. The efficacy of the two routes of administration has also been compared in a real-world setting.

An evaluation of the effectiveness of TCZ-IV and TCZ-SC, using the Pan-European register, was conducted in terms of treatment compliance and disease activity in patients with RA across eight European registries [12]. In regards to the route of administration, TCZ-IV vs. TCZ-SC, both forms have been shown to be effective in treatment of moderate-to-severe RA, however in the comparison the study of Tocilizumab IV vs. Tocilizumab SC by Nakashima Y *et al.*, the TCZ-SC weekly regimen showed a more rapid effect in terms of C-reactive protein (CRP) normalization [13].

In the Republic of North Macedonia, tocilizumab (monotherapy or in combination with methotrexate) is approved by the Health Insurance Fund for the following indications:

- treatment of severe, active and progressive RA in adults not previously treated with methotrexate (MTX).
- treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more cs DMARDs or TNF antagonists. In these patients, tocilizumab can be given as monotherapy in case of MTX intolerance or MTX adverse effects [14].

Since January 1st 2018 the subcutaneous formulation of tocilizumab became available for RA patients at University Clinic of Rheumatology (UCR) in Skopje, where 48 patients were enrolled on the treatment with TCZ-SC.

MATERIALS AND METHODS

Objectives

The objectives of this observational study were to assess the subcutaneous treatment satisfaction level among RA patients at the UCR Skopje, treated with subcutaneous formulation of Tocilizumab and to gain insight regarding the epidemiological characteristics and the profile of RA patients, including patient's adherence and preferences in relation to the subcutaneous treatment with Tocilizumab.

Determination of subcutaneous treatment satisfaction level among the patients receiving TCZ-SC is a very valuable milestone for future treatment with tocilizumab and other bDMARDs at the UCR Skopje and might lead to the optimisation of the conditions under which patients receive the therapy. Fulfilling the patient's needs and providing epidemiological data will be an additional asset for the patients and clinicians at UCR Skopje.

Design

The study was conducted by using questionnaires, specifically tailored for this purpose, developed by experts from UCR Skopje. They included questions related to demographic data, clinical data, previous biologic therapy and reason for switch, treatment satisfaction level, patient's knowledge about storage conditions of the subcutaneous TCZ and self-administration training attendance.

The questionnaires comprised of Yes/No questions, descriptive questions and numerical questions (Appendix 1 and 2). The collected data were related to each individual patient treated with TCZ SC. The summarized report did not include any personal data of the patients.

The patients have signed the written consent to participate in the study, the study was approved by the Ethical Comitee of Rheymatology Clinic Skopje and the authors have followed the recommendation of the Declaration of Helsinki.

Study Population

All patients included in the study were previously diagnosed with rheumatoid arthritis according to 2010 classification criteria by Aletaha *et al*. [15]. They were assessed to be eligible to receive Tocilizumab SC by the commission of three rheumatologists, which decided that they had failed treatment with at least 2 csDMARDS in the last 6 months and still had high or moderate disease activity. They were previously evaluated for tuberculosis, hepatitis A, B and C and serologically tested for HIV. They were thoroughly examined and the disease activity was evaluated using

DAS 28 score with erythrocyte sedimentation rate. The QoL was evaluated by HAQ score, which was previously translated and validated in Macedonian language.

Statistical Analysis

Data was obtained from the questionnaires collected during the study period of two months (October 1st- December 3rd 2018). Collected data was anonymous, and was analysed as available, without source data verification. The database was locked by the end of November 2018. During the period of December 3rd to December 15th a summarized final report was prepared by analysing each questionnaire and the summarized data was calculated as an absolute number and percentages.

RESULTS

In this observational study we have enrolled 48 RA patients, who received treatment with TCZ-SC.

Demographic Data

In this cohort there were 42 (87,6%) females and 6 males (12,5 %). All the patients involved in the cohort agreed to fill the questionnaires and there were no cancelled surveys.

The majority of RA patients treated with subcutaneous tocilizumab i.e. 39 out of 48 or 81%, were between the age of 31-60 years, which represents the most productive and work-capable population in North Macedonia. The mean age of the patients was 50.9 years (range 30 – 74) Figure **1**.

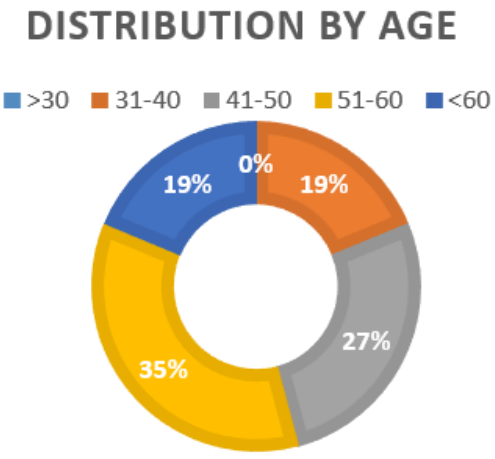

Figure 1: Distribution by age.

In order to take into consideration their traveling costs which may impact their treatment satisfaction level, patients were divided according to place of living. In this regard 22 patients (45.83%) were residents of the capital city Skopje and 20 out of 48 patients (41,6 %) had to travel more than 100 kilometres in one way to receive the treatment with TCZ SC. We have noted the cities in Table **1**.

Table 1: Geographical Distribution of Patients Enrolled on Treatment with Subcutaneous Formulation of Tocilizumab

City	Number of patients	Percentage of patients (%)
Skopje	22	46
Ohrid	1	2
Struga	2	4
Kumanovo	3	6
Prilep	2	4
Bitola	3	6
Stip	3	6
Strumica	3	7
Kavadarci	1	2
Tetovo	2	4
Gostivar	1	2
Others	5	11

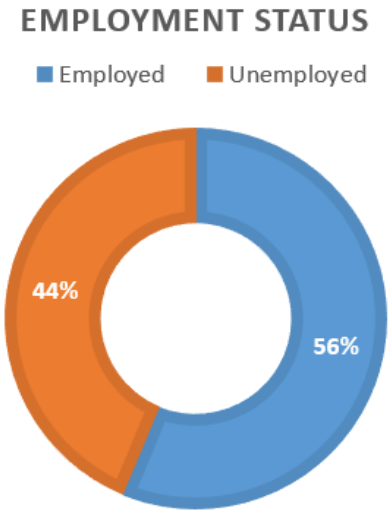

Figure 2: Employment status.

The employment status of RA patients was also assessed- 27 patients were working, while the other 21 patients were unemployed. Taking into consideration the chronic and disabling nature of RA, the unemployed participants were asked to report the reason of their unemployment. In this regard, 48% of the patients had never worked, 14% were in regular

retirement, 24% reported to have asked for an early retirement because of RA and 14% could not keep a job long term because of their disabling disease Figure **2** Employment status, Figure **3** Reason for unemployment.

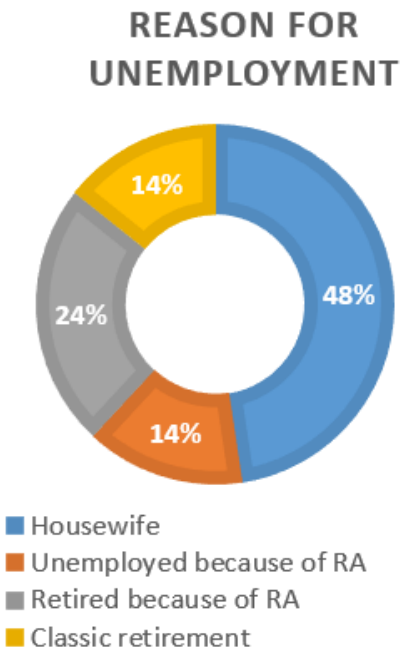

Figure 3: Reason for unemployment.

Clinical Characteristics

In regard to the clinical characteristics, the average disease duration of RA patients enrolled with the treatment was 5.35 years. There were no patients diagnosed with early RA, meaning RA diagnosed in the last year before enrolment in this study. Only 2 patients (4%) were diagnosed with RA in the period of 2 years before enrolment, and most of the patients or 69% were diagnosed with RA for more than 6 years (Figure **4**: Clinical characteristics of RA patients in terms of disease duration).

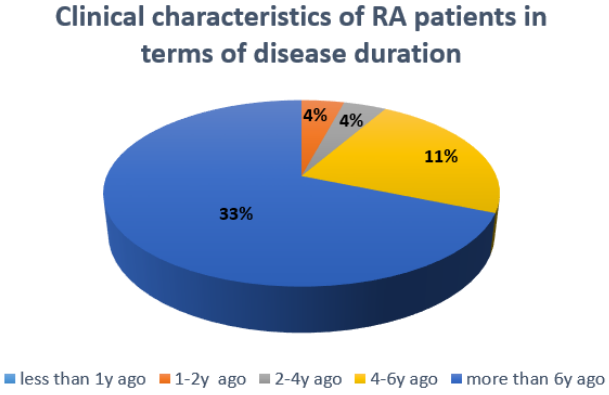

Figure 4: Clinical characteristics of RA patients in terms of disease duration.

When we speak about the disease activity, the highest number of patients enrolled on treatment with TCZ-SC, 28 patients (58%) had high disease activity, 15 patients (31%) had moderate disease activity and 5 patients (11%) had low disease activity. The average DAS28 score of the RA patients enrolled in the treatment was 5.4.

RA Treatment

All 48 patients included in the study had previously been treated with DMARDs: 29 (61%) were on cs DMARDs, 15 had previously received rituximab (31%) and 4 patients had been previously enrolled in clinical trial with b DMARD (8%). At that time, anti-TNF therapy was still not available in North Macedonia. In the patients who were treated with other b DMARDs, there was a gap of at least 6 months in between the treatment options Table **2**.

Table 2: Distribution of Patients by Type of Previous Therapy

Type of therapy	Number of patients	Percentage of patients (%)
Rituximab	15	31
anti-TNF	0	0
Other biologic treatment	4	8
sDMARDs	29	61

Regarding the reason for switch from previous treatment to Tocilizumab SC, 40 patients (83%) were switched because of the lack of the efficacy of previous treatment resulting with no response to therapy and 8 patients (17%) because of physician's advice .11.

The enrolled patients were assessed in regard to the location where they receive their treatment: 28 patients (58.3%) received their treatment at UCR, 12 in their native town hospital (25%) and 8 at their homes (16.7%) (Table **3**). Patients which received the treatment in the hospital have chosen that option because they did not feel capable to learn self treatment at that time.

Table 3: Distribution of Patients by Location of Therapy Administration

Pts. receiving tx at UCR (%)	Pts. receiving tx in native town hospital (%)	Pts. receiving tx at their home (%)
28 (58.3)	12 (25)	8 (16.7)

Regarding treatment preferences in relation to the route of administration all 48 patients included in the observational study prefer to receive TCZ subcutaneously.

TCZ-Subcutaneous Treatment Satisfaction

Out of 48 patients enrolled in the treatment with TCZ-SC, 50% or 24, reported to be very satisfied with the subcutaneous treatment and the other half i.e. 50% reported to be satisfied with the subcutaneous treatment. None of the patients answered the satisfaction question neither with “not satisfied” nor “very unsatisfied” (Figure **5**: Level of satisfaction from ACTEMRA subcutaneous administration).

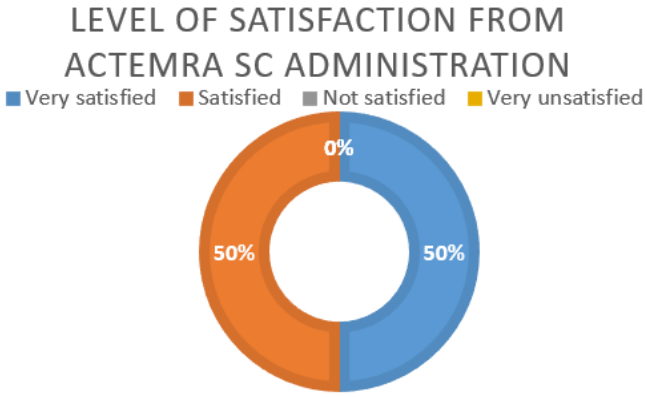

Figure 5: Level of satisfaction from Tocilizumab SC administration.

Patients were requested to denote their treatment satisfaction level with TZC-SC on a scale from 1-10, where 1 stands for the worst and 10 for the best. Table **4** and Figure **6**: Level of satisfaction on scale 1-10;

Table 4: Treatment Satisfaction Level of Patients Receiving TCZ-SC, Scale 1-10

Treatment satisfaction level, scale 1-10	Number of patients	Percentage (%)
1	0	0
2	0	0
3	0	0
4	0	0
5	8	16
6	2	5
7	7	15
8	14	29
9	6	12
10	11	23

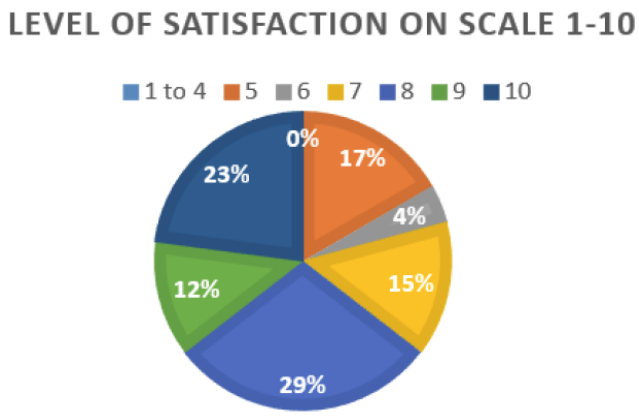

Figure 6: Level of satisfaction on scale 1-10.

None of the patients denoted their satisfaction with the marks from 1-4, 17% of the patients had chosen grade 5 and 23% reported to be completely satisfied and circled grade 10.

Out of 48 participants, only 2 had adverse effects- one had local erythema which faded in few hours and the other one lower respiratory infection for which she missed 2 doses.

Ten out of 48 patients (20.8%) reported that they need help when receiving their therapy, while 25 out of 48 patients (52%) reported that they would prefer to receive their treatment at home.

In regard to the organized self-administration training, 32 patients (66.6%) reported to have attended the training, and 41 patients (85.4 %) reported to be suitably informed about storage conditions of TCZ-SC. Since storage conditions of TCZ-SC require a temperature-controlled supply and cold chain from 2-8 °C, 29 patients (60.41%) reported to have cooling storage for transportation of the medicine.

Regarding the overall satisfaction level with treatment conditions 26 participants reported to be very satisfied (54%) and 22 patients reported to be satisfied from the treatment conditions (46%). None of the patients reported to be unsatisfied from the treatment conditions.

DISCUSSION

Patient satisfaction is an important indicator for measuring the quality of health care, including treatment with specific drugs, such as TCZ SC. Treatment satisfaction positively affects clinical outcome and increases the compliance. This finding was one of the motives to conduct this observational

study in relation with TCZ subcutaneous treatment satisfaction level, which resulted in a positive outcome. Our data confirmed that none of the patients receiving TCZ-SC had any negative experience with the treatment. All the assessed patients reported to be satisfied or very satisfied from the subcutaneous treatment with TCZ-SC.

Additionally, all patients have reported that they like to receive subcutaneous treatment. This finding indicates that the option of patients to receive TCZ-SC at their home after proper training will have a positive impact in decreasing the indirect costs related to the treatment such as traveling costs and need for additional company. Subcutaneous treatment preferably received at home is safe, cheap and convenient alternative to intravenous treatment [12].

This high rate of treatment satisfaction proved once again that TCZ SC is an effective medicine in the treatment of RA , with very convenient modality of application. TCZ-SC provides a convenient route of administration, option to receive the treatment at home and what is most important excellent clinical outcomes, as reported in the literature [10-12].

The efficacy and safety of subcutaneous form of TCZ was confirmed in the previous studies of Nakashima, Burmester and Choy [12,16-18]. Moreover, TCZ SC has been shown to improve signs and symptoms of active RA, inhibiting X-ray progression and significantly improving physical function and HRQOL by satisfying the patients' needs and preferences [7,9-11,13,14].

Tocilizumab, originally approved by the FDA as an IV medicine in 2010, is the first and only humanised interleukin-6 (IL-6) receptor-antagonist monoclonal antibody approved by the FDA for both SC and IV 2/4 administration. The approval is based on data from the phase III clinical trials SUMMACTA and BREVACTA [16]. For TCZ-SC, the FDA recommended dosage is 162 mg administered subcutaneously every other week, followed by an increase to 162 mg every week based on clinical response for patients less than 100 kg in weight. For patients at or above 100 kg, the dosing is 162 mg administered subcutaneously every week [8,10,18,19].

There are many studies about the efficacy of intravenous ant subcutaneous tocilizumab. In the study of Dougados and coworkers, iv tocilizumab was efficacious in achieving DAS-ESR remission in 40% patents in combination with methotrexate and in 34,8 % as monotherapy [20]. Similar remission index also was achieved in the study of Choy and colleagues in a common framework of 11 studies in 22 countries; this phase 4 study programme confirmed TCZ-SC's known efficacy and safety profile with comparable effects as monotherapy and in combination with csDMARDs [18].

In the UK real world ACT-MOVE study by Isaac *et al.,* there was a mean decrease in DAS28-ESR score among all patients (-3.68), and within TCZ-SC monotherapy (-3.75) and combination therapy with cs DMARDs (-3.67) groups, after 52 weeks [19].

In the study of Burmester *et al*. the long-term efficacy and safety of TCZ-SC was maintained and comparable to that of TCZ-IV, except for injection site reactions (ISRs) which were more frequent after 97 weeks [16].

Besada and coworkers have mentioned in their article that the only difference between the intravenous and subcutaneous formulation is that the dosage and intervals of subcutaneous TCZ administration should be adjusted during the course of treatment especially in non-Japanese RA patients with usually higher body weight. He also said that subcutaneous form of t TCZ could facilitate not only patients' emancipation from the hospital, but reduce both societal and medical costs [21].

McLaughlin and colleagues also agreed with that statement, and wrote that TCZ-SC might become a mainstay, along with other biologic agents, for the treatment of RA patients who have failed traditional non-biologic DMARDs [22].

In Ro-Switch French study of Darloy *et al.,* maintenance of effectiveness of subcutaneous tocilizumab six months after switching from intravenous formulation in patients with rheumatoid arthritis (RA) in a real-world setting, was shown [23]. One of limitations of our study was that we did not have iv TCZ to compare both treatment modalities.

In his newest study, Ogata and coworkers have concluded that the efficacy and safety profiles of TCZ are similar to those of tumor necrosis factor (TNF) inhibitors, The most notable advantage of TCZ is its usefulness as a monotherapy. Additionally, TCZ is favorable in the improvement of systemic inflammatory symptoms such as anemia and fatigue. The low immunogenicity of TCZ contributes favorably to long-

term drug retention.The only limitations of tocilizumab are slow taper because of possible remissions after stopping the treatment and possibility of tocilizumab to obscure some symptoms of infection [24].

Desplat and coworkers, were evaluating the difference between the intravenous and subcutaneous forms of tocilizumab and abatacept, and the patient's willingness for exchange. Even though subcutaneous treatment was more cost effective, 45,8 percent of the patients have chosen to keep the intravenous route. Reasons associated with choosing to maintain the IV route were worries about a lack of follow-up, the absence of medical assistance during the subcutaneous injection On the other hand,reasons guiding the choice of the subcutaneous route were concerns about repeated hospital day-care, greater autonomy with SC injections and economic considerations [25].

The successful use of tocilizumab in RA has encouraged the development of other biologic agents specifically targeting the IL-6 pathway, either directed against IL-6 cytokine (sirukumab, olokizumab, and clazakizumab) or IL-6 receptor (sarilumab). In particular, sarilumab as monotherapy demonstrated a clear head-to-head superiority over adalimumab in MTX-intolerant subjects. In addition, compared with tocilizumab, sarilumab showed a similar safety profile with significantly higher affinity and longer half-life, responsible for a reduction of the frequency of administration (every other week instead weekly [26].

In this study we have also shown patient's satisfaction with the subcutaneous treatment with TCZ, In addition to the evaluation of the patient's satisfaction y of the treatment with TCZ SC, we have shown some important epidemiological data about RA patients in the Republic of North Macedonia, which gives more insights about RA treatment in developing countries.

For many years we did not have any biological DMARDs except rituximab, only for a very limited number of patients, which explains the high disease activity in the RA patients of this cohort. The average DAS28 score of RA patients enrolled to be part of this observational study was 5.4 in comparison with 4,1 DAS28 score obtained from the Pan-European registers [12] Table **5**.

It is believed that the previously mentioned discrepancy in DAS28 score is because of a limited budget at the UCR Skopje, which have strongly limited the number of RA patients who have access to biological DMARds including TCZ SC. Furthermore, TCZ-SC is available at UCR Skopje since January 2018 only and we have been able to treat only 48 patients with TCZ SC since then. We have never been able to obtain intravenous form of TCZ, so we were incapable to compare subcutaneous with intravenous form of TCZ.

Even though this study is important as one of the first studies about biological therapy in the Republic of North Macedonia, this study has some limitations. The study population in this observational study consists of patients suffering from RA enrolled in a short period of time and therefore the presented results and conclusions in this article do not represent the total number of patients suffering from RA in our country. At the time of completion of this study we did not have a patient's registry, a tool which is now available to us for further studies. Also as we were not very experienced in formulations of satisfaction questionnaires, some bias might be possible in regard with the questions

Table 5: Baseline Characteristics from Pan-European Registries vs University Clinic of Rheumatology in Skopje

	Pan-European registries	University Clinic of Rheumatology in Skopje
Baseline characteristics		
total no patients	1034	48
female (%)	850 (82.2)	42 (87.5)
age, years (range)	57.3 (48.6-65.3)	50.9 (30.0-74.0)
disease duration, median years (range)	6.7 (2.8-13.0)	5.35 (1.1- ≥6)
previous bDMARDs, n (%)		
None	319 (33.1)	29 (60.4)
≥ 1 bDMARDs	645 (69.9)	19 (39.6)
DAS28 (median)	4.1 (3.3–5.5)	5.4 (2.18-8.9)

formulation which have resulted in some imprecision with the report of the results.

In conclusion, this observational study, specifically tailored to assess subcutaneous treatment satisfaction level among RA patients receiving subcutaneous tocilizumab, showed that all patients enrolled to take part in this study reported to be satisfied with this application modality. Higher treatment satisfaction is expected to lead into better quality of life and adherence to treatment. The more patients are informed about the disease and its treatments, the higher the level of treatment satisfaction they will express. Treating rheumatologists need to be aware of the importance of patient's satisfaction developing a dialogue with patients, and making shared decision with the RA patient about the disease and its treatment.

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CONFLICT OF INTEREST

Authors declare no conflict of interest in performing this study.

CONTRIBUTIONS

FG has drafted the manuscript, LDK has made all the revisions, SMP, GB, IK made the study proposal, all other authors added their patient's questionnaires and helped in collecting patients.

GLOSSARY OF ABBREVIATIONS

RA = Rheumatoid arthritis

UCR = University Clinic of Rheumatology

CRP = C-reactive protein

NSAIDs = Non steroidal anti-infiammatory drugs

DMARDs = Disease Modifying Anti-Rheumatic Drugs

Cs DMARDs = Conventional Disease Modifying Anti-Rheumatic Drugs

b-DMARDs = Biological Disease Modifying Anti-Rheumatic Drugs

DAS-28 score = Disease Activity Score 28 joints included

Pts = Patient

Sc = Subcutaneous

PRO = Patient reported outcomes

TCZ-SC = Tocilizumab subcutaneous

TCZ-IV = Tocilizumab intravenous

PDF = Pharmaceutical dosage form

HRQOL = Health related quality of life

Tx = Therapy

QoL = Quality of Life

ACR = American College of Rheumatology

REFERENCES

[1] Rheumatoid Arthritis: National Clinical Guideline for Management and Treatment in Adults. National Collaborating Centre for Chronic Conditions, Royal College of Physicians London UK 2009; 79.

[2] Sokka T, Abelson B, Pincus T. Mortality in rheumatoid arthritis: 2008 update. Clin Exp Rheumatol 2008; 26(51): S35-S61.

[3] Gabriel SE, Michaud K. Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. Arthritis Res Ther 2009; 11(3): 229. https://doi.org/10.1186/ar2669

[4] Arthritis foundation. Treatment of Rheumatoid arthritis. Available at: https://www.arthritis.org/about-arthritis/types/rheumatoid-arthritis/treatment.php

[5] Gaffo A, Saag KG, Curtis JR. Treatment of Rheumatoid Arthritis. American Journal of Health-System Pharmacy 2006; 63(24): 2451-2465. https://doi.org/10.2146/ajhp050514

[6] Barton J, Patient preferences and satisfaction in the treatment of rheumatoid arthritis with biologic therapy 2009; 3: 335-344. https://doi.org/10.2147/PPA.S5835

[7] Strand V, Burmester GR, Ogale S, Devenport J, John A, Emepy P. Improvements in health-related quality of life after treatment with tocilizumab in patients with rheumatoid arthritis refractory to tumour necrosis factor inhibitors: results from the 24-week randomized controlled RADIATE study, Rheumatology 2012; 51(10): 1860-1869. https://doi.org/10.1093/rheumatology/kes131

[8] European Medical Agency. RoActemra EMA/686079/2018 Available at. https://www.ema.europa.eu/en/medicines/human/EPAR/roactemra

[9] Kivitz A, Olech E, Borofsky M, *et al.* Subcutaneous tocilizumab versus placebo in combination with disease-modifying antirheumatic drugs in patients with rheumatoid arthritis. Arthritis Care Res 2014; 66: 1653-61. https://doi.org/10.1002/acr.22384

[10] Gabay C, Emery P, van Vollenhoven R, *et al*. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, Controlled Phase 4 Trial 2013; 381(9877): 1541-50. https://doi.org/10.1016/S0140-6736(13)60250-0

[11] Lauper K, Mongin D, Iannone F, *et al*. Comparative effectiveness of subcutaneous tocilizumab versus intravenous tocilizumab in a pan- European collaboration of registries. RMD Open 2018; 4: e000809. https://doi.org/10.1136/rmdopen-2018-000809

[12] Nakashima Y, Kondo M, Miyahara H, Iwamoto Y. Drug delivery options to increase patient adherence and satisfaction in the treatment management of rheumatoid arthritis –focus on subcutaneous tocilizumab. Drug Design Development and Therapy 2014; 8: 913-919. https://doi.org/10.2147/DDDT.S52099

[13] Ogata A, Atsumi T, Fukuda T, *et al*. Results of switching from intravenous to subcutaneous tocilizumab monotherapy in patients with rheumatoid arthritis: Extension of the MUSASHI study. Arthritis Care & Research 2015; 67(10(10): 1354-1362. https://doi.org/10.1002/acr.22598

[14] Lee SJ, Kremer J, Kavanaugh A. Consortium of Rheumatology Researchers of North America (CORRONA). Treatment disparity related to race/ethnicity and education in rheumatoid arthritis patients: comment on the article by Constantinescu, et al. Arthritis Rheum 2009; 61(8): 1141-1142. https://doi.org/10.1002/art.24727

[15] Aletaha D, Neogi T, Silman AJ, *et al*. Rheumatoid arthritis classification criteria: An ACR / EULAR collaborative initiative. Arthritis Rheum 2010; 9(62): 2569-2581. https://doi.org/10.1002/art.27584

[16] Burmester G, Rubbert-Roth A, Cantagrel A, *et al*. Efficacy and safety of subcutaneous tocilizumab versus intravenous tocilizumab in combination with traditional DMARDs in patients with RA at week 97 (SUMMACTA). Ann Rheum Dis 2016; 75: 68-74. https://doi.org/10.1136/annrheumdis-2015-207281

[17] De Mits S, Lenaerts J, Van der Cruyssen B, *et al*. A nationwide survey on patient's versus physician's evaluation of biological therapy in rheumatoid arthritis in relation to disease activity and route of administration. The Be-Raise study. PLoS ONE 2016; 11: e0166607. https://doi.org/10.1371/journal.pone.0166607

[18] Choy E, Caporali R, Xavier R, Fautrel B, Sanmarti R, Bao M, Bernasconi C, Pethö-Schramm A. Subcutaneous tocilizumab in rheumatoid arthritis: findings from the common-framework phase 4 study programme TOZURA conducted in 22 countries. Rheumatology (Oxford) 1; 57(3): 499-507. https://doi.org/10.1093/rheumatology/kex443

[19] Isaacs J, Salih A, Sheeran T. Efficacy and safety of subcutaneous tocilizumab in rheumatoid arthritis over 1 year: a UK real-world, open-label study. Rheumatology Advances in Practice 2019; 0: 1-11. https://doi.org/10.1093/rap/rkz010

[20] Dougados M, Kissel K, Sheeran T, *et al*. Adding tocilizumab or switching to tocilizumab monotherapy in methotrexate inadequate responders: 24-week symptomatic and structural results of a 2-year randomised controlled strategy trial in rheumatoid arthritis (ACT-RAY). Ann Rheum Dis 2013; 72(1): 43-50. https://doi.org/10.1136/annrheumdis-2011-201282

[21] Besada E. Potential patient benefit of a subcutaneous formulation of tocilizumab for the treatment of rheumatoid arthritis: a critical review. Patient Prefer Adherence 2014; 8: 1051-9. https://doi.org/10.2147/PPA.S34958

[22] McLaughlin M, Östör A. Safety of subcutaneous versus intravenous tocilizumab in combination with traditional disease-modifying antirheumatic drugs in patients with rheumatoid arthritis. Expert Opin Drug Saf 2015; 14(3): 429-37. https://doi.org/10.1517/14740338.2015.998198

[23] Darloy J, Segaud N, Salmon JH, *et al*. Tocilizumab Effectiveness After Switching from Intravenous to Subcutaneous Route in Patients with Rheumatoid Arthritis: The RoSwitch Study. Rheumatol Ther 2019; 6(1): 61-75. https://doi.org/10.1007/s40744-018-0138-y

[24] Ogata A, Kato Y, Higa S, Yoshizaki K. IL-6 inhibitor for the treatment of rheumatoid arthritis: A comprehensive review. Mod Rheumatol 2019; 29(2): 258-267. https://doi.org/10.1080/14397595.2018.1546357

[25] Desplats M, Pascart T, Jelin G, *et al*. Are abatacept and tocilizumab intravenous users willing to switch for the subcutaneous route of administration? A questionnaire-based study. Clin Rheumatol 2017; 36(6): 1395-1400. https://doi.org/10.1007/s10067-017-3587-8

[26] Raimondo MG, Biggioggero M, Beccolini A, Crotti C, Favalli EG. Profile of sarilumab and its potential in the treatment of rheumatoid arthritis. Drug Design Development and Therapy 2017; 11: 1593-1603. https://doi.org/10.2147/DDDT.S100302

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