American Journal of Arthritis Research

Review Article
Published: 06 Jun, 2018

The Efficacy and Safety of Tocilizumab in the Treatment of Rheumatoid Arthritis: An Austrian Non-Interventional Study

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Abstract

Tocilizumab (TCZ) has variously been approved in combination with Methotrexate for the treatment of Rheumatoid Arthritis (RA) in adults. The objectives of this Non-Interventional Study (NIS) were to assess the efficacy and safety of TCZ in routine clinical use.

Clinical response to TCZ was evaluated by collecting Disease Activity Score 28 (DAS28) and other efficacy parameters. The number and type of Adverse Events (AEs) and concomitant medication were documented. The median treatment duration was 52 weeks.

The efficacy and safety analyses included 590 patients, 97.8% of whom had been pretreated with disease-modifying anti-rheumatic drugs. DAS28 scores were available for 484 patients, of whom 67.98% experienced disease remission and 83.06% low disease activity at any time during treatment. AEs were reported for 21.02% of the patients, with 10% serious events.

The results confirm that TCZ is efficacious and well tolerated in routine use for the treatment of RA. As the results of this NIS are in line with existing data, a reevaluation of the risk-benefit balance of TCZ for the treatment of RA does not seem necessary.

Keywords: RoActemra; Tocilizumab; Rheumatoid arthritis; Non-interventional study; DAS28

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Received Date: *15 Feb 2018*
Accepted Date: *29 May 2018*
Published Date: *06 Jun 2018*

Citation:
Bröll H, Lunzer R, Nothnagl T, Bauer B, Leeb BF. The Efficacy and Safety of Tocilizumab in the Treatment of Rheumatoid Arthritis: An Austrian Non-Interventional Study. Am J Arthritis Res. 2018; 2(1): 1012.

Introduction

Rheumatoid Arthritis (RA) is a progressive, systemic autoimmune disease characterized by inflammation of the synovial membrane lining the joints. This inflammation causes bone erosion leading to deformity and loss of function, resulting in pain, stiffness and swelling, and ultimately to irreversible joint destruction and disability [1]. The systemic symptoms of RA include fatigue, anemia and osteoporosis. RA is the most common chronic inflammatory disease in the Western world with a prevalence of some 0.5% to 1.0% [2]. It affects men and women of all ages with a peak incidence of onset between 40 and 60 years of age.

Over the past decades, there have been major advances in the medical treatment of RA. However, there remains an obvious need for more effective therapies based on a more precise understanding of the pathophysiology underlying the course of the disease. Biologic compounds that target Tumor Necrosis Factor (TNF), B-cells or T-cells have been used successfully to treat RA, while early diagnosis and treatment of the disease have added to improved outcomes. However, despite these advances, the effects of biological on systemic manifestations are limited and approximately 30% to 40% of patients fail to achieve an adequate clinical response or to tolerate these new agents [3].

The anti-interleukin (IL)-6 receptor antibody Tocilizumab (TCZ) has been shown to reduce the rate of progression of joint damage as measured by x-ray and to improve physical function when given in combination with Methotrexate (MTX). TCZ has generally been seen to be well tolerated, with the majority of Adverse Events (AEs) being of mild to moderate intensity.

While real-life data from a variety of Austrian RA patients has been collected in the BioReg

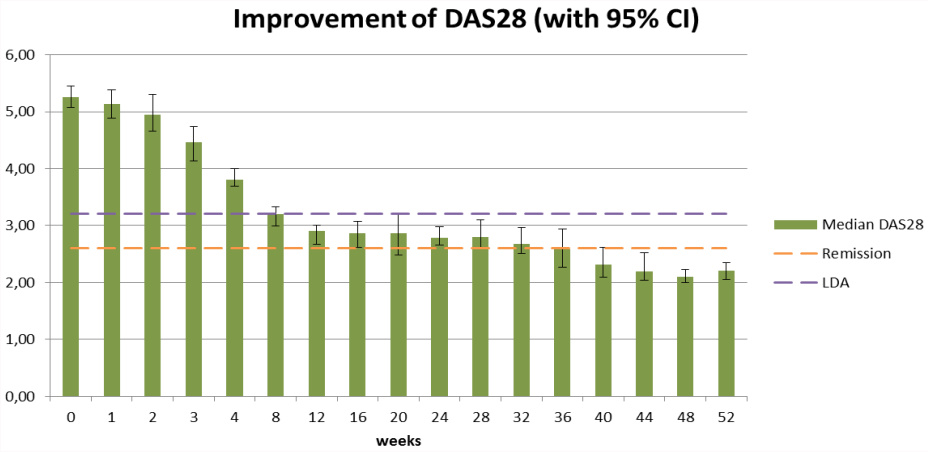

Figure 1: Improvement in DAS28 values from screening to week 52.

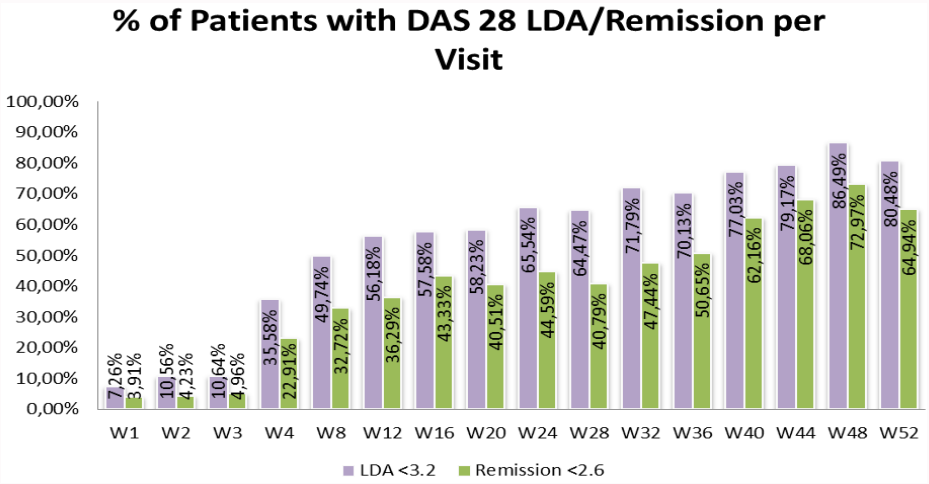

Figure 2: Percentage of patients with DAS28 remission or LDA at each visit.

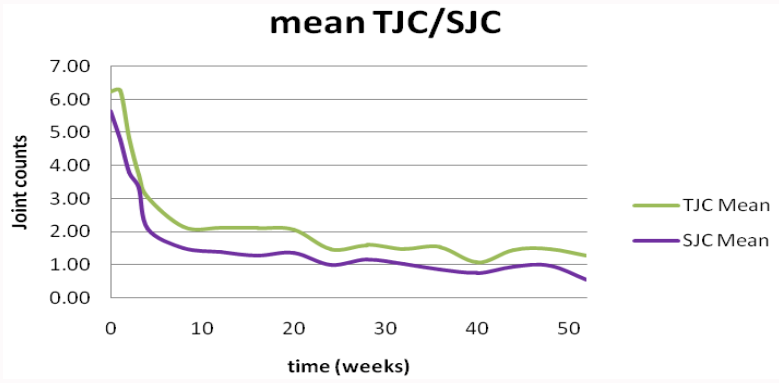

Figure 3: TJC and SJC during therapy.

Project (www.bioreg.at), the primary and secondary objectives of the present Non-Interventional Study (NIS) were to evaluate the efficacy and safety of TCZ in the treatment of RA in real-life, routine clinical practice.

Materials and Methods

Study design and data sources

This study was designed as a multicenter, open-label, single-arm Phase IV NIS. The study was planned to start in March 2009 and planned to end in December 2015. No inclusion or exclusion criteria were specified. Patient inclusion was based on the investigators' decisions.

This NIS was conducted according to the Austrian Medicinal Products Act (§ 2a (3) *Arzneimittelgesetz*) as applicable in 2009. It was local practice at that time to submit the NIS protocol to one of the leading ethics committees in order to receive a confirmation that

Table 1: Schedule of assessments.

	Baseline	Treatment period (every 4 weeks, until week 52)			
Weeks	BL	Week 4 / week 8 / week 16	Week 12 / week 24	Week 20 / week 28 – week 48 (every 4 weeks)	Week 52 / end of documentation
Demographics & diagnosis[1]	X				
Previous therapies	X				
Pregnancy test	X	X	X	X	X
Disease activity[2]	X	X	X	X	X
Infusion[3]	X	X	X	X	
Therapy assessment[4]			X		X
Concomitant medication	X	X	X	X	
Drug compatibility	X	X	X	X	X

[1]Height, weight, gender, year of birth
[2]Disease activity score 28, simplified disease activity index score, clinical disease activity index score, tender joint count/swollen joint count, American college of rheumatology score, rheumatoid factor, anti-cyclic citrullinated peptide, erythrocyte sedimentation rate, C-reactive protein, others. Additionally assessed at week 1, week 2, week 3
[3]Administered dose, dose change
[4]Continuation of treatment, therapy success/response

the NIS does not meet the criteria of an interventional trial. The study protocol was submitted to the Ethics Committee of Upper Austria and the corresponding confirmation letter was dated February 5, 2009. According to the law, it was not necessary for patients to provide written informed consent.

By recommendation, the dose of TCZ for the treatment of RA is 8 mg/kg body weight every four weeks and the route of administration i.v. Patients eligible for this trial were to be treated at the physician's discretion according to the approved label for TCZ. Patient eligibility was neither defined nor controlled, as this was a NIS according to Austrian law. Patient selection by the treating physicians was not controlled, as far as the subjects were eligible for TCZ treatment according to label. The data were collected between March 2009 and December 2014. The treating physicians recorded the data from patient files. The clinical parameters reflecting the course of disease during treatment with the study drug were calculated by the participating investigators and documented in the clinical report forms (CRFs). The types of AEs were evaluated alongside clinical response to TCZ.

The data were initially recorded using hardcopy CRFs and were entered into a database. No quality checks were implemented for the paper CRF data. In the course of the data cleaning process, implausible values were removed from the dataset and self-evident corrections were conducted (e.g., for visit dates in the case that a given year was falsely entered). Beginning with March 2013, electronic CRFs (eCRFs) were used for data collection. To ensure high data quality, routine, automated range and edit checks were programmed into the eCRFs. Only mandatory fields were visible, depending on the investigator's entries. The data were not verified against electronic health records or other source data. Diagnoses justifying treatment with TCZ were collected, yet diagnostic procedures were not reported.

Table 1 summarizes the variables collected in the course of this investigation.

Statistical analyses

A sample size justification showed the statistical probability to collect the most commonly reported adverse drug reactions (occurring in ≥ 5% of patients treated with TCZ monotherapy or in combination with Disease-Modifying Anti-Rheumatic Drugs [DMARDs]) to be 99.4% with the patient sample originally planned for this NIS.

Table 2: Median DAS28 from screening to week 52.

Visit	Median	95% CI	n
Screening	5.31	5.18-5.47	452
Week 0 (pre-dose)	5.25	5.04-5.43	125
Week 1	5.14	4.90-5.40	179
Week 2	4.95	4.60-5.24	142
Week 3	4.47	4.20-4.80	141
Week 4	3.8	3.60-3.90	371
Week 8	3.2	3.07-3.41	382
Week 12	2.9	2.80-3.13	372
Week 16	2.86	2.64-3.10	330
Week 20	2.87	2.55-3.25	79
Week 24	2.78	2.58-2.91	296
Week 28	2.8	2.50-3.00	76
Week 32	2.67	2.38-2.83	78
Week 36	2.58	2.23-2.90	77
Week 40	2.31	2.00-2.53	74
Week 44	2.19	1.86-2.34	72
Week 48	2.1	1.97-2.20	74
Week 52	2.2	2.05-2.35	251

Descriptive statistics were used to analyze the data. Occurrences, both in total and percent, were calculated for nominal and ordinal data. The minimum and maximum values and the median and arithmetic means were calculated for decimal numbers. Efficacy was investigated by calculating total and relative numbers of patients in remission or those who showed Low Disease Activity (LDA).

As no hypothesis was to be tested, no sample size was calculated. No data were transformed, except for the calculation of age groups and for time intervals. Missing data were not queried, nor was a replacement strategy such as the last observation carried forward method implemented for such data. Invalid data were excluded from the analysis (e.g., if patients included in this study failed to receive a single dose of TCZ). No sensitivity analyses were carried out and there were no amendments to the statistical analysis plan.

Results and Discussion

Study population

The present NIS included a total of 592 patients. For two of these subjects, no more than screening visits were documented and no infusion of study drug was reported. These patients were thus excluded from the analyses. The data from the remaining 590 patients were used for the demographic, efficacy and safety analyses. The documented key parameters of Disease Activity Score 28 (DAS28) values, Tender Joint Count (TJC)/Swollen Joint Count (SJC), Simplified Disease Activity Index (SDAI)/Clinical Disease Activity Index (CDAI), and American College of Rheumatology (ACR) scores were analyzed for the efficacy analysis. At least a single DAS28 value was reported for 484 (82.03%) of the 590 patients with documented TCZ infusions. AEs were documented for 124 (21.02%) and concomitant medication for 430 patients (72.88%).

Among the 590 patients, 490 were female, 99 were male and gender was not documented for one patient. The median and mean ages were 58 and 57.53 years, respectively. The age range was 18 to 85 years. The most strongly represented age groups were 50-59 (n=167; 28.55%), 60-69 (n=147; 25.13%) and 70-79 years (n=109; 18.63%). The median interval from diagnosis of disease to start of therapy with TCZ was 5.38 years.

Nearly all patients with documented pre-treatments (n=584) had already been treated with DMARDs (n=577, 98.80%), and only 7 patients were DMARD-naïve (1.20%). Biologics had been administered to 412 patients (71.03%) who thus showed an inadequate response to such treatment. Inadequate response to DMARDs had been seen in 167 subjects (28.79%) who had not yet been given biologics. One patient (0.17%) had received neither DMARDs nor biologics.

The most frequent previous treatments with biologics were with Adalimumab (n=254; 61.65%), Etanercept (n=229; 55.58%) and Infliximab (n=97; 23.54%). In the course of their previous treatment, 347 patients (70.10%) had received concomitant MTX, and 148 patients (29.90%) had received other concomitant medication.

A median of 52 treatment weeks were documented. Dose changes occurred mainly on account of changes in patient weight or adverse reactions.

Due to the study setup (NIS, no monitoring of the participating sites, no source data verification); some of the key parameters were poorly documented.

Efficacy

DAS28: At least a single DAS28 value after the first TCZ infusion was documented for 484 (82.03%) of all patients. At any time during the treatment with study drug, 329 subjects experienced a DAS28 remission (DAS28 <2.6; 67.98%). Four hundred and two patients (83.06%) showed LDA (DAS28 <3.2) at least once during therapy.

The median DAS28 values were 5.31 at screening and 2.20 at week 52 (Table 2 and Figure 1).

The percentage of patients presenting with LDA or remission at each visit compared to those with no remission or LDA at that visit was calculated (Figure 2).

TJC/SJC: TJC/SJC was assessed during the visits. At screening, the median TJC was 7 and the mean TJC was 7.67 (n=287). At week 24, the median TJC was 1 (mean TJC 1.47; n=195). A median TJC of 0 (mean TJC 1.27; n=171) was observed at the last infusion visit at week 52.

The median SJC measured at screening was 5 (mean 5.74; n=287). At week 24, the median SJC had improved to 0 (mean 0.99; n=195), and, at week 52, the median SJC was also 0, with a mean SJC of 0.54 (n=173) (Figure 3).

SDAI/CDAI: The SDAI and CDAI parameters were sparsely documented during treatment with TCZ. Only 59 patients had at

Table 3: AEs.

AEs	n	%
Upper respiratory tract infections	42	16.2
Leucocytopenia	30	11.5
Oral herpes simplex	29	11.2
Increase of liver transaminase	20	7.69
Neutrocytopenia	5	1.92
Hypercholesterolemia	4	1.54
Cough	3	1.15
Exanthema	3	1.15
Pneumonia	3	1.15
Abdominal pain	2	0.77
Gastritis	2	0.77
Herpes zoster	2	0.77
Pruritus	2	0.77
Dyspnea	1	0.38
Hypersensitivity reaction	1	0.38
Vertigo	1	0.38
Other	110	42.3
Total	260	100

Table 4: Serious AE line listing.

Prolonged wound healing after neurolysis of the left median nerve
Allergic reaction
Allergic reaction under therapy
Cardiac atrial fibrillation
Cardiac insufficiency
Dilatation of the common femoral and left popliteal artery
Dyspnea
Planned percutaneous transluminal coronary angioplasty
Herpes zoster
Hypersensitivity reaction
Increase of liver transaminase
Leucocytopenia (5x)
Neutrocytopenia (4x)
Peripheral arterial occlusive disease
Pneumonia
Sinus thrombosis
Sick sinus syndrome: frequency 31/min PM: 12.10 2013
Stroke right side of the brain, carotid stenosis right side
Tachycardiac atrial fibrillation

Table 5: Treatment and outcomes of graded AEs.

Treatment	n	%
Interruption of therapy	61	32.8
No intervention	49	26.3
Drug therapy	22	11.8
Discontinuation of therapy	12	6.45
Dose modification	11	5.91
Other	31	16.7
Total	186	100
Outcomes	**n**	**%**
Recovered	141	75.8
Not yet restored	23	12.4
Improved	12	6.45
Unknown	9	4.84
Persistent damage	1	0.54
Total	186	100

least a single documented SDAI score after their first infusions, and 25 of those subjects showed a remission (SDAI <3.3; 42.37%) during treatment with the study drug. In terms of the CDAI, a remission (<2.8) at any visit after the first infusion was observed in 68 of 204 patients (33.33%) with at least a single CDAI documented after the first TCZ infusion.

Safety

Concomitant medication: For 430 patients (72.88%), at least one concomitant medication was documented. In total, 1,250 concomitant medications were reported in the CRFs. The concomitant medications were grouped by class using the World Health Organization International Nonproprietary Names (WHOINN) dictionary. The most frequent concomitant medications were corticosteroids (n=287; 22.96%), Antimetabolites (n=232; 18.56%) and non-steroidal anti-inflammatory (n=164; 13.12%). Conventional DMARDs were reported for 244 subjects (41.36%). Two hundred and six patients received MTX during therapy with TCZ (34.92%) and 38 received Leflunomide (6.44%).

AEs and adverse reactions: Two hundred and sixty AEs were reported during this trial. Of the 590 patients who received study medication, 124 (21.02%) experienced at least one AE. The most common expected adverse reactions were directly selectable in the CRFs, with the possibility to enter any other events as free text (Table 3). For 74 events, no grading was documented. Nearly three-fourths of the reported AEs were mild (n=135; 72.58%), 42 AEs were moderate (22.58%) and 9 (4.84%) were severe. Twenty-six serious AEs were reported (10.00%). A relation to TCZ was documented for 129 AEs (49.62%). Table 4 summarizes the serious AEs.

Table 5 lists treatments given for and the outcomes of AEs.

The key results of the present NIS demonstrated that TCZ in routine use is an effective and well tolerated treatment for RA. Utilizable data from 590 patients from 33 participating sites in Austria were documented in the CRFs. The median length of treatment was 52 weeks.

Disease improvement was identified with a DAS28 remission in 329 patients (67.98%) and 402 patients (83.06%) showing DAS28 LDA in the course of TCZ therapy. The TJC/SJC parameter underlined these efficacy outcomes.

Supplementary Table 1: Investigators, institutions and numbers of study participants included in the study.

Investigator	Institution, city	Patients n
Raimund Lunzer	Hospital of the brothers of mercy, Graz	120
Thomas Schwingenschlögl	Private practice, Wiener Neudorf	92
Martin Reither	Private practice, St. Pölten	70
Thomas Nothnagl	Private practice, Krems	67
Lothar Boso	Bludenz hospital, Bludenz	34
Burkhard Leeb	Private practice, Hollabrunn	34
Thomas Müller	Private practice, Graz	26
Hans Bröll	Private practice, Vienna	15
Attila Dunky	Private practice, Vienna	15
Rene Fallent	Güssing hospital, Güssing	13
Elke Böttcher	Rheumatism center oberlaa, Vienna	11
Gabriela Eichbauer-Sturm	Private practice, Linz	11
Miriam Stetter	Private practice, Amstetten	11
Omid Zamani	Rheumatism center favoriten, Vienna	10
Armin Vesenmayer	Private practice, Salzburg	7
Gerhard Kessler	Private practice, Feldkirch	6
Fritz Köppl	Private practice, Vöcklabruck	6
Stefan Egger	Ordination gesundheitsquadrat, Vienna	5
Horst Just	Private practice, Klagenfurt	4
Gabriella Cerna	Private practice, Innsbruck	3
Wolfgang Haider	Private practice, Innsbruck	3
Angelika Kraus	Rheumatism center oberlaa, Vienna	3
Jürgen Lenz	Private practice, Dornbirn	3
Manfred Linkesch	Private practice, Linz	3
Peter Peichl	Private practice, Vienna	3
Werner Piber	Private practice, Stolzalpe	3
Angelika Hasslacher	Private practice, Wolfsberg	2
Manfred Herold	Private practice, Innsbruck	2
Thomas Horvath	Private practice, Hard	2
Christian Moll	Private practice, Kufstein	2
Rudolf Brugger	Private practice, Bregenz	1
Christoph Riezler	Private practice, Bürs	1
Oliva Schnetzer	Private practice, Bludenz	1
Oliver Wilhelm	Private practice, Götzis	1

With respect to drop-outs from the study, our post-hoc analysis revealed a similar rate at week 24 (14.41%) as compared to the pivotal clinical phase III trials analyzing TCZ plus MTX, ranging from 6.6% to 14% [4-8].

Only 21.02% of the patients treated with the study drug experienced AEs, totaling to 260 events documented in the CRFs. Grading was reported for 186 AEs. Most of these AEs were either mild or moderate (n=177; 95.16%) and 90% of all reported AEs were non-serious (n=234).

The results of another prospective NIS to investigate the routine clinical use of TCZ in the treatment of RA have recently been published.

Conducted in Germany, the multicenter routine study was a prospective NIS aiming to assess the tolerability, effectiveness and utilization of TCZ administration [9]. Of the 850 patients with baseline demographic traits and pretreatments that were similar to those encountered in the present trial, 60.5% received TCZ in combination with other RA medication.

The mean baseline DAS28 value of 5.5 ± 1.3 decreased to 2.6 ± 1.6 by week 52 of treatment. At week 52, LDA state was achieved in 66.4% and DAS28 remission in 55.1% of the subjects. Any infections and severe infections occurred in 37.6% and 7.2% of the patients, respectively; serious infections were seen in 5.3%.

The routine study likewise showed TCZ given in a real-life clinical setting to induce improvements in terms of efficacy and safety that were consistent with data reported from pre-approval Phase III studies.

Still, the present trial suffered from several limitations. First, as this was a NIS, patient inclusion was only based on the treating physicians' decisions. Then, no randomization process or formal evaluation of the patients was carried out, nor data verification by comparison with source data. Finally, the data underlying the present analyses were incomplete, as they were initially collected on hardcopy CRFs only before switching to eCRFs and implementing routine automated checks.

Conclusion

The objectives of this trial to investigate the efficacy and safety of TCZ in the treatment of RA in routine, real-life clinical use were met.

Disease remission and LDA were demonstrated with improvements in efficacy as reflected by the DAS28 scores and TJC/SJC parameters. The type and frequency of AEs were as expected and in line with previously reported Phase III and IV study results.

In view of the results of this NIS, no re-evaluation of the risk-benefit balance of TCZ for the treatment of RA would seem necessary.

Acknowledgment

The following investigators and institutions participated in the study and included the following numbers of patients respectively (Supplementary Table 1). The authors gratefully acknowledge their co-investigators' invaluable contributions to this study. We also thank Roche Austria GmbH, Vienna/Austria, for supporting this work financially and Karl Thomanek, Vienna/Austria, for medical writing.

Conflict of Interest

HB has received research grants from Roche Austria, Pfizer and BMS. BFL has received research grants from Celltrion, Schering-Plough, Wyeth, Roche, MSD, Centocor, Abbott, Amgen, Aesca, as well as honoraria not exceeding €5,000 each from Centocor, Abbott, Amgen, Aesca, UCB, Roche, MSD, Celltrion, GSK Schering-Plough, Wyeth, Pfizer, BMS, Janssen-Cilag, Eli-Lilly, Novartis, Sandoz, Gebro and Celgene. BB is an employee of Roche Austria GmbH.

All other authors have declared no conflict of interest.

Clinical Trial Registration: ClinicalTrials.gov identifier NCT02721004.

References

1. Schett G, Gravallese E. Bone erosion in rheumatoid arthritis: mechanisms, diagnosis and treatment. Nat Rev Rheumatol. 2012;8(11):656-64.
2. Silman AJ. Epidemiology and the rheumatic diseases. In: Maddison PJ, Isenberg DA, Woo P, Glass DN, editors. Oxford textbook of rheumatology. New York: Oxford University Press; 1993. p. 499-513.
3. Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. N Engl J Med. 2000;343(22):1586-93.
4. Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J, Alecock E, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (Option study): A double-blind, placebo-controlled, randomised trial. Lancet. 2008;371(9617):987-97.
5. Genovese MC, McKay JD, Nasonov EL, Mysler EF, da Silva NA, Alecock E, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: The tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. Arthritis Rheum. 2008;58(10):2968-80.
6. Emery P, Keystone E, Tony HP, Cantagrel A, van Vollenhoven R, Sanchez A, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: Results from a 24-week multicentre randomised placebo-controlled trial. Ann Rheum Dis. 2008;67(11):1516-23.
7. Kremer JM, Blanco R, Brzosko M, Burgos-Vargas R, Halland AM, Vernon E, et al. Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: Results from the double-blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structural joint damage at one year. Arthritis Rheum. 2011;63(3):609-21.
8. Jones G, Sebba A, Gu J, Lowenstein MB, Calvo A, Gomez-Reino JJ, et al. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: The ambition study. Ann Rheum Dis. 2010;69(1):88-96.
9. Iking-Konert C, von Hinüber U, Richter C, Schwenke H, Gürtler I, Kästner P, et al. Routine: A prospective, multicentre, non-interventional, observational study to evaluate the safety and effectiveness of intravenous tocilizumab for the treatment of active rheumatoid arthritis in daily practice in Germany. Rheumatology (Oxford). 2016;55(4):624-35.