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Multicenter, Open-Label, Long-term Extension to Describe the Safety of Tocilizumab in Patients with Early, Moderate to Severe Rheumatoid Arthritis

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Abstract: Introduction: Biologic DMARDs (Disease Modifying Anti Rheumatic Drugs) have shown to be effective in the treatment of rheumatoid arthritis (RA) resistant to the use of synthetic DMARDs. The primary goal of this study was to assess the long-term safety of the use of tocilizumab in patients with early rheumatoid arthritis, moderate to severe disease activity. The secondary goal was to assess the efficiency of tocilizumab in achieving and maintaining clinical remission of the disease. Methods: ML28133 is a long-term, extended study of 13 patients with rheumatoid arthritis treated with tocilizumab. Two patients were male (15.4%), 11 (84.61%) female. The average age of patients was 53.27+/-10.68. Patients received 8 mg/kg tocilizumab i.v. every four weeks, 104 weeks overall. Safety was assessed following side effects, blood tests, physical examination and vital signs. Efficiency was assessed by achieving and maintaining clinical remission according to DAS28 (Disease Activity Score 28), global assessment of disease activity, VAS score and HAQ-DI (Health Activity Score) questionnaire. Results: Incidence of side effects was 76.92%. Infections were of special interest and were most common (15.3%). Four patients had serious adverse events, three of which associated with tocilizumab, and therapy was stopped. In 11 (84.6%) of the 13 treated patients clinical remission was achieved at times. At the end of the study, 8 out of 9 patients were in remission. Conclusion: The results have shown significant therapeutic effect of tocilizumab even in the most severe forms of the disease, which gives hope for its use as a monotherapy.

Keywords: Rheumatoid Arthritis, Tocilizumab, Safety, Adverse Effects, Efficiency

1. Introduction

Rheumatoid arthritis (RA) is a multisystem, autoimmune disease characterized by peripheral synovitis. The natural course of the disease leads to disability. Long standing chronic synovitis leads to structural changes in the joints, deformities and malfunctioning leading to disability [1]. The use of an intensive treatment strategy is especially important in patients with aggressive disease and the presence of factors indicating difficult prognosis [2-4]. The treatment should be tailored to achieving remission or low disease activity quickly according to the recommendations (EULAR 2013). Biologic DMARDs (Disease Modifying Anti Rheumatic Drugs) specifically attack the molecules in the cascade of the inflammatory response and interfere with it. They calm the inflammation, the synovial hyperplasy, degeneration and degradation of the cartilage and the destruction of the subchondral bone and joints. They have been shown to be very effective in the treatment of rheumatoid arthritis, in the early forms of the disease, as well as in patients with developed disease and severe disease activity resistant to the standard treatment with synthetic DMARDs.

Tocilizumab (Actemra) is a first-line biologic agent for

treatment of adult patients with moderate to severely active rheumatoid arthritis [5, 9]. It can be used as a monotherapy, or in combination with methotrexate or other synthetic DMARDs [10, 18]. Tocilizumab is a recombinant humanized anti-human interleukin-6 (IL-6) receptor monoclonal antibody from the IgG1 subclass. It is the first biologic drug to specifically inhibit interleukin-6, a very important proinflammatory cytokine in the pathogenesis of RA. The drug connects to the membrane and soluble receptors for IL-6 and inhibits its action. It blocks signal transmission and cell activation through IL-6. Interleukin-6 is a proinflammatory cytokine which regulates many processes in the developement of the autoimmune rheumatoid inflammation. It is associated with disease activity, as well as systemic manifestations of RA such as anaemia, osteoporosis and increased risk for cardiovascular diseases. Locally, in the joint itself, IL-6 is found in high concentrations in the rheumatoid synovium and actively supports the process leading to joint damage. IL-6 is the main stimulator in the producion of acute phase proteins such as C-reactive protein (CRP) and serum amyloid alpha [2]. Besides the multiple proinflammatory effects, CRP is an independent predictor of increased cardiovascular risk in patients with RA [1]. High levels of IL-6 contribute to anemia. Blocking its receptor leads to significant improvements in the signs and symptoms of the disease.

2. Aims

The primary aim of this study was to evaluate the long-term safety of TCZ therapy in patients who had completed the WA19926 core study (a multicentric, randomized, double-blind study of parallel groups evaluating the safety, disease remission and the prevention of structural joint damage in patients treated with tocilizumab as a monotherapy, or in combination with methotrexate, compared to methotrexate monotherapy in patinents with early rheumatoid arthritis, with medium to severe disease activity) and may have benefited from TCZ treatment.

The secondary aims were to assess efficacy of TCZ over time using endpoints such as clinical remission based on the DAS28-ESR, total tender joint count (TJC) and total swollen joint count (SJC) and to assess sustained drug-free remission via DAS28-ESR remission criteria.

3. Materials and Methods

This was a Phase III, open-label, single arm, multicenter, long-term extension study. The study population consisted of 17 enrolled patients, previously treated with TCZ, with early, moderate to severe rheumatoid arthritis (RA) from 1 center at the University Clinic of Rheumatology in Skopje, Macedonia. Inclusion criteria were: patients who were able and willing to provide a written informed consent and to comply with the requirements of the study protocol, were aged > 18 years, patients who completed WA19926 core study (visit at Week 104 and 2 follow-up telephone visits) and who may have benefited from study medication according to the investigator's assessment, no current or recent adverse event (AE) or laboratory finding preventing the use of the study medication dose of TCZ 8 mg/kg at screening, receiving treatment on an outpatient basis; for women who were not postmenopausal (12 months of amenorrhea) or surgically sterile (absence of ovaries and/or uterus), agreement was required to use at least 1 adequate method of contraception, including at least 1 method with a failure rate of < 1% per year (e.g., hormonal implants, combined oral contraceptives, vasectomized partner), during the treatment period, while females of childbearing potential must have had a negative serum pregnancy test at screening.

Exclusion criteria: females who were pregnant, patients who had prematurely withdrawn from the WA19926 core study for any reason, treatment with any investigational agent or cell-depleting therapies since the last administration of study medication in the WA19926 core study, treatment with an anti-tumor necrosis factor or anti-interleukin (IL) 1 agent, or a T-cell co-stimulation modulator since the last administration of study medication in the WA19926 core study, immunization with a live/attenuated vaccine since the last administration of the study drug in the WA19926 core study, diagnosis since visit at Week 104 of the core WA19926 study of rheumatic autoimmune disease other than rheumatoid arthritis (RA), including systemic lupus erythematosus, mixed connective tissue disease, scleroderma, and polymyositis, or significant systemic involvement secondary to RA (e.g., vasculitis, pulmonary fibrosis or Felty's syndrome). Secondary Sjögren's syndrome and/or nodulosis with RA were permitted, diagnosis since visit at Week 104 of the core WA19926 study of inflammatory joint disease other than RA (e.g., gout, reactive arthritis, psoriatic arthritis, seronegative spondyloarthropathy, Lyme disease), laboratory parameters at screening period: aspartate aminotransferase (AST) or alanine aminotransferase (ALT) 1.5 times upper limit of normal (ULN), total bilirubin > ULN, absolute neutrophil count < 1000/mm^3 (1 × 109/L), platelet count < 100,000/mm^3 (100 × 109/L), history of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies or hypersensitivity to TCZ (the active substance or to any of the excipients), evidence of serious uncontrolled concomitant cardiovascular, nervous system, pulmonary (including obstructive pulmonary disease), renal, hepatic, endocrine (including uncontrolled diabetes mellitus), immunologic or gastrointestinal (GI) disease; history of diverticulitis, diverticulosis requiring antibiotic treatment or chronic ulcerative lower GI disease such as Crohn's disease, ulcerative colitis or other symptomatic lower GI conditions that might predispose to perforations for whom a favorable benefit/risk assessment for study continuation could not be documented, known active or history of recurrent bacterial, viral, fungal, mycobacterial or other infections (including but not limited to tuberculosis (TB) and atypical mycobacterial disease, clinically significant abnormalities on chest X-ray as determined by the investigator, human immunodeficiency virus [HIV], hepatitis

B [hepatitis B surface antigen {HBsAg} and total hepatitis B core antibody {HBcAb}] and hepatitis C virus [HCV] antibody and Herpes zoster, but excluding fungal infections of nail beds), or any major episode of infection requiring hospitalization or treatment with intravenous (IV) antibiotics within 4 weeks prior to baseline or oral antibiotics within 2 weeks prior to baseline, evidence of active malignant disease, malignancies diagnosed within the previous 10 years (including hematological malignancies and solid tumors, except basal cell carcinoma of the skin that had been excised and cured), or breast cancer diagnosed within the previous 20 years, uncontrolled disease states, such as asthma or inflammatory bowel disease where flares were commonly treated with oral or parenteral corticosteroids, current liver disease as determined by the investigator, active TB requiring treatment within the previous 3 years. Patients were required to be screened for latent TB following local practice guidelines and should not have been admitted to the study if latent TB was detected. Patients should have had no evidence of active TB infection at enrollment. Patients treated for TB with no recurrence in 3 years were permitted.

There were 17 patients enrolled, with 13 (76.47%) treated with TCZ (3 patients with a history of infection or active infection and one patient with latent TB).

Demographic data and disease characteristics at baseline were consistent with the patient population and the requirements of the study protocol. Of the enrolled patients 2 (15.4%) were male and 11 (84.6%) were female. The mean (standard deviation [SD]) age of all patients in the intent-to-treat (ITT) population. Population was 53.27 (10.68) years with a range of 32 to 72 years. Majority of patients belongs in group 18 to 64 year (92.3%), and 1 patient belongs in the age group 65 to 72 years (7.7%).

A detailed physical examination was conducted in all patients (cardiovascular, pulmonary, abdominal, neurological, head, neck, extremities, lymph nodes, skin, musculosceletal system) at baseline and on weeks 12, 24, 56, 80 and at the end of the study. Vital signs (heart rate, systolic and diastolic blood pressure), body temperature, laboratory testing including hematologic tests (hemoglobin, hematocrit, erythrocyte, leukocyte, neutrophil, basophil, eosinophil, lymphocyte count, platelets, erythrocyte sedimentation rate, MCV, MCH, MCHC), bloot tests (AST, ALT, ALP, the highly sensitive CRP, total proteins, albumin, LDL, HDL, total cholesterol, urea, creatinine, uric acid, sodium, potassium, chloride, calcium, phosphorus, triglycerides), urine analysis (for potential presence of protein, blood or sugar) were done at baseline and on weeks 12, 36, 48, 56, 80, 92 and at the end of the study. All data were analyzed electornically in the eCRF.

The effect of the therapy with tocilizumab was assessed through the changes of DAS28-ESR, total number of tender joints and total number of swollen joints; the percent of patients who achieved clinical remission according to DAS28-ESR <2.6 in two following visits (every 12 weeks); physicians global assessment of disease activity with visual analogue score (VAS) scale; patient global assessment of disease activity with visual analogue score (VAS) scale; pain assessment with visual analogue score (VAS) scale; health assessment questionnaire (HAQ). All of these parameters were assessed with the same dynamic as the vital signs, lab tests, meaning at baseline and on weeks 12, 36, 48, 56, 80, 92 and at the end of the study.

Eligible patients, who met all inclusion criteria, received an IV infusion of 8 mg/kg TCZ (maximum of 800 mg for patients over 100 kg) every 4 weeks on an outpatient basis for a total of 104 weeks (with two phone controls at weeks 108 and 112). Dose modifications of TCZ were allowed for safety reasons, which was done in two patients because of viral infections. A concomitant non-biologic disease-modifying antirheumatic drug (DMARD) could be added at any visit at the investigator's discretion and as tolerated by the patient. Of all ITT patients (13), 11 patients (84.61%) reported at least 1 concomitant background medication. There were 11 (84.61%) patients who received concomitant DMARDs, 12 (92.30%) MTX, 5 (38.46%) patients who received non-steroidal anti-inflammatory drugs (NSAIDs) and 2 (15.38%) patients who received corticosteroids. The most frequently reported concomitant medications were methotrexate (92.30%) and folic acid (76.9%). Two (2) patients (15.38%) reported at least 1 prior medication. It was 1 NSAIDs (ketoprofen) and one folic acid.

Safety was assessed using the ITT Population and by reporting of adverse events (AEs) with special emphasis on infections and other AEs of special interest, clinical laboratory results, and physical examination including vital signs. Adverse events were summarized by intensity and by relationship to study drug. The primary safety outcome measures were as follows: incidence and severity of AEs, incidence and severity of serious adverse effects (SAEs), incidence and severity of AEs of special interest (AESIs) including: infections including all opportunistic infections and non-serious infections as defined by those treated with IV anti-infective drugs, myocardial infarction/acute coronary syndrome, gastrointestinal perforations and related events, malignancies, anaphylaxis/hypersensitivity reactions, demyelinating disorders, stroke, bleeding events, hepatic events, rates of AEs leading to dose modification or study withdrawal, incidence of clinically significant laboratory abnormalities. All safety data were reported regarding all patients enrolled in the study and who received at least 1 TCZ dose during the study. A total of 13 patients were reported in this population.

For statistical analysis we used nonparametric statistical tests (Friedman test, Kruskal Wallis test, Spearman's correlation test). Baseline was defined as the day of first TCZ dose in the study. Statistical signification was on level $p<0.05$, $p<0.01$ and $p<0.001$. Changes in parameters were analyzed by nonparametric Friedman test (for differences between more than two times periods). For analysis of differences between two periods Wilcoxon test was performed. Categorical data were analyzed by Chi-square and Fisher's exact test, as appropriate. In all tests, p value <0.05 was considered to be statistically significant. For

laboratory test data (N), mean, standard deviation, median, minimum, maximum was reported, whereas for qualitative variables absolute and relative frequency distribution was described. The incidence of clinically significant laboratory adverse effects, death or discontinuation of treatment were reported with percents. The incidence of adverse effects was taken from the total number of patients with a particular adverse effect divided by the number of years treated (number of patients/patient years).

4. Results

ML28133 is a local study to evaluate the long-term safety of tocilizumab in patients who have successfully completed the WA19926 study and had benefited from the treatment. A total of 17 patients were screened and enrolled for the study of whom 13 (76.47%) were treated with TCZ and included in the Population. Of the 4 patients who were screening failures and did not receive treatment, 3 were due to active (or known history of) recurrent bacterial, viral, fungal, mycobacterial or other infections and 1 had active tuberculosis treatment. About half of treated patients (10 [58.82%]) completed the study according to the protocol. Of the 3 (23.07%) patients who did not complete the study, the primary reason was an adverse event (patient ID 3 had tumor on right ovarium, patient ID 13 had thrombocytopenia and patinet ID 16 had paronychia). Three patients had temporary discontinuation because of an adverse event (patient ID 1 – bronchopneumonia, patent ID 2 - rhinorrhea and nasopharyngeal inflammation and patient ID 7 – tonsillopharyngitis). After temporary termination, all of these patients returned to the study.

At screening, 5 (38.46%) patients reported a previous or ongoing clinically significant medical condition other than RA. These patients had 6 clinically significant previous or concomitant diseases. Two (33.33%) of these events has resolved status, while 4 (66.66%) are ongoing with treatment.

Table 1. *Overall summary of adverse events (ITT Population) n/total patients.*

	n/total patients (%)	n Events
Any AEs	10/13 (76.92%)	16
Related AEs	6/13 (46.15%)	7
SAEs	4/13 (30.76%)	4
Related SAEs	3/13 (23.07%)	3
Severe AEs	1/13 (7.69%)	1
Related Severe AEs	1/13 (7.69%)	1
AEs of Special Interest	2/13 (15.38%)	3
Infections	2/13 (15.38%)	2
Myocardial Infarction/Acute Coronary Syndrome	0/13 (0.00%)	0
Gastrointestinal Perforations and Related Events	1/13 (7.69%)	1
Malignancies	0/13 (0.00%)	0
Anaphylaxis/Hypersensitivity Reactions	0/13 (0.00%)	0
Demyelinating Disorders	0/13 (0.00%)	0
Stroke	0/13 (0.00%)	0
Bleeding Events	0/13 (0.00%)	0
Hepatic Events	0/13 (0.00%)	0
Related AEs of Special Interest	2/13 (15.38%)	3
SAEs of Special Interest	2/13 (15.38%)	2
AEs Leading to Dosage Modification	2/13 (15.38%)	2
Related AE Leading to Dosage Modification	0/13 (0.00%)	0
Withdrawn from Study Due to AEs	1/13 (7.69%)	1

Abbreviations: AE±adverse event, ITT±Intent-to-Treat, N±number of patients in group, n±number of events, SAE±serious adverse event.

Table 2. *Summary of all adverse (ITT Population) events.*

SOC/ PT	n/total patients (%)	n Events
Infections and infestations	5/13 (38.46%)	8
Tonsillitis	1/13 (7.69%)	1
Virosis	2/13 (15.38%)	2
Tonsillopharyngitis	2/13 (15.38)	2
Bronchopneumonia	1/13 (7.69%)	1
Paronychia	1/13 (7.69%)	2
Gastrointestinal signs and symptoms	1/13 (7.69%)	1
Unknown* (Chronic gastritis, reflux esophagitis gr. A)	1/13 (7.69%)	1
Vomiting	1/13 (7.69%)	1
Respiratory, thoracic and mediastinal disorders	1/13 (7.69%)	1
Rhinorrhea	1/13 (7.69%)	1

SOC/ PT	n/total patients (%)	n Events
Reproductive system and breast disorders	1/13 (7.69%)	1
Ovarian tumors	1/13 (7.69%)	1
Investigations	1/13 (7.69%)	3
Blood triglycerides increased	1/13 (7.69%)	1
Blood cholesterol increased	1/13 (7.69%)	1
Thrombocytopenia	1/13 (7.69%)	1
Injury, poisoning and procedural complications	1/13 (7.69%)	1
Traumatic fracture	1/13 (7.69%)	1

Abbreviations: AE±adverse event, ITT±Intent-to-Treat, N±number of patients in group, n±number of events, SAE±serious adverse, SOC=system organ class, PT=preferred term.

*Unknown –patient had AE with "unknown" name in database, classified as "Gastrointestinal Perforations and Related Events". After investigation of patient file, investigator confirmed that respected AI is chronic gastritis, reflux esophagitis gr. A (Documented in NTF from 13-Sep-2016).

At baseline, the mean (SD) DAS28-ESR, total TJC, and total SJC values were: 3.51 (1.09), 5.38 (4.62), and 2.1 (2.30), respectively. The mean values across all 3 measures were numerically lower than baseline (indicating improvement) at all subsequent visits from Week 4. At the end of the study the mean (SD) DAS28-ESR, total TJC, and total SJC values were: 1.37 (1.01), 2.11 (4.59), and 0.0 (0.0), 19 respectively. This change is statistically significant ($p<0.01$) (Figure 1).

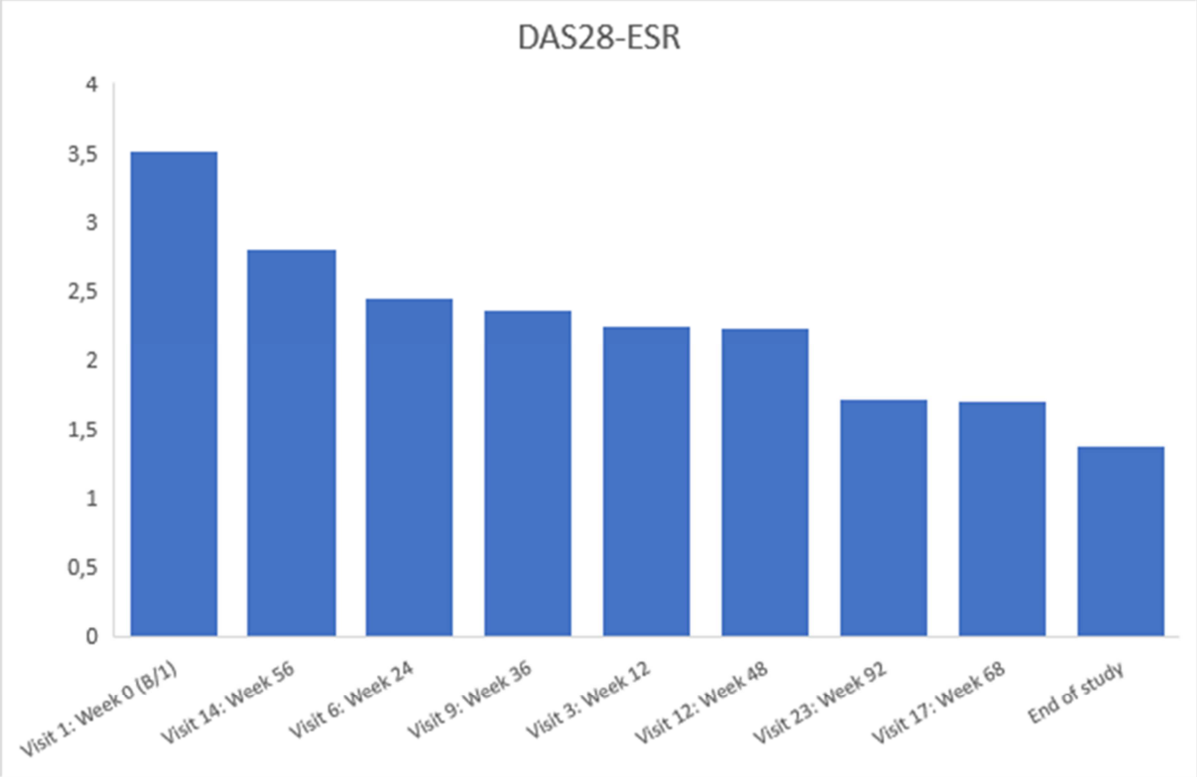

Figure 1. *Mean DAS28-ESR scores by visit (ITT Population).*

Mean values for the changes for TJC scores in patients treated with tocilizumab in visit 1 (week 0), 3 (week 12), 6 (week 24), 9 (week 36), 12 (week 48), 14 (week 56), 17 (week 68), 23 (week 92) and at the end of the study (week 104) were 2.15, 1.08, 1.08, 1.0, 0.91, 0.58, 0.44, 0.56 and 0 respectively, showing a significant decrease of the number of swollen joints. At the end of the study all patients were without swollen joints.

DAS28-ESR was categorized according to the EULAR criteria defining the therapeutical response using the DAS28 index as presented in table 3.

Table 3. *Categorization of DAS28-ESR according to EULAR criteria.*

Range	Remission	Low	Moderate	High
0-9.4	< 2.6	≥ 2.6 - < 3.2	≥ 3.2 - ≤ 5.1	> 5.1

The mean values of the DAS28-ESR measures were continually numerically lower than baseline (indicating improvement) at all subsequent visits from Week 4 (Figure 2), showing disease suppression by the medication.

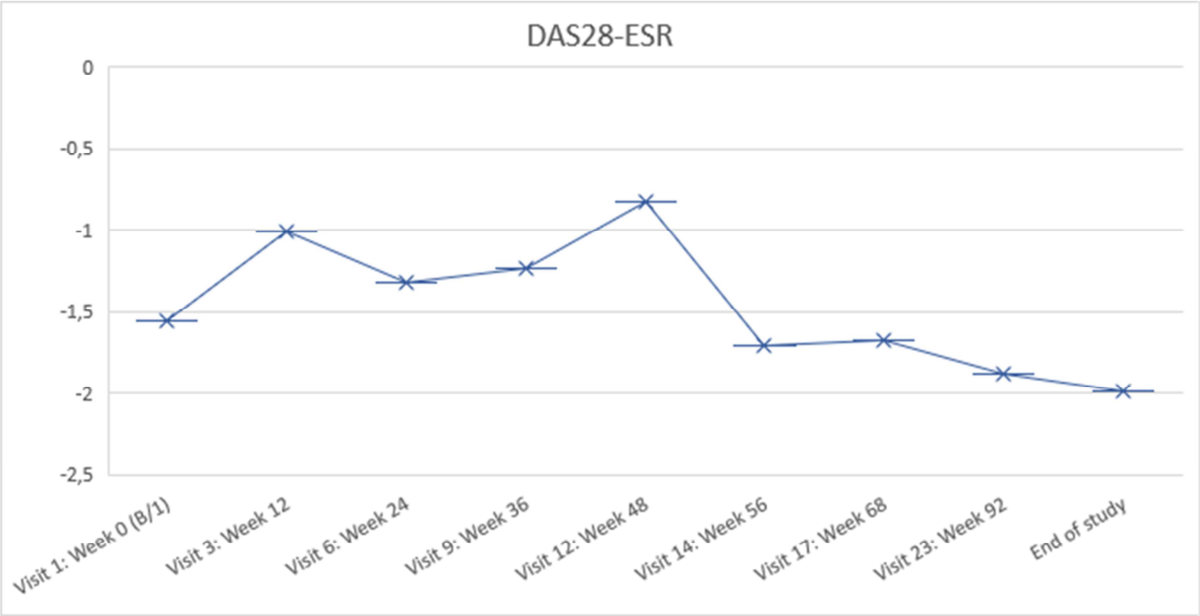

Figure 2. *Mean changes of DAS28-ESR scores from baseline.*

There were 11 patients (84.6%) who achieved clinical remission at any time during the study, defined as DAS28-ESR <2.6. At baseline, 2 patients (16.6%) had achieved clinical remission, rising to 8 patients (88.9%) at the end of the study. After 4 weeks the number of patients in remission jumped from 2 (16.6%) to 8 (66.6%) (Figure 3).

Figure 3. *Summary of clinical remission by visit (ITT Population).*

At baseline, the mean (SD) PGA of disease activity, patient's global assessment (PtGA) of disease activity and Patient's Assessment of Pain VAS values were 24.30 (13.04), 30.15 (13.95) and 29.69 (13.99), respectively. The mean values across all 3 measures were numerically lower than baseline (indicating improvement) at all subsequent visits from Week 4. This change is statistically significant ($p<0.01$).

At baseline, the mean (SD) HAQ-DI was 0.43 (0.43). The mean value was lower across all subsequent visits. This change is statistically significant ($p<0.01$).

All enrolled patients received 8 mg/kg tocilizumab. Two patients required dose modification, thereason for both patients being AEs (virosis). In case of 2 patients with body weight above 100 kg, 800 mg tocilizumab was administered in line with the provisions of the study protocol.

Overall, 10 patients (76.92%) experienced 16 events during the study. The mean number of AEs per patient was (M±SD) (1.60±1.26). Maximum number of AEs experienced by one patient was 5 AEs. One patient had AEs of ovarian tumor as a severe intensity AEs, all other AEs were mild or moderate in intensity. There were 6 patients (46.15%) who experienced 7 AEs that were considered remotely, possibly, or probably related to TCZ. There were

9 unrelated AEs. There were no deaths, life-threatening AEs. There was one SAEs possibly related to TCZ. Two (2) patients had 2 AEs, which led to dosage modification. Six (6) patients had 7 AEs, which led to discontinuation of drug administration. Three (3) patients had temporary discontinuation and three (3) permanent discontinuation. The primary reason why 3 (23.07%) patients permanently discontinued the study was an adverse event (patient ID 3 had tumor on right ovarium, patient ID 13 had thrombocytopenia and patinet ID 16 had paronychia). In three patients who had temporary discontinuation the reason was also an adverse event (1 – bronchopneumonia, 2 - rhinorrhea and nasopharyngeal inflammation and 3 – tonsillopharyngitis). After temporary discontinuation, all 3 patients returned to the study treatment. There were no mortalities during the study. None of the AEs led to discontinuation of the medication application. There were no vitally dangerous AEs. There was only one possible SAE associated with tocilizumab (Tables 1 and 2).

Investigators rated initial intensity of adverse events as moderate in 4 (25.00%) cases and mild in 12 cases (75.00%). The intensity of AEs was: mild 11 (68.75%), moderate 4 (25.00%) and severe 1 (6.25%) of all AEs.

Regarding laboratory tests, 1 patient (7.69%) had elevated triglyceride levels, 1 (7.69%) had elevated cholesterol and 1 (7.69%) had thrombocytopenia.

5. Discussion

The primary goal of this study was to evaluate the safety of tocilizumab used for a long time period, in patients who had completed the basic WA 19926 study and who had benefited from the treatment. The secondary goals were to assess the efficacy of tocilizumab, using clinical remission of the disease as defined by the Disease Activity Index 28 with erythrocyte sedimentation rate (DAS28-ESR), total number of tender joints (TJC), total number of swollen joints (SJC) and the assessment of remission persistence using the DAS28 criteria. All patients recruited were diagnosed with rheumatoid arthritis and had moderate to severe disease activity without a satisfactory response to synthetic DMARDs, at a single center at the University Clinic of Rheumatology in Skopje, Macedonia. Patients were treated with tocilizumab i.v. 8 mg/kg every 4 weeks. A total of 17 patients were considered for participation in the study, of whom 13 were included, having satisfied the inclusion criteria. Of the 4 patients that were not included, 3 had active (or a history of repetitive) infections, and one was being actively treated for tuberculosis. The safety of tocilizumab was assessed with a special accent on following potential infections, serious adverse effects and events of special significance associated with the study medication. The incidence of adverse effects was 46.15%. Out of all adverse effects, infections were the most common (15.3%). Four patients had serious adverse events (SAEs). Three of these were associated with the tested drug (pneumonia, ovarian tumor, paronychia). All three had stopped the treatment, two permanently. A serious adverse event was reported in a single patient. There were no deaths or life-threatening events. Two patients (15.3%) had a total of 3 adverse effects of interest, two of which were infections and one with chronic gastritis with esophagial reflux gradus A. To assess the safety of the drug, laboratory tests, physical examinations, EKG recordings, tuberculosis testing, chest x-rays, data regarding admission to hospital/death were used. The mean value of the data collected to assess the efficacy of tocilizubam, such as DAS28-ESR, TJC and SJC showed significant improvement compared to baseline after the week 12 visit (visit 4) in all three measurments ($p<0.05$). Of the 13 treated patients, 11 (84.6%) had achieved clinical remission in certain visits during the study. At the last visit, 8 out of the 9 remaining patients were in remission (DAS28-ESR<2.6).

Tocilizumab (Actemra) is a first-line biologic agent for treatment of adult patients with moderate to severely active rheumatoid arthritis. It can be used as a monotherapy, or in combination with methotrexate or other synthetic DMARDs [4, 5]. Tocilizumab was registered in Macedonia in 2009 [5] as it was in Europe, but it was used for the first time in 2008 in Japan. It is the first biologic drug which specifically inhibits the actions of interleukin-6 (IL-6), an important proinflammatory cytokine in the pathogenesis of RA [7].

Tocilizumab is used at a dose of 8 mg/kg of body weight in an intravenous infusion, in duration of one hour. Premedication is not needed. The infusion is repeated every 4 weeks.

Searcing the literature showed that over 4000 patients were included in clinical developmental programs before the official registering of the medication. They confirm that the inhibition of the IL-6 receptor with tocilizumab results in significant clinical improvement and a clear benefit for patients with RA and a stable safety profile. Tocilizumab was studied as a monotherapy in patients previously not treated with methotrexate (AMBITION) [13], in combination with methotrexate in patients with an inadequate response to DMARDs (OPTION, TOWARD and LITHE) [14, 15], and in patients with an inadequate reponse to anti-TNF therapy (RADIATE) [16]. Tociluzumab was proven to be effective in all three investigated groups, used as a monotherapy or in combination with methotrexate or other synthetic DMARDs in treatment of patients with an inadequate response to synthetic DMARDs or TNF antagonists. Time to effect of the clinical response to tocilizumab is fast and is seen after just 2 weeks of application, and the magnitude of the effect increases with the increase of the time treated. Treatment with tocilizumab at the dose of 8 mg/kg shows powerful inhibition of joint damage. Tocilizumab is an approved biologic agent with proven superiority compared to methotrexate in monotherapy for 6 months in patients with RA with moderate to severe disease activity [18, 19]. This therapy also provides a clinical remission which is stable and the effect improves with every following application according to the DAS28-ESR. The reports from the multycentric study, phase III, with 4211 patients [19] shows that tocilizumab is generally well tolerated, most of the

adverse effects are mild to moderate in severity. Of these, the most common are infections, mainly upper respiratory, such as nasopharyngitis. Pneumonia, mainly bacterial, is the most common serious adverse effect. There are reports of rare SAE, such as gastrointestinal perforation of the lower GI tract, mostly associated with infections and diverticulitis. Neutrophilia has been reported, but it is unclear whether it is associated with the medication and its dosing or with an infection.

6. Conclusion

Our study data has shown that the safety profile, the efficiacy and benefit of the treatment with tocilizumab, even in the most severe forms of RA resistant to previous DMARD therapy is excellent. Thus, tocilizumab provides a great and positive hope. This drug has been shown to be efficient in treating systemic manifestations of the disease. It can also be applied as a monotherapy. Data regarding the efficiency and the safety profile of this drug support the positive attitude towards the "cost-benefit" in using tocilizumab in early rheumatoid arthritis with moderate to severe disease activity.

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