

A Study of the Efficacy and Safety of Subcutaneous Injections of Tocilizumab in Adults with Rheumatoid Arthritis

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ABSTRACT **Background:** Tocilizumab is an interleukin 6 (IL-6) receptor antagonist used to treat moderate to severe active rheumatoid arthritis (RA). Both intravenous (IV) and subcutaneous (SC) routes are approved for the treatment of adults with RA. **Objectives:** To evaluate SC tocilizumab in a real-life clinical setting. **Methods:** Our study was a multi-center, open-label, single-arm study. Participants were adults with a diagnosis of active RA, previously treated with disease-modifying antirheumatic drugs (DMARDs), with or without biologic agents. Participants received a weekly SC injection of tocilizumab 162 mg as monotherapy or in combination with methotrexate or DMARDs for 24 weeks. Efficacy, safety, and immunogenicity were assessed. **Results:** Treatment of 100 patients over 24 weeks resulted in improvement in all efficacy parameters assessed: Clinical Disease Activity Index, Disease Activity Score using 28 joint counts and erythrocyte sedimentation rate, American College of Rheumatology response scores, Simplified Disease Activity Index, tender and swollen joint counts, and patient-reported outcomes including fatigue, global assessment of disease activity, pain, and Health Assessment Quality of Life Disease Index. Improvement was achieved as early as the second week of treatment. There were 473 adverse events (AEs)/100 patient-years (PY) and 16.66 serious AEs/100 PY. The most common AEs were neutropenia (12%), leukopenia (11%), and increased hepatic enzymes (11%). Of a total of 42 PY, the rates of serious infections and AEs leading to discontinuation were 4.8, and 11.9 events/100 PY, respectively. **Conclusions:** The safety, tolerability, and efficacy profile of tocilizumab SC were comparable to those reported in other studies evaluating the IV and SC routes of administration.

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KEY WORDS: rheumatoid arthritis, subcutaneous (SC), tocilizumab

Rheumatoid arthritis (RA) is a chronic, progressive systemic autoimmune disease. Its natural history is characterized by sustained inflammation of the synovium as well as disease activity flares that lead to progressive joint damage, functional disability, and impaired quality of life [1]. RA has a prevalence of 0.5% to 1.0% and a peak incidence between 40 and 60 years of age, and affects women primarily. The cause of RA is not known. Various clinical, genetic, and laboratory markers have been associated with poorer outcomes.

Long-term efficacy and safety of drugs are of paramount importance to the pharmacological management of RA. Nonsteroidal anti-inflammatory drugs (NSAIDs) provide only symptomatic relief. Disease-modifying anti-rheumatic drugs (DMARDs) are the standard treatment for RA throughout all stages of the disease, and they maintain or improve physical function and slow radiographic joint damage [2]. Patients who show inadequate response to DMARDs (DMARD-IR) are treated with biological compounds that act in various mechanisms of action. These treatments include targeting cytokines and cellular subsets of the immune system. In a real-life setting approximately 30–40% of patients treated with biologic DMARDs discontinue their treatment because of inefficacy or adverse events [3]. Biomarkers or demographic and clinical features may aid in predicting response to treatment. However, even among responders, many patients do not achieve clinical or radiographic remission and may experience toxicity or lose their response to treatment within several years of starting a biologic agent. Therefore, there is a continuous need to offer more treatment options to RA patients.

Elevated tissue and serum levels of interleukin-6 (IL-6) have been implicated in the pathogenesis of RA [4,5]. Tocilizumab is a recombinant humanized anti-human monoclonal antibody of the immunoglobulin G (IgG) subclass directed against the IL-6 receptor. The efficacy and safety of treatment with intravenous (IV) tocilizumab has been well established in many clinical studies as well as in real-life settings. Recently, a subcutaneous (SC) route of administration has become available, allowing patients to administer the drug at home.

To date, the development program of SC tocilizumab in RA patients included three studies showing that combined treatment of SC tocilizumab with DMARDs was superior to treatment with placebo and non-inferior to IV tocilizumab plus DMARDs. In addition, SC tocilizumab monotherapy showed non-inferiority to IV tocilizumab monotherapy [6].

The current study (ClinicalTrials.gov number: NCT01988012) was part of a Roche multinational, open-label, single-arm umbrella study (TOZURA), comprising seven single-country and four regional multi-country protocols to evaluate the SC tocilizumab treatment regimen of 162 mg once weekly as monotherapy or in combination with methotrexate or other DMARDs in a real-life clinical setting [7].

PATIENTS AND METHODS

PATIENTS

The study group comprised 100 patients. Their demographics and baseline characteristics are summarized in Table 1. The vast majority of the patients were Caucasian (99%) and most were female (80%). At baseline, the mean age of the patients was 54.3 ± 11.8 years and the mean duration of RA was 8.7 ± 9.2 years. Mean disease activity according to disease activity score using 28 joint counts, and erythrocyte sedimentation rate (DAS28-ESR), clinical disease activity index (CDAI), and simplified disease activity index (SDAI) was 4.98 ± 0.98 , 31.89 ± 14.35 , and 33.73 ± 14.83 , respectively.

STUDY DESIGN AND SETTING

This multi-center, open-label single-arm study was performed at 13 medical centers in Israel between January 2014 and July 2015. Each center received approval for performing the study from its institutional independent ethics committee as required by Israeli Ministry of Health regulations.

STUDY POPULATION

Study participants were adults above 18 years of age with a diagnosis of active RA according to the revised (1987) American College of Rheumatology (ACR) or European League Against Rheumatism (EULAR) (2010) criteria who received treatment on an outpatient basis (not including tocilizumab). The participants were either previously treated with three DMARDs

and not treated with any biologic agent, or were previously treated with one biologic agent (alone or in combination with DMARDs) and discontinued that agent for any reason.

Exclusion criteria included rheumatic autoimmune disease other than RA (secondary Sjögren's syndrome with RA was permitted), functional Class IV as defined by the ACR classification of functional status in rheumatoid arthritis, diagnosis of juvenile idiopathic arthritis or juvenile RA, and/or RA before the age of 16 and prior history of current inflammatory joint disease other than RA.

Table 1. The baseline demographics and rheumatoid arthritis characteristics of the patients

Gender, N (%)	Tocilizumab N=100
Female (%)	80 (80)
Age, years, mean \pm SD	54.3 ± 11.8
Weight, kg, mean \pm SD	76.7 ± 15.1
Height, cm, mean \pm SD	164.8 ± 8.2
RA duration, years, mean \pm SD*	8.7 ± 9.2
RF positive, N (%)**	56 (56)
ACPA positive, N (%)**	38 (38)
Evidence of structural joint damage, N (%)**	29 (29)
RA-related surgical procedures, N (%)	8 (8)
DAS28-ESR, mean \pm SD	4.98 ± 0.98
SJC, mean \pm SD	21.42 ± 15.20
TJC, mean \pm SD	10.30 ± 10.27
ESR, mm/hr, mean \pm SD***	41.64 ± 25.88
CRP, mg/L, mean \pm SD#	1.79 ± 2.77
Patients receiving one or more DMARDs, N (%)	74 (74)
DMARD-IR, N (%)	65 (65)
Biologic-IR, N (%)	35 (35)

*n=99

**only valid data is shown (i.e., patients who were not tested are not shown)

***n=94

#n=98

ACPA = anti-citrullinated protein antibody, biologic-IR = inadequate response to biologics, CRP = C-reactive protein, DAS28-ESR = disease activity score for 28 joints-erythrocytes sedimentation rate, DMARDs = disease modifying antirheumatic drugs, DMARD-IR = inadequate response to DMARDs, ESR = erythrocyte sedimentation rate, RF = rheumatoid factor, SD = standard deviation, SJC = swollen joint count, TJC = tender joint count

TREATMENT

Study participants received a weekly SC injection of tocilizumab 162 mg (in a single fixed dose irrespective of body weight) as monotherapy or in combination with methotrexate or other DMARDs for 24 weeks. All patients had a follow-up visit (via a telephone call) 4 weeks after the end of the treatment study visit (week 24), or after an early withdrawal visit from the study, to assess adverse events (AEs), concomitant medications, and plans for further treatment. DMARDs were allowed if the participant was on a stable dose for at least 4 weeks prior to baseline. Oral corticosteroids (≤ 10 mg/day prednisone or equivalent) and NSAIDs (up to the maximum recommended dose) were permitted if the participant was on a stable dose regimen for more than 4 weeks prior to baseline.

ENDPOINTS

The primary endpoint of the study was the proportion of patients achieving remission and proportion of patients achieving low disease activity (LDA) according to the CDAI after 24 weeks of treatment with SC tocilizumab. Secondary efficacy endpoints included the change in SDAI up to 24 weeks, the proportion of patients achieving SDAI remission and LDA after 24 weeks, change in the DAS28-ESR up to 24 weeks. Additional endpoints included proportion of patients achieving ACR responses up to 24 weeks, proportion of patients achieving EULAR responses up to 24 weeks, and change in tender joint count (TJC) and swollen joint count (SJC) over time. Furthermore, patient-reported outcomes were assessed, including patient pain visual analogue scale (VAS), patient global assessment of disease activity VAS, the Stanford health assessment questionnaire disability index (HAQ-DI© Stanford University, 1980) [8], and patient functional assessment of chronic illness therapy-fatigue (FACIT-F) [9].

Pharmacokinetics and immunogenicity (anti-tocilizumab antibodies) were assessed at baseline, 12 weeks, and 24 weeks. Anti-tocilizumab antibodies were measured using the bridging enzyme-linked immunosorbent assay. Safety was assessed by adverse events reports.

STATISTICAL ANALYSIS

The analysis population included all patients who received at least one dose of SC tocilizumab. Study results were summarized by descriptive statistics at baseline and over time. Change in efficacy parameters between baseline and 24 weeks were analyzed using the Wilcoxon signed rank test. A *p* value of < 0.05 was considered significant. Statistical analyses were performed using SAS 9.3 software (SAS Institute Inc., Cary, NC, USA).

RESULTS

At baseline, 74% of the patients were treated with DMARDs, while the rest began treatment with tocilizumab as a monotherapy. The most common DMARD was methotrexate, taken

by 59% of patients. During the study 12 additional patients (12%) stopped DMARD treatment completely (3 other patients stopped DMARD treatment temporarily during the study). Therefore, a total of 38% of patients were treated with tocilizumab monotherapy during the study. An inadequate response to a RA biologic treatment (biologic-IR) was experienced by 35 patients (35%) prior to the study and the rest of the patients (65%) were DMARD-IR.

Eighty-five patients (85.0%) completed the study as planned and 15 patients (15.0%) withdrew early from the study. The primary reasons for discontinuation of the study were AEs (4 patients), decision of patient to withdraw (4 patients), insufficient therapeutic response (4 patients), loss to follow-up (1 patient), physician decision (1 patient), and a protocol violation (1 patient). None of the patients withdrew due to anaphylaxis or a hypersensitivity reaction.

EFFICACY

As shown in Figure 1A, mean CDAI decreased by 18.29 ± 14.52 between baseline and 24 weeks ($P < 0.0001$). The minimal clinically meaningful difference (MCMD) of CDAI score (reduction ≥ 12) was evident as early as 2 weeks of treatment [Figure 1B]. After 24 weeks of treatment, 16.5% of patients achieved clinical remission (CDAI ≤ 2.8) and 34.1% of patients achieved LDA (CDAI > 2.8 and ≤ 10). There was no statistically significant difference in the mean change in CDAI from baseline between the DMARD-IR patient population and the biologic-IR population. In addition, no difference was observed between the patients who received tocilizumab monotherapy at baseline compared to those who received a combination of tocilizumab and DMARDs at baseline.

DAS28-ESR remission (DAS28-ESR < 2.6) increased from 13% (13 of 99 patients) after 2 weeks of treatment to 57.1% (48 of 84 patients) after 24 weeks of treatment. DAS28-ESR LDA rate (DAS28-ESR ≥ 2.6 and < 3.2) increased from 11.1% (11 of 99 patients) at 2 weeks of treatment to 16.7% (14 of 84 patients) at 24 weeks. SDAI remission rate (SDAI ≤ 3.3) increased from 3.0% (2 of 66 patients) at week 2 to 19.2% (10 of 52 patients) after 24 weeks, while SDAI LDA (SDAI ≤ 11) increased from 8.1% (8 of 66 patients) to 38.5% (20 of 52 patients). The proportion of patients achieving an ACR 20/50/70 response at week 24 was 62.4%/37%/20%.

Figure 2 shows the percent of patients achieving MCMD in CDAI (reduction ≥ 12), SDAI (reduction ≥ 13), pain VAS (decrease ≥ 20), patient global activity (PGA) of disease activity (decrease ≥ 18), FACIT-F (increase ≥ 4), and HAQ-DI (decrease ≥ 0.375) [10]. The proportion of patients who achieved a minimal clinically meaningful reduction in SDAI increased from 31.3% at week 2 to 65.4% at 24 weeks. A statistical and clinical significant mean decrease from baseline in pain VAS score was observed from baseline to week 16 and onwards. At 24 weeks, 61.2% of patients achieved a minimal clinically meaningful decrease from baseline in pain VAS score.

Patient and physician global assessment of disease activity also decreased significantly during the study period with 68.2% of patients achieving a clinically meaningful decrease in patient global assessment of disease activity at 24 weeks. A statistically and clinically significant mean increase from baseline in FACIT-F score was evident from week 8 onwards and the proportion of patients who achieved a minimal clinically meaningful increase from baseline was 65.9% at 24 weeks. The proportion of patients who achieved MCMD in HAQ-DI increased from 18.2% at week 2 to 44.7% at 24 weeks.

The effect of SC tocilizumab treatment on the acute phase reactants ESR and C-reactive protein (CRP) was already evident at week 2 with mean CRP decreasing from 1.79 ± 2.77 mg/L to 0.22 ± 0.78 mg/L ($P < 0.0001$) and mean ESR decreasing from 41.64 ± 25.88 mm/hour to 19.79 ± 18.54 mm/hour ($P < 0.0001$) at week 2. At 24 weeks, mean CRP was 0.08 ± 0.08 mg/L and mean ESR was 9.15 ± 11.99 mm/hour [Table 2].

Of the patients assessed for EULAR response, more than two-thirds (67.4%) achieved good to moderate response at week 2. Between week 8 and week 24 over 90% of patients with valid data achieved good to moderate response; at 24 weeks, 96.4% of patients achieved good to moderate response.

Mean hemoglobin levels increased by a mean of 0.96 ± 0.99 g/dl from baseline to 24 weeks in the overall population. The increase in hemoglobin levels was more pronounced in the 11 patients who were anemic at baseline (Hemoglobin ≤ 11 g/dl): in these patients, hemoglobin increased by a mean of 1.91 ± 1.23 g/dl (from 10.90 ± 0.94 g/dl at baseline to 12.34 ± 1.37 g/dl at week 24).

Table 2. Change in parameters from baseline to week 24. Patients with no valid data for any of the components required to calculate the parameters were omitted from the calculation

Parameter	Change from baseline to 24 weeks Mean \pm SD (n)	P value
CDAI	-18.29 \pm 14.52 (85)	< 0.0001
DAS28-ESR	-2.47 \pm 1.29 (83)	< 0.0001
SJC	-7.54 \pm 9.60 (85)	< 0.0001
TJC	-11.91 \pm 13.59 (85)	< 0.0001
SDAI	-21.41 \pm 14.99 (52)	< 0.0001
ESR	-33.41 \pm 25.37 (78)	< 0.0001
CRP	-1.68 \pm 2.21 (52)	< 0.0001
Pain VAS	-29.11 \pm 29.16 (85)	< 0.0001
PGA of disease activity	-25.84 \pm 29.16 (87)	< 0.0001
PhGA of disease activity	-37.69 \pm 24.92 (85)	< 0.0001
FACIT-F	6.95 \pm 9.70 (85)	< 0.0001
HAQ-DI	-0.34 \pm 0.62 (85)	< 0.0001
Hemoglobin	0.96 \pm 0.99 (78)	
Hemoglobin (≤ 11 g/dl at baseline)	1.91 \pm 1.23 (8)	

CDAI = clinical disease activity index, CRP = c-reactive protein, DAS28-ESR = disease activity score for 28 joints-erythrocytes sedimentation rate, ESR = erythrocyte sedimentation rate, FACIT-F = functional assessment of chronic illness therapy-fatigue, HAQ-DI = health assessment questionnaire-disability index, PGA = patient global activity, PhGA = physician global activity, SD = standard deviation, SDAI = simplified disease activity index, SJC = swollen joint count, TJC = tender joint count, VAS = visual analogue scale

Figure 1. Efficacy in treatment

[A] Mean CDAI score over time **[B]** Percent of patients in CDAI remission and low disease activity over 24 weeks of treatment. Clinical remission was defined as CDAI ≤ 2.8 . Low disease activity was defined as CDAI > 2.8 and ≤ 10 . CDAI = Clinical Disease Activity Index

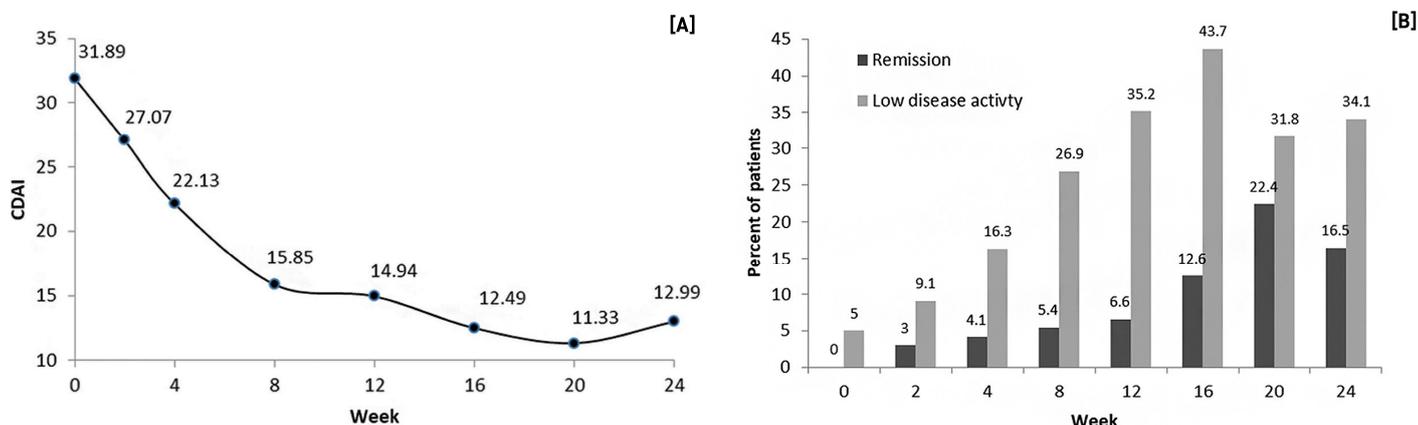
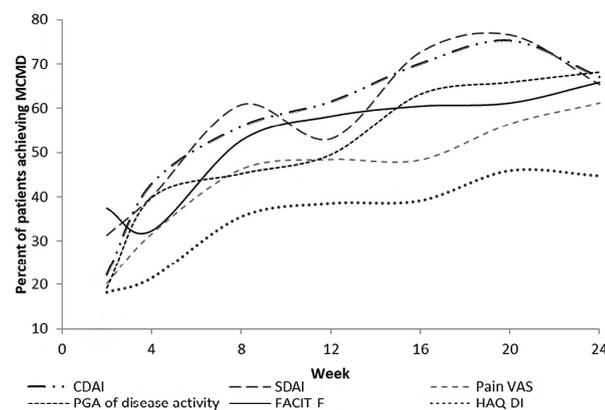


Figure 2. Percent of patients achieving minimal clinically meaningful differences from baseline over 24 weeks of treatment

CDAI MCMD: reduction \geq 12, SDAI MCMD: reduction \geq 13, pain VAS MCMD: decrease \geq 20
 PGA of disease activity MCMD: decrease \geq 18
 FACIT-F MCMD: increase \geq 4, HAQ-DI MCMD: decrease \geq 0.375
 CDAI = clinical disease activity index, FACIT-F = functional assessment of chronic illness therapy-fatigue, HAQ-DI = health assessment questionnaire-disability index, MCMD = minimal clinically meaningful differences, PGA = patient global activity, SDAI = simplified disease activity index, VAS = visual analogue scale



PHARMACOKINETICS AND IMMUNOGENICITY

Mean tocilizumab and soluble IL-6R levels increased from baseline and appeared to remain stable between 12 and 24 weeks. Mean tocilizumab levels were $35.49 \pm 17.81 \mu\text{g/ml}$ (n=91) and $41.63 \pm 22.79 \mu\text{g/ml}$ (n=84) after 12 and 24 weeks of treatment, respectively. Mean soluble IL-6R levels increased from $38.33 \pm 10.30 \text{ ng/ml}$ (n=98) at baseline to $512.77 \pm 122.84 \text{ ng/ml}$ (n=91) and $542.21 \pm 128.38 \text{ ng/ml}$ (n=85) at 12 and 24 weeks, respectively. None of the patients was positive for anti-tocilizumab antibodies at 12 or 24 weeks. One patient had a moderate hypersensitivity reaction (non-serious adverse event of significant interest) but did not develop anti-tocilizumab antibodies.

SAFETY

At least one AE was reported by 70% of patients (473 events/100 patient years [PY]). The most common AEs were neutropenia (12%), leukopenia (11%), and increased hepatic enzymes (11%). In addition, increased alanine aminotransferase (ALT) and increased aspartate aminotransferase (AST) were observed in 8% and 6% of patients, respectively and upper respiratory tract infection and urinary tract infection were each observed in 7% of patients. Five patients (5%) discontinued from the study because of treatment-emergent AEs and none of the AEs that led to discontinuation from treatment occurred within 24 hours of SC tocilizumab injection.

Dose modifications were necessary for 16 patients (16%) because of AEs. The most common reason for dose modification was change in hepatic enzymes (8% of patients), leukopenia

(4%), and neutropenia/decreased neutrophil count (4%). Seven treatment-emergent serious adverse events (SAEs) were reported in 6% of the patients. Two serious infections (both cellulitis) were reported in one patient; and both of the events resolved. Injection-site reactions were reported in 7% of patients. Each injection site reaction (erythema, irritation, pain, pruritus, rash, swelling, and urticaria) occurred only once during the study. All of them except for one were mild; injection-site erythema was rated moderate. No severe hypersensitivity, anaphylaxis, malignancies, pregnancies, or deaths were reported during the study.

Twenty-three patients (23%) reported 31 AEs of hepatic enzymes elevation; 22 of the events were considered to be related to tocilizumab. None of the events was severe or serious, and none of them fulfilled the definition of Hy's law (AST or ALT elevations that are more than threefold the upper limit of normal [ULN] and concurrent elevation of total bilirubin more than twofold ULN) during the study. Tocilizumab treatment was temporarily interrupted in two patients (2%) as a result of elevations in liver enzyme. In six patients (6%), tocilizumab dose was decreased or its frequency was reduced. Tocilizumab was permanently discontinued in two patients (2%).

LABORATORY FINDINGS

ALT elevations of one to fivefold ULN were observed at least once in 55 patients (55%) during the study. These elevations were transient (i.e., happened once and resolved) in 19 patients (19%), fluctuated (i.e., happened more than once) in 6 patients (6%), and were persistent (i.e., did not resolve) in 30 patients (30%). AST elevations at onefold to threefold ULN were observed at least once in 49 patients (49%) during the study, which were transient in 27 patients (27%), fluctuated in 4 patients (4%), and persistent in 18 patients (18%). Eleven patients (11%) had total bilirubin above ULN range at any time during the study. All but one had levels below twofold ULN and none of them fulfilled the criteria for Hy's law.

Neutrophils below the lower limit of normal range (1.5 GI/L) but above 1 GI/L were reported by 36 patients (36%) at least once during the study. None of the patients had neutrophil values below 0.5 GI/L during the study.

Total cholesterol above ULN was measured at least once during the study in 11 patients (11%) and 3 of the patients had a medical history of hyperlipidemia. Low-density lipoprotein (LDL) cholesterol ULN was measured in 4 patients (4%) at least once during study laboratory tests; three of them had total cholesterol above ULN. Twenty-five patients (25%) had triglycerides values above ULN during the study; 8 of them had triglyceride elevations already at screening or baseline.

Mean weight increased by $1.40 \pm 2.19 \text{ kg}$ from baseline to 12 weeks and by $1.80 \pm 3.18 \text{ kg}$ from baseline to 24 weeks. An increase of more than 10% in body weight was measured in 3 patients (3%) from baseline and 23 additional patients (23%) had weight increases between 5-10%. The body weight of 2 patients (2%) decreased by more than 10% from baseline.

DISCUSSION

The present study was conducted in a real-life setting. Treatment with SC tocilizumab over 24 weeks resulted in an improvement in all efficacy parameters assessed: CDAI, DAS28-ESR, ACR response scores, EULAR response criteria, SDAI, TJC/SJC, and patient-reported outcomes. At baseline 26% of patients were treated with monotherapy, increasing to 38% during the course of the study. This is consistent with available publications on clinical trials and real-life data [6] describing tocilizumab IV and SC and local data from Israel [12,13].

The proportion of patients in CDAI remission ($\text{CDAI} \leq 2.8$) at 24 weeks was 16.5%, similar to the proportion of patients in CDAI remission in the MUSHASHI study, and of 18.5% and 17.2% in the ADACTA study [6]. Unlike DAS28 and SDAI scores, CDAI does not include CRP levels. This mitigates potential overestimation of remission rates, which may be present with these scores.

The observed changes in CDAI from baseline to 24 weeks as well as remission and LDA rates were similar in patients who received monotherapy at baseline compared to those who were treated with a combination of tocilizumab and DMARDs, highlighting the efficacy of tocilizumab monotherapy, which is closely linked to its low immunogenic potential.

Interestingly, DAS28-ESR remission was higher than in the SUMMACTA [11] and BREVACTA [24] trials while the ACR 20/50/70 were similar. A particularly interesting finding of our study is the rapid achievement of improvement as early as week 2. A minimal clinically meaningful reduction of CDAI score was observed in 22 patients (22.2%) at week 2, including 3 patients who achieved CDAI remission, comparable with the rapid onset of response reported for IV tocilizumab treatment [14-17].

The effect of SC treatment on fatigue was not assessed in the studies that assessed SC administration of tocilizumab and only a few studies reported the impact of IV tocilizumab on fatigue. In the current study MCMD (increase of FACIT-F score of above 4) from baseline was evident from week 8 onward, and at 24 weeks the proportion of patients who achieved a MCMD from baseline was 65.9%. This finding is similar to previous reports for IV tocilizumab: the ACTIVE study (56.8% at 24 weeks) [13] and the PEPS study (62% at 16 weeks) [25]. The RADIATE and TOWARD studies showed statistically significant mean improvement vs. placebo in FACIT-Fatigue scores from baseline at week 24.

In the current study, mean tocilizumab and soluble IL-6R levels increased from baseline to week 12, and remained stable through week 24. Mean tocilizumab levels at 24 weeks ($41.63 \pm 22.79 \mu\text{g/ml}$) were similar to the observed steady-state trough concentration in the SUMMACTA study ($42 \pm 27.4 \mu\text{g/ml}$). The high variance of tocilizumab and soluble IL-6R levels among patients may be explained by the variance in systemic absorption via the SC route, in body weight, or in intervals between injections, caused by dose adjustments or non-adherence to the

treatment regimen. Immunogenicity risk was very low, as expected, in accordance with previous publications [18-21], with none of the patients testing positive for the anti-tocilizumab antibodies test at week 12 or at week 24.

In this real-life trial, the proportion of SAEs and of serious infections (SIs) was low and similar to the rate reported in other randomized clinical trials. Seventy percent of patients reported at least one AE (473 events/100 patient years [PY]) compared to 62.7% of patients in the BREVACTA study, 76% in the SUMMACTA study and 89% in the MUSASHI study [21].

Of a total of 42 PY in our study, the rates of SAEs, SIs, and AEs leading to discontinuation were 16.7, 4.8, and 11.9 events per 100 PY, respectively. These results compare well with a long-term safety analysis of IV tocilizumab (mean treatment duration of 3 years, and up to 4.6 years, with a total of 12,293 PY) that showed rates of SAE, SI, and AEs leading to discontinuation in the first year of treatment of 15.5, 4.5, and 5.2 events per 100 PY, respectively [23].

The rate (7.0%) and type of injection site reactions was similar to that reported in other SC studies. The percentage of leukopenia and increased ALT in the present study was similar to that observed in other studies in which tocilizumab was administered IV or SC and is in accordance with tocilizumab's labeling [22]. Total cholesterol above ULN was measured at least once during the study in 11 patients (11%); 3 patients had a medical history of hyperlipidemia. Four patients (4%) had LDL cholesterol ULN at least once during study laboratory tests; three had total cholesterol above ULN. These laboratory findings seem lower than those reported in the prescribing information [22], where 24% of patients receiving tocilizumab in clinical trials experienced sustained elevations in total cholesterol of above 6.2 mmol/L and 15% experienced sustained increase in LDL of ≥ 4.1 mmol/L. Twenty-five patients (25%) had triglyceride values above ULN during the study; 8 had triglyceride elevations already at screening or baseline.

Weight gain is a common AE of SC and IV tocilizumab treatment [22]. In the current study, 23% had weight increases between 5-10%. An increase of over 10% in body weight compared to baseline was observed in three patients (3%). The body weight of two patients decreased by more than 10% from baseline with no known reason. No malignancies were reported during the study.

LIMITATIONS

The study limitations include its non-blinded, non-randomized nature and the relatively short period of follow-up of up to 32 weeks.

CONCLUSIONS

The overall safety, tolerability, and efficacy profile of tocilizumab administered by the SC route in this real-life setting were comparable to those reported from other studies both in studies evaluating IV and in studies evaluating the SC route of administration. Our findings add to the established body of knowledge, and strengthen previous findings from clinical trials and real-world data.

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Qualified researchers may request access to individual patient level data through the clinical study data request platform <https://vivli.org/>.

Further details on Roche's criteria for eligible studies are available at <https://vivli.org/members/ourmembers/>

For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm.

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Every adversity, every failure and every heartache carries with it the seed of an equivalent or greater benefit.

Napoleon Hill (1883-1970), American author

Everybody needs his memories. They keep the wolf of insignificance from the door.

Saul Bellow (1915-2005), Canadian-American writer, awarded the Pulitzer Prize, the Nobel Prize for Literature, and the National Medal of Arts