

Effect of Tocilizumab on Fatigue and Bone Mineral Density in Patients with Rheumatoid Arthritis

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ABSTRACT: **Background:** Chronic fatigue is common among patients with rheumatoid arthritis (RA), affecting quality of life. Osteoporosis is a prevalent co-morbidity in RA patients.

Objectives: To assess the effect of long-term treatment with tocilizumab on fatigue and bone mineral density (BMD) in RA patients with inadequate response to synthetic or biologic disease-modifying anti-rheumatic drugs.

Methods: In this multicenter, open-label, non-controlled, single-arm study, patients ≥ 18 years of age received intravenous tocilizumab 8 mg/kg every 4 weeks for 96 weeks. The primary outcome was the change in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score from baseline to weeks 24, 48, 72, and 96. BMD was assessed before and 96 weeks after treatment.

Results: The study comprised 145 patients (mean age 53.4 ± 13.4 years, 83.4% women). Of these, 88 (60.7%) completed the 2 year treatment period. The mean FACIT-Fatigue score improved consistently starting from week 4 and showed a statistically significant increase of 5.0 ± 9.7 , 6.8 ± 10.5 , 7.3 ± 10.9 , and 7.3 ± 10.4 from baseline to weeks 24, 48, 72, and 96, respectively ($P < 0.0001$). Mean BMD of femoral neck and total spine remained stable. Disease activity, acute phase reactants, and composite efficacy measures decreased during the study, while hemoglobin levels increased. Adverse events

and serious adverse events were as expected for the known and previously described data.

Conclusions: Tocilizumab therapy for 2 years significantly and clinically decreased fatigue. BMD remained stable and no new safety issue was reported.

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KEY WORDS: tocilizumab, rheumatoid arthritis (RA), fatigue, bone mineral density (BMD), obesity

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by inflammation of the synovial membrane lining the joints and significant disability in uncontrolled cases.

Chronic fatigue is a common complaint among patients with RA [1]. It often affects daily activity and is associated with a decrease in quality of life [2]. The reported prevalence of fatigue in adults with RA ranges from 42% to more than 80% [1]. Co-morbid conditions, disease duration, functional status, and RA disease activity have been reported as predictors of fatigue

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in RA [3]. In addition, pain, disturbed sleep, and depression are also associated with fatigue in patients with RA [1,4,5].

Interleukin 6 (IL-6) is a pro-inflammatory cytokine produced by a variety of cell types. It is involved in T-cell activation, B-cell differentiation, induction of acute phase proteins, stimulation of hematopoietic precursor cell growth and differentiation, differentiation of osteoclasts from precursor cells, proliferation of hepatic, dermal and neural cells, and promotion of bone and lipid metabolism [6-8]. IL-6 exerts its effects through a ligand-specific receptor (IL-6R), present both in soluble and membrane-expressed forms. Elevated serum and synovial fluid IL-6 levels have been reported in RA patients [9]. IL-6 levels correlate with disease activity in RA [9], induce bone resorption [10], and contribute to the development of osteoporosis [11,12]. Osteoporosis is twice as prevalent in patients with RA compared to individuals who do not have RA [13], with a 50% increase in the risk of osteoporotic fractures [14].

Tocilizumab is a recombinant humanized anti-human monoclonal antibody of the immunoglobulin IgG1 subclass directed against the IL-6R and produced by recombinant DNA technology. Treatment with tocilizumab has demonstrated high efficacy and favorable safety in previous clinical studies.

The aim of this open-label study was to assess whether treatment with tocilizumab 8 mg/kg every 4 weeks for a period of 96 weeks improves fatigue in RA patients with inadequate response to prior synthetic disease-modifying antirheumatic drugs (sDMARDs) and/or biologic disease-modifying antirheumatic drugs (bDMARDs). We also assessed long-term tocilizumab treatment on fatigue and bone mineral density (BMD).

METHODS

ETHICS APPROVAL

The protocol for the research project was approved by the local ethics committee in each of the 16 medical centers within which the work was conducted and with the 1964 Helsinki declaration and its later amendments or comparable ethics standards. Informed consent was obtained from all patients prior to their inclusion in the study.

STUDY DESIGN

This multicenter, open-label, non-controlled, single-arm study was conducted at 16 centers in Israel from October 2010 to July 2014. RA patients with moderate to severe active disease (determined by 28-joint Disease Activity Score [DAS28] ≥ 3.2) and inadequate clinical response to a stable dose of anti-rheumatic therapy (sDMARDs and/or bDMARDs) for a period of at least 8 weeks prior to baseline were included in the study. Exclusion criteria were: rheumatic autoimmune diseases or inflammatory joint diseases other than RA, any condition affecting bone homeostasis, malignancies diagnosed within 5 years prior to

screening (except non-melanoma skin cancer that has been excised and cured), and severe widespread pain.

Patients were treated with intravenous (IV) tocilizumab 8 mg/kg every 4 weeks for a period of 96 weeks. Patients could receive concomitant treatment with DMARDs, background corticosteroids (≤ 10 mg/d prednisone or equivalent), non-steroidal anti-inflammatory drugs (NSAIDs), and analgesics throughout the study period at the discretion of the investigator.

ENDPOINTS

The primary outcome of the study was the change in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score from baseline to weeks 24, 48, 72, and 96. The FACIT-Fatigue Scale is a 13-item tool that measures an individual's level of fatigue during their usual daily activities over the week prior to completing the questionnaire. The level of fatigue is measured on a 5 point fatigue Likert scale (4 = not at all fatigued to 0 = very much fatigued). The assessment was developed for chronic illnesses and has been validated for patients with RA [15]. The total score of FACIT ranges from 0 to 52. An increase of 4 points in the FACIT-Fatigue score is considered as clinically meaningful.

The secondary outcomes were:

- Changes in BMD
- Proportion of patients achieving remission according to disease activity score (DAS28) < 2.6 , according to clinical disease activity index (CDAI < 2.8)
- Changes in American College of Rheumatology (ACR) 20, ACR50, and ACR70 response compared to baseline
- Changes in hemoglobin levels compared to baseline
- Change in the Stanford Health Assessment Questionnaire-Disability Index (HAQ-DI© Stanford University, 1980) [16]
- Tocilizumab long-term (96 weeks) safety and changes in weight and body mass index (BMI).

BMD of lumbar spine, femoral neck, and total femur was measured using dual energy X-ray absorptiometry at baseline and after 96 weeks of treatment. T-scores \pm standard deviation (SD) compared with the peak BMD value of an adult aged from 20 to 30 years were calculated. Osteopenia was defined by a T-score between -1 and -2.5 and osteoporosis as a T-score below -2.5, according to the World Health Organization guidelines [17].

STATISTICAL ANALYSIS

All analyses used the intention-to-treat (ITT) population. Study results were summarized by descriptive statistics at baseline and over time. The number of patients contributing to assessments decreased over time because of early withdrawals.

FACIT-Fatigue score change between weeks 24, 48, 72, and 96 to baseline were analyzed using paired sample *t*-test or

Wilcoxon signed rank test as appropriate. $P < 0.05$ were considered statistically significant.

The study was planned for 150 subjects with a primary endpoint improvement by at least 4 units in FACIT-Fatigue score. Eighty-eight subjects completed the study according to the protocol. Despite the high withdrawal rate, the study's primary endpoint was achieved with 90% power and was found statistically significant.

RESULTS

A total of 145 patients were enrolled in the study, 88 of them (60.7%) completed the 2 year treatment period as planned. Fifty-seven patients (39.3%) withdrew prematurely from the study. The main causes for withdrawal were: treatment inefficiency/lack of response (16 patients, 11.0%), adverse effects (AEs) (13 patients, 9.0%), and patient refusal to complete study visit/procedures/withdrawal of consent (9 patients, 6.2%). Patient baseline demographics are shown in Table 1. The mean BMI of the patients with diabetes mellitus at baseline was 31.7 ± 5.3 kg/m².

Clinical characteristics are described in Table 2. Prior to the study, 90 patients (62.1%) were treated with sDMARDs (68.3% with hydroxychloroquine, 62.1% with sulfasalazine, and 29% with methotrexate). Fifty-five patients (37.9%) were treated with at least one bDMARDs (mainly etanercept or adalimumab) prior to the study. During the study, 98 patients (68%) were treated with methotrexate; 48.3% of the patients received glucocorticoids at baseline and 18.6% were treated with bisphosphonates.

Table 1. Patient demographics and baseline characteristics

Parameter	Study population N=145
Age, mean ± SD, years	53.4 ± 13.4
Age, median (range), years	54.4 (22.1–82.9)
Gender, n (%)	
Male	24 (16.6)
Female	121 (83.4)
Ethnicity, n (%)	
Caucasian	142 (97.9)
Other	3 (2.1)
Weight, mean ± SD, kg	74.7 ± 16.9
Height, mean ± SD, cm	163.3 ± 7.5
BMI, mean ± SD, kg/m ²	28.0 ± 5.9
BMI, median (range), kg/m ²	27.4 (15.6–44.3)
BMI, n (%)	
Underweight (BMI < 18.5)	4 (2.8)
Normal range (18.5 < BMI < 25)	53 (36.6)
Overweight (25 < BMI < 30)	35 (24.1)
Obese (30 BMI < 35)	34 (23.4)
Morbid obesity (BMI > 35)	19 (13.1)
Diabetes	29 (20)

SD = standard deviation, BMI = body mass index

FACIT-FATIGUE SCORES

The mean FACIT-Fatigue score increased consistently starting from week 4, showing a statistically significant increase of 5.0 ± 9.7 , 6.8 ± 10.5 , 7.3 ± 10.9 , and 7.3 ± 10.4 from baseline to weeks 24, 48, 72, and 96, respectively ($P < 0.0001$ for the change from baseline to each time point). The threshold for minimal clinically significant difference is 4 points. More than 50% of the patients achieved an increase of at least 4 points at weeks 24, 48, 72, and 96 (56.8%, 61.9%, 60.0%, and 62.7% of patients, respectively). The mean FACIT-Fatigue score remained higher than baseline at the follow-up visit 4 weeks after termination of treatment (29.0 ± 13.2).

Multivariate analysis on the ITT population showed that anemia, BMI category at baseline, or previous bDMARDs treatment, did not have an effect on the change in FACIT-Fatigue scores at weeks 24, 48, 72, or 96.

BONE MINERAL DENSITY

The mean change in T-score from baseline to the end of the study visit was not statistically significant in any of the regions assessed. No statistically significant changes were observed for the changes in BMD even when the results were adjusted for the number of days in the study. Between study baseline and the end of the study, for each of the regions assessed, most of the patients remained within their initial categorization indicating stable BMD. None of the patients who started the trial with a normal BMD had a T-score in the osteoporosis range at the end of the study.

DAS28 AND CDAI RESPONSE

Clinically meaningful decreased disease activity was observed during the study with mean DAS28 statistically significantly decreasing by 2.9 ± 1.3 , 3.1 ± 1.4 , 3.1 ± 1.6 , and 3.3 ± 1.5 from baseline to weeks 24, 48, 72, and 96, respectively ($P < 0.0001$ for the change from baseline to each time point). The proportion of patients in remission according to DAS28 (DAS28 < 2.6) increased from 30.4% at week 24 to 45.8% at week 96, and

Table 2. Baseline disease activity and previous treatments

Parameter	Study population N=145		
	N	Mean ± SD	Median (range)
Duration of disease, years	145	10.5 ± 9.1	8.0 (0.3–43.5)
DAS28 score (calculated)	129	6.2 ± 1.1	6.2 (2.9–8.3)
Pain (VAS), mm	139	69.5 ± 21.0	71.0 (1.0–100.0)
ESR, mm/hr (n)*	138	45.3 ± 27.1	40.0 (1.0–130.0)
CRP, mg/dL (n)*	133	2.8 ± 5.6	1.1 (0.0–53.5)
sDMARDs-IR, n (%)	90	(62.1)	
bDMARDs-IR, n (%)	55	(37.9)	

SD = standard deviation, ESR = erythrocyte sedimentation rate, IR = response, sDMARDs = synthetic disease-modifying antirheumatic drugs, bDMARDs = biologic disease-modifying antirheumatic drugs, DAS28 = 28-joint Disease Activity Score, VAS = visual analog scale

*values were taken from baseline visit

the proportion of patients with low disease activity according to DAS28 ($\text{DAS28} \leq 3.2$) increased from 43.5% at week 24 to 52.8% at week 96.

Stratification of the change in DAS28 by BMI category at baseline showed a statistically significant decrease in DAS28 in all of the BMI categories between baseline and weeks 24, 48, 72, and 96, indicating that BMI at baseline does not affect response as measured by improvement in DAS28.

The proportion of patients in remission according to the clinical disease activity index ($\text{CDAI} < 2.8$) increased from 6.7% at week 24 to 9.3% at week 48, 10.7% at week 72, and 17.5% at week 96. The proportion of patients with low disease activity ($\text{CDAI} \leq 10.0$) also increased during the study from 37.5% at week 24 to 47.5% at week 96.

The proportion of patients achieving ACR20, ACR50, and ACR70 increases from baseline are shown in Table 3. Over 90% of subjects, for whom data for calculating European League Against Rheumatism (EULAR) response was available, achieved good to moderate EULAR responses at weeks 24, 48, 72, and 96 [18].

The mean values of both erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) decreased during the study from 45.3 ± 27.1 mm/h at baseline to 7.4 ± 8.4 mm/h at week 96 for ESR and from 2.8 ± 5.6 mg/dl at baseline to 0.5 ± 1.1 mg/dl at week 96 for CRP. For both of these acute phase reactants, the decrease was already observed at week 8. The vast majority of patients (131/145, 95.6%) had normal CRP levels (i.e., lower than 1 mg/dl) at week 8. ESR and CRP values remained lower than baseline for the duration of the study.

The mean hemoglobin levels increased from a mean level of 12.4 ± 1.4 g/dl at baseline to 13.4 ± 1.5 g/dl at week 96. Specifically, the increase was more pronounced in patients who had anemia at baseline (hemoglobin < 11 g/dl), increasing by a mean of 1.6 ± 1.1 g/dl and 2.4 ± 1.3 g/dl after 20 and 96 weeks, respectively. The increase in hemoglobin was also higher than that of the ITT population in those patients whose baseline hemoglobin was lower than 12 g/dl.

PATIENT-REPORTED OUTCOMES

Mean pain score, assessed by visual analog scale (VAS), decreased during the study from 69.5 ± 21.0 mm at screening to 44.9 ± 28.0

mm at week 96, indicating a clinically meaningful improvement of more than 20 mm as suggested by Ward and colleagues [19]. A clinically significant decrease in mean pain score (more than 10 points) was already seen at week 8 (51.6 ± 26.7 mm) and remained low until the end of the study.

The mean HAQ score showed a decrease that was greater than 0.375 points from baseline to weeks 24, 48, 72, and 96, indicating clinically meaningful improvement in the disability index of the patients [16]. This improvement was already evident at week 8.

WEIGHT AND BMI

A mean increase in weight and BMI was observed during the study. Weight increased from 74.7 ± 16.8 kg at baseline to 76.4 ± 17.8 kg. Twenty-two patients (15.2%) gained over 10% of their weight (kg) over the course of 1 year during the study. A less pronounced increase in BMI was observed in the population of diabetic patients. Sixty-one subjects (42.1%) moved from one BMI category to another during the study. A similar proportion of subjects moved from normal range BMI to overweight and from overweight to obese (20.6% and 19.4%, respectively); however, 18.1% of subjects moved from the obese category to the overweight category and 16.8% of subjects moved from the overweight category to the normal range category.

Table 4 details the number of patients who shifted from their baseline BMI category to a different category by the end of their study. Seven subjects (4.8%) became morbidly obese. Of these subjects, two were also diabetic.

SAFETY

A total of 687 AEs were reported in 137 patients (94.5%) during the study. The vast majority of AEs (662/687, 96.4%) were mild or moderate and resolved without sequelae. The most common AEs were liver enzyme elevations that occurred in 32.4% of patients, leukopenia (22.1% of patients), upper respiratory tract infection (17.2% of patients), neutropenia (7.6% of patients), and thrombocytopenia (3.4% of patients). Drug-related AEs were

Table 3. The Proportion of Patients achieving ACR20, ACR50, and ACR70

Visit	N (total)	Patients achieving ACR20		Patients achieving ACR50		Patients achieving ACR70	
		N	(%)	N	(%)	N	(%)
Week 24	121	59	(48.8)	30	(24.8)	14	(11.6)
Week 48	96	61	(63.5)	27	(28.1)	15	(15.6)
Week 72	76	46	(60.5)	26	(34.2)	16	(21.1)
Week 96	81	47	(58.0)	29	(35.8)	17	(21.0)

Patients with no valid data for any of the components required to calculate ACR20, ACR50 and ACR70 were omitted from the table
ACR = American College of Rheumatology

Table 4. Changes in BMI categories at end of study visit vs. baseline

BMI categories	Study population N=145	
	N	(%)
Normal range ($18.5 < \text{BMI} < 25$) to overweight ($25 < \text{BMI} < 30$)	6	(4.1)
Normal range ($18.5 < \text{BMI} < 25$) to underweight ($\text{BMI} < 18.5$)	1	(0.7)
Obese ($30 < \text{BMI} < 35$) to morbid obesity ($\text{BMI} > 35$)	3	(2.1)
Obese ($30 < \text{BMI} < 35$) to overweight ($25 < \text{BMI} < 30$)	1	(0.7)
Overweight ($25 < \text{BMI} < 30$) to normal range ($18.5 < \text{BMI} < 25$)	2	(1.4)
Overweight ($25 < \text{BMI} < 30$) to obese ($30 < \text{BMI} < 35$)	5	(3.5)
Overweight ($25 < \text{BMI} < 30$) to morbid obesity ($\text{BMI} > 35$)	1	(0.7)

BMI = body mass index

reported in 37.9% of subjects, the most common of which were liver enzyme elevations (22.8% of patients), leukopenia (19.3% of patients), and upper respiratory tract infection (4.8% of patients).

Infusion reactions were reported in 17.9% of subjects. These reactions were mostly mild and resolved without sequelae. One event, a type IV hypersensitivity reaction, was a serious AE (SAE) and led to withdrawal of the subject from the study. No anaphylaxis was reported during the study. Nine AEs of special interest (AESIs) were reported in 5.5% of patients during the study. All of the AESIs were mild in severity. Five AESIs were considered to be related to tocilizumab: hypersensitivity reactions, ALT/AST elevations, and allergic dermatitis. Two AESIs led to dosage modification or drug interruption. All of the AESIs but one resolved without sequelae.

Fifty-three SAEs were reported for 36 subjects (24.6%). Nine SAEs in 8 subjects (5.5%) were considered related to tocilizumab. These included ALT/AST elevations, type IV hypersensitivity reaction, erysipelas, pneumonia, urinary tract infection, two events of diverticulitis, and two events of cellulitis. These treatment-related SAEs are consistent with the known and previously described safety profile of tocilizumab.

Eight serious infections were reported in six patients (4.1%), corresponding to 3.6 events per 100 patient years of tocilizumab treatment. There were no reports of opportunistic infections, including tuberculosis. None of the serious infections resulted in death.

During the study, three malignancies were reported in three subjects (one in each patient). These malignancies included breast carcinoma, breast cancer metastases, and cervical carcinoma. Thirteen patients (9.0%) withdrew from the study due to AEs (breast carcinoma, metastatic breast cancer, cerebral hemorrhage, ALT/AST elevations, type IV hypersensitivity reaction, unstable angina, subarachnoid hemorrhage, chronic otitis media, diverticulitis, gastric perforation, and cerebrovascular accident). No deaths were reported during the study.

DISCUSSION

The present study showed that treatment with tocilizumab consistently increased the mean FACIT-Fatigue score starting from week 4 and showed a statistically significant increase from baseline at weeks 24, 48, 72, and 96 ($P < 0.0001$). Clinically significant improvement was observed starting from the second infusion. Minimum scores increased with time, from 1 at baseline to 18 at week 64.

Multivariate analysis showed that anemia, BMI category at baseline, or previous bDMARDs treatment did not have an effect on the change in FACIT-Fatigue scores at weeks 24, 48, 72, or 96. In addition, BMI categories did not have an effect on FACIT-Fatigue scores during the same period of time.

During 96 weeks of tocilizumab treatment, BMD remained stable. However, several patients shifted to a better BMD cat-

egory, while several others shifted to a worse category. Kume and co-workers [20] showed that BMD of the lumbar spine and femoral neck remained stable after 1 year of tocilizumab treatment and a significant increase in BMD of the lumbar spine and femoral neck in 33/78 patients who had osteopenia at baseline [20].

The overall remission rate of 45.8% according to DAS28 is similar to that reported in other studies reflecting clinical trial data. An increase in the proportion of subjects in remission and in the proportion of subjects with low disease activity was observed by the Simplified Disease Activity Index.

An effect of tocilizumab treatment on the acute phase reactants ESR and CRP was already evident at Week 8; 95.6% of the patients had normal CRP levels by week 8. This finding is compatible with the mechanism of action of tocilizumab. A clinically meaningful decrease in mean VAS pain score (more than 10 points) was already evident at Week. Pain scores remained lower than baseline for the duration of the study. Furthermore, a clinically meaningful improvement in the functional status of the subjects (assessed by HAQ-DI) was observed from week 24 onward.

Although the BMI category at baseline did not affect the decrease in disease activity, weight gain is a known side effect of tocilizumab [21]. Although it probably does not depend on the activity of RA, the reasons for this phenomenon are not known. In the present study, a mean increase in weight and BMI was observed from study initiation. The change in BMI was less pronounced in the diabetic population.

Drug-related AEs and SAEs reported during the study were expected and consistent with the known and previously described safety profile of tocilizumab.

The study limitations include its non-blinded, non-randomized, and non-controlled nature. As a result of these limitations, various sources of bias could not be excluded. In addition, the higher than expected drop-out rate may have been due to the long duration of the study (effectively 2 years), which may have given way to more cases than usual of patient preferences and other administrative causes for withdrawal.

CONCLUSIONS

The present study demonstrated that treatment with 8 mg/kg IV tocilizumab once every 4 weeks rapidly alleviates fatigue in RA patients, regardless of previous treatments or BMI at baseline. Although the BMD of the patients remained stable, the effect of tocilizumab on bone turnover status remains to be elucidated.

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Capsule

Socioeconomic predictors of incident depression in systemic lupus erythematosus

McCormick and co-authors assessed different measures of socioeconomic status (SES) as predictors of incident depression among women with systemic lupus erythematosus (SLE). Data were derived from the 2010–2015 waves of the Lupus Outcomes Study, where individuals with confirmed SLE were interviewed annually by telephone. Depression was assessed using the Center for Epidemiologic Studies Depression Scale, using a validated lupus-specific cutoff (≥ 23) for major depressive disorder. Women interviewed in ≥ 2 consecutive waves, with scores < 23 in the first wave (T1), were included. The level of financial strain was classified as high, moderate, or none based on responses to three questions. Generalized estimating equations were used to assess the impact of poverty status, income, education, and financial strain at T1 on the risk of incident depression the next year (T2), with adjustment for sociodemographic and disease status measures. Individuals could contribute more than one

2 year dyad to the analysis. In total, 682 women contributed 2097 observations, with 19% having high financial strain, 47% moderate strain, and 34% no strain. There were 166 women who had 184 episodes of incident depression (rate = 8.8/100 person-years). In bivariate analysis, poverty, lower income and education, disease activity, and high financial strain were associated with depression onset; race/ethnicity was not. Poverty, income, and education were not significant in multivariate analyses, but disease activity and high financial strain were (odds ratio 1.85; 95% confidence interval 1.06–3.23). High financial strain was a significant predictor of new-onset depression in women with SLE, controlling for disease factors and other SES measures. Determining specific, modifiable sources of financial strain may help prevent the development of depression.

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