Association of Serum Tocilizumab Trough Concentrations with Clinical Disease Activity Index Scores in Adult Patients with Rheumatoid Arthritis

Uri Arad and Ori Elkayam

ABSTRACT. ***Objective.*** To determine whether serum trough concentrations of tocilizumab (TCZ) administered as a fixed-dose subcutaneous (SC) injection for the treatment of rheumatoid arthritis (RA) are associated with disease activity responses.

Methods. We analyzed datasets from the Israeli branch of the multinational TOZURA study, which evaluated a weekly subcutaneous TCZ treatment regimen in a real-life clinical setting. Generalized estimating equations (GEE) were used to evaluate associations between the TCZ levels and the study outcomes. Linear models and GEE were used to evaluate associations between patient characteristics and TCZ levels.

Results. A significant association between the TCZ concentrations and the change in the Clinical Disease Activity Index (CDAI) score was observed. In a multivariate binary GEE model, every increase of 10 μg/ml in the concentration of TCZ was associated with being in a state of CDAI remission or low disease activity (OR 1.41) versus a moderate/high disease activity state. An OR of 1.52 was associated with being in a state of Health Assessment Questionnaire–Disability Index remission. In univariate linear models, there was an inverse association between body mass index (BMI) and improvement in the CDAI score, and the BMI score was associated with lower TCZ concentrations. Patients who weighed > 100 kg had lower TCZ concentrations.

Conclusion. In the first 24 weeks of treatment with SC TCZ injections, TCZ concentrations were associated with clinical improvement, while body weight and BMI were inversely associated with TCZ concentrations. Personalizing the dose of SC TCZ to body weight may improve outcomes of clinical disease activity in patients with RA. (First Release October 15 2019; J Rheumatol 2019;46:1577–81; doi:10.3899/jrheum.181431)

Key Indexing Terms:
RHEUMATOID ARTHRITIS TOCILIZUMAB THERAPEUTIC DRUG MONITORING
BODY MASS INDEX BIOLOGICAL PRODUCTS OBESITY

In patients with rheumatoid arthritis (RA) treated with monoclonal antibody tumor necrosis factor-α inhibitors (TNFi), the association between the serum drug trough concentrations and the clinical response to treatment is well established[1,2]. Additionally, the development of antidrug antibodies to monoclonal antibody TNFi, especially to adalimumab and infliximab, correlates with a low level of detectable drug concentration and with a worse clinical outcome in RA, psoriatic arthritis, axial spondyloarthritis, and inflammatory bowel disease[3,4,5,6].

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Tocilizumab (TCZ) is a monoclonal antibody directed against the interleukin 6 (IL-6) receptor, with an established efficacy in the treatment of RA[7]. TCZ has a low immunogenic profile; only about 1–2% of patients develop detectable antidrug antibodies, which were not found to associate with low drug levels or clinical inefficacy[8]. TCZ is administered either as a weekly subcutaneous (SC) injection at a fixed dose of 162 mg, or as an intravenous (IV) infusion with a weight-based dosing regimen of 4 or 8 mg/kg, once every 4 weeks.

Several studies have attempted to explore the relationship between serum TCZ drug levels and clinical outcomes in RA patients. In a pharmacokinetic analysis of 4 phase III studies of intravenously administered TCZ, a relationship between drug exposure and improvement in 28-joint count Disease Activity Score (DAS28) and American College of Rheumatology (ACR) response criteria and in inflammatory markers was evident[9]. A retrospective analysis of an Italian cohort of 126 TCZ-treated patients with RA, which compared between patients with TCZ concentrations < 10 μg/ml (n = 84) and > 10 μg/ml (n = 42), found a statistically significant difference between groups in the DAS28 after 6 months

of treatment (3.09 ± 1.32 vs 2.78 ± 1.32, respectively)[10]. In an observational study of 66 consecutive patients with RA treated with IV TCZ 8 mg/kg once every 4 weeks, serum trough concentrations > 1 μg/ml were sufficient to normalize the serum C-reactive protein (CRP) levels[11]. This study also demonstrated a negative association between TCZ concentration and ΔDAS28 at Week 24 of treatment. Because the majority of patients obtained TCZ concentrations > 1 μg/ml, the authors speculated that tapering the TCZ dose might be feasible in a considerable proportion of patients.

The SUMMACTA study was a randomized double-blind study that demonstrated the clinical equivalence of weekly SC 162 mg TCZ to IV TCZ at a dose of 8 mg/kg once every 4 weeks[12]. In the BREVACTA study, SC TCZ 162 mg every 2 weeks was tested against placebo[13]. In a previously published pharmacokinetic and pharmacodynamic analysis of these trials, in patients treated by SC injections, the clinical response increased with increasing TCZ trough concentration exposure quartiles, with the efficacy variables plateauing past the first quartile (mean C_{trough} ~15 μg/ml) in the once-weekly SC injection regimen[14].

To further study the relationship between TCZ trough concentrations and clinical outcomes in patients with RA treated with once-weekly SC 162 mg TCZ, we analyzed the data from the Israeli cohort of the TOZURA study. This study was a multinational phase IV, single-arm open-label study of patients with RA commencing TCZ treatment[15]. The cohort consisted of 100 patients who were periodically evaluated until Week 24, and the serum trough drug concentrations and levels of soluble IL-6 receptor (sIL6R) were measured at Week 12 and Week 24. Analyses were performed to identify variables that may affect clinical outcomes and drug levels.

MATERIALS AND METHODS

We analyzed datasets of the Israeli branch [Treatment with Actemra (TCZ) administered as Subcutaneous Injection (TASC), clinicaltrials.gov: NCT01988012] of the Roche multinational umbrella study TOZURA, which evaluated an SC TCZ treatment regimen of 162 mg once weekly as monotherapy or in combination with methotrexate (MTX) or other conventional synthetic disease-modifying antirheumatic drugs (DMARD) in a real-world clinical setting[15]. The study enrolled 100 patients. The anonymized datasets were kindly provided by the Roche Global Product Development Medical Affairs Data Sharing Team.

Study design and setting. Briefly, this was a multicenter, open-label single-arm study performed at 13 medical centers in Israel between January 2014 and July 2015, and was part of the multinational umbrella study TOZURA, whose results have been previously published[15]. In Israel, the approval number at the Tel Aviv Sourasky Medical Center ethics review board was 0319-13-TLV and each of the additional 12 sites received approval for performing the study from its independent institutional ethics committees as required by Israeli Ministry of Health regulations.

Study population. Study participants were adults (≥ 18 yrs of age) with a diagnosis of active RA according to the revised (1987) ACR or European League Against Rheumatism/ACR (2010) criteria who received treatment on an outpatient basis (not including TCZ), and who were either previously treated with 3 DMARD and were not treated with any biologic agent, or were previously treated with 1 biologic agent (alone or in combination with DMARD) and discontinued that agent for any reason.

Exclusion criteria included rheumatic autoimmune disease other than RA (secondary Sjögren 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 history of or current inflammatory joint disease other than RA.

Treatment. Study participants received a weekly SC injection of TCZ 162 mg (in a single fixed dose irrespective of body weight) as monotherapy or in combination with MTX or other DMARD for 24 weeks. DMARD were allowed if the participant had been taking a stable dose for at least 4 weeks prior to baseline. Oral corticosteroids (≤ 10 mg/day prednisone or equivalent) and nonsteroidal antiinflammatory drugs (up to the maximum recommended dose) were permitted if the participant was taking a stable dose for ≥ 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 Clinical Disease Activity Index (CDAI) after 24 weeks of treatment with SC TCZ. Pharmacokinetics and immunogenicity (anti-TCZ antibodies) were assessed at baseline, 12 weeks, and 24 weeks. Anti-TCZ antibodies were measured using the bridging ELISA. Safety was assessed by adverse events reports.

Statistical analysis. Linear regression analysis and generalized estimating equations (GEE) were used to evaluate associations between TCZ levels and the study outcomes [change in CDAI scores, change in Health Assessment Questionnaire (HAQ) scores, CDAI remission/LDA status, and HAQ–Disability Index (HAQ-DI) remission]. GEE were also used to evaluate associations between age, sex, weight, BMI, baseline CRP levels, serum TCZ, and sIL6R serum levels at Week 12 and Week 24. P values < 0.05 were considered significant. Analyses were performed with IBM SPSS Statistics software, version 24 (IBM Corp.).

Differences between TCZ levels with weight categories were analyzed with the Kruskal-Wallis test with Dunn's posthoc comparison analysis. P values of < 0.05 were considered significant. Calculations were performed with GraphPad Prism software.

RESULTS

Clinical improvement associates with serum TCZ levels. The Israeli cohort enrolled in the TOZURA study included 100 patients with RA, with a mean age of 54.3 years (SD 11.8); 80 of them were female. Sixty-five patients had an inadequate response to treatment with conventional DMARD and 35 patients did not adequately respond to treatment with biological DMARD. At baseline, the mean ± SD disease activity scores according to CDAI, Simplified Disease Activity Index, and DAS28-ESR were 31.9 ± 14.4, 33.7 ± 14.8, and 5.0 ± 1.0, respectively. At 12 weeks, 4 patients withdrew from the study and 85 patients completed the study until Week 24.

The mean (± SD) TCZ trough levels at Week 12 were 34 ± 19 μg/ml, with a further increase to 41 ± 23 μg/ml at Week 24. About 90% of patients had TCZ trough levels > 10 μg/ml (Figure 1A) at 12 weeks.

Because treatment with TCZ almost invariably results in normalization of the acute-phase reactants, we decided to focus our analysis on the change in the CDAI score, a disease activity outcome measure that uses clinical components without acute-phase reactants. The mean (± SD) CDAI score decreased to 15.8 ± 12.5 after 12 weeks of treatment with TCZ and remained stable until Week 24 (13.0 ± 12.0). We detected

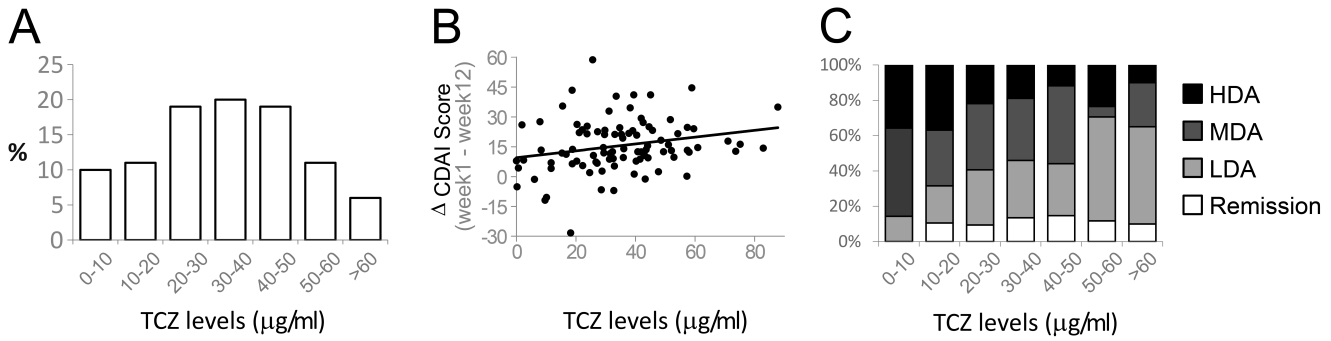

Figure 1. Tocilizumab (TCZ) levels associated with clinical response. A. The distribution of TCZ levels among the cohort. B. Change in CDAI score between Week 1 and Week 12 according to TCZ levels. A higher score represents a better improvement. The line represents the trend line ($y = 0.1713x + 9.514$, $R^2 = 0.055$). C. CDAI response (remission and low, moderate, and high disease activity states) relative to TCZ levels. CDAI: Clinical Disease Activity Index; LDA: low disease activity; MDA: moderate disease activity; HDA: high disease activity.

an association between TCZ levels and the clinical response; in a univariate linear model using data from Week 12, for every increase of 10 μg/ml in the serum concentration of TCZ, there was a corresponding decrease (improvement) of 1.71 units in the CDAI score ($p = 0.024$). Figure 1B depicts change in CDAI score between Week 1 and Week 12 according to TCZ levels. Further, the associations between TCZ levels and the change in CDAI scores remained significant after including the following factors in a multivariate linear model: BMI, sex, concomitant MTX, seropositivity (anticyclic citrullinated peptide antibodies or rheumatoid factor), screening CRP levels, centered baseline CDAI scores, and TCZ trough concentration. For every increase of 10 μg/ml in the serum concentration of TCZ there was a corresponding improvement of 2.22 units in the CDAI score ($p = 0.002$). Similarly, in a multivariate binary GEE model, every increase of 10 μg/ml in the serum concentration of TCZ was associated with an OR of 1.41 of being in a state of CDAI remission or LDA versus moderate/high disease activity state ($p = 0.001$; Figure 1C). In addition, every increase of 10 μg/ml in the serum concentration of TCZ was associated with an OR of 1.52 of being in a state of HAQ-DI remission ($p = 0.029$).

BMI inversely associates with an improvement in disease activity. Because the SC regimen uses a fixed dose instead of weight-based dosing, we analyzed whether the patients' BMI was associated with clinical response to treatment. Seventy-two percent of the patients had a BMI > 25 and the BMI of 30% of patients was > 30 (Figure 2A). An inverse association between BMI and change in CDAI score between Week 1 and Week 12 was found in a univariate linear model; for every decrease of 1 BMI unit, there was a corresponding improvement of 0.53 units in the change of CDAI score ($p = 0.043$). Figure 2B depicts change in CDAI score between Week 1 and Week 12 according to BMI categories. In a multivariate binary GEE model, the association between BMI and a state of CDAI remission or LDA versus moderate/high disease activity state did not reach statistical significance, but a trend was observed ($p = 0.074$).

TCZ levels associate inversely with BMI and weight. Because we found that TCZ levels associated with a better clinical response and that BMI associated inversely with a better clinical response, we checked whether a direct association exists between BMI and TCZ drug levels. We found that in a linear model, every increase of 1 BMI unit was associated

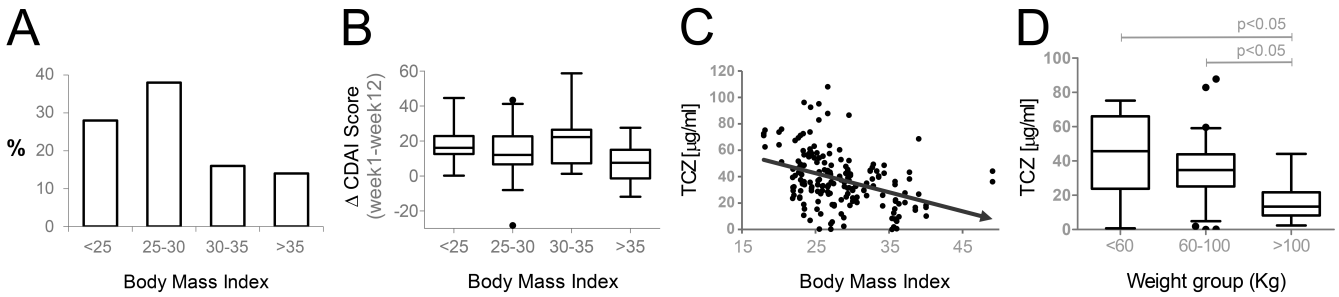

Figure 2. The relationship between clinical improvement and tocilizumab (TCZ) levels with body mass index (BMI) and weight. A. The distribution of patients' BMI by 5-point categories. B. Change in CDAI score between Week 1 and Week 12 according to BMI categories. A higher score represents a better improvement. Bars represent the median value, boxes the 25th–75th percentiles, and whiskers the 2.5th–97.5th percentiles. C. TCZ drug levels at Week 12 relative to BMI. The arrow represents the trend line ($y = –0.4934x + 29.972$, $R^2 = 0.037$). D. TCZ levels according to weight categories. Bars represent the median value, boxes the 25th–75th percentiles, and whiskers the 2.5th–97.5th percentiles. $P < 0.05$ according to Kruskal-Wallis test with Dunn's multiple posthoc comparison were considered significant. CDAI: Clinical Disease Activity Index.

with a decrease of 1.5 μg/ml in the serum TCZ concentrations ($p < 0.0001$). Figure 2C shows the relationship between BMI and TCZ drug levels.

We also analyzed TCZ levels according to weight groups (< 60, 60–100, > 100 kg). The TCZ concentrations were significantly lower in the > 100 kg weight group compared to the < 60 kg and the 60–100 weight groups (Figure 2D).

DISCUSSION

In this cohort of patients treated with once-weekly TCZ 162 mg SC injections for 24 weeks, an association was evident between the magnitude of clinical improvement (a greater decrease in CDAI score) and the trough concentrations of TCZ. None of the patients with TCZ levels < 10 μg/ml (10% of the cohort) reached a state of CDAI remission, and the majority of patients with TCZ levels > 60 μg/ml (6% of the cohort) were in either a state of LDA or remission. These results suggest that TCZ drug level monitoring might aid in tailoring treatment to improve outcomes of patients with RA. Further prospective studies or retrospective analyses of larger cohorts are indicated to determine optimal target drug levels. The results of our study suggest that TCZ drug levels should be titrated to > 10 μg/ml.

The association between obesity and a poor response to anti–TNF-α agents in rheumatologic patients has been reported repeatedly in published metaanalyses[16,17]. In contrast, the effect of obesity on the response to biological DMARD with other mechanisms of action has not been extensively evaluated yet. In a retrospective analysis of 222 RA patients treated with TCZ, the response to TCZ was not influenced by the baseline BMI[18]. A caveat to that study is that the clinical response was evaluated by DAS28-ESR, and as mentioned, normalization of the ESR levels is extremely responsive to TCZ treatment even in the face of an insufficient clinical improvement. Another retrospective study of 115 patients with RA also reported that BMI did not affect the response to TCZ[19]; none of the evaluated variables, including change from baseline in DAS28, pain on a visual analog scale, ESR and CRP levels, and tender and swollen joint counts, were different among the BMI categories. In that study the treatment regimen was a weight-based (8 mg/kg) monthly IV infusion as opposed to a fixed SC weekly dose of 162 mg of TCZ, and the proportion of obese (BMI > 30) patients was lower than in our cohort (22% vs 32%). Again, the response to treatment primarily focused on DAS28.

Two studies regarding treatment of RA patients with abatacept and one study relating to treatment with rituximab also found that BMI does not affect the response to therapy[20,21,22].

In contrast, in a univariate linear model analysis of the current cohort, an inverse association between change in CDAI score and BMI was demonstrated. This association did not reach statistical significance in a multivariate GEE model, but a trend toward significance ($p = 0.074$) was observed. These results are in accord with the lower response to TCZ treatment in patients who weighed > 100 kg relative to patients weighing < 100 kg, as was observed in the SUMMACTA study[12]. The authors speculated that this might be due to the smaller number of patients in this weight category. In our study, a significant difference in the change in CDAI score was not found between weight groups (not shown), perhaps because of a smaller study population.

More recently, a pharmacodynamics and pharmacokinetics study of the data from the SUMMACTA and BREVACTA trials was published[14]. In this analysis, with SC dosing, increase in body weight was associated with lower TCZ trough concentrations. Weight was the only strong covariate that influenced both TCZ clearance and volume of distribution variables, and the observed TCZ trough concentrations were lower in patients in the > 100 kg weight category relative to the < 60 kg and 60–100 kg weight categories. The authors concluded that the regimen of 162 mg every 2 weeks in patients weighing > 100 kg resulted in subtherapeutic drug exposure and clinical responses not different from placebo. These results are concordant with the findings of our study.

The study population in our study was not large enough to enable analysis regarding differences in adverse/side events by TCZ trough concentration. In the paper by Abdallah, *et al* that analyzed the combined data of the SUMMACTA and BREVACTA studies (1699 patients), there was no apparent association between increasing TCZ exposure and occurrence of adverse events, including infections and infestations, for any of the dosing schedules[14].

In the USA, in patients weighing < 100 kg, SC TCZ is dosed at 162 mg every 2 weeks and the dose is increased to once a week according to clinical response, while patients who weigh more are initiated with a once-a-week injection. Prospective trials are needed to determine whether therapeutic drug monitoring or adjusted weight-based dosing regimens can improve or hasten clinical responses, as opposed to the current practice.

This study demonstrates a relationship between TCZ trough concentrations and clinical improvement in patients with RA commencing treatment with TCZ. Patients with higher BMI values or who weighed > 100 kg had lower TCZ levels. These results raise the possibility that in patients with an inadequate response to TCZ treatment, especially obese ones, the clinical outcomes might be improved by monitoring and adjusting TCZ drug levels.

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We thank the Roche Global Product Development Medical Affairs Data Sharing Team for the TASC study datasets. Qualified researchers may request access to individual patient level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Further details on Roche's criteria for eligible studies are available online (clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx). 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 www.roche.com/

research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm.

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