Association of serum Tocilizumab trough concentrations with clinical disease activity index scores in adult rheumatoid arthritis patients.

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Running head: Tocilizumab levels and CDAI

ABSTRACT

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

Methods: We analyzed data sets 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 patients characteristics and TCZ levels.

Results: A significant association between the TCZ concentrations and the change in the CDAI score was observed. In a multivariate binary GEE model, every increase of 10 μg/ml in the concentration of TCZ was associated with an odds ratio of 1.41 of being in a state of CDAI remission or low disease activity versus moderate/high disease activity state, and with an odds ratio of 1.52 of being in a state of HAQ-DI remission.

In univariate linear models, there was an inverse association between BMI and improvement in the CDAI score and the BMI score was associated with lower TCZ concentrations. Patients that weighed more than 100 kg had lower TCZ concentrations.

Conclusion: In the first 24 weeks of treatment with SC TCZ injections, TCZ concentrations are associated with clinical improvement, while body weight and BMI are inversely associated with TCZ concentrations. Personalizing the dose of SC TCZ to body weight may improve outcomes of clinical disease activity in RA patients.

INTRODUCTION

In patients with rheumatoid arthritis (RA) treated with monoclonal antibody TNFα inhibitors, the association between the serum drug trough concentrations and the clinical response to treatment is well established (1,2). Additionally, the development of anti-drug antibodies (ADAs) to monoclonal antibody TNFα inhibitors, 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 (3–6).

Tocilizumab (TCZ) is a monoclonal antibody directed against the 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 ADAs, 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 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 below 10 μg/ml (n=84) and above 10 μg/ml (n=42), found a statistically significant difference between groups in the 28-joint Disease Activity Score (DAS28)

after 6 months of treatment (3.09±1.32 vs 2.78±1.32, respectively) (10). In an observational study of 66 consecutive RA patients treated with IV TCZ 8 mg/kg once every 4 weeks, serum trough concentrations above 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. Since 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 which 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) and in the BREVACTA study, SC TCZ 162 mg every 2 weeks was tested against placebo (13). In a recently published pharmacokinetic and pharmacodynamic analysis of these trials, in patients treated by SC injections, the clinical response increased with increasing TCZ trough concentrations exposure quartiles, with the efficacy parameters plateauing past the first quartile (mean C_{trough} ~15 μg/ml) in the every-week SC injection regimen (14).

To further study the relationship between TCZ trough concentrations and clinical outcomes in RA patients 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 "real-life" RA patients commencing TCZ treatment (15). The cohort consisted of 100 RA patients who were periodically evaluated until week 24 and the serum trough drug-concentrations and levels of soluble IL6 receptor (sIL6R) were measured at week 12 and week 24. Analyses were performed to identify parameters that may affect clinical outcomes and drug levels.

MATERIALS AND METHODS

We analyzed data sets of the Israeli branch (TASC, NCT01988012) of the Roche multinational umbrella study TOZURA, which evaluated a SC TCZ treatment regimen of 162 mg once weekly as monotherapy or in combination with methotrexate or other csDMARDs in a real-life clinical setting (15). The study enrolled 100 patients. The anonymized data sets were kindly provided by the Roche Global Product Development Medical Affairs Data Sharing Team.

Study design and setting: Briefly, this was a multi-center, open-label single-arm study performed at 13 medical centers in Israel between January 2014 and July 2015, which 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 committee as required by Israeli Ministry of Health regulations.

Study population: Study participants were adults (≥18 years of age) with a diagnosis of active RA according to the revised (1987) ACR or European League Against Rheumatism (EULAR)/ACR (2010) criteria who received treatment on an outpatient basis (not including tocilizumab), and who were either previously treated with 3 DMARDs, and were 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 or current inflammatory joint disease other than RA.

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. 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 ≥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 tocilizumab.

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: Linear regression analysis and generalized estimating equations were used to evaluate associations between TCZ levels and the study outcomes (Change in CDAI scores, Change in HAQ scores, CDAI remission/low disease activity status, and HAQ DI remission). Generalized estimating equations 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 below 0.05 were considered significant. Analyses were performed with IBM® SPSS® Statistics software, version 24.

Differences between TCZ levels with weight categories were analyzed with the Kruskal-Wallis test with Dunn's post-hoc 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 of RA patients that were enrolled in the TOZURA study included 100 patients of whom 80 were female, and with a mean age of 54.3 years (SD 11.8). Sixty-five patients had an inadequate response to treatment with conventional disease-modifying anti-rheumatic drugs (DMARDs) and 35 patients did not adequately respond to treatment with biological DMARDs. At baseline, the mean ± SD disease activity scores according to CDAI, SDAI and DAS28-ESR, were 31.9 ± 14.4, 33.7 ± 14.8 and 5.0 ± 1.0, respectively. At 12 weeks, four 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 above 10 μg/ml (Fig. 1A) at 12 weeks.

Since 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 which is 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 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. Furthermore, also after including the factors, body mass index (BMI), sex, concomitant MTX, seropositivity (anti-CCP or RF), screening CRP levels, centered baseline CDAI scores and TCZ trough concentration in a multivariate linear model, the associations between TCZ levels and the change in CDAI scores remained significant. 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 odds ratio of 1.41 of being in a state of CDAI remission or low disease activity versus moderate/high disease activity state (p=0.001, Fig. 1C). In addition, every increase of 10 μg/ml in the serum concentration of TCZ was associated with an odds ratio of 1.52 of being in a state of HAQ-DI remission (p=0.029).

BMI inversely associates with an improvement in disease activity.

Since 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 above 25 and the BMI of 30% of patients was above 30 (Fig. 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 low disease activity 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.

Since we found that TCZ levels associate 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 one BMI unit was associated 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 (Fig. 2D).

DISSCUSSION

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 below 10 μg/ml (10% of the cohort) reached a state of CDAI remission and the majority of patients with TCZ levels above 60 μg/ml (6% of the cohort) were either in a state of low disease activity or remission. These results suggest that TCZ drug level monitoring might aid in tailoring treatment to improve outcomes of RA patients. Further prospective studies or retrospective analyses of larger cohorts are indicated to determine optimal target drug levels. The results of this study suggest that TCZ drug levels should be titrated to above 10 μg/ml.

The association between obesity and a poor response to anti-tumor necrosis factor-α (TNF) agents in rheumatologic patients has been reported repeatedly in published meta-analyses (16,17). In contrast, the effect of obesity on the response to biological DMARDs 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 this study is that the clinical response was evaluated by DAS28-ESR, and as previously 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 RA patients also reported that BMI did not affect the response to TCZ (19); none of the evaluated parameters, including change from baseline in DAS28, pain on a visual analog scale, erythrocyte sedimentation rate and C-reactive protein level, 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 did not that find that BMI affects the response to therapy (20–22).

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 towards significance ($p=0.074$) was observed. These results are in accord with the lower response to TCZ treatment in patients who weighed above 100 kg relative to patients weighing less than 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 due to a smaller study population.

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 parameters and the observed TCZ trough concentrations were lower in the >100 kg weight patients category relative to the <60 kg and 60-100 kg weight categories.

The authors concluded that 162 mg every-2-weeks regimen in patients weighing more than 100 kg, resulted in sub-therapeutic 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 less 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.

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

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We thank Roche for the TASC study data sets. 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 here (https://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 here (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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FIGURE LEGENDS:

Figure 1: Tocilizumab 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 state) relative to TCZ levels.

Figure 2: The relationship between Clinical improvement and TCZ levels with 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 to 75th percentiles and whiskers the 2.5^{th} to 97.5^{th} percentiles. **(C)** TCZ drug levels at week 12 relative to BMI. The red line 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 to 75th percentiles and whiskers the 2.5th to 97.5th percentiles. $P<0.05$ according to Kruskal-Wallis test with Dunn's multiple post-hoc comparison were considered significant.