Relationship Between Baseline and Early Changes in C-Reactive Protein and Interleukin-6 Levels and Clinical Response to Tocilizumab in Rheumatoid Arthritis

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Objective. To clarify the relevance of measuring interleukin-6 (IL-6) and C-reactive protein (CRP) levels in order to predict clinical response to tocilizumab (TCZ) in rheumatoid arthritis patients.

Methods. In a pooled, post hoc analysis of 5 pivotal trials of TCZ, we examined the distributions of baseline serum concentrations of IL-6 and CRP, stratified by randomized treatment group, and week 24 Disease Activity Score in 28 joints (DAS28) status (DAS28 <2.6 versus DAS28 ≥2.6). Relationships between early biomarker changes and later changes in DAS28 scores were evaluated using Spearman’s correlations and scatterplots. Finally, percentage changes from baseline in IL-6 and CRP levels were evaluated.

Results. Distributions of baseline IL-6 and CRP levels were similar for patients who achieved DAS28 scores <2.6 within 6 months of TCZ initiation and those who did not. Correlations between early changes in these 2 biomarkers and change in DAS28 scores were low (rho < 0.3 for all). Mean percentage increases from baseline in IL-6 concentrations were observed in all treatment groups (highest in the 8 mg/kg dose group); mean percentage decreases in CRP concentrations were greater at week 2 and at all visits for the 8 mg/kg dose group.

Conclusion. Baseline serum concentrations of IL-6 and CRP may not be predictive of clinical outcomes after TCZ treatment. Data demonstrate the efficacy of TCZ in patients across a broad range of baseline serum IL-6 and CRP concentrations. Similarly, changes in these biomarkers after TCZ dosing are expected and may or may not correspond to changes in other clinical signs and symptoms. These results complement previous reports describing the complex interactions among biomarker changes, other therapeutic mechanisms of action, and clinical outcomes.

Introduction
In the past 15 years, therapeutic options for patients with rheumatoid arthritis (RA) have grown extensively; 9 biologic therapies and 1 novel oral medication have been approved by the US Food and Drug Administration, allowing physicians and patients more choices for disease control. However, because of the heterogeneity of RA and differences in the targeted mechanisms of action of the drugs, not every patient will respond initially or maintain response to a given therapy. The American College of Rheumatology and the European League Against Rheumatism recommend treat-to-target as a standard of care (1–3).

Supported by Hoffmann-La Roche and Genentech.
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Submitted for publication June 9, 2015; accepted in revised form October 13, 2015.

Implicit in this approach is the maintenance of tight disease control, influenced by regular assessments of disease activity, which may require switching therapies. At the same time, interest has been growing in identifying biomarkers to help clinicians stratify patients and match them to personalized, efficacious treatment options (4).

Given the targeted nature of modern medicines, the rheumatologist is tempted to attribute prognostic relevance to serum markers thought to be associated with disease. However, given the complexity of the immunologic networks that drive RA, limited progress has been made in identifying generalized or treatment-specific biomarkers. Progress has also been restricted by the intrinsic impact of a treatment’s specific mechanism of action. Wang et al (5) attempted to address these constraints by investigating the molecular pathway of the target of tocilizumab (TCZ) therapy but found that the variation in pathway activity, as measured in blood, may not be a strong predictor of treatment response in RA.

The copyright line for this article was changed on 14 August 2018 after original online publication.
TCZ is a recombinant, humanized, anti–human monoclonal antibody directed against the soluble interleukin-6 receptor (sIL-6R) and the membrane-bound IL-6 receptor (mIL-6R). IL-6 is a proinflammatory, multifunctional cytokine produced by a variety of cell types and involved in diverse physiologic and immunologic processes. Moreover, elevated tissue and serum levels of IL-6 have been implicated in the pathology of several inflammatory and autoimmune disorders, including RA. TCZ has been shown to inhibit sIL-6R– and mIL-6R–mediated signaling (6). Inhibition of this signaling is associated with the rapid reduction of acute-phase reactants, such as C-reactive protein (CRP) levels, and the elevation of serum IL-6 levels after TCZ dosing (7).

Although identifying predictive biomarkers is a desirable endeavor, equally important is the consideration of how an individual drug can be differentiated according to its mechanism of action (8). One might argue that recognizing the nonpredictive nature of otherwise “obvious” targets is imperative in order to avoid unnecessary expense and lost time (time during which a patient’s disease could progress). The objective of this brief report is to describe the relevance of measuring IL-6 and CRP levels in the context of patient selection and clinical response prediction for TCZ therapy.

**Significance & Innovations**

- The interaction between the mechanism of action and biomarkers is often assumed to be correlated with clinical effects, but may not be.
- Baseline values of C-reactive protein (CRP) and interleukin-6 (IL-6) are not predictive of clinical outcomes after tocilizumab (TCZ) treatment.
- Changes in CRP and IL-6 levels after TCZ treatment may or may not correspond to changes in other clinical signs and symptoms.

**Patients and methods**

Detailed descriptions of the pivotal trial study designs, patient populations (n = 4,186 randomized), and results that demonstrated the efficacy and safety of TCZ, leading to its initial approval for the treatment of patients with RA, have been published previously (9–13). In brief, clinical signs and symptoms were measured at baseline and every 4 weeks thereafter; CRP levels were measured at baseline, at weeks 2 and 4, and then every 4 weeks thereafter; and IL-6 was measured in all patients at baseline, at week 12, and at week 24. All serum samples except those at week 2 were drawn just before dosing. In this post hoc analysis, distributions of baseline serum concentrations of IL-6 and CRP, stratified by randomized treatment group, and week 24 Disease Activity Score in 28 joints (DAS28) status (did or did not achieve DAS28 <2.6) were examined using box plots. Spearman’s correlations and scatterplots were used to evaluate relationships between early changes in these biomarkers versus later changes in DAS28 status. Finally, means and 95% confidence intervals for percentage changes from baseline in IL-6 and CRP levels were estimated by visit and treatment group. Patients were analyzed according to their randomized assignment.

**Figure 1.** Interleukin-6 (IL6) serum concentrations during study treatment with tocilizumab (TCZ) 8 mg/kg with or without a concomitant disease-modifying antirheumatic drug (DMARD), TCZ 4 mg/kg plus DMARD, or placebo (intravenous [IV]) plus DMARD. A, Box plot showing similar distributions of baseline (BL) IL-6 levels by treatment arm and week 24 Disease Activity Score in 28 joints (DAS28) status. B, Scatterplot with Spearman’s rank correlation for change from BL to week 12 in IL6 levels versus change from baseline to week 24 in DAS28 status. C, IL6 mean percentage change from baseline with 95% confidence interval by visit.
treatment groups. DAS28 status was assessed using non-responder imputation: patients with missing data were counted as having DAS28 \( \geq 2.6 \). DAS28 change from baseline was analyzed as observed, except in the event of patient escape, when scores were set to missing. CRP and IL-6 biomarkers were analyzed as observed, with no imputation for missing data, and IL-6 values below the limit of quantitation were set at the lower limit (3.13 pg/ml).

**Results**

Mean \( \pm \) SD baseline CRP levels were 2.6 \( \pm \) 3.2 mg/dl (elevated as per the inclusion criterion), and mean \( \pm \) SD baseline IL-6 levels were 40.1 \( \pm \) 59.50 pg/ml. Neither baseline nor change from baseline level of CRP or IL-6 was associated with clinical response to TCZ in the 4 mg/kg or 8 mg/kg doses. Distributions of baseline CRP and IL-6 values were similar for patients who did and did not achieve DAS28 \( \geq 2.6 \) at week 24 (Figures 1A and 2A), and no meaningful correlations or other obvious associations were observed between early changes in these 2 biomarkers and change in DAS28 to week 24 in any treatment group (all rho \( \leq 0.30 \)).

**Discussion**

These results hold important implications for clinical practice. Although it might seem intuitive that IL-6 or CRP levels would have predictive value in identifying patients more likely to respond to the unique mechanism of action of TCZ, here we show that the baseline values of these biomarkers are not predictive of clinical outcomes after TCZ treatment. Data demonstrate that TCZ can be efficacious in patients across a broad range of serum IL-6 and CRP concentrations at baseline. Similarly, dramatic changes in these biomarkers after dosing are expected for many patients and may or may not correspond to changes in other clinical signs and symptoms. These results are similar to a previous study with TCZ. CRP levels were normalized during treatment; however, remission rates were comparable when disease activity was analyzed using an index that included CRP (Simplified Disease Activity Index) or did not include CRP (CDAI) (14,15). This study is only one example of the complex interactions between key inflammatory mediators in RA that can be further complicated by the diversity of therapeutic mechanisms of action, making identification of predictive biomarkers challenging. The lack of effective biomarkers at this stage to predict clinical response to any treatment has been highlighted by others (8). In the meantime, the rheumatologist is left to rely on evaluating therapeutic response through comprehensive clinical assessments of how the disease is progressing and how the patient feels and functions.

**Figure 2.** C-reactive protein (CRP) serum concentrations during study treatment with tocilizumab (TCZ) 8 mg/kg with or without a concomitant disease-modifying antirheumatic drug (DMARD), TCZ 4 mg/kg plus DMARD, or placebo (intravenous [IV]) plus DMARD. A, Box plot showing similar distributions of baseline (BL) CRP by treatment arm and week 24 DAS28 status. B, Scatterplot with Spearman’s rank correlation for change from BL to week 4 in CRP levels versus change from BL to week 24 in DAS28 status. C, CRP mean percentage change from BL with 95% confidence interval by visit.
AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Devenport had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Wang, Devenport, Low, Yu, Hitraya.
Acquisition of data. Wang, Devenport, Low, Yu, Hitraya.
Analysis and interpretation of data. Wang, Devenport, Low, Yu, Hitraya.

ROLE OF THE STUDY SPONSOR

Hoffmann-La Roche and Genentech sponsored this post hoc analysis using existing data from earlier pivotal studies conducted by Roche. Publication of this article was not contingent upon approval by Hoffmann-La Roche and Genentech.

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