Comment on 'Implication of baseline levels and early changes of C-reactive protein for subsequent clinical outcomes of patients with rheumatoid arthritis treated with tocilizumab'

We read with interest the article 'Implication of baseline levels and early changes of C-reactive protein for subsequent clinical outcomes of patients with rheumatoid arthritis treated with tocilizumab' by Shafran et al.[1] This was an exploratory analysis of multiple studies and concluded that baseline C-reactive protein (CRP) and its early course may inform, to some extent, the estimation of potential therapeutic success in patients with rheumatoid arthritis (RA) treated with tocilizumab. Although we appreciate the pursuit of personalised treatment decisions in RA, this conclusion is not the only interpretation, and previously published analyses of these data further characterise the relationship between CRP and clinical outcomes with tocilizumab treatment in patients with RA.[2]

Shafran et al[1] concluded that baseline and early changes in CRP levels are predictive of tocilizumab response. Although CRP levels were affected differently by tocilizumab than rituximab or methotrexate treatment, decreasing to near zero in tocilizumab-treated patients, the data show some independence between CRP and clinical outcomes and demonstrate the potential influence of disease activity on clinical outcomes. Figure 1 presents mean percentage change in CRP levels and Clinical Disease Activity Index (CDAI) over time.[1] In the tocilizumab group, percent change in CRP was numerically larger than percent change in CDAI, implying some independence of the two variables. In the methotrexate group, percent change in CRP was smaller than percent change in CDAI, also suggesting some independence of the two variables. In the rituximab group, percent changes in CRP and CDAI were similar.

Figure 2 presents mean CRP values at baseline and week 4 for patients achieving remission/low/medium/high CDAI at week 24.[1] The error bars overlap within treatment groups, implying no statistical differences; however, the authors conclude that early CRP levels predict response to tocilizumab.

Figure 3 presents mean CRP values over time for patients achieving remission/low/medium/high CDAI at week 24.[1] In the tocilizumab group, the curves are close together (error bars would be expected to overlap) because CRP levels are reduced in nearly all patients. This implies that the impact of CRP on clinical outcomes is removed early with tocilizumab treatment and that clinical response is based on treatment effectiveness and other factors, as shown in Figure 4.[1] In all treatment groups, mean disease activity is consistent with the week 24 outcome category; for example, patients with high disease activity at week 24 tend to have the highest mean disease activity throughout. This suggests a relationship between baseline and week 24 disease activity, as recently quantified.[3]

Figure 5 presents ORs for achieving CDAI remission at various CRP level cutpoints (a), comparison between treatments of ORs for achieving CDAI remission at various CRP cutpoints (an approach that cannot be clearly interpreted for these nonrandomised treatment groups) (b), and comparison between randomised treatment arms from a validation sample of ORs for achieving CDAI remission at various CRP level cutpoints (c).[1] In (a), the 95% CIs cross 1.0 for all CRP cutpoints with tocilizumab, suggesting that there is an equal likelihood of attaining CDAI remission above or below threshold. In (c), the likelihood of achieving CDAI remission is higher with tocilizumab than methotrexate, regardless of baseline CRP level, and, based on overlapping CIs, there is a similar likelihood of achieving CDAI remission in patients treated with methotrexate combined with tocilizumab versus tocilizumab alone at all baseline CRP levels.

Overall, these results are consistent with previous analyses of randomised controlled trials in which relationships between biomarkers and outcomes were summarised at the group level and at individual patient levels.[2] Serum CRP level changes after tocilizumab dosing are expected for most patients but occur independently of changes in other clinical signs and symptoms, and tocilizumab can be efficacious across a broad range of baseline CRP concentrations. Decrease in CRP levels is a pharmacodynamic marker of tocilizumab treatment but neither a surrogate for clinical activity nor a reliable predictor of clinical outcomes. This is relevant to the practising clinician, who should continue to make decisions for patients with RA treated with tocilizumab based on clinical and symptomatic response.

Attila Pethoe-Schramm,[1] **Jenny Devenport** ,[2] **William Reiss**[3]

[1]Product Development Medical Affairs, F Hoffmann-La Roche AG, Basel, Switzerland
[2]Product Development Biostatistics, F Hoffmann-La Roche AG, Basel, Switzerland
[3]United States Medical Affairs, Genentech, South San Francisco, California, USA

Correspondence to Dr Jenny Devenport, F Hoffmann-La Roche AG, Basel 4053, Switzerland; jenny.devenport@roche.com

Check for updates

Linked

► http://dx.doi.org/10.1136/annrheumdis-2020-218403

ORCID iD
Jenny Devenport http://orcid.org/0000-0003-0816-6075

REFERENCES

1 Shafran IH, Alasti F, Smolen JS, *et al*. Implication of baseline levels and early changes of C-reactive protein for subsequent clinical outcomes of patients with rheumatoid arthritis treated with tocilizumab. *Ann Rheum Dis* 2020;79:874–82.

2 Wang J, Devenport J, Low JM, *et al*. Relationship between baseline and early changes in C-reactive protein and interleukin-6 levels and clinical response to tocilizumab in rheumatoid arthritis. *Arthritis Care Res* 2016;68:882–5.

3 Rubbert-Roth A, Aletaha D, Devenport J, *et al*. Effect of disease duration and other characteristics on efficacy outcomes in clinical trials of tocilizumab for rheumatoid arthritis. *Rheumatology*.