

Response to: '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" by Pethoe-Schramm *et al*

We would like to thank Dr Pethoe-Schramm and colleagues for their comment on our paper¹ and the diligent assessment of the data we presented.² The authors addressed each of our Figures sequentially and, therefore, it will be a pleasure to respond here accordingly.

Before doing so, we would like to mention that in contrast to other studies, like the one by Wang *et al*³ which we also referred to in our paper, we approached the analyses by using Clinical Disease Activity Index (CDAI) remission criteria (endorsed by ACR-EULAR for this purpose) rather than "remission" criteria by the Disease Activity Score using 28 joint counts (DAS28).^{4,5} As often described, DAS28 <2.6 is an inappropriate remission endpoint because many patients still have residual swollen joints which are drivers of joint damage.^{6,7} Moreover, acute phase reactants are highly weighted in the formula.^{8,9} Consequently, DAS28 remission rates are exaggerated and misleading in the context of interleukin-6 (IL-6) inhibition by cytokine receptor inhibitors like tocilizumab or pathway inhibitors like Janus kinase inhibitors;^{10,11} moreover, these issues cannot be overcome by lowering the threshold for the remission cutpoint.^{5,12} Finally, since DAS28 includes an acute phase reactant, using it as an outcome to evaluate the role of C-reactive protein (CRP) cannot be seen as independent of CRP and, therefore, may be circular.

Equally importantly, we did not start by asking the question of the 'distribution of baseline... concentrations of...CRP' in relation to achieving DAS28 <2.6 or not, but rather asked the question, which CRP-levels those patients who achieved stringent remission at endpoint had at baseline and compared this with baseline CRP levels in patients who had other disease activity states at endpoint and not just non-remission. Thus, our research question, although covering similar aspects, tackled the data differently than other studies.

Figure 1 of our paper¹ shows a parallel reduction of levels of CRP and CDAI for rituximab (RTX) but not for tocilizumab (TCZ) where CRP-levels decrease much more dramatically than CDAI levels. As Pethoe-Schramm *et al* mention, this is an implication of some independence of the two variables, and also reiterates what is already known from the tocilizumab clinical trials^{13,14} and our previous work¹⁰ that on IL-6R blockade CRP may normalise independently of clinical improvement, which is neither the case for RTX nor methotrexate (MTX).

In Figure 2 of our paper the CIs indeed, overlap, but as indicated in the results and figure legend, the differences across the disease activity states were highly significant by Kruskal-Wallis test across the three disease activity groups for all variables and all treatment types. Importantly, however, while all other variables and all treatment types had the same direction of association across the various disease activity states, the direction was the reverse only for the CRP data in the TCZ treated population, while in RTX and MTX patients CRP association was again the same as seen with all other measures. Indeed, during the review process we were asked to show the results for other single variables and have chosen pain as an example, because pain, like CRP is not included in the CDAI. As expected and in line with the CDAI data, pain changes behaved opposite to CRP changes for TCZ but not RTX or MTX.

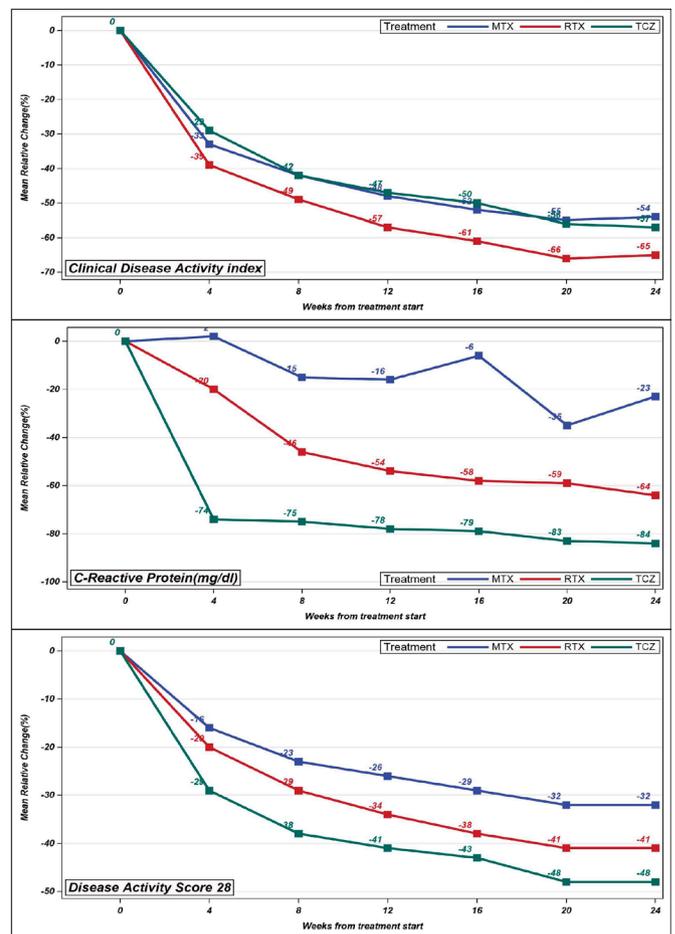


Figure 1 Changes of CDAI, CRP and DAS28 from baseline to 24 weeks for tocilizumab (TCZ), rituximab (RTX) and methotrexate (MTX). As can be seen, DAS28 changes parallel CRP changes for TCZ but not for MTX and RTX. This is not a comparative analysis of efficacy, but just to illustrate the differences of using different instruments. RTX and MTX come from the same trial in early rheumatoid arthritis patients and TCZ data come from a pool of three trials in patients with insufficient response to MTX, as detailed in the original paper.¹ Please note that for reasons of better clarity the scale of each panel is different. CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS28, disease activity score using 28 joints and erythrocyte sedimentation rate.

With respect to Figure 3 of our publication, let us please reiterate what this Figure has been developed for, namely to show the different behaviours of CRP levels in patients who reach different states at endpoint when being treated with TCZ versus other agents. In those reaching remission, TCZ led to a most dramatic and early change of CRP compared with other states and compared with other drugs (Figure 3 B, D, F in our paper).¹ This is in stark contrast to CDAI changes which were shown there in Figure 4. Just to reiterate: patients in remission start with the highest CRP levels and end with the lowest CRP levels when TCZ is used, while on RTX and MTX patients reaching remission have the lowest CRP level from beginning to end. And this is true for all drugs when the CDAI is used, thus, again, revealing the difference between CRP changes and clinical changes when TCZ is applied.

We agree with Pethoe-Schramm *et al* that in Figure 5 CIs cross 1 which is a matter of power.¹ However, our analyses revealed consistently that patients treated with TCZ had the best odds of

achieving remission with high CRP levels compared with lower ones while this was not the case for RTX and MTX. We had determined that with increasingly higher definitions of 'elevated' CRP (eg, cutpoint of ≥ 4 mg/dL) TCZ efficacy increased relative to patient with not or less 'elevated' CRP levels, which was also confirmed in a sensitivity analysis from a separate trial (Figure S1).¹

We would like to come back to the issue of using DAS28 or DAS28-based states as outcomes in trials of tocilizumab. In the FUNCTION trial TCZ monotherapy conveyed significant differences compared with MTX monotherapy when using DAS28 remission, but not CDAI, Simplified Disease Activity Index (SDAI) or even ACR responses,¹⁵ and we have pointed out the fallacy of this score in a recent review.¹⁶ To provide Pethoe-Schramm *et al* as well as the readers with some additional information why we feel the value of baseline CRP levels for TCZ treatment may have escaped previous investigations, we have now complemented the data of our paper with DAS28 changes over time. As depicted in figure 1 accompanying this response, we saw a similar pattern for DAS28 as for CRP, but not CDAI, with TCZ which was different from the data observed with RTX and especially MTX (Figure 1).

In summary, we fully agree with Pethoe-Schramm *et al* that rheumatologists should make their treatment decisions based on clinical disease activity (and, as exemplified again here, by using the CDAI). Indeed, regular *clinical* assessment is part and parcel of the treat-to-target and EULAR rheumatoid arthritis (RA) management recommendations,^{17 18} where the use of ACR-EULAR remission criteria is also addressed. While on the group level of all patients enrolled in clinical trials of RA TCZ has comparable efficacy to other biologics,^{19 20} our data suggest that those with the highest CRP values will fare even better on TCZ than they might do on other drugs. This is the essence and novelty of our findings, and a step into precision medicine to support treatment selection in clinical practice, which—although only weak overall—is ultimately shown for CRP here: positive association with later outcomes for one drug, and an inverse (negative) one for other drugs. Whether this finding also holds up in clinical practice or is just a result of a post-hoc analysis of clinical trial data, will have to be seen in future in prospective investigations.

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