Longitudinal versus cross-sectional IL-6 measurements in tocilizumab-treated GCA. Response to: 'Analysis of IL-6 measurement in GCA patients treated with tocilizumab should consider concomitant treatment with prednisone' by Samson and Bonnotte

We thank Samson and Bonnotte¹ for their interest in our study on longitudinal interleukin 6 (IL-6) measurements in tocilizumab (TCZ)-treated giant cell arteritis (GCA) patients. The authors' measured IL-6 blood levels in GCA before and after a treatment with glucocorticoids and a 3-month course of TCZ. They confirm the suppression of acute phase proteins (c-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and fibrinogen) and the increase in serum IL-6.^{2,3} The patients with higher IL-6 levels at 12 weeks were not more likely to relapse after TCZ stop than those with lower levels. This is in line with our data (as well as Gloor *et al*²), as absolute levels were also not associated with relapse outcome in our study (median 38.3 vs 36.1 vs 39.8 pg/mL for 'no', 'early' and 'late relapse').³ Instead, we found that a *longitudinal decline* (ie, the slope over several measurements) of IL-6 levels during therapy related to later relapses. Since Samson and Bonnotte did not analyse longitudinal measurements, the direct comparison is not possible.

A challenge in the interpretation of cross-sectional IL-6 measurements is the high interindividual variability. Therefore, serial measurements are critical, also to detect individual IL-6 peaks that may indicate infections or relapses. Samson and Bonnotte suggest that the prednisone dose may be a significant driver of interindividual IL-6 variability. We performed an additional analysis of our data (figure 1). Median IL-6 levels after the peak following the first TCZ dose were non-significantly higher in subjects receiving ≥ 20 mg versus < 20 mg daily prednisone (72.3 vs 44.4 pg/mL, $p=0.064$). The last measured IL-6 was comparable in those having > 5 mg prednisone and those with less than 5 mg (42.1 vs 32.6, $p=0.47$). IL-6 levels trended to be higher in the > 70 years old patients before TCZ was stopped (53.4 vs 36.1 pg/mL, $p=0.062$). This age-effect was less pronounced at the early time-point (66.9

vs 45.4 pg/mL, $p=0.39$). There was a weak direct correlation between the prednisone dose and the early IL-6 level ($r=0.51$, $p=0.008$). Combined, we found no evidence in our cohort, that higher prednisone doses explain lower IL-6 levels. The impact of age on IL-6 levels needs to be further explored.

The differences in the overall magnitude of IL-6 levels between the study of Samson and Bonnotte and our study may relate to the method and samples used. Samson and Bonnotte describe a Luminex-based assay without specifying assay validation and whether fresh or cryopreserved samples were used. We did all measurements direct ex vivo as part of the clinical routine. We use an electrochemiluminescence method (ElecSys) with a lower detection limit of < 7 pg/mL. The assay is standardised and validated for the clinical use.

Finally, we studied a patient cohort with a high frequency of previous relapses and steroid-sparing therapies. In contrast, Samson and Bonnotte describe findings from a trial of previously untreated GCA patients with a short course of TCZ in addition to prednisone. The longer treatment duration and repeated sampling allowed longitudinal IL-6 measurement and hence, assessment of the slopes that correlated with outcome after stopping TCZ.

In absence of reliable blood or imaging biomarkers to assess disease activity during TCZ therapy,⁴ it is worth to further explore the role of serial IL-6 measurements in larger patient cohorts.

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Figure 1 Stratification of interleukin 6 (IL-6) blood levels based on daily cortisone dose or age. IL-6 plasma levels in subjects: (A) receiving or ≥ 20 mg of daily prednisone (PDN) in early time-points (left) and before tocilizumab (TCZ) was stopped (right); (B) younger versus older than 70 years of age. (C) Correlation matrix of: 'n TCZ'=total numbers of TCZ doses received, IL-6 after the second dose and IL-6 before TCZ was stopped, as well as daily prednisone doses at the time of TCZ start and discontinuation. Values indicate Spearman r correlation coefficients. 'PDN at start' versus 'IL-6 after second dose' ($p=0.008$), 'PDN at stop' versus 'n TCZ' ($p=0.042$) and 'IL-6 after second dose' versus 'at TCZ stop' ($p=0.029$) were significant.

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