Analysis of IL-6 measurement in patients with GCA treated with tocilizumab should consider concomitant treatment with prednisone

We read with great interest the letter published by Berger *et al* in which the authors showed that relapse-free survival for giant cell arteritis (GCA) treated with tocilizumab (TCZ) was longer in patients with an interleukin (IL) 6 decline (slope ≤0.1).[1]

In contrast with Berger *et al*,[1] IL-6 levels at the last TCZ infusion were not found to predict the risk of relapse in our phase 2 prospective open-label clinical trial that included 20 patients with GCA (19/20 patients with new-onset GCA) treated with prednisone and TCZ (8 mg/kg/4 weeks from inclusion to week 12 (W12)). These patients were followed for 52 weeks, and IL-6 levels were monitored by luminex (eBioscience) at inclusion (W0), W12 and W26.[2] As a consequence of the blockade of the IL-6 pathway, acute-phase reaction proteins (erythrocyte sedimentation rate, C-reactive protein and fibrinogen) remained in the lowest range during the TCZ treatment period (figure 1A). Similar to Berger's study, the median (IQR) IL-6 concentration increased from 1.5 (1.5–12.7) at W0 to 20.6 (8.3–38.5) pg/mL at the last TCZ infusion (W12) (p=0.021; figure 1B), but this increase was less significant than the increase reported by Berger CT *et al*.[1] About 3 months after TCZ was discontinued (W26), median (IQR) IL-6 concentration had normalised to 1.5 (1.5–1.5) pg/mL (figure 1B). In our study, 2/6 (33.3%) patients with low serum IL-6 (< 12.9 pg/mL) at W12 relapsed during the follow-up period versus 8/13 (61.5%) patients with high IL-6 (≥12.9 pg/mL) at week 12 which did not reach significance (p=0.35). As suggested by Berger CT *et al*,[1] we also distinguished between non-relapsers, early relapsers (<90 days post-TCZ cessation) and late relapsers (>90 days post-TCZ cessation), but median IL-6 at TCZ cessation (W12) was not significantly different in the three groups: 24.7 vs 35.8 vs 19.5 pg/mL (p=0.64; figure 1C).

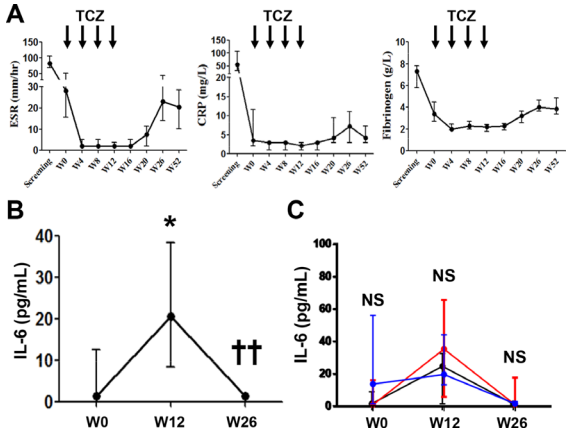

Figure 1 (A) Monitoring of acute-phase response in 20 patients with giant cell arteritis treated with prednisone and tocilizumab. (B) Median±IQR concentrations of IL-6 at week 0 (W0), W12 and W26. Wilcoxon rank tests were performed to compare data between W0 and W12 (*p<0.05; p<0.01) and between W12 and W26 (p<0.05; ††p<0.01) (C) Median±IQR concentrations of IL-6 at W0, W12 and W26 in early relapsers (red line), late relapsers (blue line) and non-relapsers (black line). Data were compared with Kruskal-Wallis tests at each visit (W0, W12 and W26). NS p≥0.05. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL, interleukin; NS, not significant; TCZ, tocilizumab.

The difference between our results and those of Berger *et al*[1] could be related to the shorter duration of TCZ treatment in our study (four intravenous infusions). However, we think the differences are more likely explained by the fact that our patients were still receiving a median (IQR) prednisone dose of 11 (9–14) mg/day at the time of the last TCZ infusion, compared with 5 (0–20) mg/day in Berger *et al*'s work.[1] Considering that glucocorticoids also decrease IL-6 concentration,[3 4] a higher dose of prednisone at the last TCZ infusion could have diminished the extent of the IL-6 increase in our study and thereby limited its ability to predict the occurrence of early relapse.[1 2]

Taken together, these data suggest that IL-6 monitoring can help clinicians to monitor GCA activity and predict relapse provided that glucocorticoids are stopped or prescribed at a low dose.

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Contributors MS and BB included patients, collected data, performed IL-6 dosages, analysed data and drafted the manuscript.

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