

Response to: 'Association of subcutaneous belimumab and long-term antimalarial treatment reduces antiphospholipid antibodies levels in systemic lupus erythematosus: post-hoc analysis of a randomised placebo-controlled trial—comment on: 'Effect of belimumab treatment on antiphospholipid antibody levels: post-hoc analysis based on two randomised placebo-controlled trials in systemic lupus erythematosus' by Chatzidionysiou *et al*' by Bettiol *et al*

We thank Dr Bettiol *et al*¹ for their interest in our article.² Dr Bettiol *et al* performed a post-hoc analysis on a different randomised controlled trial of subcutaneous belimumab in systemic lupus erythematosus (SLE). The authors evaluated the effect of treatment with belimumab on the levels of anticardiolipin antibodies (aCL) (IgG, IgM and IgA) but also of anti-β₂-glycoprotein I (antiβ₂GPI) antibodies. The latter was unfortunately not available in BLISS-76 and BLISS-52 trials, as acknowledged in the limitations of our post-hoc analysis. The authors have also extended our observation about the effect of co-treatment with antimalarials on antiphospholipid antibody (aPL) titres in the belimumab versus the placebo group, by examining the duration of their use. We agree with the authors that the duration of antimalarials is of high clinical significance. In addition to previous retrospective studies,³ we have recently shown in a pilot randomised controlled trial comparing hydroxychloroquine (HCQ) plus standard care versus standard care in patients with primary antiphospholipid syndrome that the long-term HCQ use was associated with a significant decrease in aPL titres over an average 2.6-year follow-up.⁴ We had also previously shown that the duration of HCQ, and not just the use of HCQ, had a protective role against thrombosis in both aPL-positive and aPL-negative patients with SLE.⁵

Regarding the effect on aPL levels, Dr Bettiol *et al* report a significant median per cent change in the IgM aCL and IgA antiβ₂GPI levels in the belimumab versus placebo group only in the subgroup of patients with concomitant antimalarials treatment and not in the overall comparison between the entire belimumab and placebo groups. No significant effect on aCL or antiβ₂GPI titres was observed in patients not receiving antimalarials from the belimumab and the placebo groups, supporting the predominant role of antimalarials in aPL levels reduction in accordance to our results. In our post-hoc analysis, we did not find any significant overall effect of belimumab treatment on the titres of aCL antibodies, apart from a significant effect of belimumab versus placebo on IgG and IgA aCL titres over time only in the subgroup of patients treated with antimalarials.

As the authors acknowledge, the number of patients is small and therefore the risk of type II error is present. In many subgroups the number of patients was <10, which makes the application of statistical methodology very difficult. Additionally, since we know that aCL fluctuate with time, it is unlikely to be able to draw safe conclusions when only two measurements at two different time points are available. In our study, we undertook a longitudinal data analysis so as to include multiple time points. Finally, no adjustment for potential confounders was performed in the data analysis by Dr Bettiol *et al* in contrast with our analysis.

Despite the limitations, these results add a valuable information about the potential effect of belimumab, especially in combination

with antimalarials, in reducing aPL levels in SLE patients. In both our study and in the study by Dr Bettiol *et al*, a reduction of the titres of some isotypes of aPL (especially of IgA type) was seen in the belimumab + antimalarials group, but no clear overall effect was seen. The independent role of belimumab on aPL titre reduction, and the clinical significance of its effect on IgA isotype of aPL, needs to be further evaluated in larger, long-term prospective studies.

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