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

We read with interest the article by Chatzidionysiou et al,[1] which reported a post-hoc analysis of two trials on intravenous belimumab in systemic lupus erythematosus (SLE), showing a significant reduction of antiphospholipid antibodies (aPL) only in patients cotreated with antimalarials.

However, this post-hoc analysis focused on anticardiolipin antibodies (aCL) only, with no data on anti-β2-glycoprotein I (antiβ2GPI) antibodies, which display the best diagnostic/prognostic value in antiphospholipid antibodies syndrome (APS). Moreover, although long-term use of antimalarials was reported to reduce aPL levels by itself,[2] no information on the duration of antimalarials cotreatment was reported.[1] Interestingly, treatment with belimumab was recently reported to induce aCL and antiβ2GPI disappearance in a small case series of patients with SLE-associated APS.[3] We also reported a significant reduction in aCL and antiβ2GPI titres in 12 patients with SLE on belimumab, either alone or associated with antimalarials.[4]

This study aimed to assess the effect of subcutaneous belimumab (200 mg/week) versus placebo, in association with standard therapy +/- antimalarials, on aCL and antiβ2GPI titers in
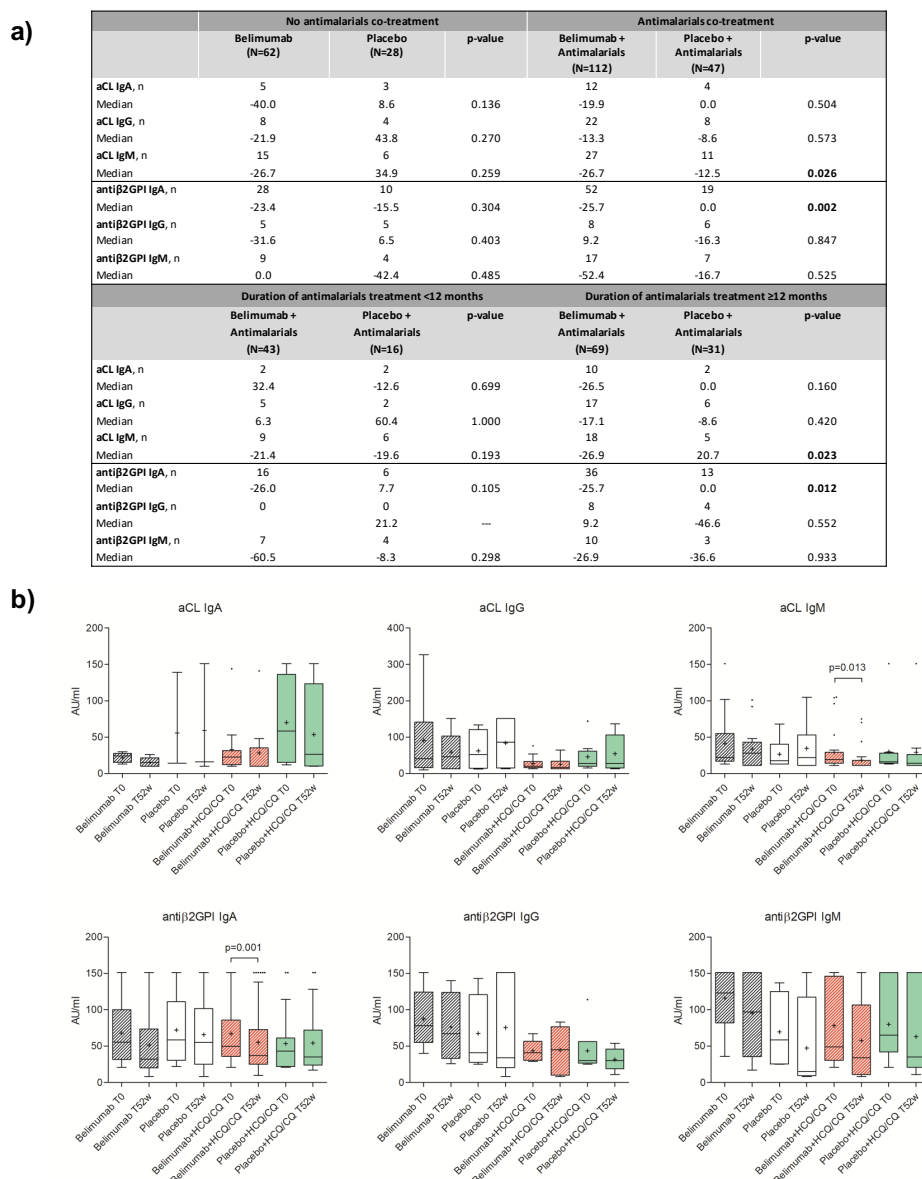
a)

	No antimalarials co-treatment			Antimalarials co-treatment		
	Belimumab (N=62)	Placebo (N=28)	p-value	Belimumab + Antimalarials (N=112)	Placebo + Antimalarials (N=47)	p-value
aCL IgA, n	5	3		12	4	
Median	-40.0	8.6	0.136	-19.9	0.0	0.504
aCL IgG, n	8	4		22	8	
Median	-21.9	43.8	0.270	-13.3	-8.6	0.573
aCL IgM, n	15	6		27	11	
Median	-26.7	34.9	0.259	-26.7	-12.5	**0.026**
antiβ2GPI IgA, n	28	10		52	19	
Median	-23.4	-15.5	0.304	-25.7	0.0	**0.002**
antiβ2GPI IgG, n	5	5		8	6	
Median	-31.6	6.5	0.403	9.2	-16.3	0.847
antiβ2GPI IgM, n	9	4		17	7	
Median	0.0	-42.4	0.485	-52.4	-16.7	0.525
	Duration of antimalarials treatment <12 months			Duration of antimalarials treatment ≥12 months		
	Belimumab + Antimalarials (N=43)	Placebo + Antimalarials (N=16)	p-value	Belimumab + Antimalarials (N=69)	Placebo + Antimalarials (N=31)	p-value
aCL IgA, n	2	2		10	2	
Median	32.4	-12.6	0.699	-26.5	0.0	0.160
aCL IgG, n	5	2		17	6	
Median	6.3	60.4	1.000	-17.1	-8.6	0.420
aCL IgM, n	9	6		18	5	
Median	-21.4	-19.6	0.193	-26.9	20.7	**0.023**
antiβ2GPI IgA, n	16	6		36	13	
Median	-26.0	7.7	0.105	-25.7	0.0	**0.012**
antiβ2GPI IgG, n	0	0		8	4	
Median		21.2	---	9.2	-46.6	0.552
antiβ2GPI IgM, n	7	4		10	3	
Median	-60.5	-8.3	0.298	-26.9	-36.6	0.933

b)

Figure 1 (A) Median per cent change in anticardiolipin antibodies (aCL) and anti-β2-glycoprotein I (antiβ2GPI) antibodies titers at 52 weeks of follow-up as compared with the baseline level in patients treated with belimumab or placebo, stratified according to the cotreatment with antimalarials hydroxychloroquine (HCQ) or chloroquine (CQ) and to the duration of antimalarials treatment. (B) Anticardiolipin and antiβ2GPI antibodies titres in patients treated with belimumab or placebo, alone or associated with antimalarials, at baseline and at 52 weeks of follow-up.

patients with SLE, using data from the randomised controlled trial "A study of belimumab administered subcutaneously in subjects with systemic lupus erythematosus (SLE)" (BLISS-SC).[5]

The median values and median per cent change from the baseline levels of IgG/IgM/IgA aCL and antiβ2GPI antibodies were evaluated at 24 and 52 weeks in the BLISS-SC trial[5] and compared between treatment arms by the Mann-Whitney test. Analyses were stratified according to the antimalarials cotreatment and its duration.

A total of 249 patients with SLE from the BLISS-SC trial tested positive for aPL using different commercial ELISA kits; 174 received belimumab and 75 placebo; antimalarials were coadministered in 112 and 47 patients, respectively.

A significant reduction in antiβ2GPI IgA titres was observed in the belimumab group as compared with the placebo one (median per cent change of −22.0 vs −4.4, p=0.012) at 24 weeks. A significantly greater median per cent change in the belimumab group was confirmed for antiβ2GPI IgA (−25.6 vs −4.8, p=0.002), and for aCL IgM (−26.7 vs −7.1, p=0.017) at 52 weeks (data not shown). No aPL disappearance was found in the treatment arms. When stratifying the analysis according to antimalarials cotreatment, we found no significant difference in aPL titers reduction between the belimumab and the placebo groups in patients not receiving antimalarials, neither at 24 weeks (data not shown) or 52 weeks (figure 1A,B). Conversely, cotreatment with antimalarials significantly reduced median levels and was associated with a significantly greater change in antiβ2GPI IgA levels in the belimumab +antimalarials group as compared with the placebo +antimalarials group at both 24 weeks (median per cent change of −22.1 vs −2.2,p=0.010) and 52 weeks (−25.7 vs −0.0; p=0.002). Comparable results were found in aCL IgM levels at 52 weeks (−26.7 vs −12.5, p=0.026) as well. Notably, reduction in antiβ2GPI IgA and in aCL IgM titers in the belimumab +antimalarials group was statistically significant only for patients treated with antimalarials for ≥12 months (figure 1A).

This post-hoc analysis suggests a beneficial synergistic effect of subcutaneous belimumab and antimalarials in reducing not only aCL, but also antiβ2GPI antibody levels. Interestingly, this effect was significant in patients on long-term antimalarials treatment only.

The main limitations of this analysis are the relatively small sample size, and the fact that only data related to two follow-up time points were available, thus, despite the presence of a control group, spontaneous aPL fluctuations over time cannot be excluded.

Nevertheless, aPL are associated with an increased risk of cardiovascular events, which represent the leading cause of mortality in SLE. Since there is evidence that IgA aPL display a predictive value for thrombosis in patients with SLE[6] the combined treatment with belimumab and antimalarials is a promising therapeutic tool that deserves further studies.

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REFERENCES

1 Chatzidionysiou K, Samoli E, Sfikakis PP, et al. Effect of belimumab treatment on antiphospholipid antibody levels: post-hoc analysis based on two randomised placebo-controlled trials in systemic lupus erythematosus. Ann Rheum Dis 2020;79:304–7.

2 Nuri E, Taraborelli M, Andreoli L, et al. Long-term use of hydroxychloroquine reduces antiphospholipid antibodies levels in patients with primary antiphospholipid syndrome. Immunol Res 2017;65:17–24.

3 Sciascia S, Rubini E, Radin M, et al. Anticardiolipin and anti-beta 2 glycoprotein-I antibodies disappearance in patients with systemic lupus erythematosus and antiphospholipid syndrome while on belimumab. Ann Rheum Dis 2018;77:1694–5.

4 Emmi G, Bettiol A, Palterer B, et al. Belimumab reduces antiphospholipid antibodies in SLE patients independently of hydroxychloroquine treatment. Autoimmun Rev 2019;18:312–4.

5 Stohl W, Schwarting A, Okada M, et al. Efficacy and safety of subcutaneous belimumab in systemic lupus erythematosus: a Fifty-Two-Week randomized, double-blind, placebo-controlled study. Arthritis Rheumatol 2017;69:1016–27.

6 Frodlund M, Vikerfors A, Grosso G, et al. Immunoglobulin A anti-phospholipid antibodies in Swedish cases of systemic lupus erythematosus: associations with disease phenotypes, vascular events and damage accrual. Clin Exp Immunol 2018;194:27–38.