

Targeting BAFF/BLyS in lupus: is the glass half-full or half-empty?

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BAFF/BLyS, a pivotal cytokine in B-cell development, survival and proliferation,¹ became a trusted target in systemic lupus erythematosus (SLE) more than 15 years ago when the growth factor was shown to be involved in the pathogenesis of both preclinical models and human SLE.^{2,3}

Anti-BLyS monoclonal antibody belimumab (BEL) was licensed in 2011 for the treatment of SLE based on the results of the BLISS 52 and 76 phase III trials, which showed superiority compared with placebo, based on the percentage of patients achieving the SLE Responder Index 4 (SRI-4), a composite endpoint requiring (a) a reduction of ≥ 4 points in SELENA-SLEDAI score, (b) no new British Isles Lupus Assessment Group 2004 (BILAG) B score and (c) no worsening (increase ≥ 0.3 points from baseline) in Physician's Global Assessment. At week 52, the delta efficacy between BEL and placebo (both on top of standard of care) was 14.0% and 9.7% in favour of the study drug in BLISS 52 and 76, respectively.^{4,5} A post-hoc analysis demonstrated that the drug was more efficacious in clinically and serologically active patients⁶ and postmarketing data suggested safety with long-term use.⁷ BEL is currently studied in lupus nephritis (NCT01639339) on top of standard immunosuppression (BLISS-LN).

Tabalumab (TAB) is a human IgG4 monoclonal Ab neutralising soluble and membrane-bound BAFF/BLyS, in contrast to BEL, which blocks only soluble BLyS. The results of two Phase III trials (ILLUMINATE 1 and ILLUMINATE 2) are reported.^{8,9} The studies, performed as independent trials, share inclusion criteria (SELENA-SLEDAI score ≥ 6) and treatment regimens. Thus, two TAB arms,

120 mg every 2 weeks (Q2W) or 240 mg every 4 weeks (Q4W) were compared with placebo, on top of standard of care. The primary endpoint was the proportion of patients achieving an SRI-5 at week 52, which differs from the SRI-4 by the requirement of a reduction ≥ 5 points in SELENA-SLEDAI score. In both trials, patients in whom antimalarials (AM) and immunosuppressants (IS) were added or increased were considered as non-responders. In ILLUMINATE 1, patients in whom AM or IS was decreased were surprisingly considered *de facto* as non-responders. The SRI-5 primary endpoint was met with the 120 mg Q2W TAB regimen only in ILLUMINATE-2 (table 1; line 1), contributing to the decision of the company not to develop the drug further in SLE.

The designers of the TAB trials took several risks. First, they decided to embark directly in Phase III studies, instead of going through a classical dose-ranging Phase II trial. Although pharmacokinetics models suggest that optimal efficacy is achieved on B cells with the Q2W 120 mg TAB regimen, the possibility that higher doses and/or more frequent dosing would have led to greater efficacy is not too far-fetched. Moreover, it must be remembered that careful interpretation of the results of the (failed) BEL Phase II trial¹⁰ was key to the success of the BEL story, by allowing additional analyses which lead to construct the primary endpoint used in the Phase III studies, *in casu* SRI-4, and to select serologically active patients.

Second, and most importantly, the results of ILLUMINATE-1 would have been different if patients in whom AM/IS was decreased had not been considered as non-responders. The rationale was likely to avoid modification in the background treatment and a possible increase in glucocorticoid (GC) use, which would have biased the GC-sparing analysis, but this was not an inspired choice. Thus, in a post-hoc analysis not considering patients tapering AM/IS as non-responders, a statistical difference in the rates of SRI-5 responders between TAB and placebo was unmasked in ILLUMINATE-1, at least with the Q4W arm (table 1; line 2).

Last, the primary outcome was not a 'standard' SRI-4, but a more stringent

SRI-5 target. While the hope was to decrease the placebo response, a hypothesis that turned out to be correct, a delta of 5 points is hard to achieve in trials including mainly mucocutaneous and musculoskeletal patients. Noteworthy, the SRI-4 target was met in ILLUMINATE-2 (table 1, line 3) and in ILLUMINATE-1 (table 1, line 4), the latter at least when AM/IS taper was not considered as a non-response (*vide supra*), with deltas well in line with those observed in the BLISS trials.

On the whole, the results of the two TAB trials discussed here illustrate—once again—the difficulty we face in choosing the most appropriate outcome measures to capture treatment efficacy in SLE trials. Of note, this is also true for lupus nephritis studies, where outcome measures may seem easier to define. Thus, it was recently demonstrated that the use of different renal outcome measures, performed on the same data set, leads to different conclusions regarding study drug efficacy.¹¹

The purpose of this editorial is obviously not to suggest that trials which missed their primary and key secondary outcomes are success stories! Rather, we propose a balanced interpretation of the two TAB trials, which does not jeopardise the concept that BAFF/BLyS is a reasonable target in SLE. In other words, we propose that the glass remains half-full, rather than being already half-empty.

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Table 1 Results of the ILLUMINATE and BLISS trials†

Outcome measure	Analysis	ILLUMINATE-1			ILLUMINATE-2			BLISS 52		BLISS 76	
		PBO	TAB 120 mg Q2W	TAB 120 mg Q4W	PBO	TAB 120 mg Q2W	TAB 120 mg Q4W	PBO	BEL 10 mg/kg	PBO	BEL 10 mg/kg
SRI-5	Original	29.3	31.8 (NS)	35.2 (0.052)	27.7 (NS)	38.4 (0.002)	34.8 (0.051)	Not available	Not available	20.4	32.6 (<0.001)
	Modified‡	29.8	34.1 (NS)	37.0 (0.021)	NA	NA	NA	NA	NA	NA	NA
SRI-4	Original	Not available	Not available	Not available	37.8 (NS)	49.2 (<0.05)	44.9 (NS)	44	58 (0.0006)	33.5	43.2 (<0.05)
	Modified‡	39.8	47.2 (<0.05)	47.4 (<0.005)	NA	NA	NA	NA	NA	NA	NA

†Figures are percentage of patients achieving the target; figures between brackets are p values, with significant differences indicated in bold.

‡In the modified analyses performed for ILLUMINATE-1, patients in whom antimalarials and/or immunosuppressants were tapered were not considered as *de facto* non-responders. BEL, belimumab; NA, not applicable; NS, not significant; PBO, placebo; SRI, SLE responder index; TAB, tabalumab.

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