From BLISS to ILLUMINATE studies: "Blys repetita placent"?

Although disappointing, the results of the ILLUMINATE trials are read with great attention.[1][2] These trials assessed the efficacy of tabalumab, a B lymphocyte stimulator (Blys) inhibitor, in systemic lupus erythematosus (SLE). Unfortunately, the results were not considered by Lilly worth following the development of this new agent, of the same therapeutic class than belimumab, the first biologic to be labelled in SLE.[3][4] Overall, what retained our attention were the similarities between designs and results of ILLUMINATE and BLISS studies, while the fates of the two corresponding drugs were so different (table 1).

Indeed, apart from slight differences in the design concerning the management of standard of care treatments, the inclusion of patients from different countries and the choice of a different cut-off for the outcome criteria, these four studies addressed large populations of patients with SLE with similar characteristics that were evaluated with the same composite outcome measure SLE Responder Index[5] and showed only a modest (around 10%) response rate difference between active treatment and placebo. Notably, there were differences between the two ILLUMINATE studies as observed between the two BLISS studies (table 1). A significant effect was reached in ILLUMINATE 2 study only in the high-dose tabalumab arm (120 mg Q2W),[2] while in ILLUMINATE 1, a small but not significant effect was observed only with the intermediate dose of tabalumab (120 mg Q4W),[1] then failing to confirm the dose effect observed in ILLUMINATE 2.[2] The two BLISS studies were considered positive, but, conversely to BLISS 52,[3] BLISS 76 showed the benefit of belimumab only in the group receiving the higher dose (10 mg/kg), and the effect observed at week 52 was lost at week 76.[4]

Table 1 Phase III studies conducted in non-renal patients with SLE targeting Blys

Phase III	BLISS 52	BLISS 76	ILLUMINATE 1	ILLUMINATE 2
N	865	819	1138	1124
Type of SLE	AAN+SLEDAI≥6	AAN+SLEDAI≥6	AAN+SLEDAI≥6	AAN+SLEDAI≥6
Drug	Belimumab	Belimumab	Tabalumab	Tabalumab
SOC (%)				
Corticoids	96	76	78	73
Antimalarials	67	63	63	70
Immunosuppressant	42	56	43	40
Dosages	1 or 10 mg/kg Q4W*	1 or 10 mg/kg Q4W*	120 mg Q4W or Q2W†	120 mg Q4W or Q2W†
Anti-dsDNA+ (%)	75	64	60	59
Administration	Intravenous	Intravenous	Scut	Scut
Black/Asian (%)	4/38	14/3	10/17	12/10
Countries (%)				
North America	–	53	35	38
South America	50	11	23	16
Europe	11	25	20	22
Asia	38	–	16	11
Endpoint	SRI-4 W52	SRI-4 W52	SRI-5 W52	SRI-5 W52
Response rate,‡ placebo/dose 1/dose 2 (%)	44/**51**/**58**	34/41/**43**	29.3/35.2§/31.8	27.7/34.8/**38.4**
Delta max (%)	14	9	5.9	10.7
Long-term response rate, placebo/dose 1/dose 2 (%)	–	W76 32/39/39	–	–
Corticoid–sparing effect	No¶	No	No	No**
Qol				
Indices	SF36 PCS	SF36	BFI	BFI
Effect	Yes but NCS	No††	No§	No
Biological effect				
Anti-dsDNA	Yes	Yes	Yes	Yes
Complement	Yes	Yes	Yes	Yes
Sensitivity analyses‡‡				
Ethnicity	Yes (negative)	Yes (negative)	No	No
DNA+ Comp–	Yes (positive)	Yes (positive)	No	No

*After two first injections 2 weeks apart.
†After a 240 mg initial dosage.
‡Significant results are shown in bold.
§Nearly significant for Q4W.
¶Prednisone dose reduced by ≥25% to ≤7.5 mg/day during weeks 40–52.
**Nearly significant for Q2W.
††Not significant for 10 mg/kg.
‡‡Predefined only for ILLUMINATE studies.
AAN, antinuclear antibodies; BFI, Brief Fatigue Inventory; Blys, a B lymphocyte stimulator; Comp–, complement fractions consumption; DNA+, positive DNA antibodies; NCS, not clinically significant; PCS, physical component score; Qol, quality of life; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SOC, standard of care; SRI, SLE Responder Index.

From a pathological perspective, that tabalumab failed where belimumab 'succeeded' was unexpected, since Blys blockade by tabalumab was expected to be stronger, due to its effect not only on soluble but also on membrane-bound Blys.[6] As many European lupologists, we continue to use rituximab, a drug that failed phase III studies[7][8] but showed nice results in various registries,[9] instead of prescribing belimumab, the first biologic with a label obtained with positive phase III studies.[3][4] Of course, the limited prescription of belimumab is influenced partly by the absence of trials addressing severe forms of SLE (ie, renal), but mainly by authorities that authorised belimumab but at the charge of hospitals in France,[10] or even refused to label belimumab in the UK[11] because of its too modest effect, measured with a dedicated outcome measure derived from a negative phase II study,[12] and the absence of a clear benefit on major secondary endpoints such as quality of life and corticosteroid-sparing effect (table 1).

In this complex context, the fact that tabalumab development programme was ended in spite of very similar effect size may reinforce doubts of the SLE community about the real clinical significance of the results obtained in BLISS studies.[3][4] It also raises questions on B cell dysregulation in SLE and the exact role of Blys, but also of related molecules such as A proliferation-inducing ligand (APRIL) and their respective effects on B cell subsets.[13] Finally, the results of ILLUMINATE studies should be considered as a starting point to question the drug development model applied in recent years with huge populations and significant p values, but low or absent clinical impact was obtained with expensive new drugs. Importantly, the Blys inhibitors story is not going to end with tabalumab negative trials or the poor development of belimumab in some European countries. Blisibimod, a selective peptibody antagonist of the Blys cytokine, displayed a moderate efficacy in a phase II study,[14] justifying ongoing phase III trials (NCT01395745 and NCT02514967). Furthermore, in response to the negative results of rituximab trials in SLE[7][8] (of note, the effect was around 11% in Lupus Nephritis Assessment with Rituximab Study (LUNAR)), new perspectives in B cell targeting therapies were developed: (1) trials conducted in other systemic autoimmune diseases such as anti-neutrophil cytoplasmic antibodies (ANCA) vasculitis[15][16] or Sjogren syndrome;[17][18] (2) new ongoing trials in SLE with different designs/populations such as the Trial of Rituximab and Mycophenolate Mofetil Without Oral Steroids for Lupus Nephritis (RITUXILUP) (NCT01773616) or Rituximab for Lupus Nephritis With Remission as a Goal (RING) (NCT01673295) studies addressing organ-specific (renal) or refractory forms of SLE instead of more heterogeneous non-severe forms and (3) combination of rituximab and belimumab (NCT02284984; NCT02260934) to counteract the high levels of Blys observed after B cell depletion and considered as a possible cause of relapses after rituximab.

To conclude, as others, we realise that such B cell targeted therapies may be relevant only for a subset of patients and ineffective in other subsets (eg, black patients did not seem to benefit from belimumab). Blys levels at baseline[19] or immunological abnormalities identified by post hoc analyses[20] but unconfirmed in real life are not sufficient to define patients who are likely to respond. We think that the data/samples collected during the ILLUMINATE and BLISS trials are fantastic opportunities to develop biomarkers to identify responders to these new drugs. High-throughput immune monitoring should be applied to this important task,[21] using several broad-spectrum technologies in association as developed, for example, in the collaborative European Molecular Reclassification to Find Clinically Useful Biomarkers for Systemic Autoimmune Diseases (PRECISESADS) project.[22] Public access to these data sets, as in the GlaxoSmithKline (GSK) initiative,[23] should also help in the design of new outcome measures that reach clinical and not only statistical significance.[24] In the meantime, we will have to deal with the paradox of these three biologics targeting B cells directly or indirectly in SLE: one (rituximab), with no label but prescribed; a second (belimumab), difficult to prescribe in spite of its label and a third (tabalumab), quite similar to the second but that even did not get the chance to get a label.

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