Achieving lupus low-disease activity and remission states under belimumab in refractory systemic lupus erythematosus: time and organ involvement matter

We read with much interest the contribution of Oon *et al*¹ that was published recently in *Annals of the Rheumatic Diseases*, describing attainment of the lupus low-disease activity state (LLDAS) in a post-hoc analysis of the BLISS trials. At week 52, LLDAS was reached by 12.5% and 14.4% of patients treated with belimumab 10 mg/kg in BLISS-52 and BLISS-76, respectively. The authors conclude that LLDAS is a potential response indicator for future systemic lupus erythematosus (SLE) trials. As opposed to SLE responder index 4 (SRI4),² which represents a change from baseline activity, LLDAS³ and remission⁴ are clinical states that should be targeted as they are associated with damage accrual reduction and include the notion of a low prednisone dose.⁵ Yet, these indicators should be further studied before being introduced into clinical trials. In particular, Oon *et al*'s study lacks data on the time needed to achieve LLDAS and the clinical factors influencing its achievement. It is also important to consider the absence of relapse after an improvement of the disease. In this letter, we wish to provide additional data on the time needed, the probability of and the clinical predictors for achieving stable (ie, without subsequent relapse until month 12) LLDAS and remission state under belimumab. We included all patient with SLE treated with belimumab (intravenous 10 mg/kg on day 0, 14, 28 and then every 28 days) in our centre from March 2013 to May 2018 for an active disease despite standard therapy. Follow-up was conducted on a monthly basis during the first 6 months and at months 9 and 12 (± 1) after belimumab initiation. Primary endpoints were defined as reaching stable SRI4, LLDAS or remission state.^{2-4 6} Patients who did not achieve a primary endpoint and stopped belimumab before 12 months were considered as non-responders. Patients who achieved a primary endpoint but stopped belimumab before 12 months were excluded from the final analysis for this endpoint. The secondary endpoint was the time to obtain a stable British Isles Lupus Assessment Group (BILAG) D from a baseline BILAG A or B or C in the musculoskeletal and mucocutaneous systems at month 6 (± 1) and alternatively, at month 12 (± 1).⁷

A total of 50 patients fulfilling the SLICC criteria for SLE were enrolled.⁸ Belimumab indications were persistent arthritis in 44 (88%) cases, active cutaneous lupus in 26 (52%) cases (6 acute cutaneous lupus, 11 subacute cutaneous lupus, 6 discoid rash, 5 chilblains lupus, 7 alopecia, 2 mucosal ulcers and 1 cryoglobulin vasculitis) and serositis in 2 (4%) cases. Disease activity and previous/ongoing treatments at the beginning of belimumab are displayed in table 1. Eleven (22%) patients stopped belimumab before 12 months: 7 treatment failures, 2 adverse events, 1 pregnancy wish and 1 lost to follow-up.

The probability of reaching stable SRI4, LLDAS or remission at month 12 according to Kaplan-Meier estimator were: 81.7%, 58.1% and 37.1%, respectively (figure 1A). The median (25%–75% interquartile range) time to meet stable SRI4 was 91 (48–275) days, stable LLDAS 213 (78.5–283.5) days and stable remission 270 (262.5–283.0) days. Survival curves and log-rank test analyses showed that baseline IgG level <12 g/L predicted an increased probability and a shorter timeframe for attaining LLDAS (HR=3.5 (95% CI 1.4 to 6.9), p=0.04) and that the baseline SLICC/American College of Rheumatology (ACR) damage index ≥ 1 predicted

Table 1 Disease characteristics, previous treatments and ongoing treatments at the beginning of belimumab

	Patients (n=50)
Disease characteristics at the start of belimumab	
SELENA-SLEDAI* score—median (range)	6 (2–14)
SELENA-SLEDAI score <4	2 (4)
SELENA-SLEDAI score 4–7	31 (62)
SELENA-SLEDAI score ≥ 8	17 (34)
≥ 1 BILAG† A or B score	48 (96)
PGA*—median (range)	0.6 (0.4–1.5)
Mild/moderate flare*	41 (82)
Severe flare*	8 (16)
SDI score‡—median (range)	0 (0–3)
Positive Farr assay	20 (40)
Low C3	15 (30)
Previous treatments	
Number of drugs used per patient, median (range)	4 (2–9)
HCQ	49 (98)
Chloroquine	5 (10)
Prednisone	49 (98)
Methotrexate	38 (76)
MMF or MPA	9 (18)
Azathioprine	10 (20)
Rituximab	3 (6)
Thalidomide	5 (10)
Leflunomide	1 (2)
Colchicine	3 (6)
Topical tacrolimus	6 (12)
Ongoing treatments at the start of belimumab	
Hydroxychloroquine	45 (90)
Patients with (HCQ)>750 ng/mL§	38/45 (84)
Prednisone	45 (90)
Prednisone dose—mg/day, median (range)	10 (4–50)
Increase¶ of corticosteroids	16 (32)
Increase of daily prednisone	13 (26)
Intravenous high-dose methylprednisolone	9 (18)
Methotrexate	30 (60)
MMF or MPA	5 (10)
Azathioprine	4 (8)
Colchicine	3 (6)
Thalidomide	2 (4)
Chloroquine	2 (4)
Leflunomide	1 (2)
Topical tacrolimus	1 (2)

Values are expressed as, n (%), unless stated otherwise.

(HCQ), HCQ blood concentration.

*Defined using Petri *et al*.⁹

†Defined using Isenberg *et al*.⁷

‡Defined using Gladman *et al*.¹⁰

§Considered to be the therapeutic target.

¶Defined as an increase of daily prednisone and/or intravenous high dose (>250 mg) methylprednisolone infusion between day 0 (the day of the start of belimumab) and month 1.

BILAG, British Isles Lupus Assessment Group; C3, complement fraction 3; HCQ, hydroxychloroquine; MMF, mycophenolate mofetil; MPA, mycophenolic acid; PGA, physician's global assessment; SDI, SLICC Damage Index; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus: National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index.

a decreased probability and a longer timeframe for attaining SRI4 (HR=0.4 (95%CI 0.2 to 0.4), p=0.04). No significant association was found between the time to achieve SRI4,

Figure 1 SRI4, LLDAS and remission under belimumab treatment. Kaplan-Meier curves. (A) Percentage of patients achieving stable (ie, without subsequent relapse) SRI4, LLDAS and remission. Patients with SLE treated with belimumab were followed for 12 ($\pm$ 1) months. Each corner in the curve represents a patient who achieved a stable SRI4, LLDAS or remission until 12 ($\pm$ 1) months. Vertical tick marks along each curve represent patients who did not reach the outcome and had a follow-up shorter than 12 ($\pm$ 1) months (censored data). Patients who achieved a primary endpoint but who stopped belimumab before 12 ($\pm$ 1) months were excluded from the final analysis for this endpoint. Numbers of patients at risk for event are reported on a monthly basis for each outcome. The time at which 50% of the initial population reached the endpoint was 174 days for SRI4 and 386 days for LLDAS. (B and C) Musculoskeletal versus mucocutaneous response at 6 and 12 months. Percentage of patients with a baseline BILAG A, B or C in the musculoskeletal system and the mucocutaneous system attaining stable (ie, without subsequent relapse) BILAG D in this system at 6 ($\pm$ 1) months (B) and 12 ($\pm$ 1) months (C). Each corner in the curves represents a patient who achieved a stable BILAG D. Data were analysed and censored with the method applied to the primary endpoints. Curves were compared using log-rank tests. BILAG, British Isles Lupus Assessment Group; LLDAS, Lupus Low Disease Activity Score; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus: National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index; SLE, systemic lupus erythematosus; SRI4, SELENA-SLEDAI Responder Index.

LLDAS or remission and the following baseline parameters: Safety of Estrogens in Lupus Erythematosus: National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) ≥ 6 or 8, low C3 serum level, positive Farr assay, daily prednisone dose ≥ 10 mg and concomitant treatment with an immunosuppressant. At month 6, patients with baseline BILAG A, B or C had an increased probability and a shorter timeframe to meet a stable BILAG D in the musculoskeletal system compared with the mucocutaneous system ($p=0.003$). The difference was no longer significant at 12 months ($p=0.11$) (figure 1B,C).

In conclusion, our study provides evidence that stable LLDAS and remission under belimumab are reached slowly, with a substantial number of patients reaching one or the other after 6 months of treatment and with a faster control of articular activity compared with the cutaneous one. These data suggest that belimumab should probably be maintained for more than 6 months before concluding that there has been an inadequate response, especially in the case of cutaneous lupus. The greater likelihood of obtaining LLDAS in our study compared with the Oon *et al's*¹ study was probably related to the higher baseline disease activity seen in the BLISS trials where a SELENA-SLEDAI of at least six was an inclusion criterion.

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