How to use the Lupus Low Disease Activity State (LLDAS) in clinical trials

Recently, two different studies^{1,2} applied the criteria of the Lupus Low Disease Activity State (LLDAS)³ to the data sets of the BLISS-52⁴ and BLISS-76⁵ phase III trials of belimumab. The studies reported similar LLDAS attainment frequencies at key time points; however, not identical. We herein discuss possible explanations in order to guide future usage of the LLDAS.

In the study by Parodis *et al*,¹ LLDAS at week 52 was achieved by 10.0% of the patients in BLISS-52 and 7.1% in BLISS-76, with a greater percentage within patients who received belimumab 10 mg/kg compared with patients who received placebo in BLISS-52 (11.9% vs 6.2%; $p=0.030$), but not in BLISS-76 (8.3% vs 6.4%; $p=0.473$). In the study by Oon *et al*,² LLDAS at week 52 was attained by 12.5% and 14.4% in the belimumab 10 mg/kg arm versus 5.8% and 7.8% in the placebo arm in BLISS-52 ($p=0.02$) and BLISS-76 ($p=0.04$), respectively.

The small-scale differences in the two studies can be traced to the criteria used for the retrospective calculation of the LLDAS (table 1). Comparing the two setups, Parodis *et al* did not rely on British Isles Lupus Assessment Group (BILAG) evaluations claiming that the rationale for the development of LLDAS included the notion that the highly detailed BILAG index renders its use cumbersome in everyday practice.³ In contrast, Oon *et al*² used BILAG information collected as a part of the BLISS studies. More specifically, Oon *et al* defined criterion 1 as (i) a Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score ≤ 4 , (ii) zero score in the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA)-SLEDAI items seizures, psychosis, organic brain syndrome, visual disturbance, cranial nerve disorder, lupus headache, cerebrovascular accident, vasculitis, urinary casts, haematuria, proteinuria, pyuria, pleurisy, pericarditis and fever, and (iii) BILAG D or E only for the neurological, renal and cardiac systems, with no evidence of active haemolysis. The same study defined criterion 2 as (i) no new SELENA-SLEDAI items with score >0 and (ii) no BILAG items with new activity, irrespective of organ system, while Parodis *et al* defined criterion 2 as no new moderate or severe flare according to the SELENA-SLEDAI Flare Index (SFI).⁶

In fact, neither absence of new flares based on the SFI used by Parodis *et al* nor BILAG D/E scores used by Oon *et al* are validated interpretations of the LLDAS criterion 2. In retrospective settings, such assumptions may be inevitable, especially since the initial publication of the derivation of LLDAS³

does not clarify what one should consider 'new features' of SLE disease activity. The discrepancies in the two studies underscore the importance of prospective evaluation of the LLDAS where possible. In prospective settings, no new lupus disease activity could be a clinician-assessed item in the case report form.

Despite the similar results in the two studies, the authors emphasised different points. Oon *et al* stressed the discriminatory performance of LLDAS when the belimumab and placebo arms were compared, while Parodis *et al* discussed the overall low LLDAS attainment rates. Indeed, a stringent outcome might be advantageous in trials of powerful therapies where the active treatment could generate higher rates of LLDAS achievers compared with the BLISS trials, but low attainment rates across all arms might impede approval by drug regulatory agencies despite adequate separation between the active substance and placebo arms.

The LLDAS was designed to reflect low SLE disease activity rather than changes in lupus activity; it can, therefore, be considered a more clinically relevant outcome in SLE studies compared with the SLE Responder Index (SRI)-4, and should preferably be assessed prospectively. Perhaps the time has come to put forth a standardised approach to the calculation the LLDAS components to ensure uniformity across both prospective and retrospective studies.

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Table 1 Definitions of the LLDAS criteria used in the two *post hoc* studies

Parodis <i>et al</i> ¹	Oon <i>et al</i> ²
1. SLEDAI-2K score ≤ 4 with no activity in the renal descriptors (proteinuria, pyuria, haematuria and cellular casts), no pleurisy, no pericarditis and no fever.	1. SLEDAI-2K score ≤ 4 with no activity in major organ systems (renal, central nervous system, cardiopulmonary, vasculitis and fever) and no haemolytic anaemia or gastrointestinal activity.
2. No new features of SLE activity, defined as no new moderate or severe flare according to the SELENA-SLEDAI Flare Index compared with baseline.	2. No new features of lupus disease activity, defined as no new SELENA-SLEDAI item score >0 and no new BILAG activity compared with the previous assessment.
3. SELENA-SLEDAI PGA score ≤ 1 (scale: 0–3).	3. SELENA-SLEDAI PGA score ≤ 1 (scale: 0–3).
4. Daily prednisone or prednisone equivalent dose ≤ 7.5 mg.	4. Current prednisone equivalent dose ≤ 7.5 mg/day.
	5. Standard maintenance dosages of immunosuppressive drugs and approved biologic agents.

All criteria had to be met for attainment of LLDAS.

. BILAG, British Isles Lupus Assessment Group; LLDAS, Lupus Low Disease Activity State; PGA, physician's global assessment; SELENA, Safety of Estrogens in Lupus Erythematosus National Assessment; SLE, systemic lupus erythematosus; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

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