Original article

Attainment of treat-to-target endpoints in SLE patients with high disease activity in the atacicept phase 2b ADDRESS II study

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Abstract

Objective. Low disease activity (LDA) and remission are emerging treat-to-target (T2T) endpoints in SLE. However, the rates at which these endpoints are met in patients with high disease activity (HDA) are unknown. Atacicept, which targets B lymphocyte stimulator and a proliferation-inducing ligand, improved disease outcomes in SLE patients with HDA (SLEDAI-2K $\geq$10) at baseline in the phase 2b ADDRESS II study. This is a *post hoc* analysis of T2T endpoints in these patients.

Methods. Patients received weekly atacicept (75 or 150 mg s.c.) or placebo for 24 weeks (1:1:1 randomization). Attainment of three T2T endpoints, LDA (SLEDAI-2K $\leq$2), Lupus Low Disease Activity State (LLDAS) and remission (clinical SLEDAI-2K = 0, prednisone-equivalent $\leq$5mg/day and Physician's Global Assessment <0.5), was assessed and compared with SLE Responder Index (SRI)-4 and SRI-6 response.

Results. Of 306 randomized patients, 158 (51.6%) had baseline HDA. At week 24, 37 (23.4%) HDA patients attained LDA, 25 (15.8%) LLDAS and 17 (10.8%) remission. Each of these endpoints was more stringent than SRI-4 ($n = 87$; 55.1%) and SRI-6 ($n = 67$; 42.4%). Compared with placebo ($n = 52$), at week 24, patients treated with atacicept 150 mg ($n = 51$) were more likely to attain LDA [odds ratio (OR) 3.82 (95% CI: 1.44, 10.15), $P = 0.007$], LLDAS [OR 5.03 (95% CI: 1.32, 19.06), $P = 0.018$] or remission [OR 3.98 (95% CI: 0.78, 20.15), $P = 0.095$].

Conclusion. At week 24, LDA, LLDAS and remission were more stringent than SRI-4 and SRI-6 response, were attainable in the HDA population and discriminated between treatment with atacicept 150 mg and placebo. These results suggest that T2T endpoints are robust outcome measures in SLE clinical trials and support further evaluation of atacicept in SLE.

Trail registration. ClinicalTrials.gov, http://clinicaltrials.gov, NCT01972568.

Key words: SLE, atacicept, low disease activity, remission, treat to target, lupus low disease activity state

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Rheumatology key messages

- The utility of treat-to-target endpoints in SLE trials with high baseline disease activity is unknown.
- Low disease activity and remission were attainable, and more stringent than SLE Responder Index-4 and -6 response.
- Low disease activity endpoints discriminated between atacicept and placebo treatment.

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Introduction

SLE is a multisystem autoimmune disease associated with significant morbidity and mortality that have changed little in recent decades [1, 2]. With current (mostly legacy) treatments, incomplete control of disease activity is common, and patients endure progressive organ damage accrual and poor quality of life [3, 4]. As new and more effective treatments emerge, following the example set in other rheumatic diseases, treat-to-target (T2T) approaches are likely to become part of the standard of care in SLE [5, 6]. In support of this, T2T endpoints for SLE have begun to be defined and validated. In SLE, both disease activity and treatment, especially corticosteroids (CS), contribute to long-term adverse outcomes [7]. As a result, T2T endpoints in SLE should combine the attainment of lower disease activity with lower-dose CS use [8].

A consensus on definitions of remission in SLE is emerging [9, 10]. Although further validation studies are still required, achieving remission-endpoints, defined by the absence of clinical activity and very low or zero oral CS doses, is associated with protection from damage accrual [11, 12]. With currently available treatments, the frequency of achieving sustained remission is variable, but generally low [13, 14]. Low disease activity (LDA) endpoints such as the Lupus Low Disease Activity State (LLDAS) are more attainable, yet still associated with reduced damage accrual [11, 15–17] and improved health-related quality of life [18].

The few studies reported so far suggest that these potential T2T definitions have utility as endpoints in SLE clinical trials. LLDAS has been shown to be feasible and clinically meaningful [19–21], although to date, remission has not been examined in the clinical trial setting. Whether these endpoints can be realistically attained in a sufficient number of patients, who begin a trial with high disease activity (HDA), to allow discrimination of placebo and active treatment in these patients, warrants study.

Activation and differentiation of B lymphocytes to autoantibody-producing plasma cells are hallmarks of SLE. This process is regulated by two cytokines: B lymphocyte stimulator (BLyS) of the TNF family (also known as B cell Activating Factor, or BAFF) and a proliferation-inducing ligand (APRIL) [22]. BLyS and APRIL are elevated in the serum of SLE patients and correlate with disease activity [23, 24], severe organ manifestations [25], organ damage [26] and autoantibody production [27]. BLyS and APRIL ligate a common receptor, transmembrane activating factor and cyclophilin ligand interactor [22]. Atacicept is a recombinant human transmembrane activating factor and cyclophilin ligand interactor-immunoglobulin fusion protein that binds to both BLyS and APRIL. Atacicept treatment has been associated with reductions in SLE disease activity in two large phase 2 studies [28, 29]. In the phase 2b ADDRESS II study, the primary endpoint was not met. However, in a pre-specified analysis of patients with baseline HDA [defined as SLEDAI-2K [30] ≥10 at screening], atacicept treatment resulted in significant improvements in SLE Responder Index (SRI)-4 and SRI-6 response rates and flares [28].

To determine the utility of potential T2T endpoints in the analysis of treatment responses, specifically in subpopulation of patients who enter clinical trials with HDA, we conducted a *post hoc* analysis in the predefined ADDRESS II HDA subpopulation. For completeness, results from the whole [modified intention-to-treat (mITT)] population are also reported.

Methods

Study design

The design of the ADDRESS II study has been described previously [28]. Briefly, ADDRESS II was a 24-week, multicentre, randomized, double-blind, placebo-controlled phase 2b study to evaluate safety and efficacy of atacicept in patients with active, autoantibody-positive SLE (ClinicalTrials.gov NCT01972568). The study was performed in accordance with the Declaration of Helsinki, International Conference on Harmonization Guidance on Good Clinical Practice and local regulatory requirements. No patient consent was necessary or obtained for this specific analysis, which was a *post hoc* analysis of trial data. Patient consent for the trial was described in the original report. Patients received weekly s.c. injections of atacicept 75 or 150 mg or placebo for 24 weeks (1:1:1 randomization). The primary endpoint was SRI-4 response [31] at week 24 in the mITT population. The HDA subpopulation was prespecified and defined as patients with SLEDAI-2K ≥10 at screening.

Assessment of potential T2T endpoints

Potential T2T endpoints analysed included LLDAS, remission and LDA. LLDAS was defined according to the recent prospective validation study as a state comprising all of the following: SLEDAI-2K ≤4 without major organ activity; no new features of lupus disease activity compared with previous assessment measured on SLEDAI-2K; Physician's Global Assessment (PGA) ≤1 (0–3); prednisone-equivalent ≤7.5 mg/day; and standard maintenance doses of immunosuppressants [15]. Remission was defined using the Definitions of Remission in SLE (DORIS) framework [9] (clinical SLEDAI-2K = 0; prednisone-equivalent ≤5 mg/day; PGA <0.5). In addition, a simple definition of LDA was defined as SLEDAI-2K ≤2.

Statistical analysis

Attainment of LDA, LLDAS and remission was assessed at each post-baseline visit up to week 24. Patients with missing data were imputed as non-responders for each of the analysed endpoints. The association of LDA, LLDAS and remission with SRI-4 and SRI-6 at week 24 was explored in the mITT population and HDA subpopulation using descriptive statistics. The proportions of

patients attaining LDA, LLDAS and remission were compared with SRI-4 and SRI-6 attainment using the McNemar test. The attainment of the LDA, LLDAS, remission and SRI-6 response over 24 weeks according to treatment group was graphically presented using heat maps [19, 32]. Differences in LDA, LLDAS and remission attainment at week 24 between HDA patients treated with atacicept 75 or 150 mg *vs* placebo were analysed using odds ratios (ORs) estimated from logistic regression. These analyses were considered exploratory and no multiplicity adjustments were made.

Results

Study population

The ADDRESS II study included 306 patients fulfilling the revised ACR classification criteria for SLE [33] who were autoantibody-positive with active disease (SLEDAI-2K $\geq$6), despite standard of care. Patients received treatment with placebo ($n = 100$), atacicept 75 mg ($n = 102$) or atacicept 150 mg ($n = 104$) from day 1 to week 24 [28]. There were 158 (51.6%) patients with HDA at screening who were included in this *post hoc* analysis: 52 received placebo, 55 atacicept 75 mg and 51 atacicept 150 mg. Baseline characteristics in the HDA subpopulation were balanced except for some minor differences in race and ethnicity, and mean disease duration between treatment arms (Table 1). Safety data have been reported previously [28].
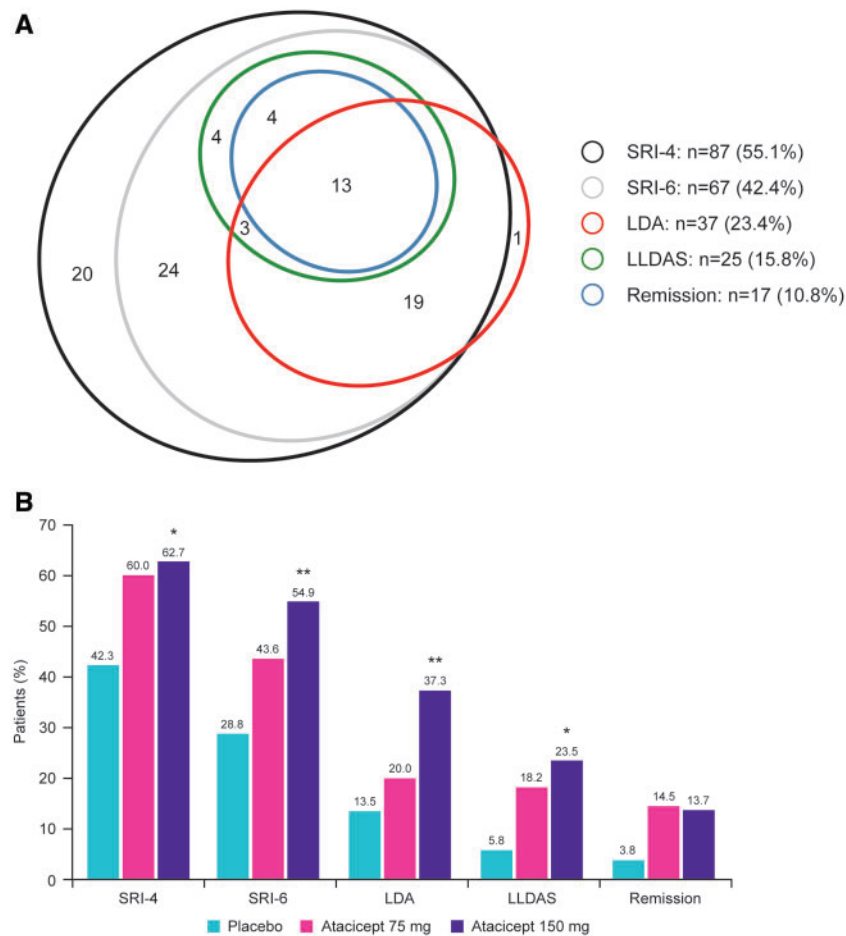
Post hoc analysis of T2T endpoint attainment in the HDA subpopulation

SRI-4 and SRI-6 responses in the HDA subpopulation have been reported previously [28]. Across treatment arms, 87 (55.1%) and 67 (42.4%) patients had an SRI-4 and SRI-6 response at week 24, respectively. LDA, LLDAS and remission were attained at week 24 by 37 (23.4%), 25 (15.8%) and 17 (10.8%) HDA patients, respectively (Fig. 1A). Almost all patients attaining LDA, LLDAS and remission also had an SRI-4 and SRI-6 response (94.6, 96.0 and 100% for both endpoints, respectively). One patient with LDA and one patient who attained both LDA and LLDAS were not SRI-4 or SRI-6 responders. Conversely, only 40.2, 27.6 and 19.5% of SRI-4 responders and 52.2, 35.8 and 25.4% of SRI-6 responders also attained LDA, LLDAS and remission, respectively. Thus, each of the T2T endpoints were significantly more stringent than SRI-4 and SRI-6 ($P < 0.0001$; Fig. 1A). Of note, all patients in remission also met the definition for LLDAS, consistent with the concept of these states being concentric [8]. In contrast, four subjects who attained remission did not meet the definition for LDA (SLEDAI-2K $\leq$2) because they had clinical SLEDAI $= 0$, but SLEDAI-2K >2 due to positive anti-dsDNA antibodies and low complement.

TABLE 1 Baseline characteristics of ADDRESS II patients with HDA (SLEDAI-2K $\geq$10) at screening

	Placebo (n = 52)	Atacicept 75 mg (n = 55)	Atacicept 150 mg (n = 51)
Age, mean (s.d.), years	39 (13.7)	35 (11.1)	37 (10.4)
Female, *n* (%)	47 (90.4)	50 (90.9)	49 (96.1)
Race or ethnicity, *n* (%)			
White	40 (76.9)	35 (63.6)	31 (60.8)
Black/African American	2 (3.8)	3 (5.5)	4 (7.8)
Hispanic or Latino	30 (57.7)	30 (54.5)	23 (45.1)
Disease characteristics			
SLE disease duration, mean (s.d.), years	6.8 (7.6)	7.1 (7.6)	5.5 (5.0)
SLEDAI-2K score, mean (s.d.)	12 (2.3)	12 (3.0)	12 (2.4)
Serologically active disease,[a] *n* (%)	38 (73.1)	43 (78.2)	35 (68.6)
Medication history			
Prednisone-equivalent dose at screening, mean (s.d.), mg/day	10.4 (8.0)	11.8 (8.6)	11.1 (8.5)
>7.5 mg/day prednisone equivalent, *n* (%)	30 (57.7)	35 (63.6)	29 (56.9)
Antimalarial, *n* (%)	39 (75.0)	42 (76.4)	38 (74.5)
AZA, *n* (%)	11 (21.2)	13 (23.6)	7 (13.7)
MTX, *n* (%)	9 (17.3)	7 (12.7)	7 (13.7)
MMF, *n* (%)	8 (15.4)	11 (20.0)	9 (17.6)
Serum biomarkers, *n* (%)			
ANA $\geq$1:80	49 (94.2)	53 (96.4)	48 (94.1)
Anti-dsDNA $\geq$15 IU/ml	36 (69.2)	39 (70.9)	32 (62.7)
Low C3 <LLN (0.9 g/l)	23 (44.2)	29 (52.7)	20 (39.2)
Low C4 <LLN (0.1 g/l)	16 (30.8)	14 (25.5)	15 (29.4)

[a]Positive anti-dsDNA antibodies or low complement at screening. C: complement; HDA: high disease activity, LLN: lower limit of normal; SLEDAI-2K: SLEDAI 2000.

FIG. 1 Endpoint stringency of LDA, LLDAS and remission attainment *vs* SRI responses in HDA patients

(**A**) Euler diagram to illustrate the distributional shift for SRI-4 and SRI-6 responder *vs* attainment of each of the three evaluated T2T endpoints at week 24 in all HDA patients regardless of treatment. (**B**) Attainment of SRI and T2T endpoints by treatment arm at 24 weeks. *$P < 0.05$ (*vs* placebo); **$P < 0.01$ (*vs* placebo). HDA: high disease activity; LDA: low disease activity; LLDAS: Lupus Low Disease Activity State; SRI: SLE Responder Index; T2T: treat-to-target.

Post hoc analysis of T2T endpoint attainment with atacicept *vs* placebo in the HDA subpopulation

As previously reported [28], SRI-4 and SRI-6 responses at week 24 in the HDA subpopulation were significantly increased with atacicept 150 mg *vs* placebo [SRI-4: 62.7 *vs* 42.3%, OR 2.30 (95% CI: 1.04, 5.06), $P = 0.039$; SRI-6: 54.9 *vs* 28.8%, OR 3.00 (95% CI: 1.33, 6.78), $P = 0.008$]; the treatment effect of atacicept was evident from week 4 (SRI-4) and week 8 (SRI-6) (Fig. 1B). Both LDA and LLDAS at week 24 were also significantly increased with atacicept 150 mg *vs* placebo [LDA: 37.3 *vs* 13.5%, OR 3.82 (95% CI: 1.44, 10.15), $P = 0.007$; LLDAS: 23.5 *vs* 5.8%, OR 5.03 (95% CI: 1.32, 19.06), $P = 0.018$] (Fig. 1B). Increased remission attainment with atacicept 150 mg *vs* placebo at week 24 was also observed, but this did not reach statistical significance [13.7 *vs* 3.8%, OR 3.98 (95% CI: 0.78, 20.15), $P = 0.095$] (Fig. 1B). Differences between atacicept 150 mg and placebo in LDA, LLDAS and

remission were observed from 16 weeks of treatment (Fig. 2). Increased attainment of all three T2T endpoints was also observed with atacicept 75 mg *vs* placebo at week 24, but the differences did not reach statistical significance.

Fig. 3 shows heat maps of the attainment and retention of SRI-4, SRI-6, LDA, LLDAS and remission over 24 weeks in the HDA subpopulation in each treatment group: consistently more atacicept-treated than placebo-treated patients attained LDA, LLDAS and remission, and this was maintained over time.

The performance of the T2T endpoints was also examined in the whole trial (mITT) population (supplementary Fig. S1, available at *Rheumatology* online). As previously reported [28], SRI-4 and SRI-6 response rates increased with atacicept 150 mg *vs* placebo at week 24, but the differences did not reach statistical significance. Similarly, atacicept 150 mg treatment increased the proportion of patients achieving LDA, LLDAS and remission

Fɪɢ. 2 Attainment of LDA, LLDAS, remission and SRI endpoints in HDA patients over 24 weeks
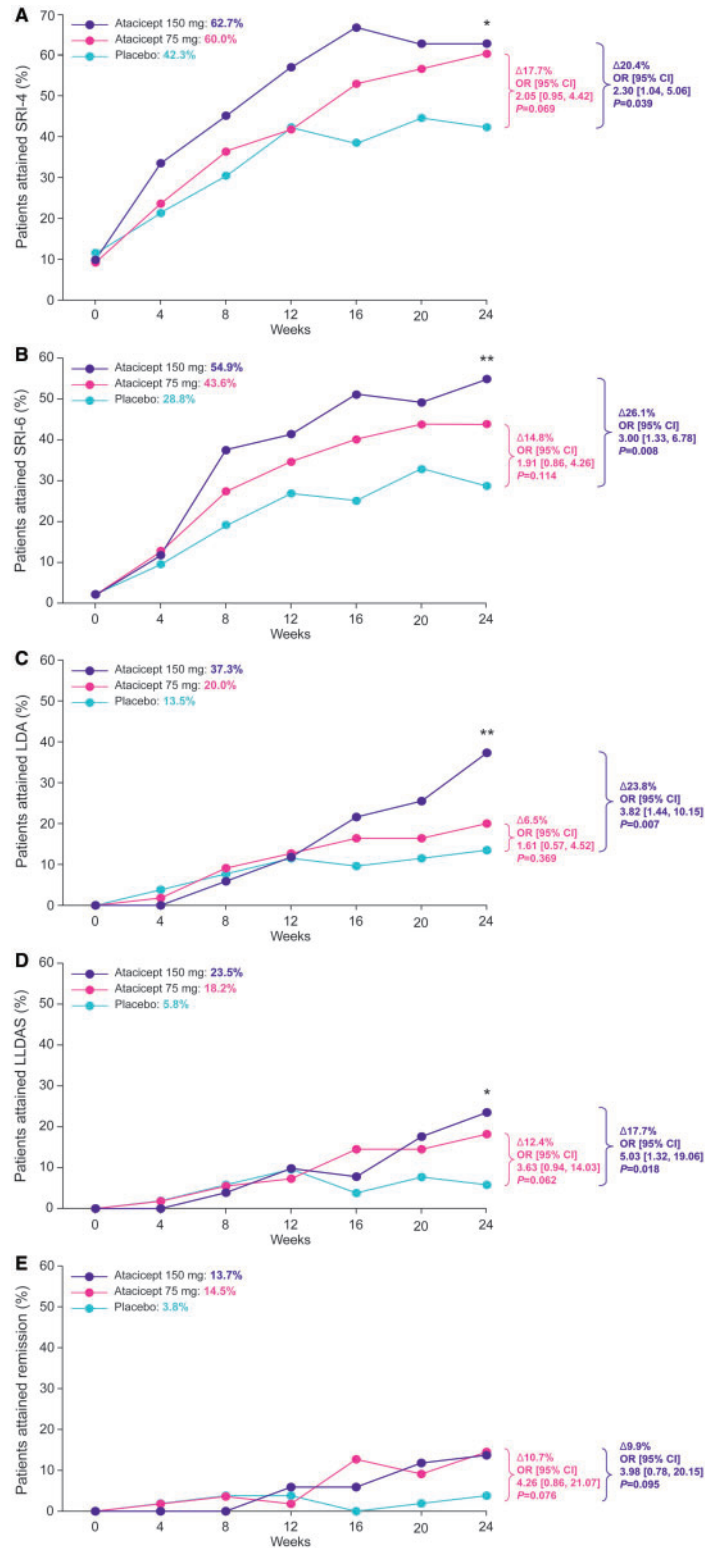
Rates of attainment of (**A**) SRI-4, (**B**) SRI-6, (**C**) LDA, (**D**) LLDAS and (**E**) remission over 24 weeks in HDA patients treated with placebo, atacicept 75 mg or atacicept 150 mg. *$P < 0.05$ (*vs* placebo); **$P < 0.01$ (*vs* placebo). HDA: high disease activity; LDA: low disease activity; LLDAS: Lupus Low Disease Activity State; OR: odds ratio; PGA: Physician's Global Assessment; SLEDAI-2K: SLEDAI 2000; SRI: SLE Responder Index.

FIG. 3 Individual patient response heat maps for SRI, LDA, LLDAS and remission over 24 weeks
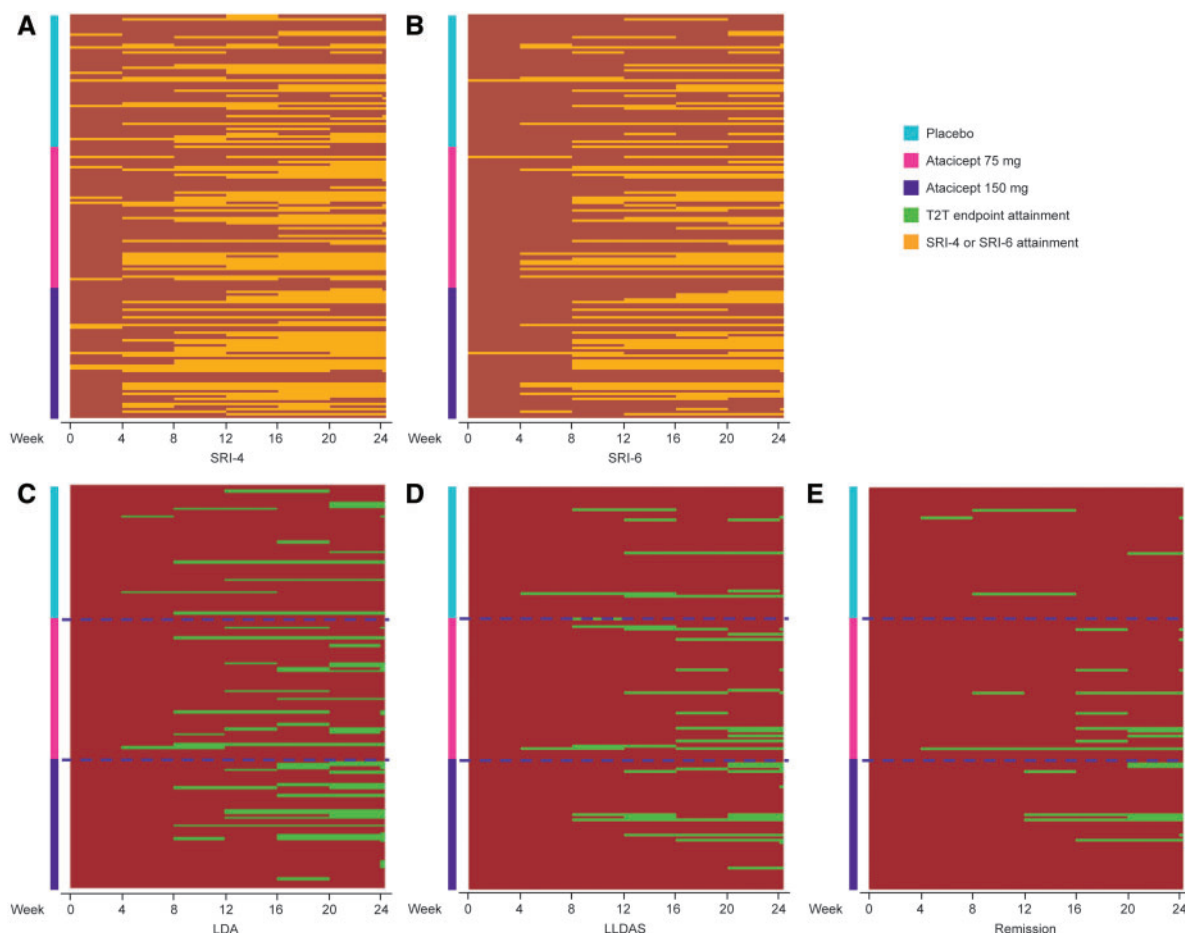
Individual patient attainment of (**A**) SRI-4, (**B**) SRI-6, (**C**) LDA, (**D**) LLDAS and (**E**) remission over 24 weeks in HDA patients treated with placebo, atacicept 75 mg or atacicept 150 mg. LDA: low disease activity; LLDAS: Lupus Low Disease Activity State; PGA: Physician's Global Assessment; SLEDAI-2K: SLEDAI 2000; SRI: SLE Responder Index; T2T: treat-to-target.

at week 24, but the differences did not reach statistical significance *vs* placebo.

Among patients in the HDA subpopulation who were serologically active (anti-dsDNA and low complement) at screening ($n = 69$), atacicept 150 mg treatment still resulted in an increase in SRI-4 and SRI-6 response rates and more frequent attainment of LDAS, LLDAS and remission *vs* placebo; none of these increases reached statistical significance (data not shown).

Discussion

Robust treatment endpoints have been defined and validated for multiple rheumatic diseases, and in RA a T2T approach has been demonstrated to achieve meaningfully improved outcomes [34]. Obtaining the same goal in SLE is more challenging, partly because of the complexity of assessing disease activity, and also because of the lack of data from studies using highly effective

therapies to help analyse the utility of potential T2T endpoints. It has been suggested that the development and validation of T2T endpoints for SLE [5, 6] may contribute discriminatory outcomes for use in trials and allow prospective metrics-based studies. A key step towards this goal is examination of the utility of potential T2T endpoints in clinical trial settings. Several potential endpoints for SLE have now been described. A multinational collaborative group proposed and preliminarily validated LLDAS as a T2T endpoint [15]. LLDAS attainment has now been shown in multiple cohort studies to be associated with both reduced damage accrual [11, 15, 16] and improved health-related quality of life [18], and was recently formally validated in a prospective study [17]. Recently, LLDAS has been shown to discriminate active treatment from placebo more robustly than most commonly used measures [19–21], although in the one study reported to date, remission did not [35]. Based on the concept that remission and LLDAS should represent concentric, increasingly stringent cutoffs, the DORIS

working group has proposed a framework for remission definitions for SLE [9]. A large cohort study has confirmed that remission is relatively uncommon in SLE compared with LLDAS, but when attained—even for a short time—it confers protection from damage accrual [11]. However, it is unclear whether the use of potential T2T endpoints such as LLDAS and remission are feasible in patients who enter a clinical trial with HDA.

Our findings in the HDA subpopulation from the ADDRESS II trial at week 24 indicate that each of the three endpoints analysed is a robust outcome measure more stringent and discriminatory than SRI-4 or SRI-6. At week 24, of the three endpoints assessed, LLDAS yielded the highest OR for discrimination between active treatment and placebo. These results are consistent with findings reported by Ordi-Ros *et al.* [20] and Morand *et al.* [19] in studies of MMF and of anifrolumab, respectively. These data also support the utility of the DORIS remission definition used here in a trial setting. Remission and LLDAS were less frequently attained than a simple definition of LDA based on SLEDAI-2K alone, consistent with the observation in a large prospective cross-sectional study that all domains of LLDAS contribute to the validity of this definition [36]. The definitions of remission and LLDAS include PGA as an outcome measure, which may be critical to balance omissions in the SLEDAI-2K measure [37]. Of note, while LLDAS and remission were concentric in this study, differences in definitions meant that some patients who met the definitions of LLDAS and remission did not meet the definition of LDA because they had SLEDAI-2K >2 due to positive anti-dsDNA antibodies and low complement. While the simple LDA measure may be a useful, discriminatory endpoint for trials, its prognostic utility remains to be examined.

Compared with placebo, treatment with atacicept 150 mg was associated with an ~4-fold relative increase in the odds of reaching LDA, a 5-fold relative increase in the odds of reaching LLDAS and a 4-fold relative increase in the odds of achieving remission in HDA patients at week 24, although the last of these was rarer and did not reach statistical significance. Parodis *et al.* also recently reported that remission did not significantly separate active treatment from placebo in *post hoc* analyses of the belimumab phase 3 trial datasets [35], whereas LLDAS did [21]. These findings are consistent with the treatment benefits previously reported with atacicept 150 mg compared with placebo in HDA patients, using SRI-4, SRI-6 and reduction in first severe flares as endpoints [28]. Atacicept benefit on these potential T2T endpoints was first observed at week 16, which contrasts with the improvements in SRI-4 and SRI-6 with atacicept *vs* placebo that were evident from weeks 4 and 8, respectively. However, further prospective studies with greater statistical power would be required to determine the timing of onset of benefit for potential T2T endpoints. Early onset of response may be informative for long-term outcomes, since a recent study demonstrated that meeting the LLDAS definition within 6 months of commencing treatment was associated with improved outcomes in SLE [38].

When examining the full (mITT) ADDRESS II trial population, we found that although atacicept 150 mg treatment increased the proportion of patients achieving all three T2T endpoints at week 24 *vs* placebo, the differences did not reach statistical significance. These results are consistent with the increases in SRI-4 and SRI-6 response rates observed with atacicept 150 mg *vs* placebo in the mITT population [28], which also showed a trend for treatment effect that did not reach statistical significance. These findings suggest that the potential T2T endpoints evaluated in this *post hoc* analysis may be more relevant to patients with HDA.

Several limitations apply to the interpretation of these data. The analysis of potential T2T endpoints was a *post hoc* analysis, suitable for generating hypotheses that must be confirmed by future testing in a formal T2T strategy trial. Response rates in the trial setting, as reported here, may under- or overestimate responses because the dataset analysed here was not powered for assessment of these endpoints and the duration of their attainment. However, in a previously reported analysis of LLDAS in a trial dataset, with a 12-month duration, significant differences in duration of LLDAS attainment were detected [19]. The 6-month duration of this study was insufficient for analysis of the impact of potential T2T endpoint attainment on damage accrual, but the association of LLDAS and remission attainment with protection from damage accrual has been well described [11, 12, 15, 16].

In conclusion, we report that LLDAS, LDA and remission are feasible endpoints in SLE trials, attainable in patients with highly active disease at baseline, which discriminate active treatment from placebo at week 24. LLDAS had the most optimal performance characteristics (based on ORs) of the three measures studied. Since LLDAS and remission have been demonstrated to be stepwise more stringent endpoints in terms of their attainability and association with protection from damage accrual, they may be particularly meaningful trial endpoints. In summary, these data indicate that atacicept 150 mg demonstrated a significant treatment effect *vs* placebo at week 24 on these potential T2T endpoints in patients with HDA, supporting the continued development of this treatment in SLE.

Acknowledgements

Supplementary data

Supplementary data are available at *Rheumatology* online.

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