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Original article

Predictors of low disease activity and clinical remission following belimumab treatment in systemic lupus erythematosus

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Abstract

Objectives. To identify predictors of low disease activity and clinical remission following belimumab treatment in SLE.

Methods. SLE patients who received belimumab 10 mg/kg ($N = 563$) in the BLISS-52 and BLISS-76 clinical trials were surveyed. The performance of baseline factors in predicting attainment of low disease activity (defined as Lupus Low Disease Activity State) or clinical remission [defined as clinical (c)SLEDAI-2K = 0] at week 52 from treatment initiation was evaluated using logistic regression. Organ damage was assessed using the SLICC/ACR Damage Index (SDI).

Results. We demonstrated a negative impact of established organ damage on attainment of Lupus Low Disease Activity State [SDI > 0; odds ratio (OR): 0.44; 95% CI 0.22, 0.90; $P = 0.024$] and the primary Lupus Low Disease Activity State condition, i.e. SLEDAI-2K ⩽ 4 with no renal activity, pleurisy, pericarditis or fever (SDI > 1; OR: 0.46; 95% CI 0.27, 0.77; $P = 0.004$); cognitive impairment/psychosis was found to mainly account for the latter association. Baseline SDI scores > 1 predicted failure to attain cSLEDAI-2K = 0 (OR: 0.53; 95% CI 0.30, 0.94; $P = 0.030$), with cutaneous damage mainly driving this association. Anti–dsDNA positivity increased (OR: 1.82; 95% CI 1.08, 3.06; $P = 0.025$) and cardiovascular damage reduced (OR: 0.13; 95% CI 0.02, 0.97; $P = 0.047$) the probability of attaining cSLEDAI-2K = 0 along with a daily prednisone equivalent intake restricted to ⩽7.5 mg.

Conclusion. Belimumab might be expected to be more efficacious in inducing low disease activity and clinical remission in SLE patients with limited or no organ damage accrued prior to treatment initiation. Patients with positive anti–dsDNA titres might be more likely to achieve clinical remission along with limited or no CS use.

Key words: systemic lupus erythematosus, biologics, belimumab, outcome measures, treat-to-target, treatment, B cell–targeted therapies

CLINICAL SCIENCE

Rheumatology key messages

- Neuropsychiatric and cardiovascular damage prior to initiation of belimumab treatment is associated with reduced probability of achieving Lupus Low Disease Activity State.
- Mucocutaneous and cardiovascular damage is associated with a reduced probability of achieving clinical remission, defined as cSLEDAI-2K = 0.
- Anti-dsDNA–positive patients were more likely to achieve clinical remission along with limited CS use.

Introduction

Belimumab, a monoclonal antibody towards the soluble counterpart of the cytokine B cell–activating factor, also known as B lymphocyte stimulator, is the first biologic agent approved for the treatment of SLE [1]. *Post-hoc* analyses of the pivotal phase III randomized controlled trials (RCTs) of belimumab BLISS-52 [2] and BLISS-76 [3] revealed superiority of belimumab over placebo in patients with SLE with high baseline disease activity, positive anti-double stranded (ds)DNA titres and low complement levels, as well as in patients receiving CSs [4]. Later, real-life observations demonstrated that established organ damage prior to treatment initiation predicted reduced belimumab efficacy based on the SLE Responder Index 4 (SRI-4) [5], which was recently corroborated in a *post-*

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hoc analysis of data from the BLISS-52 and BLISS-76 trials [6].

The SRI-4 response rate at week 52 from treatment initiation was the primary outcome measure in the BLISS-52 [2] and BLISS-76 [3] trials. The SRI-4 was created for use in RCTs of belimumab [2, 3, 7] and was designed to detect changes in overall SLE disease activity [8]. However, achievement of SRI-4 response does not necessarily signify a state of remission or low SLE disease activity. From a clinical point of view, clinical remission is a more meaningful target, or low SLE disease activity if clinical remission is not achievable.

According to the SRI-4, treatment response is defined as (i) a reduction of $\geqslant 4$ points in the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA)-SLEDAI [9] score, (ii) no new flare based on the BILAG index [10], defined as no new BILAG A and no more than one new BILAG B, and (iii) no worsening in the Physician's Global Assessment by $\geqslant 30\%$ compared with the evaluation at treatment initiation. SRI-4 response is not achieved unless all three criteria are met. The Lupus Low Disease Activity State (LLDAS) [11] was introduced as a composite tool to detect low SLE disease activity, being achieved when all of the following conditions are met: a SLEDAI 2000 (SLEDAI-2K) [12] score of $\leqslant 4$, no activity in major organ systems (renal activity, central nervous system involvement, cardiopulmonary activity, vasculitis, fever), no haemolytic anaemia or gastrointestinal activity, no new features of SLE disease activity, a SELENA-SLEDAI Physician's Global Assessment of $\leqslant 1$ (on a 3-point scale), a prednisone or prednisone equivalent dose of $\leqslant 7.5$ mg/day, and well-tolerated doses of immunosuppressive drugs and/or approved biologic agents.

Ongoing activity in the descriptors rash, alopecia, mucosal ulcers and proteinuria is always scored in the SLEDAI-2K [12], in contrast to only new occurrences in the original SLEDAI [13]. The clinical SLEDAI-2K (cSLEDAI-2K) is a variant of the SLEDAI-2K, in which the serological descriptors (anti-dsDNA and complement levels) are omitted [14], introduced for use in the evaluation of SLE disease activity in clinical practice, where test results for the serological SLEDAI items are not always available. From a clinical perspective, the information provided by cSLEDAI-2K may in most cases be considered sufficient for decision making; in fact, treatment intensification is not recommended in cases of serologically active but clinically inactive SLE [15].

Recent *post-hoc* analyses of the BLISS-52 and BLISS-76 trials applied the LLDAS and zero scores of cSLEDAI-2K, and found adequate separations of the frequencies attained in the different treatment groups and ability to delineate the superiority of belimumab over placebo [16, 17]. In the present *post-hoc* analysis of the same RCTs, we investigated the performance of different baseline factors, especially characteristics previously shown to affect belimumab efficacy [4–6], as predictors of LLDAS and cSLEDAI-2K = 0 attainment, in order to further clarify in which SLE patient subsets belimumab treatment may be expected to be beneficial, and contribute to the optimization of its use in clinical practice.

Methods

Patients

In total, 1684 patients were included in the BLISS trials; the BLISS-52 trial (ClinicalTrials.gov identifier NCT00424476) [2] comprised 865 and the BLISS-76 trial (ClinicalTrials.gov identifier NCT00410384) [3] comprised 819 adult ANA- and/or anti-dsDNA antibody–positive SLE patients with a SELENA-SLEDAI score of $\geqslant 6$ at screening. The patients were randomized to receive belimumab 1 mg/kg, belimumab 10 mg/kg or placebo, along with standard of care treatment, and the primary efficacy end point was attainment of SRI-4 response at week 52 in both trials. Based on the findings from both RCTs, belimumab 10 mg/kg was the dose later approved by pharmaceutical regulatory agencies for use in clinical practice. For this reason, we investigated the performance of baseline clinical and serological items as predictors of LLDAS or cSLEDAI-2K = 0 attainment in the belimumab 10 mg/kg patient group only ($N = 563$). Although the patients were followed until week 52 in the BLISS-52 trial and until week 76 in the BLISS-76 trial, the two RCTs had almost identical designs, facilitating *post-hoc* analyses of pooled data from the two trials. Access to data from the BLISS trials for the present analysis was granted by GlaxoSmithKline (Uxbridge, UK) through the Clinical Study Data Request (CSDR) consortium.

Definitions

We applied the LLDAS and cSLEDAI-2K = 0 definitions as previously described [16]. In brief, for the complete LLDAS we required that the following four conditions were met: (i) a SLEDAI-2K score of $\leqslant 4$ with no activity in the renal descriptors (proteinuria, pyuria, haematuria, cellular casts), no pleurisy, no pericarditis and no fever, based on evaluations at week 52 from treatment initiation, (ii) no new features of SLE activity, defined as no new moderate or severe flare according to the SELENA-SLEDAI flare index from baseline through the 52-week follow-up visit [9, 18], (iii) a SELENA-SLEDAI Physician's Global Assessment score of $\leqslant 1$ at week 52, and (iv) a daily prednisone or prednisone equivalent dose of $\leqslant 7.5$ mg at week 52. Due to low attainment rates of the complete LLDAS [16], we analysed the main condition of LLDAS (LLDAS condition 1: a SLEDAI-2K score of $\leqslant 4$ with no activity in the renal descriptors, no pleurisy, no pericarditis and no fever) separately.

Moreover, we analysed the combination of cSLEDAI-2K = 0 together with a daily prednisone equivalent dose of $\leqslant 7.5$ mg (LLDAS condition 4). It is worth noting that while the serological SLEDAI-2K items (positive anti-dsDNA titres and low complement levels) are suppressed in the cSLEDAI-2K, they are both retained in the SLEDAI-2K condition of LLDAS (condition 1). In cases of persistent or new onset of serological activity, LLDAS may thus constitute an even more stringent outcome measure

compared with the cSLEDAI-2K = 0. Nevertheless, the fact remains that the two measures reflect dissimilar states of SLE disease activity.

Levels of anti-dsDNA immunoglobulin G ⩾30 IU/ml (detectable range of the assay: 30–3600 IU/ml) indicated positivity, and baseline C3 and C4 complement levels were dichotomized into low and normal/high [2, 3]. Organ damage was assessed using the SLICC/ACR Damage Index (SDI) [19].

Based on previous literature [4, 6, 20], we included the following baseline items in the analyses: CS use, low C3/C4 levels, positive anti-dsDNA titres, SELENA-SLEDAI scores ⩾10, SDI scores > 0 and >1, as well as age and duration of SLE from the time of diagnosis until enrolment in the BLISS programme, since factors unrelated to SLE and/or age-associated factors may contribute to organ damage accrual, and organ damage is known to increase over the course of the disease [21].

The patients' rights, safety and well-being were protected in compliance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrolment. All participating centres obtained ethics committee or institutional review board approval of the study protocols.

Statistics

Logistic regression models were used to evaluate the association of baseline items with LLDAS or cSLEDAI-2K = 0 attainment at week 52 from belimumab treatment initiation. Baseline items showing significant associations in simple (univariable) models qualified for further analysis in multiple logistic regression models for assessment of priority, independence and confounding potentiality. *P* values < 0.05 were considered statistically significant. The statistical analyses were performed using the SPSS Statistics 25 software (IBM Corp., Armonk, New York, USA).

Results

Baseline characteristics of the patients in the belimumab 10 mg/kg treatment arms of the BLISS-52 and BLISS-76 trials are presented in Table 1, both separately and combined.

Predictors of low disease activity

At week 52 from treatment initiation, 10.2% (number of positive observations, *n* = 46; number of patients with available data, *N* = 449) of the patients in the belimumab 10 mg/kg group met the criteria of LLDAS. Among the baseline factors investigated as potential predictors of LLDAS attainment, the only observed association was a negative impact of SDI > 0 [odds ratio (OR): 0.44; 95% CI 0.22, 0.90; *P* = 0.024] (Fig. 1). No specific SDI domain or item was found to account for this association (see Supplementary Table S1, available at *Rheumatology* online), probably due to the low LLDAS rates.

For the latter reason, we also investigated the performance of baseline factors as predictors of the primary condition of LLDAS, i.e. SLEDAI-2K ⩽ 4 with no renal activity, no pleurisy, no pericarditis and no fever, which was attained by 55.9% (*n* = 251; *N* = 449) of the patients. Low C3 levels, low C4 levels, longer disease duration and SDI scores of >1 were negative predictors of attainment of LLDAS condition 1 in simple logistic regression analysis (Fig. 1), but SDI scores of >1 was the only baseline factor that remained significantly associated with failure to achieve the outcome in multiple logistic regression (OR: 0.46; 95% CI 0.27, 0.77; *P* = 0.004). In separate analysis of SDI domains and items, cognitive impairment and/or major psychosis prior to belimumab treatment initiation was found to significantly reduce the likelihood of attaining LLDAS condition 1 at week 52 (OR: 0.35; 95% CI 0.14, 0.88; *P* = 0.025), and previous cerebrovascular accidents exhibited a trend in the same direction (OR: 0.29; 95% CI 0.08, 1.10; *P* = 0.068) (see Supplementary Table S2, available at *Rheumatology* online).

Predictors of clinical remission

We next investigated baseline factors as predictors of cSLEDAI-2K = 0 at the 52-week follow-up evaluation, which was attained by 39.6% (*n* = 178; *N* = 449) of the patients. CS use and anti-dsDNA positivity were found to predict achievement of the outcome in simple logistic regression models, whereas higher age, SDI scores of > 0 and SDI scores of >1 were negative predictors (Fig. 2). In multiple logistic regression, SDI scores of >1 was the only baseline factor among the ones in the model showing a significant association with failure to attain clinical remission, defined as cSLEDAI-2K = 0 (OR: 0.53; 95% CI 0.30, 0.94; *P* = 0.030).

We also analysed the SDI domains and items separately (see Supplementary Table S3, available at *Rheumatology* online). In this analysis, damage in the musculoskeletal (OR: 0.54; 95% CI 0.29, 0.99; *P* = 0.047) and the skin domain (OR: 0.33; 95% CI 0.12, 0.88; *P* = 0.027), as well as in the cognitive impairment/major psychosis SDI item (OR: 0.32; 95% CI 0.11, 0.97; *P* = 0.044), showed associations with failure to achieve cSLEDAI-2K = 0 in simple logistic regression. However, only the association of damage in the skin domain remained significant in the multiple logistic regression model (OR: 0.33; 95% CI 0.12, 0.89; *P* = 0.028) (see Supplementary Table S3, available at *Rheumatology* online).

Predictors of clinical remission with limited or no CS use

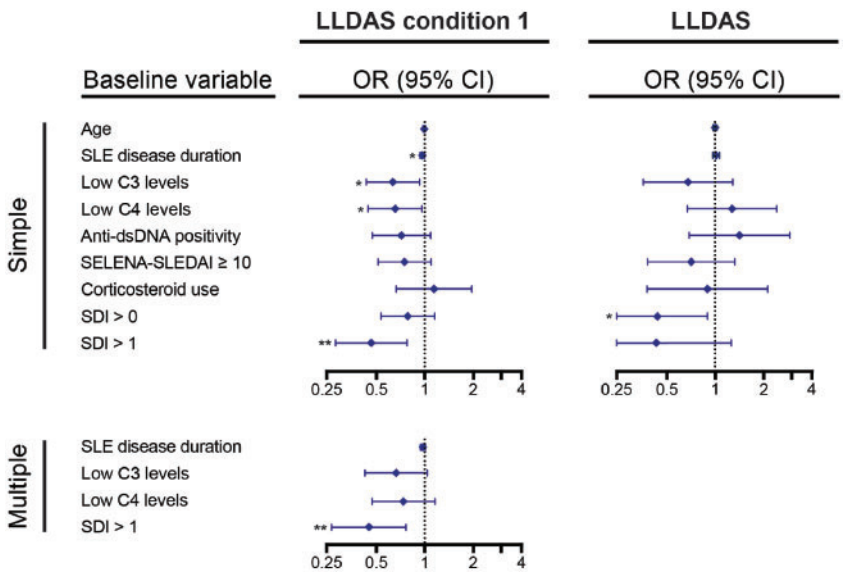
Finally, we applied a CS dose restriction to cSLEDAI-2K = 0, i.e. a maximum daily prednisone or prednisone equivalent dose of 7.5 mg (Fig. 2); this composite outcome was achieved by 23.2% (*n* = 104; *N* = 449) of the patients. In simple logistic regression models, anti-dsDNA positivity at baseline increased the probability of achieving clinical remission defined as cSLEDAI-2K = 0 and a prednisone equivalent dose of ⩽7.5 mg/day at week 52 (OR: 1.82; 95% CI 1.08, 3.06; *P* = 0.025). In contrast, baseline SDI scores of > 0 were found to decrease the likelihood of achieving the same outcome (OR: 0.61; 95% CI 0.38,

Table 1 Baseline characteristics of patients in the belimumab 10 mg/kg treatment arm

	BLISS-52 *N* = 290	BLISS-76 *N* = 273	Pooled data *N* = 563
Female sex; *n* (%)	280 (96.6%)	259 (94.9%)	539 (95.7%)
Ethnic origin; *n* (%)			
Indigenous American[a]	91 (31.4%)	34 (12.5%)	125 (22.2%)
White/Caucasian	71 (24.4%)	189 (69.3%)	260 (46.2%)
Black/African American	11 (3.8%)	37 (13.6%)	48 (8.5%)
Asian	116 (40.0%)	10 (3.7%)	126 (22.4%)
Multiracial	1 (0.3%)	3 (1.1%)	4 (0.7%)
Age, mean (S.D.), years	35.4 (10.8)	40.5 (11.1)	37.9 (11.3)
SLE disease duration (years); median (IQR)	3.6 (1.3–7.3)	4.7 (1.3–10.9)	3.8 (1.3–8.8)
SELENA-SLEDAI; mean (S.D.)	10.0 (3.9)	9.5 (3.6)	9.8 (3.8)
SLEDAI-2K; mean (S.D.)	10.4 (3.9)	9.7 (3.7)	10.0 (3.8)
Prednisone equivalent (mg/day); median (IQR)	10.0 (7.5–20.0)	7.5 (0.0–10.0)	10.0 (5.0–15.0)
CS use; *n* (%)	278 (95.9%)	200 (73.3%)	478 (84.9%)
Positive anti-dsDNA titres; *n* (%)	218 (75.2%)	179 (65.6%)	397 (70.5%)
Low C3 levels; *n* (%)	147 (50.7%)	115 (42.1%)	262 (46.5%)
Low C4 levels; *n* (%)	180 (62.1%)	147 (53.8%)	327 (58.1%)
SDI score; median (IQR)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.0 (0.0–1.0)

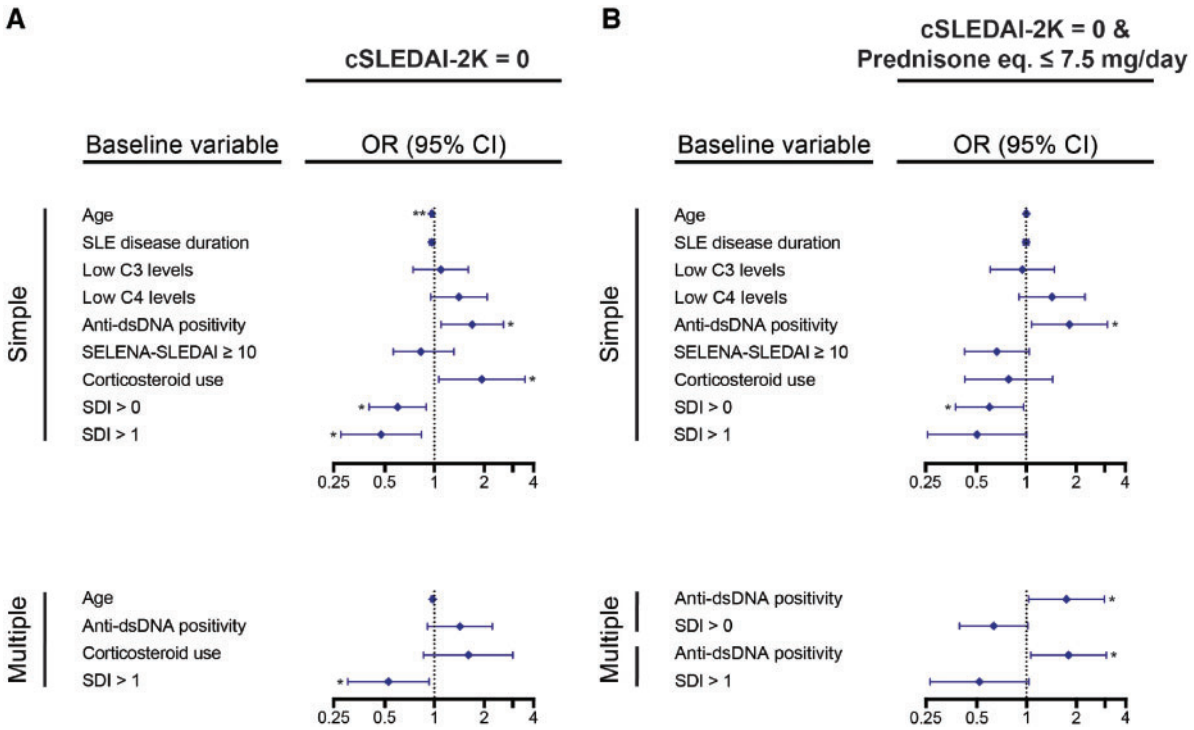
For dichotomous variables, data are presented as counts (percentage, %). For continuous variables, data are presented as means (S.D.) if they were normally distributed, or medians (IQR) if they were not. [a]Alaska Native or American Indian from North, South or Central America. SELENA-SLEDAI: Safety of Estrogens in Lupus Erythematosus National Assessment version of the SLEDAI; SLEDAI-2K: SLEDAI 2000; SDI: SLICC/ACR Damage Index; IQR: interquartile range.

Fig. 1 Baseline predictors of LLDAS



The forest plots illustrate the performance of baseline items in predicting attainment of the complete LLDAS definition, as well as the primary LLDAS condition defined as a SLEDAI-2K score of $\leqslant 4$ with no activity in the renal descriptors (proteinuria, pyuria, haematuria, cellular casts), no pleurisy, no pericarditis and no fever, at week 52 from initiation of treatment with belimumab 10 mg/kg. The results are based on simple and multiple logistic regression models. Following simple logistic regression analyses, multiple logistic regression models were constructed for selected baseline variables in order to assess independence, priority and confounding potentiality. P values < 0.05 were considered statistically significant. Statistical significance: $^{*}P < 0.05$; $^{**}P < 0.01$. LLDAS: Lupus Low Disease Activity State; SLEDAI-2K: SLEDAI 2000; SDI: SLICC/ACR Damage Index; SELENA-SLEDAI: Safety of Estrogens in Lupus Erythematosus National Assessment-SLEDAI; OR: odds ratio.

FIG. 2 Baseline predictors of cSLEDAI-2K = 0



The forest plots illustrate the performance of baseline items in predicting attainment of cSLEDAI-2K = 0 (**A**) and cSLEDAI-2K = 0 along with a maximum daily prednisone or prednisone equivalent dose of 7.5 mg (**B**) at week 52 from initiation of treatment with belimumab 10 mg/kg. The results are based on simple and multiple logistic regression models. Following simple logistic regression analyses, multiple logistic regression models were constructed for selected baseline variables in order to assess independence, priority and confounding potentiality. *P* values < 0.05 were considered statistically significant. Statistical significance: $^{*}P < 0.05$; $^{**}P < 0.01$. SLEDAI-2K: SLEDAI 2000; SDI: SLICC/ACR Damage Index; SELENA-SLEDAI: Safety of Estrogens in Lupus Erythematosus National Assessment-SLEDAI; OR: odds ratio.

0.97; $P = 0.036$). In multiple logistic regression analysis, only anti-dsDNA positivity was associated with the outcome, yielding a nearly 2-fold increased probability of achieving cSLEDAI-2K = 0 along with a prednisone (or prednisone equivalent) dose of $\leqslant$7.5 mg/day (OR: 1.74; 95% CI 1.03, 2.94; $P = 0.040$), whereas the association between baseline SDI scores of > 0 and failure to achieve clinical remission with the CS restriction did not reach statistical significance (OR: 0.63; 95% CI 0.40, 1.02; $P = 0.06$).

In separate analysis of the SDI domains and items (see Supplementary Table S4, available at *Rheumatology* online), damage in the cardiovascular domain at baseline yielded an ~8-fold reduced probability of achieving clinical remission with the CS dose restriction (OR: 0.13; 95% CI 0.02, 0.97; $P = 0.047$). In contrast, diabetes was shown to increase the probability of achieving the same outcome (OR: 4.31; 95% CI 1.14, 16.34; $P = 0.032$). These associations remained significant and independent of one another in multiple logistic regression analysis, and when anti-dsDNA positivity was added to the model (see Supplementary Table S4, available at *Rheumatology* online).

Discussion

In the present study, we demonstrated that organ damage accrued prior to initiation of treatment with belimumab resulted in reduced likelihood of attaining low disease activity, either the complete LLDAS definition or SLEDAI-2K $\leqslant$ 4 with no renal activity, no pleurisy, no pericarditis and no fever, as well as clinical remission defined as a cSLEDAI-2K score of zero. Interestingly, addition of a CS dose restriction of a daily prednisone (or prednisone equivalent) dose of $\leqslant$7.5 mg revealed that SLE patients with positive anti-dsDNA titres at the time of treatment initiation were more likely to achieve the outcome.

Previous analysis of BLISS data comparing belimumab-treated SLE patients with patients who received placebo revealed superiority of belimumab over placebo in serologically active patients, more specifically patients with positive anti-dsDNA titres or low C3/C4 levels at baseline, based on the SRI-4 [4], which was recently also corroborated regarding the attainment of LLDAS [17]. Our analysis was non-comparative; we investigated the performance of baseline factors as predictors of LLDAS or cSLEDAI-2K = 0 attainment in the belimumab 10 mg/kg arm only,

i.e. the dose approved by regulatory agencies for use in clinical practice. In this analysis, established organ damage prior to treatment initiation was the strongest and most consistent baseline predictor of failure to attain low SLE disease activity and clinical remission at the 52-week follow-up visit. The finding is in conformity with previous reports of established organ damage reducing belimumab efficacy, both in real-life [5] and clinical trial [6] settings. In accordance with another real-life setting [22], serological activity at treatment initiation was not found to impact the likelihood of attaining LLDAS.

In the present study, hypocomplementaemia at baseline was not associated with attainment of either low activity state or clinical remission. Interestingly, serological activity in the form of positive anti-dsDNA titres was found to substantially increase the likelihood of attaining clinical remission when the CS dose restriction of a maximum daily prednisone or prednisone equivalent dose of 7.5 mg was added to the cSLEDAI-2K = 0. This finding is in accordance with the aforementioned comparative *post-hoc* analysis of BLISS data, in which anti-dsDNA positivity indicated increased likelihood of achieving reduced SLE activity (based on the SRI-4 criteria) in belimumab-treated patients compared with patients who only received background therapy [4]. Although CSs are highly effective in managing flares or persistently moderate to high disease activity in SLE, long-term usage is associated with a number of adverse effects, including osteoporosis, osteonecrosis, cardiovascular disease, infections, diabetes and cataracts, with serious toxicity reported at doses of prednisone or prednisone equivalents exceeding 7.5 mg per day [23]. For these reasons, limiting CS usage is an important target of the pharmaceutical intervention along with clinical remission in patients with SLE, providing the rationale for the additional analysis with the CS dose restriction along with attainment of cSLEDAI-2K = 0. Collective results from both analyses indicate that anti-dsDNA–positive SLE patients and patients with limited or no organ damage accrued prior to belimumab treatment initiation may be more likely to benefit from belimumab treatment in terms of achievement of a low-steroid clinical remission.

Since organ damage is known to increase with disease duration [21], it is worth noting that the association between established organ damage and non-attainment of clinical remission or low disease activity was not confounded by SLE duration. The mechanisms underlying the association between organ damage and reduced belimumab efficacy have yet to be explored, but the consistency in several studies and analyses is reassuring. Organ damage in SLE patients is associated with unfavourable course of disease and premature mortality [21, 24], which hypothetically, at least partly, accounts for the observations in the present study. However, little is known about the influence that organ damage may have on the sensitivity of SLE disease activity assessment instruments such as the LLDAS and cSLEDAI-2K, which should also be taken into consideration when interpreting the results.

Recently, dissection of the SDI into its separate items revealed that cognitive impairment/psychosis and previous thrombotic events were the SDI items mainly driving the association between organ damage and reduced belimumab efficacy [6], the latter also being observed in a real-life setting [5], suggesting that antiphospholipid antibodies, the antiphospholipid syndrome and/or use of anticoagulants may play an important mechanistic role. In the present study exploring the performance of baseline factors in predicting attainment of low disease activity or clinical remission, cognitive impairment and/or major psychosis was still a prominent factor associated with failure to achieve low SLE disease activity 52 weeks after belimumab treatment initiation, and the cardiovascular component in the form of cerebrovascular accidents exhibited a trend in the same direction. Interestingly, cutaneous damage was found to substantially decrease the probability of attaining clinical remission without the restriction of CS dose, whereas the cardiovascular component was again the strongest predictor of failure in attaining clinical remission along with limited or no CS use. A striking observation was that diabetes developed prior to treatment initiation paradoxically increased the likelihood of achieving this combined outcome. Although the reason for this observation is not clear, an explanation might be an increased intentionality among clinicians to limit CS exposure in diabetic patients, acknowledging the well-known negative impact of CSs on this specific comorbid condition.

The retrospective nature of the study was a limitation. Since patients with active LN and NPSLE were excluded from the trials, the implications derived from the present study may not be applicable to these SLE patient subsets. Moreover, SLE patients of African American origin (8.5%) were not represented at the same extent as patients of other ethnic origins, such as Caucasian (46.2%) or Asian (22.4%) subjects, which may limit the applicability of the findings to the African American SLE population. Nevertheless, the BLISS trials comprise the largest to date SLE populations with a conscientious follow-up, being ideal for retrospective investigations regarding optimization of the use of belimumab therapy. The similar design of the BLISS trials facilitated analysis of pooled data, which increased the magnitude of the statistical power to generate more accurate estimates.

The findings in the present study suggest that belimumab might be expected to be more efficacious in inducing low disease activity in SLE patients with limited or no organ damage accrued prior to treatment initiation. Patients with positive anti-dsDNA titres might be more likely to achieve clinical remission along with low CS use. The associations were irrespective of age, SLE disease duration or SLE activity grade, and provide important clinical implications regarding optimization of the use of belimumab.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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