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Effectiveness of belimumab after rituximab in systemic lupus erythematosus

A Randomized Controlled Trial

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ABSTRACT

Background: B cell depletion with rituximab is commonly used for patients with systemic lupus erythematosus (SLE) refractory to conventional therapy but yields variable responses. We hypothesised that high B cell activating factor (BAFF) levels after rituximab can cause disease flares thereby limiting its effectiveness.

Objective: To obtain preliminary evidence for efficacy of the anti-BAFF therapeutic belimumab after rituximab in SLE.

Design: Phase II randomised, double-blind (patient, assessors, researchers, providers of care) placebo-controlled, parallel group, superiority trial (ISRCTN: 47873003)

Setting: England

Participants: 52 patients with SLE refractory to conventional treatment, for whom their physician had recommended rituximab therapy, were recruited between February 2, 2017 and March 28, 2019.

Interventions. Participants were treated with rituximab and then 4 to 8 weeks later were randomised (1:1) to receive intravenous belimumab or placebo for 52-weeks.

Measurements The pre-specified primary endpoint was serum IgG anti-dsDNA antibody levels at 52-weeks. Secondary outcomes included incidences of disease flares and adverse events.

Results At 52 weeks, IgG anti-dsDNA antibody levels were lower in patients treated with belimumab compared to placebo (geometric mean 47 IU/ml, 95% CI 25-88 vs 103 IU/ml, 95% CI 49-213, treatment effect 70% greater reduction from baseline, 95% CI 46-84%, p<0·001). Belimumab reduced the risk of severe flare (BILAG A flare) compared to placebo after rituximab (hazard ratio 0·27, 95% CI 0·07 -0·98, log-rank p=0·033), with 10 severe flares in the placebo and 3 in the belimumab group. Belimumab did not increase the incidence of serious adverse events. Belimumab significantly suppressed B cell repopulation compared to placebo (geometric mean 0.012 $x10^9$/L, 95% CI 0.006-0.014 vs 0.037 $x10^9$/L, 95% CI 0.021-0.081) at 52 weeks in a subset of patients (n=25) where data were available.

Limitations: Small sample size, biomarker primary endpoint.

Conclusion: Belimumab after rituximab significantly reduced serum IgG anti-dsDNA antibody levels and reduced the risk of severe flare in SLE patients who are refractory to conventional therapy. Our results suggest that this combination could be developed as a therapeutic strategy.

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem, autoimmune disease, predominantly affecting women of reproductive age, which is associated with substantial morbidity and was among the leading causes of death in young women between 2000 and 2015 in the United States (1). Over recent decades, improvements in the outcome for patients with SLE has slowed due to the paucity of novel effective therapies (2). Reliance on treatment with corticosteroids remain, often prescribed at high doses, which increases the risk of end organ damage. Immunosuppressive agents such as azathioprine, mycophenolate and methotrexate are frequently used off-label, in part, to minimise the use of corticosteroids, but a proportion of patients are refractory to these conventional therapies and are likely to have higher morbidity and mortality (3, 4).

For the last twenty years B cell depletion with rituximab, a chimeric anti-CD20 monoclonal antibody, has shown benefit in open labelled studies (5-12) but two large, phase III, double-blind randomised placebo-controlled trials in non-renal lupus (13) and renal lupus (14) did not find statistically significant differences for their primary end-points. Nevertheless, national and international guidelines recommend rituximab for patients with lupus refractory to conventional therapy, supported by real world evidence from registries that continue to report its widespread use and effectiveness (3, 4, 15-19). In England, rituximab is recommended for patients with moderate or severe SLE who have failed to respond to at least two immunosuppressive therapies, and either continue to have clinically significant disease activity or require high dosages of prednisolone (4, 20). The B cell activating factor (BAFF)-neutralizing monoclonal antibody belimumab was the first biologic licensed for the treatment of lupus following two large phase III clinical trials, BLISS 52 (21) and BLISS 76 (22), and has recently been shown to be effective for renal lupus (23). However, the limited criteria permitting the use of belimumab treatment in England (4), based on an assessment by National Institute for Clinical Excellence which takes into account therapeutic benefit and cost effectiveness, results in far fewer patients with active, refractory disease receiving belimumab compared to rituximab (24).

A number of explanations have been proposed for the variable responses reported for rituximab (25). One mechanism that may limit rituximab's effectiveness is the rise in BAFF levels after B cell depletion (26, 27). Elevated serum BAFF levels can be sustained beyond initial B cell repopulation and can distinguish lupus relapse from ongoing disease remission following rituximab (28). For some lupus patients repeated cycles of rituximab resulted in ever higher serum anti-dsDNA antibody levels, which were associated with disease flares and escalation of serum BAFF levels (28). We therefore hypothesised that targeting BAFF would reduce the frequency of flares after rituximab (29). Inhibition of BAFF may also delay B cell repopulation, which has been associated with improved clinical outcome after rituximab (30). Thus, we designed a phase II clinical trial to gather preliminary evidence for the effectiveness and safety of this treatment regime for patients with lupus. To maximise relevance to real world practise, only patients for whom their physician had already recommended rituximab therapy in accordance with national commissioning criteria (4, 20) were enrolled in the trial.

METHODS

Design Overview

A detailed protocol and statistical analysis plan for BEAT LUPUS (BElimumab After b cell depletion Therapy in patients with systemic LUPUS erythematosus) have been published (31, 32). BEAT-LUPUS is a 52-week phase IIb, multicentre, UK based (16 centres), randomised, double blind, placebo-controlled parallel group superiority clinical trial investigating the safety and efficacy of belimumab administered 4 to 8 weeks after the first infusion of B cell depletion therapy (rituximab) in patients with SLE. The Hampstead Research Ethics Committee-London (reference 16/LO/1024) and the Medicines and Healthcare products Regulatory Agency (MHRA) approved the protocol. University College London sponsored the trial. The study was conducted in accordance with the principles of the Declaration of Helsinki Good Clinical Practice guidelines. All patients provided written informed consent before enrolment.

Setting and Participants

Eligible patients were aged between 18 and 75 years fulfilling classification criteria for SLE (4) and had to have a positive anti-dsDNA antibody test at least once in the past 5 years, and due to be treated with rituximab due to failure of conventional therapy according to NHS England guidelines and the British guidelines for the management of SLE in adults (4, 20). A second eligibility screen occurred no less than 10 days before randomisation to exclude patients who had required intravenous antibiotics for infections developing after rituximab therapy, or low IgG (<4g/L) or neutropenia ($<1x10^9$/L). A full list of the inclusion and exclusion criteria has been previously published (31) and the full protocol is available in Supplementary material.

Randomisation and Interventions

After providing written informed consent, participants were allocated to receive either belimumab or placebo treatment (1:1) using a secure online randomisation service provider. Treatment allocation was performed using a minimisation approach incorporating a random element, with an overall probability of 85% that the under-represented treatment would be selected, to ensure balance in the stratifying factors between the two randomised groups (33). Minimisation reduces the imbalance of certain key characteristics in the active treatment and placebo arm at treatment allocation. The characteristics (factors) minimised on were CD19 count (performed locally at each site in the routine laboratory) 7-10 days before randomisation (above or below $0{\cdot}01x10^9$/l) to account for variability in B cell depletion which could affect response, the presence or absence of anti dsDNA antibodies (positive or negative at first screen), and whether patients had active renal disease at first screen (BILAG-2004 A or B renal score; see Outcomes and Follow up section and Supplement for further explanation). The participants, investigators, sponsor and the clinical team caring for each patient were masked to treatment assignment until unblinding occurred in December 2020 (last patient last visit, April 2020). Only the allocated pharmacist preparing the trial treatment, the unblinded site monitor and the trial statistician were aware of the treatment allocation.

Before randomisation, in particular during the 4 to 8 weeks period after first screening, when intravenous rituximab was administered, treatment was entirely at the physician's discretion, although the rituximab dose was fixed (1g administered twice, 2 weeks apart). The first infusion of rituximab occurred within 1 week after the first

screen. Participants received intravenous belimumab (as per standard dosage regime - 10mg/kg) or placebo, at randomisation (week 0), 2, 4 weeks, and then every 4 weeks through to 52 weeks. Adherence was assessed as being the successful administration by infusion of the participant's trial treatment (placebo or belimumab) at each visit between randomisation and week 48 inclusive.

Participants were permitted to receive up to 20mg prednisolone/day from randomisation. Investigators were encouraged to taper prednisolone dosage to half the initial dose by 6 months after randomisation. Only the immunosuppressants methotrexate, mycophenolate or azathioprine were allowed after randomisation; the maximum advised dose of mycophenolate was 1g/day, azathioprine 1mg/kg, and methotrexate 15mg/week. Background anti-malarial drugs were permitted at first screen but no dose changes allowed thereafter.

Outcomes and Follow-up

The primary outcome measure was serum IgG anti-dsDNA antibody levels at 52 weeks. Serum total IgG anti-dsDNA antibody levels (normal value < 20 IU/ml), was analysed by a commercially available ELISA (Abnova, Taiwan) in a central lab at University College London. Secondary outcomes included time from randomisation to first moderate (defined as ≥2 BILAG-2004 B flares, but no A flare) or severe disease flare (defined as ≥1 BILAG-2004 A flare) (34, 35). BILAG categorises disease activity into five levels (Grade A: highest activity to E: never active) for each of 9 organ systems. A flare requires worsening or new manifestations of lupus (34, 36).

Other key secondary outcomes were cumulative dose of steroid, proportion of participants with a prednisolone dose ≤ 7·5 mg/day at weeks 48 and 52, and proportion of patients successfully reducing steroid dose by 50% (if randomisation dose ≥ 10 mg) or ≤5mg/day (if randomisation dose <10 mg) without flaring. To assess safety, the proportion of patients with (serious) adverse events at 52 weeks were included as secondary outcomes. Adverse events were systematically captured at study visits every 4 weeks. Patients who stopped trial treatment were encouraged to attend subsequent trial visits (particularly week 52) to collect data. See Supplement for additional information.

Statistical analysis

The statistical analysis plan for BEAT-LUPUS has previously been published (32). The sample size calculation was based on change in anti-dsDNA antibody levels in a previous cohort of lupus patients treated with rituximab. From this dataset, assuming the standard deviation of the week 52 log anti-dsDNA measurements was 1.7 and the correlation between baseline and week 52 to be 0.55, we calculated that 22 evaluable participants per group would be sufficient to detect a difference of 1.2 in log anti-dsDNA antibody levels at 5% significance with 80% power. We assumed that 20% of participants would fail to attend the 12-month follow-up visit, so aimed to recruit 28 participants per group.

An intention to treat approach was adopted for the primary and secondary endpoints. The intention-to-treat analysis set included all participants who were randomised and contributed the relevant data at the time point analysed. A secondary analysis of the primary outcome was also performed in the per protocol group, i.e. those who adhered to trial treatment before providing a serum sample at 52 weeks.

Separate linear regression ANCOVA (analysis of covariance) models, as pre-specified in the statistical analysis plan (32), were used to evaluate the difference in IgG anti-dsDNA antibody (log-transformed) between treatment arms at weeks 24 and 52. This model adjusted for CD19 count at randomisation ($<0{\cdot}01x10^9$/l or $\geq 0{\cdot}01x10^9$/l), previous renal involvement at screening, log anti-dsDNA levels at screening, and at randomisation. At the request of Annals editors, we also estimated our primary outcome using a longitudinal linear mixed effect model via restricted maximum likelihood. This model included fixed effects for log anti-dsDNA levels at screening and at randomisation, renal involvement at screening, CD19 at randomisation and log anti-dsDNA levels over (continuous) time on trial; and a random patient effect to account for clustering by patient. The primary outcome was the average difference between treatment groups, estimated as the treatment term plus the treatment-by-time interaction term at 52 weeks. Supportive analyses of the primary outcome measure were performed for those patients adhering fully to trial treatment (per protocol sample) using the ANCOVA and longitudinal linear mixed effect models as described above.

Analysis of secondary endpoints and biomarkers was performed using linear regression ANCOVA models for continuous outcomes, and logistic regression for proportions. Kaplan-Meier curves were used for time to flare (where between-group difference was assessed with an unadjusted log-rank test) using Cox regression to estimate hazards between treatment arms. Mean cumulative steroid and immunosuppressant dose were compared between groups by a two-sample t test. For all analyses, p values less than 0·05 were considered significant.
Statistical analysis was performed using STATA (15·1) and R software version 4·0·2 for Mac OS (R Foundation for Statistical Computing, Vienna, Austria). See Appendix for additional information.

Role of the funding source

This trial was supported by Versus Arthritis (grant number 20873), and the University College London Hospitals (UCLH) Biomedical Research Centre (BRC), which is funded through a grant from the National Institute of Health Research. GSK provided belimumab free of charge, as well as additional funding. One of the authors (MP) was supported in part by the Medical Research Council (MRC) through the MASTERPLANS (MAximizing Sle ThERapeutic PotentiaL by Application of Novel and Stratified approaches) Consortium, and by Versus Arthritis. Lupus UK provided some additional funding. Versus Arthritis and the UCLH BRC reviewed the relevant grant proposals and monitored progress of relevant aspects of the study. None of the funders of the study had any role in study design, data collection, adjudication, sample analysis, statistical analysis, data interpretation, manuscript preparation, or decision to submit results.

RESULTS

Patients

A total of 172 patients were assessed for eligibility, 67 were subsequently consented and screened, 65 received rituximab, and 52 patients were randomised to receive either belimumab or placebo between 2nd February 2017 and 28th March 2019 (Figure 1). The numbers of patients screened and randomised at each of the 16 sites are shown in Supplementary Figure 1. In the intention to treat sample that contributed to the primary endpoint at 52 weeks, 88% and 89% of trial treatment infusions were administered in the belimumab and placebo groups respectively. Of the 52 randomised patients, 43 patients attended and provided serum samples at week 52 and were included in the intention to treat analysis of the primary endpoint; 32 patients completed trial treatment as per protocol through to 52 weeks. Withdrawals from trial treatment were similar between belimumab and placebo (Figure 1). In those patients that withdrew from trial intervention, a lupus flare was present in 7 out of the 10 patients receiving placebo, and 3 out of the 10 patients on belimumab. Table 1 presents participants' baseline characteristics. The majority of patients were taking immunosuppressant therapy, had active disease (defined as at least one BILAG B score), and the median dose of prednisolone was 10mg/day in both groups (Table 1). 26 in the placebo and 24 in the belimumab arms were taking prednisolone and/or an immunosuppressant. Mean serum IgG anti-dsDNA antibody levels were slightly higher in the belimumab arm, though the median values were similar. Renal related baseline parameters in those patients with active renal disease (defined as BILAG-2004 A/B score) are provided separately (Supplementary Table 1).

Outcome Measures

In the primary, pre-specified ANCOVA model, at 52 weeks, IgG anti-dsDNA antibody levels were lower in patients treated with belimumab (geometric mean 47 IU/ml, 95% CI 25-88) compared to placebo (103 IU/ml, 95% CI 49-213); belimumab led to a 70% greater reduction from baseline, 95% CI 46-84%, p<0·001) (Figure 2); a greater reduction in IgG anti-dsDNA antibody levels was also observed in the belimumab group compared to placebo at 24 weeks (p<0·001). Serum IgG anti-dsDNA antibody levels are shown for each participant included in the intention to treat analysis (Supplementary Figure 2). The mixed-effect model produced similar results to our pre-specified model: patients randomised to belimumab achieved a 71% (95% CI 58-81%) greater reduction in IgG anti dsDNA levels relative baseline compared to placebo. Analysis of the per protocol sample of 16 patients in each arm that completed the trial treatment (pre-specified ANCOVA model), demonstrated that serum IgG anti-dsDNA antibody levels at 52 weeks were lower in patients treated with belimumab (geometric mean 43 IU/ml, 95% CI 20-96) compared to placebo (89 IU/ml, 95% CI 36-217); belimumab led to a 70% greater reduction from baseline, 95% CI 35-86% (Appendix Figure 1). A similar difference in the reduction in IgG anti-dsDNA in the per protocol sample from the belimumab group compared to placebo was also demonstrated using the longitudinal linear mixed model (reduction of 69%, CI 47-82%, p<0.001).

Compared to placebo, belimumab also reduced the risk of a severe flare (BILAG-2004 A) over the 52 weeks by 73% (hazard ratio 0·27, 95% CI 0·07-0·98, unadjusted log-rank p=0·033) (Figure 3A); there were 10 severe flares in the placebo and three in the belimumab group. Differences in treatment effect on the combined outcome of moderate and severe flares did not achieve statistical significance (hazard ratio 0·50, 95% confidence interval

0·21-1·20, unadjusted log-rank p=0·124) (Figure 3B). The details of each first severe BILAG 2004 A flare from randomisation are shown in Supplementary Table 2.

There was approximately 50% reduction in average daily dose of prednisolone from screening to week 52 in both groups (Appendix Figure 2). There was no difference between groups with respect to the cumulative steroid dose, proportion of patients successfully reducing steroid dose by 50% without flaring at 6 and 12 months and proportion of participants with a prednisolone dose ≤7·5 mg/day at weeks 48 and 52 (Supplementary Table 3). In the patients who received mycophenolate there was no difference in the cumulative dose between the two arms of the trial (Supplementary Table 3).

Safety

Table 2 presents the safety outcomes. There were no deaths. There were no differences in the incidence of infections of any grade including serious infections, serious (SAE) or total adverse events, nor withdrawals due to adverse events (Figure 1) between those patients treated with belimumab compared to placebo after rituximab. Two patients reported suicidal ideation captured by the Columbia-Suicide Severity Rating Scale in the belimumab treated group, but none in those receiving placebo. Depression-like symptoms were similarly frequent in both treatment arms (Table 2). Serum total IgG levels remained within the normal range in the majority of patients (Supplementary Figure 3A, B). At 52-weeks serum total immunoglobulin IgM and IgA levels were slightly lower in belimumab treated patients compared to placebo (Supplementary Figure 3C, D).

Secondary outcomes and post-hoc analysis

We did not observe any difference in serum C3 levels at 52 weeks (Supplementary Figure 4). For a subset of patients in whom samples were provided by patients for analysis, peripheral blood B cell numbers were very similar between the two arms up to 24 weeks, but were higher in the placebo group at 52 weeks (geometric mean in the belimumab group 0.012 $x10^9$/L, 95% CI 0.006-0.014 vs the placebo group geometric mean 0.037 $x10^9$/L, 95% CI 0.021-0.081, p = 0.031) (Supplementary Figure 5). No clinically meaningful differences were observed between the treatment-arms for other key secondary endpoints in the Statistical Analysis Plan (32) (Supplementary Table 4). In a post-hoc analysis, we found a greater proportion of patients with renal involvement during the trial achieved a complete renal response (and no new renal flare through to week 52) following belimumab treatment compared to placebo but the numbers of patients studied are small (Supplementary Table 5).

DISCUSSION

This investigator-initiated trial showed that among patients with SLE receiving standard of care for whom rituximab was indicated, treating with belimumab after rituximab significantly reduced serum IgG anti-dsDNA antibody levels by 70% (95% CI 46-84%) at 52 weeks when compared to rituximab alone. Combination therapy also reduced severe lupus flares by three-fold (hazard ratio 0·27, 95% CI 0·07-0·98) in the context of patients that had refractory active disease at the outset of the trial -- the majority were receiving one immunosuppressant and concomitant steroid therapy, as well as hydroxychloroquine.

Serum IgG anti-dsDNA antibody levels are associated with disease activity in patients with SLE and predict worsening disease (4, 37, 38), including flares after rituximab (28). Both rituximab and belimumab have been shown to decrease IgG anti-dsDNA antibodies in their respective placebo controlled trials though the former was not associated with clinical benefit (13, 14, 21, 22). Thus, it was reassuring that the combination therapy significantly reduced the risk of a severe (BILAG-2004 A) flare compared to rituximab alone. Severe lupus flares have been strongly associated with organ damage accrual or death over the 5 ensuing years (39). The observation that there were more patients who experienced worsening lupus disease associated with withdrawal from trial treatment in the placebo group (n=7) compared to the belimumab arm (n=3) is consistent with the effectiveness of belimumab in preventing disease exacerbation after B cell depletion with rituximab.

The frequency of adverse effects was as expected for patients with active SLE, and there was no difference between those receiving belimumab compared to placebo after rituximab. The total serum IgG levels remained above the normal range in the majority of participants and none of the patients had a serum IgG level below 5g/L after randomisation, a threshold considered to substantially increase the risk of infection (40). It is notable that 20% (n=13) of the participants who were screened and received rituximab failed a second screen a week before randomisation; five of these 13 participants required intravenous antibiotics for infection, highlighting the value of this safety check just before proceeding with belimumab therapy. Although the open label placebo-controlled CALIBRATE trial (Combination of Antibodies in Lupus Nephritis: Belimumab and Rituximab Assessment of Tolerance and Efficacy) did not find a significant difference in complete or partial renal response between belimumab and placebo when after cyclophosphamide and rituximab, it did provide reassuring safety data in patients with refractory lupus nephritis (41). Consistent with our results, B cell repopulation after rituximab was delayed by belimumab in the CALIBRATE study. In contrast to BEAT-LUPUS, all patients in the CALIBRATE study received cyclophosphamide at the start of the trial, which may have blunted the differences between the two arms.

National and international guidelines recommend prescribing the lowest possible corticosteroid dosage to minimise short and long adverse effects (3, 4). At least half of the patients in both groups halved their prednisolone dose in our study. In a trial of belimumab alone in SLE, only 25% of 865 patients achieved a 50% corticosteroid dose reduction (21), and in a combined analysis of the two principal trials of belimumab alone, average exposure to all corticosteroids increased from baseline for both treatment groups during the trial period (42). The dose of corticosteroids in an earlier trial of rituximab (above 6g over 52 weeks) (14) was much higher compared to below

316 3g in BEAT-LUPUS. Of relevance, the reduction in steroid dose was equivalent in the active and placebo arms
317 in a recent trial that demonstrated the beneficial effects of voclosporin in lupus nephritis (43).

318 This trial has limitations. Firstly, the sample size is small because at the time of the trial's inception there were no
319 published safety data on the combination of rituximab and belimumab; therefore, the trial was powered on anti-
320 dsDNA antibody levels as a surrogate endpoint. Generalizability is also likely reduced because to limit the risk of
321 adverse events due to immunosuppression, the dosages of concomitant DMARDs were lower than routinely
322 prescribed for patients with active disease, particularly renal patients receiving mycophenolate. This likely
323 reduced recruitment of patients with active nephritis by some physicians, although this restriction in dosage could
324 also be an advantage with respect to distinguishing between active drug and placebo. The trial was conducted in
325 England where rituximab is used as part of standard of care according to NHS England commissioning policy (4,
326 20) and thus the applicability of the results of this trial may be strongest for patients with SLE whose disease
327 remains active and are refractory to conventional therapy and/or requiring high dosages of corticosteroids. These
328 criteria, and the standard of care administered in England, may not match the use of rituximab in other countries.
329 About 60% remained on trial treatment through to 52 weeks, which was similar to the investigator initiated
330 CALIBRATE trial (41), and indeed retention of lupus patients in routine care (44).

331 Our data provide preliminary evidence of clinical benefit of belimumab after rituximab in a double-blind placebo-
332 controlled trial, and is consistent with the hypothesis that a surge in BAFF levels after rituximab can trigger
333 exacerbations in SLE (28). These findings support further exploration of belimumab after rituximab as the first
334 combination biologic therapy for patients with SLE, at least in patients who are refractory to conventional therapy
335 and/or requiring high dosages of corticosteroids.

Contributors

PM, KC, DAI, CD, CG, and MRE planned and designed the study. MS, LRS, BEAT-LUPUS Investigators, DAI, CG, and MRE recruited the patients and contributed to the data collection. MS, CG and MRE adjudicated the disease activity scoring. MS and MP analysed the central lab ELISA and flow cytometry. MS, AET, LRS, KC, CD, CG and MRE analysed and interpreted the data. MS, AET and KC accessed and verified the underlying data. All the authors contributed to critical review, revision and approval of the results and manuscript.

Declaration of interest

MRE has received grant/research support from GSK. MRE and CG have been members of the speaker's bureau for GSK and have received consultancy fees for attending advisory boards. CG also reports consultancy fees from AbbVie, Amgen, Astra-Zeneca, the Center for Disease Control and Prevention, Sanofi and UCB, personal fees for speakers' bureau from UCB, fees for contributing to manuscripts from MGP and grant funding to Sandwell and West Birmingham Hospitals NHS Trust from UCB for systemic lupus erythematous (SLE) research studies unrelated to any therapeutic product. DAI reports personal fees from ImmuPharma, personal fees and non-financial support from Merck Serono, personal fees from Eli Lilly, personal fees from Astra Zeneca, personal fees from Servier, during the conduct of the study.

Data sharing

Data that underlie the results presented here will be shared upon reasonable request whilst preserving patient anonymity.

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Figure Legends

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram of trial participants. The number of patients who contributed to the primary endpoint analysis at 52 weeks is shown. The numbers of patients who contributed to each set of results is presented in the relevant figure or table and depended on attendance at relevant trial visits and provision of samples.

Figure 2. Serum IgG anti-dsDNA antibody levels during the trial from screening to 52-weeks (intention-to-treat analysis). Separate linear regression ANCOVA models were fitted to evaluate the difference in IgG anti-dsDNA antibody levels at 24 and 52 weeks from randomisation between belimumab or placebo adjusted for baseline (screening* and randomisation) IgG anti-dsDNA antibody values, CD19 at randomisation (above or below $0{\cdot}01x10^9$/l), and the presence of renal involvement at screening. Geometric means (unadjusted) with 95% confidence intervals are shown, and the p values at week 52 (primary endpoint) and 24 (secondary endpoint) are provided. All patients who had undergone randomisation were eligible to be included in the intention to treat analysis but samples were not provided by patients at some time points as indicated.
** Screening refers to the first screening visit before rituximab; randomisation (week 0) occurred 4 to 8 weeks after this screening.*

Figure 3. Time to first flare over the 52 weeks of the trial (intention-to-treat analysis). (A) Time to first severe flare (defined as BILAG-2004 ≥ 1A). **(B)** Time to first severe (defined as BILAG-2004 ≥ 1A) or moderate flare (defined as BILAG-2004 ≥ 2B). Kaplan-Meier curves show time to flare (where between-group difference was assessed with an unadjusted log-rank test) and cox regression was used to estimate hazards between treatment arms. BILAG-2004 = British Isles lupus assessment group – 2004.

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