

Low-dose belimumab for patients with systemic lupus erythematosus at low disease activity: protocol for a multicentre, randomised, double-blind, placebo-controlled clinical trial

Fangfang Sun ,¹ Wenyan Huang,¹ Jie Chen,¹ Liling Zhao,¹ Danting Zhang,¹ Xiaodong Wang,¹ Weiguo Wan,² Sheng-Ming Dai,³ Sheng Chen,¹ Ting Li,¹ Shuang Ye¹

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¹Department of Rheumatology, Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

²Department of Rheumatology, Huashan Hospital, Fudan University, Shanghai, China

³Department of Rheumatology and Immunology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China

Correspondence to

Dr Shuang Ye; ye_shuang2000@163.com

ABSTRACT

Introduction SLE is a chronic inflammatory systemic autoimmune disease with relapsing–remitting pattern. B-lymphocyte stimulator was involved in the pathogenesis of SLE. The humanised monoclonal antibody belimumab with 10 mg/kg was effective for active patients. However, the efficacy of low-dose belimumab for prevention of disease flares in patients with SLE with low disease activity is to be explored.

Methods and analysis This is a multicentre, randomised, double-blind, placebo-controlled clinical trial. Patients who have Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) scores no higher than 6; with no A score or no more than one B score on the British Isles Lupus Assessment Group (BILAG) scale; and who are treated with prednisone (≤ 20 mg per day) at screening will be enrolled. 334 adults will be randomly assigned in a 1:1 ratio to receive intravenous 120 mg belimumab or placebo (saline) arm on weeks 0, 2, and 4, and then every 4 weeks until 48 weeks, with standard of care. The primary outcome measure is a composite index of severe or mild-to-moderate disease flares (SELENA-SLEDAI Flare Index) within 52 weeks. Secondary outcomes include the percentage of severe flare, the percentage of mild-to-moderate flare, time to first disease flare, changes in prednisone dose, SELENA-SLEDAI, as well as BILAG score, the percentage of patients achieving prednisone free and safety analysis.

Ethics and dissemination The protocol has been approved by the Ethics Committee of the Renji Hospital, Huashan Hospital and the Sixth People's Hospital. The trial has been registered and the detailed information is available at <https://clinicaltrials.gov/ct2/show/NCT04515719>. The results of this clinical trial will be submitted for publication in peer-reviewed journals and key findings will also be presented at national and international conferences.

Trial registration number NCT04515719.

INTRODUCTION

SLE is a chronic systemic autoimmune disease with the features of recurrent disease flares. B-lymphocyte stimulator (BLyS) is a

key molecule which is associated with active SLE.¹ Belimumab, a human monoclonal antibody targeting BLyS, was the first Food and Drug Administration (FDA)-approved biological agent for patients with active SLE. The BLISS-52, BLISS-76 and BLISS-North East Asia (NEA) phase III trials demonstrated that treatment with 10 mg/kg belimumab intravenously on the background of standard of care was effective in reducing disease activity compared with placebo.^{2–3} Post hoc analysis of the BLISS trials also suggested that belimumab was effective in attaining Lupus Low Disease Activity State (LLDAS).^{4,5} Besides, the NEA trial identified that patients in the belimumab group had a significant lower risk of severe flare than that in the placebo group (22% vs 12%, $p=0.0004$).⁶ Taking a deeper look at the data, the efficacy of 1 mg/kg belimumab was similar with that of 10 mg/kg in terms of both Systemic Lupus Erythematosus Responder Index-4 (SRI-4) and LLDAS, especially in BLISS-76 with longer follow-up.⁴

However, in the real world, besides from reducing disease activity for active patients, prevention of recurrent disease flares is another important clinical problem to be solved in relative stable patients.⁷ Keeping lupus in quiescence is of importance for long-term organ protection. Nevertheless, the mechanism of relapse is still unknown, and the contribution of BLyS to lupus flares is yet to be explored. As the first FDA-approved biological in SLE, the efficacy of belimumab in patients with low disease activity in prevention of disease flares has not been thoroughly studied.

Here, we try to carry out this study to evaluate the efficacy and safety of low-dose belimumab in Chinese patients with low-grade SLE.

METHODS AND ANALYSIS

Study design

This multicentre, China-based, randomised, double-blind, placebo-controlled clinical trial will be carried out at four centres in Shanghai, China. The study is aimed to investigate the efficacy and safety of low-dose belimumab in patients with lupus with low disease activity for prevention of disease flares. We hypothesise that there will be a reduced flare rate in low-dose belimumab arm compared with placebo arm within 52 weeks. Considering that the belimumab is 120 mg per vial, and the average body weight of Asian population is around 60 kg,⁸ thus a fix dose of 120 mg belimumab, that is, approximately 2 mg/kg is administrated in this study. Belimumab and placebo will be given intravenously until week 48. The observation period is 52 weeks.

The trial began recruitment in March 2021.

Study population

Patients with SLE aged 18 years or older, fulfilled the 2012 Systemic Lupus International Collaborating Clinics criteria⁹ and manifested low disease activity, defined as Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI)¹⁰ score ≤ 6 at the time of enrolment, no British Isles Lupus Assessment Group (BILAG)¹¹ A score and at most one BILAG B score, will be included. All candidates receive a stable treatment of no more than 20 mg per day prednisone, hydroxychloroquine or immunosuppressive agents for more than 30 days. Detailed inclusion and exclusion criteria are shown in [box 1](#).

Randomisation and blinding

This is a randomised, double-blinded trial. Stratified blocked randomisation is applied. Participants will be randomly assigned (1:1) to receive either a fixed dose of 120 mg (~2 mg/kg) belimumab or placebo (saline) on the background of their standard therapy in block sizes of four by a computer algorithm. Block randomisation is applied to ensure the balance of sample sizes between groups. Randomisation is stratified according to trial centre (Renji Hospital South Campus, Renji Hospital West Campus, Huashan Hospital, the Sixth People's Hospital) and a state of LLDAS or non-LLDAS at baseline. LLDAS is defined as SELENA-SLEDAI score ≤ 4 points, no activity in any major organ or no new disease activity features, daily prednisone ≤ 7.5 mg and Physician's Global Assessment of disease activity (PGA) ≤ 1 .⁵ Randomisation codes and lists will be generated online by a statistician.

Patients and investigators involved in patient assessments, follow-up and statistical analyses are masked to group allocation. The trial pharmacist and statistician involved in the randomisation procedure are unblinded

Box 1 Inclusion and exclusion criteria

Inclusion criteria

- ▶ Aged 18 years or older.
- ▶ Participants meeting the 2012 Systemic Lupus International Collaborating Clinics criteria: (1) fulfilment of at least four criteria, with at least one clinical criterion and one immunological criterion or (2) lupus nephritis as the sole clinical criterion in the presence of ANA or anti-dsDNA antibodies.
- ▶ With low disease activity: Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index score ≤ 6 at the time of enrolment, no British Isles Lupus Assessment Group (BILAG) A score and no more than one BILAG B score.
- ▶ Candidates receive stable treatment of no more than 20 mg per day prednisone, hydroxychloroquine or immunosuppressive agents (mycophenolate mofetil, azathioprine, cyclosporine, tacrolimus, methotrexate, leflunomide) for more than 30 days.
- ▶ Participants are willing to join the trial and sign the informed consent.

Exclusion criteria

- ▶ Liver dysfunction (alanine aminotransferase >2 times the upper normal limits).
- ▶ Renal dysfunction (creatinine clearance rate <60 mL/min).
- ▶ Current pregnancy or breast feeding.
- ▶ Participants who were treated with cyclophosphamide within 6 months or B-cell targeted therapy (such as rituximab or belimumab) within previous 1 year.
- ▶ Herpes zoster infection within 3 months before screening.
- ▶ Participants with a history of malignancy within the last 5 years, except fully treated skin tumours (basal cell or squamous epithelial cell tumours) or cervical intraepithelial neoplasia.
- ▶ Active infection (such as hepatitis B defined by positive for hepatitis B surface antigen, HIV, tuberculosis, etc) at screening.

to the treatment. After initiation of the trial, the pharmacist who is unblinded will prepare the randomised infusion for each participant according to the randomisation code. Diluted belimumab was identical in appearance, size and colour with the placebo (normal saline).

An emergency hotline available 24 hours a day and 7 days a week will be provided for all the participants in case they experience a serious adverse event (SAE). Unblinding will only occur when the management of the SAE largely depends on the treatment allocation.

Trial treatment

Belimumab will be administrated intravenously at a fixed dose of 120 mg in week 0, week 2 and week 4, and then every 4 weeks until week 48. The placebo group will receive the same volume of normal saline at the same time points. A final efficacy and safety evaluation will be carried out at 52 weeks. The trial may be discontinued in case of adverse events (AEs) according to the severity and investigators' clinical decision.

All the participants receive the standard care of lupus, including ≤ 20 mg per day prednisone, hydroxychloroquine and/or immunosuppressive agents (mycophenolate mofetil, azathioprine, cyclosporine, tacrolimus, methotrexate, leflunomide, etc).

The doses of prednisone and immunosuppressive agents could be adjusted downward according to participants' disease activity and physicians' decision. If LLDAS is attainable, attempt to taper off prednisone is encouraged within 48 weeks.

When participants had a disease flare, escalation of immunotherapy will be needed according to the severity of lupus flares.

Trial endpoints

The primary outcome measure is the percentage of participants with disease flares within 52 weeks defined by SELENA-SLEDAI Flare Index (SFI). Mild-to-moderate flares are defined as one or more of the following criteria: (a) a change in SELENA-SLEDAI score of 3 points or more (but not to more than 12); (b) new or worsening rashes, cutaneous vasculitis, nasopharyngeal ulcers, serositis, arthritis or fever attributable to lupus; (c) increase in prednisone, but less than 0.5 mg/kg/day; (d) added non-steroidal anti-inflammatory drugs or hydroxychloroquine; (e) ≥ 1 increase in PGA (0–3). Severe flares are defined as one or more of the following: (a) change in SELENA-SLEDAI score to more than 12; (b) new or worsening central nervous system involvement, vasculitis, nephritis, myositis, thrombocytopenia (platelet count $< 60 \times 10^9/L$), or haemolytic anaemia (haemoglobin level $< 70 g/L$ or decrease in haemoglobin level $> 30 g/L$); (c) any SLE manifestation requiring doubling or an increase in dosage of prednisone to greater than 0.5 mg/kg per day; (d) added cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil or hospitalisation for lupus activity; (e) increased PGA to > 2.5 .

Secondary outcome measurements include the percentage of mild-to-moderate flares, the percentage of severe flares, the time to first disease flare, changes in prednisone dose, SELENA-SLEDAI and BILAG score from baseline to last visit, and the percentage of patients achieving prednisone free successfully within 52 weeks. Safety issue will also be collected until 4 weeks after the last infusion.

Exploratory outcomes include changes of complements, anti-dsDNA as well as immunoglobulin, and subgroup analysis aiming to investigate which population will benefit most from belimumab with prespecified factors including age, gender, SLE duration, SELENA-SLEDAI, BILAG, PGA, serology, baseline LLDAS attainment and prednisone dose.

Sample size calculation

The NEA study showed that 10 mg/kg belimumab reduced the severe flare rates in patients with active SLE significantly better than placebo (22% vs 12%, $p=0.0004$). Besides, according to the BLISS-52, BLISS-76 and the post hoc analysis, 1 mg/kg belimumab helped patients achieve comparable endpoints with 10 mg/kg group. Therefore, low-dose belimumab (120 mg per infusion, about 2 mg/kg) is chosen for the trial to prevent lupus flares among patients with low-grade SLE.

The sample size estimation was thus carried out with the reference to the flare rate of the placebo arm in our previous 'Met Lupus' trial enrolling similar population¹² and the reduction magnitude of flare rate borrowed from the NEA trial.

A sample size of 167 participants per group including an estimated 10% drop-out would provide the trial with 80% power at a two-sided alpha error of 0.05, yielding a minimum required enrolment of 334 participants.

Procedure

A total of 334 patients with lupus with low disease activity will be recruited in four centres: Renji Hospital South Campus and West Campus; Shanghai Jiaotong University School of Medicine; Huashan Hospital, Fudan University; the Sixth People's Hospital Affiliated to Shanghai Jiaotong University School of Medicine. The objective, protocols, potential benefits and risks of the trial will be thoroughly introduced to the candidates. All the participants will sign the informed consent as their will. Participants are able to withdraw the informed consent at any time during the trial.

Preliminary eligible patients with low lupus activity will be scheduled for a screening and the assignment of the informed consent. Medical history especially concerning the 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE, physical examination including temperature and body weight, concomitant medications and comorbidities will be collected. Laboratory examinations include complete blood cell count, urine routine test, hepatic and renal function, C reactive protein, erythrocyte sedimentation rate, anti-dsDNA body, ANA profile, immunoglobulin, and C3 and C4, anti-hepatitis antigen and T-SPOT.TB test. Disease activity including SELENA-SLEDAI score, BILAG score and PGA will be evaluated. Eligible candidates meeting the inclusion criteria will be scheduled for the first visit within 2 weeks of the screening day. Treatment allocation will be randomly assigned according to the random code generated by the statistician, and the participants receive the first infusion accordingly after complete evaluation.

Participants in the belimumab or placebo arm will receive 120 mg belimumab or normal saline in the scheduled time points until 48 weeks. An additional visit will be carried out at 52 weeks.

Physical examination, possible AEs and concomitant medication will be recorded and disease activity (SELENA-SLEDAI, BILAG and PGA) as well as laboratory examinations will be evaluated at a 4-week interval. The laboratory tests include complete blood cell count, urine routine test, hepatic and renal function, C reactive protein, erythrocyte sedimentation rate, anti-dsDNA body, immunoglobulin, and C3 and C4. Disease flares according to SFI criteria will be evaluated at each visit. A hotline will be also available for all the participants to ensure whether they experience a disease flare or an unexpected AE. At this condition, an additional visit will

Table 1 Flow chart of this trial

Visits	Screening	Follow-up					
		Visit 1	Visit 2	Visit 3	Visit 4–13	Visit 14	Visit 15
Time points	–2 weeks	Week 0	Week 2	Week 4	4-week interval	Week 48	Week 52
Informed consent	√						
Medical history	√						
Physical examination	√		√	√	√	√	√
HbsAg	√						
T-SPOT	√						
BILAG	√			√	√	√	√
SLEDAI	√			√	√	√	√
PGA	√			√	√	√	√
SFI			√	√	√	√	√
Lab routine*	√			√	√	√	√
ANA profile	√						
Anti-dsDNA	√			√	√	√	√
C3 and C4	√			√	√	√	√
Randomisation		√					
Belimumab/placebo	√	√	√	√	√	√	
Concomitant medication	√		√	√	√	√	√
Adverse event	√	√	√	√	√	√	√

*Includes complete blood cell count, urine routine test, hepatic and renal function, C reactive protein and erythrocyte sedimentation rate. BILAG, British Isles Lupus Assessment Group; PGA, Physician's Global Assessment of disease activity; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index; SFI, SELENA-SLEDAI Flare Index.

be scheduled, and thorough information as well as examinations will be documented. There will be an evaluation by investigators about whether participants will be withdrawn or continue in the trial. Subjects who experience a severe flare will be considered as having finalised the trial, and they will not be evaluated for further outcomes. Participants with mild-to-moderate flares will continue to be followed up. Patient compliance can be told by the counts of visits and infusion.

An AE is defined as any unwanted reaction during the trial, which is not always related to the medication. SAE is defined as conditions leading to unscheduled hospitalisation or extension of the original hospitalisation duration and severe disability or death. The collection of AEs will last until 4 weeks after the last infusion.

Any participant who is unwilling to continue for any reason could withdraw informed consent at any time during the trial. Discontinuation of study may occur when participants experience SAE or pregnancy or fatal comorbidities or any other conditions that investigators consider that the subject is unsuitable to continue. The detailed protocol according to the criteria of Standard Protocol Items: Recommendations for Interventional Trials is demonstrated in [table 1](#).

Statistical analysis

The full analysis set is according to the criteria of intention-to-treat population, including all eligible subjects meeting

the inclusion criteria who underwent treatment allocation and received at least one infusion of the treatment. The per-protocol population includes subjects from the intention-to-treat population and excludes patients with major protocol violations. Continuous data are presented as mean±SD, and categorical variables are presented as number (per cent).

The primary and secondary efficacy as well as safety analysis will be interpreted in the intention-to-treat population using the χ^2 test for categorical variables and the two-sample Student's t-test for continuous variables. Flare-free and severe flare-free survivals were analysed by Kaplan-Meier curve. Subgroup analysis will be plotted by forest map. The per-protocol set will be applied to sensitivity analysis to validate the robustness of the results.

An alpha level of 0.05 was used to define statistical significance. All statistical analyses will be performed with SAS software, V.9.4 (SAS Institute), SPSS software (V.22.0) and GraphPad (V.5.0).

Data collection

All data will be collected by investigators and recorded on a paper Case Report Forms. The participant's initials, data of birth, gender and enrolment number will be used for identification. The trial has been registered in ClinicalTrials.gov, and will be overseen by an independent Data Safety Monitoring Board.

DISCUSSION

SLE is a complicated systemic autoimmune disease. Numerous targeted treatments, such as type I interferon blockers, anti-interleukin-12/23 and Janus kinase inhibitors, have been tested aiming to control or reduce disease activity in patients with active SLE in the past decade.^{13–16} The efficacy measurements, therefore, are largely based on disease activity indexes, such as SRI (SLEDAI dominant) or BICLA¹⁷ (BILAG-based Composite Lupus Assessment). Belimumab is the first FDA-approved biologics for active lupus with a time-merit robustness of clinical evidence.^{2,3,6}

It is noteworthy that only few trials designated to address flare prevention as the primary endpoint in lupus, which is another key question in the management of SLE. According to our previous randomised trials and retrospective studies, on the background of standard of care, the annual flare risk of a patient with low-grade SLE (SLEDAI ≤ 6) was still approximately 30%–40%,^{12,18,19} indicating the unmet needs in clinical practice. Whether belimumab could serve as a flare-prevention tool among patients with SLE with low-grade disease is yet to be explored in a serious randomised controlled trial. The dosage of belimumab used in the current trial is based on the data of BLISS-52, BLISS-76 trials and their post hoc analysis, where the efficacy of both 1 mg/kg and 10 mg/kg belimumab was evaluated.^{2,3,6} Only a slight lower rate of SRI-4 and LLDAS attainment was observed in patients treating with 1 mg/kg belimumab compared with 10 mg/kg, especially in BLISS-76 with longer follow-up (SRI-4, 40.7% vs 43.2%; LLDAS 11.6% vs 14.4%).⁴ Thus, a fix dose of 120 mg, that is, approximately 2 mg/kg of belimumab is decided by investigators in the current clinical trial.

Using SFI as the primary endpoint has been validated in similarly designed previous trials,^{12,19} with the advantage of intention-to-treat component over solely BILAG-based or SLEDAI-based flare definitions, making it reliable and clinically meaningful. In addition, increasing evidence showed the importance of treat-to-target (T2T) strategy, that is aiming at LLDAS if remission cannot be achieved in patients with SLE for long-term organ protection.⁵ Baseline T2T is also associated with fewer disease flares.^{20,21} Patients with low-grade disease but not achieving T2T endpoint yet have greater needs of this flare-prevention endpoint compared with participants with T2T at screening. Whether belimumab has differential effect in these two subpopulations is one of the important issues to be demonstrated. Therefore, prestratification on LLDAS is applied.

Another important question which has been addressed as one of the secondary endpoints is the prednisone free issue. The glucocorticoid-sparing effect has been well established in BLISS trials among patients with active lupus. Nevertheless, the withdrawal of glucocorticoid remains to be difficult.^{22–24} A recent French randomised trial showed that prompt discontinuation of 5 mg/day prednisone in clinically quiescent patients of SLE may

increase the risk of disease flares by threefold.²⁵ However, gradual withdrawal seemed to be a safe choice according to the results from a Toronto cohort.²⁶ To minimise the damage of chronic glucocorticoid exposure,²⁷ whether belimumab could help participants with mild disease achieving this goal will be evaluated in this study.

In conclusion, this trial will focus on low-dose belimumab as an option of flare-prevention strategy for patients with low-grade activity SLE.

Contributors WH and FS contributed equally to the drafting of the manuscript. SY and TL designed the trial. FS and DZ did the sample size calculations and statistical planning of the trial. WH, DZ, JC and LZ participated in data collection. XW, WW, S-MD and SC were involved in supervision of the study. All authors revised the manuscript and agreed on the final version.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The clinical trial is conducted in accordance with the Good Clinical Practice Guidelines, Declaration of Helsinki and regulations of clinical studies in China. All the participants will sign the informed consent before the initiation of the procedures. The study was approved by the Ethics Committee of the Renji Hospital, Huashan Hospital and the Sixth People's Hospital. All the significant amendment to the protocol will be submitted to each ethics for approval. Any SAE with detailed information about date, severity, causal relationship to the medication and the clinical management should be reported to the principal investigator and ethics within 24 hours.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

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ORCID iD

Fangfang Sun <http://orcid.org/0000-0003-2570-4576>

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