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ORIGINAL ARTICLE

Response to belimumab among patients with refractory lupus nephritis: a real-world observational retrospective multicenter study

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Abstract

Objectives Belimumab is a biological agent approved for the treatment of active lupus nephritis (LN), but its efficacy on refractory lupus nephritis (LN) is unknown. This study aims to evaluate the efficacy and safety of belimumab in Chinese patients with refractory LN.

Methods This multicenter, observational, and retrospective study enrolled patients with refractory LN who failed induction therapy with steroids, cyclophosphamide, mycophenolate, and calcineurin inhibitors and received 24-week belimumab treatment before data analysis. Treatment outcomes include the overall clinical response (physician judgment, disease activity, organ damage) and renal response (complete renal response, partial renal response, no renal response). Laboratory indices and adverse events were recorded as well.

Results Of the 45 patients enrolled in the study, 6 (13.3%) achieved complete renal response, 19 (42.2%) achieved partial renal response, and the overall renal response rate was 55.6%. Median rSLEDAI decreased from 12 (IQR 8–12) at baseline to 8 (IQR 4–8) ($p < 0.0001$), 4 (IQR 4–8) ($p < 0.0001$) at 12 and 24 weeks. Mean urinary protein decreased more than 50% from 3.2 g/24 h at baseline to 1.0 g/24 h at 24 weeks ($p < 0.0001$). The conditions of hypoalbuminemia and hypocomplementemia had also gradually improved. The levels of autoantibodies showed a significant downward trend. Additionally, 9 (20.0%) patients successfully reduced the dosage of prednisone to a safe range, and 3 of them achieved their treatment goal of prednisone cessation. The mean prednisone dosage decreased from 32.7 mg/day at baseline to 18.6 mg/day ($p < 0.0001$), 13.3 mg/day ($p < 0.0001$) at 12 and 24 weeks. There were 3 adverse events reported, including 2 cases of infection, and 1 case of allergy. No serious events occurred during the follow-up.

Conclusions Belimumab is effective and safe when used in clinical practice, which can be considered as an add-on therapy for refractory LN.

Key Points
- *A multicenter observational study in the real clinical settings of China.*
- *First revealed the efficacy and safety of belimumab in Chinese patients with refractory LN.*

Keywords Belimumab · Effectiveness · Refractory lupus nephritis · Safety · Systemic lupus erythematosus

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Introduction

Systemic lupus erythematosus (SLE) is a chronic, remitting autoimmune disease with multiple organ involvement [1]. Lupus nephritis (LN) is one of the most common manifestations of SLE, which occurs in 25 to 60% of SLE patients [2]. LN is associated with a high risk of infection as well as damage accumulation and is considered as a major cause of morbidity and mortality in SLE [2–4]. In recent decades, although the therapy of glucocorticoids combined with immunosuppressive drugs has significantly improved the long-term prognosis of LN patients [5], a significant number of them remain non-responsive to first-line immunosuppressive drugs or experience a relapse during maintenance therapy. Ten to 30% of LN patients will eventually progress to end-stage renal disease (ESRD) [6, 7].

Refractory lupus nephritis implies an insufficient or no response to lupus nephritis therapy, but there is still no clear and consensus definition for it. Different definitions are mainly based on the use of immunosuppressive drugs and the course of treatment [8]. As for the treatment for refractory LN, the 2019 updated EULAR and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of LN indicated that mycophenolate mofetil (MMF), cyclophosphamide (CYC), and calcineurin inhibitors (CNIs, especially tacrolimus (TAC)) as multi-target therapy are recommended in refractory LN. B cell depletion treatment with Rituximab (RTX) is also recommended as monotherapy or add-on therapy. Furthermore, the guideline mentioned that other biological agents such as obinutuzumab and belimumab may be beneficial in refractory LN [9].

Belimumab, a biological agent targeting B lymphocyte-stimulating factor (BLyS), inhibits BLyS binding to B cells, which regulates B cell activation [10, 11]. Its efficacy and safety in the treatment of SLE have gradually been confirmed in clinical trials. In 2020, the BLISS-LN study [12], a 2-year, randomized, controlled trial of belimumab in lupus nephritis, leads to the approval of belimumab for the treatment of active LN in the USA and the European Union. However, it is still unknown whether it is effective in refractory LN. In this study, we observed the efficacy and safety of belimumab in refractory LN patients who were followed in the real clinical settings of China.

Methods

Patients and study design

Physicians enrolled patients who received 24-week belimumab treatment in four medical centers (Guangdong, China) during December 2019 to March 2022. All patients were diagnosed as SLE and LN according to the American College of Rheumatology (ACR) criteria [13]. And all fulfilled the criteria of refractory LN, defined as failure to respond to the induction therapy with CYC, MMF, or multi-target treatment for at least 6 months [9]. Patients with unexplained discontinuation or loss to follow-up who simultaneously received other biological agents, or combined with acute infectious diseases, malignant tumor, or renal transplantation, were excluded (Fig. 1).

All patients were treated with belimumab by intravenous infusion (single dose of 10 mg/kg) at weeks 0, 2, 4, 8, 12, 16, 20, and 24 for a total of 8 treatments. Patients used glucocorticoids and immunosuppressive drugs simultaneously, of which dosages were determined by physicians.

Evaluation of outcomes

Response to belimumab treatment included the overall clinical response and renal response. The assessment of the overall clinical response was as follows: Physician's Global Assessment (PGA)-like scale [14] to see physician judgment, the SLE Disease Activity Index-2000 (SLEDAI-2K) [15] to assess disease activity, and the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) to evaluate irreversible damage. In addition, renal SLEDAI (r-SLEDAI) was used to assess LN activity, which consists of the four renal-related items of SLEDAI-2K. It includes hematuria (> 5 red blood cells/high-power field), pyuria (> 5 white blood cells/high-power field), proteinuria (> 0.5g/24 h or urine protein/creatinine ratio > 0.5), and urinary casts (heme, granular, or red blood cell), each of which is scored as 4 points. Patients with r-SLEDAI score ≥ 8 were considered as active LN [16].

The primary endpoint was the renal response to 6 months of belimumab treatment, including complete renal response (CRR), partial renal response (PRR), and no renal response (NRR) [17]. CRR is defined as proteinuria less than 0.5 g/24 h, while PRR is defined as an over 50% reduction of proteinuria from baseline and less than 3 g/24 h. Both CRR and PRR require an estimated glomerular filtration rate (eGFR) that was normal or elevated no more than 10% of the normal range and no active urinary sediments. Failure to CRR or PRR is considered NRR.

Safety assessments comprised the records of adverse events during the observation period according to the definition of Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [18], and statistics on any reasons for drug discontinuation, including adverse events, disease flare, and other subjective factors.

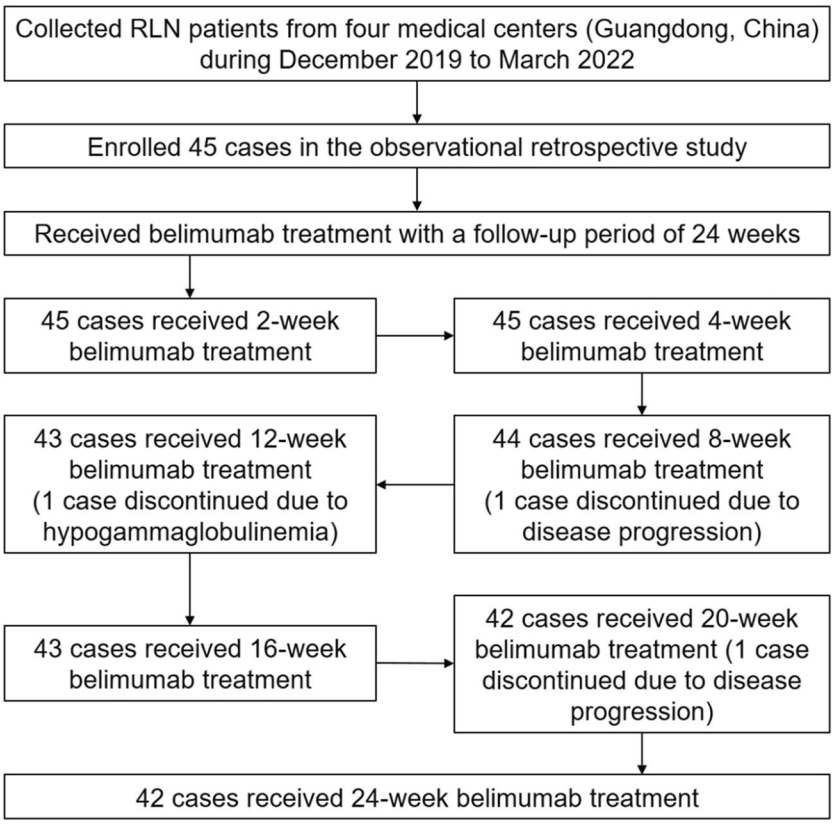

Fig. 1 Flow chart of the study design and patient disposition

Statistical analyses

The results of categorical variables were expressed as frequency, using a chi-square test to compare differences. Quantitative variables that were normally distributed were expressed as mean and standard deviation (SD) compared by a paired *t* test, while non-normally distributed variables were expressed as median with interquartile range (IQR) compared by Wilcoxon test. All $p < 0.05$ was considered statistically significant. SPSS 26.0 software and R software package lme4 were used for statistical analysis in this study.

Results

Baseline patient characteristics

The study included a total of 45 RLN patients from 4 Chinese medical centers who had received belimumab treatment with a follow-up period of 24 weeks. Demographic, pathological, and serologic features and concomitant treatments are summarized in Table 1. There were 41 (91.1%) female patients and 4 (8.9%) male patients, with a mean age of 29.0 ± 9.7 years, a mean SLE duration of 101.6 ± 64.7 months, and a mean LN duration of 88.0 ± 58.7 months. Renal biopsy was available in 17 patients, of which 9 cases were diagnosed as class IV LN, 4 cases were diagnosed as class IV + V LN, 2 cases were diagnosed as class III + V LN, 1 case was diagnosed as class III LN, and 1 case was diagnosed as class V LN.

Compared with the general SLE patients, RLN patients had a certain degree of renal impairment according to the baseline laboratory parameters. Enrolled RLN patients showed poor renal function, with a mean eGFR of 93.9 ± 46.4 ml/min/1.73 m^2 and a mean urinary protein level of 3.2 ± 2.6 g/24 h. In terms of serological characteristics, 28 (62.2%) patients had hypoalbuminemia, and 40 (88.9%) patients had hypocomplementemia. Besides, 38/38 (100%) patients were positive for autoantibodies, with either elevated ANA antibodies (37/38, 97.4%) or anti-dsDNA antibodies (28/37, 75.7%).

In baseline assessment, the median SLEDAI-2K was 16 (IQR 12–18), the median PGA was 3.0 (IQR 3.0–3.0), the median rSLEDAI was 12 (IQR 8–12), and median SDI was 1 (IQR 1–2). Overall, 41 (91.1%) patients were in a state of moderate to severe disease activity, and 36 (80.0%) patients had pre-existing organ damage.

As for concomitant medications, all the patients initiated belimumab treatment combined with conventional strategies which had showed poor response in the past more than 6 months. The average dose of glucocorticoids at baseline was 32.7 ± 21.1 mg, and 34 (75.6%) patients received oral

Table 1 Baseline characteristics of patients with refractory LN before belimumab treatment

	N = 45
General information	
Gender (female) (*N*, %)	41 (91.1)
Age (years) (mean ± SD)	29.0 ± 9.7
Duration of SLE (months) (mean ± SD)	101.6 ± 64.7
Duration of LN (months) (mean ± SD)	88.0 ± 58.7
Kidney-biopsy LN classification (*N*, %)	
III class	1 (2.2)
IV class	9 (20.0)
V class	1 (2.2)
III and V class	2 (4.4)
IV and V class	4 (8.9)
No biopsy	28 (62.2)
Laboratory parameters	
eGFR (ml/min/1.73 m^2) (mean ± SD)	93.9 ± 46.4
Urinary protein (g/24 h) (mean ± SD)	3.2 ± 2.6
Active urinary sediments (*N*, %)	20 (50.0)
Antinuclear antibody (ANA) positivity (*N*, %)	37/38 (97.4)
Anti-double-stranded DNA (anti-dsDNA) antibody positivity (*N*, %)	28/37 (75.7)
Hypoalbuminemia (*N*, %)	28 (62.2)
Hypocomplementemia (*N*, %)	40 (88.9)
Disease assessment	
SLEDAI-2K score (median, IQR)	16 (12, 18)
Moderate to severe SLE disease activity (N, %)	41 (91.1)
PGA score (median, IQR)	3 (3, 3)
SDI score (median, IQR)	1 (1, 2)
Pre-existing organ damage (*N*, %)	36 (80.0)
rSLEDAI score (median, IQR)	12 (8, 12)
Concomitant medications	
Prednisone dose (oral, mg/day) (mean ± SD)	32.7 ± 21.1
Glucocorticoids in medium to large dosage (*N*, %)	34 (75.6)
HCQ (*N*, %)	36 (80.0)
HCQ dose (oral, g/day) (mean ± SD)	0.39 ± 0.05
MMF (*N*, %)	33 (73.3)
MMF dose (oral, g/day) (mean ± SD)	1.38 ± 0.39
Used months of MMF initiated belimumab treatment (mean ± SD)	58.96 ± 45.65
CsA (*N*, %)	5 (11.1)
CsA dose (oral, mg/kg/day)	3.50 ± 0.70
Used months of CsA initiated belimumab treatment (Mean ± SD)	14.5 ± 2.12
FK506 (*N*, %)	3 (6.7)
FK506 dose (oral, mg/kg/day)	0.06 ± 0.03
Used months of FK506 initiated belimumab treatment (mean ± SD)	23.33 ± 21.46
CYC (*N*, %)	4 (8.9)
CYC dose (intravenous, g/2 weeks)	0.45 ± 0.10
Used months of CYC initiated belimumab treatment (mean ± SD)	52.0 ± 31.05

glucocorticoid in medium to large dosage. Also, there was 80% concomitant use of hydroxychloroquine as a background therapy, with a mean dosage of 0.39 ± 0.05 g/day. Regarding immunosuppressive agents, 33 cases (73.3%) were on a maintenance regimen of MMF, as well as CsA in 5 cases (11.1%), CYC in 4 cases (8.9%), and FK506 in 3 cases (6.7%).

Efficacy

At the end of a 24-week belimumab treatment, complete renal response was achieved in 6 (13.3%) patients and partial renal response was achieved in 19 (42.2%) patients. The overall response rate was approximately 55.6%. According

to the analysis of the follow-up data, belimumab showed the advantage in controlling disease activity, improving renal function, and reducing glucocorticoid dosage, as shown in Table 2.

Disease activity and organ damage

We conducted the assessments of general disease activity and renal disease activity respectively at weeks 12 and 24 of the study, including SLEDAI-2K, PGA, and rSLEDAI scores (Fig. 2). The results showed a significant decrease in the activity indices among RLN patients treated with belimumab, indicating that the disease condition was under effective control. Median SLEDAI-2K significantly decreased from 16.0 (IQR 12.0–18.0) at baseline to 10.0 (IQR 4.0–12.0) ($p < 0.0001$), 6.0 (IQR 4.0–10.0) ($p < 0.0001$) at 12 and 24 weeks. Median PGA decreased from 3.0 (IQR 3.0–3.0) at baseline to 2.0 (IQR 1.0–2.0) ($p < 0.0001$), 1.0 (IQR 0–2.0) ($p < 0.0001$) at 12 and 24 weeks. Median rSLEDAI decreased from 12.0 (IQR 8.0–12.0) at baseline to 8.0 (IQR 4.0–8.0) ($p < 0.0001$), 4.0 (IQR 4.0–8.0) ($p < 0.0001$) at 12 and 24 weeks, respectively. In addition, the median SDI scores was 1.0 (IQR 1.0–2.0) at baseline. No significant damage progression was observed during the follow-up ($p = 0.06$).

Table 2 Follow-up indexes of patients with refractory LN during the belimumab treatment

	Baseline	12 weeks	*p*1 value	24 weeks	*p*2 value
Disease assessment (median, IQR)					
SLEDAI-2K score	16.0 (12.0, 18.0)	10.0 (4.0, 12.0)	< 0.0001	6.0 (4.0, 10.0)	< 0.0001
PGA score	3.0 (3.0, 3.0)	2.0 (1.0, 2.0)	< 0.0001	1.0 (0.0, 2.0)	< 0.0001
SDI score	1.0 (1.0, 2.0)	—	—	2.0 (1.0, 3.0)	0.06
rSLEDAI score	12.0 (8.0, 12.0)	8.0 (4.0, 8.0)	< 0.0001	4.0 (4.0, 8.0)	< 0.0001
Laboratory manifestations (mean ± SD)					
eGFR (ml/min/1.73 m^2)	93.9 ± 46.4	103.9 ± 45.5	0.07	106.6 ± 44.2	0.08
Urinary protein(g/24 h)	3.2 ± 2.6	1.8 ± 1.5	0.0013	1.0 ± 1.3	< 0.0001
Albumin (ALB)(g/l)	28.3 ± 6.5	34.8 ± 5.1	< 0.0001	36.1 ± 5.6	< 0.0001
C3 (g/l)	0.5 ± 0.2	0.7 ± 0.2	< 0.0001	0.7 ± 0.2	< 0.0001
C4 (g/l)	0.1 ± 0.1	0.2 ± 0.1	< 0.0001	0.2 ± 0.1	< 0.0001
ANA (U/ml)	188.7 ± 121.3	157.7 ± 125.9	0.02	150.0 ± 131.6	0.02
Anti-dsDNA (IU/ml)	183.6 ± 123.0	127.8 ± 117.2	0.001	122.7 ± 115.7	0.0007
IgG (g/l)	10.5 ± 5.5	8.6 ± 4.5	0.0009	9.2 ± 4.2	0.01
Concomitant medications (mean ± SD)					
Prednisone (mg/day)	32.7 ± 21.1	18.6 ± 11.7	< 0.0001	13.3 ± 8.9	< 0.0001
MMF (g/day)	1.4 ± 0.4	1.2 ± 0.4	0.0046	1.1 ± 0.4	< 0.0001

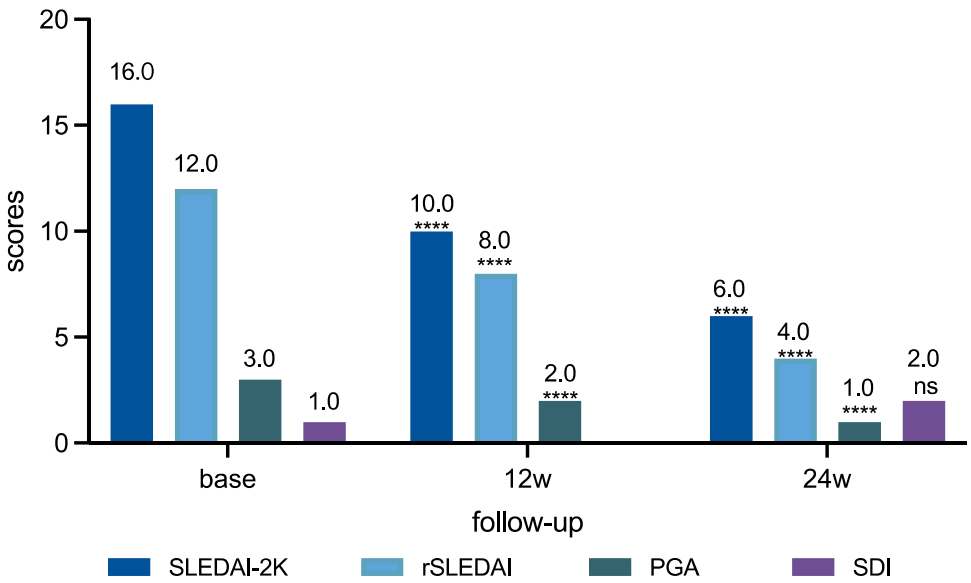

Fig. 2 Clinical outcomes in patients with refractory LN at baseline and after 12 and 24 weeks of belimumab treatment. SLEDAI-2K, rSLEDAI, and PGA score all showed a gradual decline. SDI was observed a slight increase, indicating no significant organ damage occurred during belimumab treatment (****$p < 0.0001$, ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$; ns, no significance)

Effects on kidney function

After initiating belimumab treatment, we observed a general improvement in kidney function, manifested in eGFR, urinary protein, and serum albumin. Mean eGFR slightly increased from 93.9 ± 46.4 ml/min/1.73 m^2 at baseline to 103.9 ± 45.5 ml/min/1.73 m^2 ($p = 0.07$), 106.6 ± 44.2 ml/min/1.73 m^2 ($p = 0.08$) at 12 and 24 weeks (Fig. 3A). Mean urinary protein decreased more than 50% from 3.2 ± 2.6 g/24 h at baseline to 1.8 ± 1.5 g/24 h ($p = 0.0013$), 1.0 ± 1.3 g/24 h ($p < 0.0001$) at 12 and 24 weeks (Fig. 3B). Mean serum albumin increased from 28.3 ± 6.5 g/l at baseline to 34.8 ± 5.1 g/l ($p < 0.0001$), 36.1 ± 5.6 g/l ($p < 0.0001$) at 12 and 24 weeks (Fig. 3C).

Effects on immune function

The conditions of immune system had also gradually improved over the study. Mean C3 level increased from 0.5 ± 0.2 g/l at baseline to 0.7 ± 0.2 g/l ($p < 0.001$) at 12 weeks and remained stable in the later 12 weeks (Fig. 4A). Additionally, the levels of autoantibodies including ANA and anti-dsDNA showed an obviously downward trend during the follow-up (Fig. 4B, C). The IgG level decreased slightly at the beginning of the study and then remained stable with the mean value fluctuating from 8.6 g/l to 9.2 g/l (Fig. 4D), indicating that the patient's humoral immunity was correspondingly suppressed by the treatment.

Reduction in concomitant medications

During the follow-up, the overall use of both the glucocorticoid and immunosuppressants showed a steady downward trend. The mean prednisone dosage decreased significantly from 32.7 ± 21.1 mg/day at baseline to 18.6 ± 11.7 mg/day ($p < 0.0001$) at 12 weeks, and further to 13.3 ± 8.9 mg/day ($p < 0.0001$) at 24 weeks (Fig. 5A). At the end point of study period, 20.0% (9/45) patients achieved a prednisone dose of ≤ 7.5 mg/day, which is considered as a relatively safe dose range (Fig. 5C). And 6.7% (3/45) patients achieve the goal of glucocorticoid discontinuation during the 6-month belimumab treatment. Meanwhile in patients taking MMF, there was an observed reduction in the mean dose of MMF from 1.4 ± 0.4 g/day at baseline to 1.2 ± 0.4 g/day ($p = 0.0046$), 1.1 ± 0.4 g/day ($p < 0.0001$) at 12 and 24 weeks (Fig. 5B). For the few remaining patients on other immunosuppressants

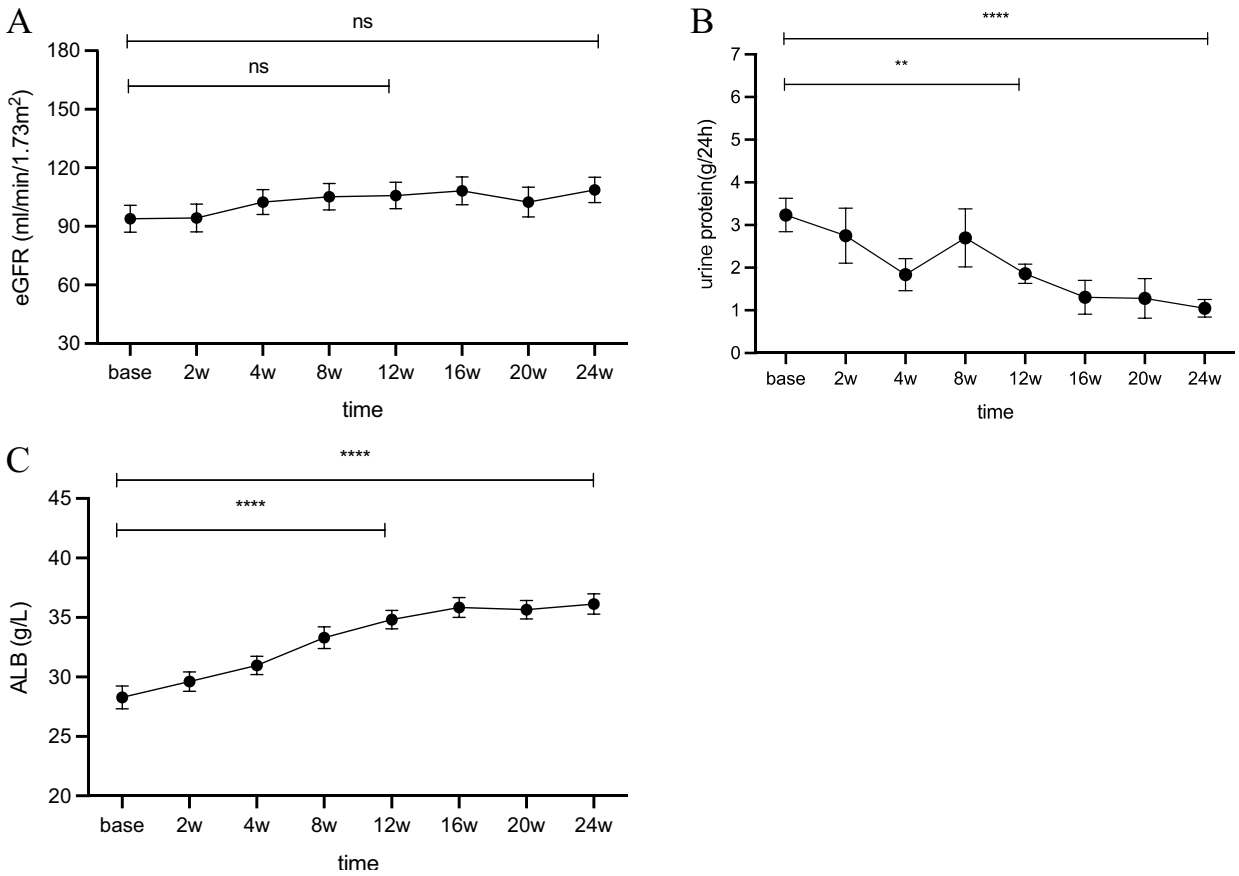

Fig. 3 Renal response to belimumab treatment. Changes in A eGFR, B urine protein, and C ALB

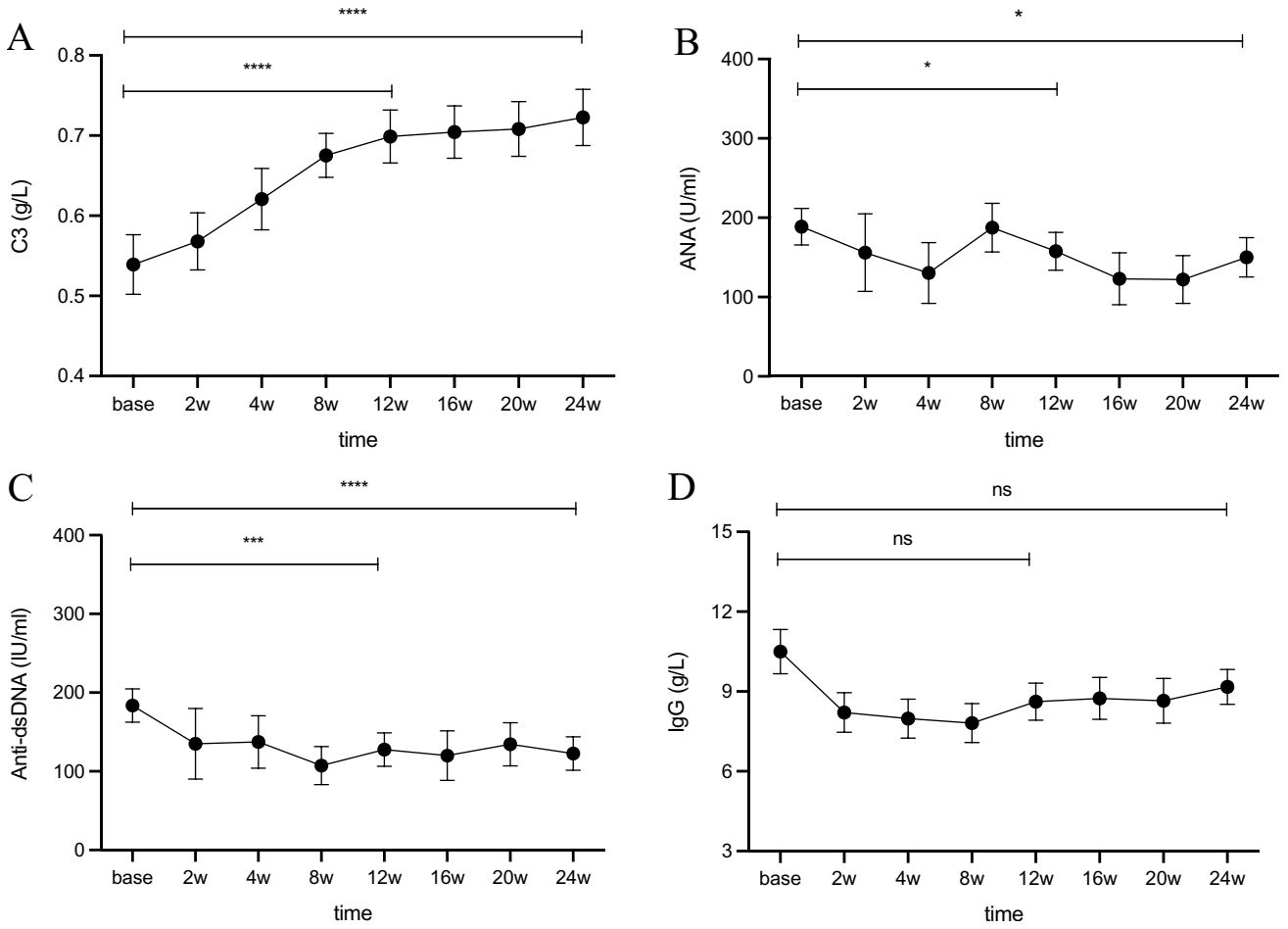

Fig. 4 Immunological response to belimumab treatment. Changes in (**A**) C3, (**B**) ANA, (**C**) anti-dsDNA, and (**D**) IgG

(CsA, CYC, FK506), doses of the drugs were at maintenance levels without changes.

Safety

Adverse events (AEs) and drug discontinuation are listed in Table 3. No severe AEs were observed during belimumab treatment period. AEs were reported in 3 patients, including infection ($N=2$) and allergy ($N=1$). Drug discontinuation was observed in 3 patients due to disease progression ($N=2$) and hypogammaglobulinemia ($N=1$), and one of them was progressed to ESRD.

Discussion

According to the current guidelines, treatment of refractory LN mainly includes multi-target therapy, biological agents, plasma exchange, and stem cell transplant [9]. However, belimumab has not yet been indicated for patients with refractory LN, and there have been no relevant studies on its effectiveness in refractory LN. In this study, we evaluated the efficacy and safety of belimumab in 45 patients with refractory LN in China clinical practice.

Over the 6-month treatment period, our study indicated that 13.3% of the patients achieved complete renal response and 42.2% achieved partial renal response, together with significant reductions in disease activity and glucocorticoid dosage. Compared with European LN patients mentioned in a poster of EULAR 2023 [19], the patients included in our study showed a lower CRR rate (35% vs 13.3%). This might be the result of different inclusion criteria and follow-up time. Firstly, the poster referred to patients with active lupus nephritis and the patients included in our study were with refractory lupus nephritis, defined as failure to respond to the induction therapy with CYC, MMF, or multi-target treatment for at least 6 months. Worse response to treatment and more severe chronic renal damage may be responsible for the lower CRR rate in RLN patients. Secondly, the follow-up period of the poster was 1 year, while our study lasted only 6 months. According to the BLISS-LN study, the CRR

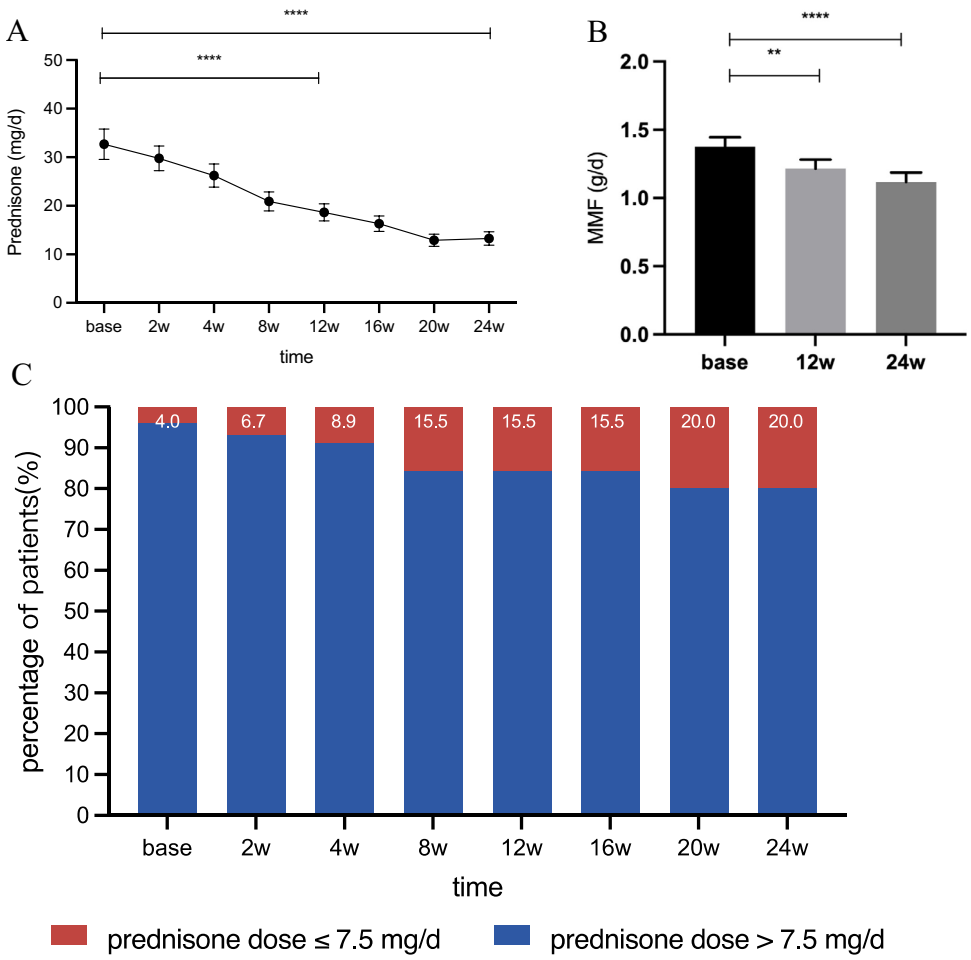

Fig. 5 Reduction in prednisone and MMF. Changes in dosage of prednisone (**A**) and MMF (**B**), and the percentage of patients with a dose reduction to ≤ 7.5 mg/day (**C**) during belimumab treatment period

Table 3 Adverse events and discontinuation during belimumab treatment

	Frequency	Discontinued
Adverse events		$N=0$
Upper respiratory tract infection	1	No
Urinary tract infection	1	No
Allergy (rash)	1	No
Disease progression		$N=2$
Refractory thrombocytopenia	1	Yes
ESRD	1	Yes
Others		$N=1$
Hypogammaglobulinemia	1	Yes

rate of patients treated with belimumab was on an upward trend early in the study and stabilized at around week 52, indicating that it took a long time for LN patients to achieve CRR. Patients might not have achieved an optimal response to belimumab therapy at week 24 in our study, resulting in the low CRR rate.

Similar to the results of our research, a retrospective study from South Korea reported that the renal response rate of patients with refractory LN was 53.9% after multi-target therapy (MMF combined TAC) at 6 months and increased to 55.5% at 12 months. However, it should be noted that the decline of SLEDAI score, glucocorticoid dosage, and urinary protein under the multi-target therapy was obviously slower than that in our study. Moreover, it was observed that the SLEDAI score and glucocorticoid dosage had rebounded in the later period (6–12 months) of multi-target therapy, showing a tendency to relapse [20]. While in our study, there was no increase in glucocorticoid dosage after the enrollment for a short term, as well as within 3 months prior to the enrollment, which might suggest the advantage of belimumab in glucocorticoid reduction.

We also found that the median SDI scores changed from 1.0 (IQR 1.0–2.0) (mean ± SD, 1.7 ± 1.5) at baseline to 2.0 (IQR 1.0–3.0) (mean ± SD, 1.8 ± 1.5) ($p > 0.05$) at the endpoint of follow-up with no significance (Table 2). 88.9% (40/45) of RLN patients showed no change from baseline in SDI score; 11.1% (5/45) experienced an SDI score increase of + 1. Previous studies have shown that SLE patients' organ

damages have accrued gradually and irreversibly during the course of the disease, especially in patients with renal involvement [21]. That is why a slight increase of SDI score was observed in our study. While effective treatment may prevent the increase of chronic damage, both Study 206,347 and BeRLiSS found that patients treated with belimumab had less damage accumulation than those treated with only background therapy [22, 23]. In our study, the high proportion of patients without SDI increasing indicated that therapy with belimumab might reduce the risk of organ damage. However, a longer follow-up period is necessary to draw more reliable conclusions.

Another recent study showed that low-dose CsA combined with MMF could effectively treat induction-resistant and flared LN. But both the dosages of CsA and MMF gradually increased during the follow-up period [24]. While in our study, the dose of MMF had showed a downward trend among 33 patients during the 6-month belimumab treatment. These findings indicate that belimumab has a faster onset of action, effectively controls disease activity in the short term, and rapidly achieves renal remission as well as concomitant medication reduction, which may have potential advantages in the treatment of refractory LN over multi-target therapy.

A reduction of autoantibody was also observed in this study. This finding corroborates the effects of belimumab on interfering with the survival and function of B cell. While a significant trend in IgG levels was not observed in enrolled patients, this may indicate that the patients did not take a significantly increased risk of infection during treatment.

Regarding safety, belimumab was well tolerated in this study with no serious adverse events. During the observation period, a total of 3 patients discontinued belimumab due to disease progression. Among them, the incidence of ESRD was 2.5%, which was significantly lower than that reported in RTX studies (4.8–13.6%)[25].

This study has some limitations. First, the relatively low patient number and the short follow-up may affect the accuracy of the analysis. We chose a 6-month length of follow-up in this study based on the following situation. According to the treatment recommendations on biologics use and product information of belimumab, treatment efficacy should be assessed at 6 months to decide whether to continue the therapy. On the other hand, due to the actual situation in our country (such as medical insurance restrictions, financial burden, compliance), many patients discontinued the belimumab after 6 months of treatment. Second, since this study was a retrospective analysis in a real clinical setting, the therapeutic effects were affected by various factors and were difficult to accurately assess, which poses some objective restrictions to our conclusions and prevents further inference. Therefore, we will continue to follow up patients with long-term treatment and carry out further studies to evaluate the efficacy and safety of belimumab on RLN in real clinical settings.

Conclusion

In conclusion, this study provides preliminary evidence that belimumab as an add-on therapy is effective and safe and that it may be a novel treatment for refractory LN. The prospective, randomized, and controlled studies are urgently needed to confirm our findings in the future.

Author contribution HX, SZ1, and QQ conceived and designed the study. SZ1, SZ2, HL, LJ, and XH collected data. SZ1, LX, and QQ performed statistical analysis. HX, SZ1, and QY drafted the manuscript. YX, DC, ZZ, and LL made critical revision on the manuscript. HX, QY, and LL supervised the study. All authors contributed to the interpretation of data. All authors approved the final version before submission.

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Data availability The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Declarations

Ethical approval The studies involving human participants were reviewed and approved by the First Affiliated Hospital, Sun Yat-sen University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Disclosures None.

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