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Efficacy and Safety of Belimumab in Lupus Nephritis Patients: A Real-World Observational Study in China

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Keywords
Belimumab · Systemic lupus erythematosus · Lupus nephritis · Steroid sparing · Disease activity

Abstract
Background: This study aimed to describe disease activity, clinical outcome, and overall patterns of lupus nephritis care in patients who received belimumab in a real-world clinical setting in China. ***Materials and Methods:*** This observational cohort study included lupus nephritis patients who received belimumab as adjunct therapy. We deeply investigated the characteristics of those patients including clinical response to belimumab and safety. ***Results:*** All 61 lupus nephritis patients were included with a median follow-up period of 9 months (6, 19). Prevalence of proteinuria (52.5–24.6%) and hematuria (33.3–9.8%) was decreased with a stable level of eGFR at last visit. The percentage of patients achieved complete or partial renal response increased from 47.5% to 78.7% and the proportion of complete or partial renal response in patients with proliferative lupus nephritis was higher than those with membranous lupus nephritis (75 vs. 50%) at last visit. The median SLEDAI score decreased from 6 to 2, and there was an increase in patient of LLDAS from 17 to 33 at last visit. A notable dose reduction was seen for glucocorticosteroid dose, with a median change from 10 to 5 mg/d. The proportion of patients receiving >7.5 mg/d steroids reduced from 52.5% at baseline to 23.0% at last visit. The discontinuation of belimumab was rare (3/61) for drug-induced fever, hyperthyroidism, and uveitis. ***Conclusions:*** Lupus nephritis patients with belimumab demonstrated improvements in clinical response and a reduction in glucocorticosteroids, which provided evidence of effectiveness and safety in real-world clinical practice in China.

Introduction

Lupus nephritis, the most common manifestation of SLE, continues to be a principal cause of morbidity and mortality

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[1, 2]. The majority patients with lupus nephritis have been required long-time immunosuppression to manage the disease activity and protect the renal function. However, the proportion of remission in lupus nephritis remains unacceptably low, and 10–30% of these patients progresses to end-stage renal disease [3–5]. New targeted treatment of lupus nephritis was urgently needed considering the adverse effect of long-time immunosuppression, such as infection and cumulative organ damage.

B lymphocyte stimulator, also known as B-cell-activating factor, plays an important role in the development, selection, and survival of B cells [6–8]. Belimumab is a recombinant human IgG-1λ monoclonal antibody that inhibits B lymphocyte stimulator. In 2011, two randomized-controlled phase III trials (BLISS-52 and BLISS-76) showed better clinical responses in refractory SLE patients with belimumab than those in the patients with standard treatment alone [9, 10]. Then, several observation studies investigated effectiveness and safety of belimumab among patients with SLE in clinical practice settings, such as OBSErve studies and BeRLiss study, which confirmed the efficacy of belimumab to decrease SLE disease activity, glucocorticoid use, and flares, thereby hindering damage progression [11–15]. In lupus nephritis, the post hoc analysis of RCTs suggested the significantly reduction of proteinuria in the subgroup of lupus nephritis with belimumab [16]. The latest analysis of BLISS-LN confirmed that belimumab reduced flares and preserved kidney function in lupus nephritis [17]. In the BeRLiss-LN, a real-life setting of Italian cohort, belimumab led to durable renal response in patients with lupus nephritis [18]. However, questions were still remained, such as how effective and safe the belimumab would be in different renal function stages, especially patients with estimated glomerular filtration rate (eGFR) <30 mL/minute/1.73 m^2, and patients with nonstandard therapies.

Herein, the effectiveness and safety of belimumab in real-world clinical practice remained to be further determined in Chinese lupus nephritis patients. We deeply investigated the clinical efficacy and safety of lupus nephritis patients receiving belimumab in real-life setting in China.

Methods

Patient Selection and Inclusion Criteria

Patients treated with belimumab and well followed up were enrolled upon presentation in Nephrology Departments of Peking University First Hospital and Peking University International Hospital between May 2020 and July 2021. The study flowchart was shown in Figure 1.

Inclusion criteria were as follows: (1) fulfillment of the 1997 American College of Rheumatology revised criteria for SLE [19] or the SLICC/ACR classification criteria for SLE [20]; (2) diagnosed lupus nephritis by renal biopsy or by persistent positive urinalysis according to the 2021 KDIGO recommendations [21]; (3) IV belimumab (10 mg/kg on days 1, 14, and 28, and then every month) as adjunct therapy. Standard therapy was defined according to the 2021 KDIGO recommendations of therapy as steroids and antimalarials, with/without immunosuppressants [21]. Exclusion criteria were followed up less than 6 months.

Data Collection in Lupus Nephritis Patients

The patients were followed up in the outpatient clinics specified for lupus nephritis. Data were collected and analyzed at baseline, month 6, and the last visit, including clinical manifestations, levels of serum creatinine, complete blood cell count, 24-h proteinuria, hematuria, leukocyturia and cylindruria, anti-dsDNA antibodies, and serum C3 and C4. Clinical disease activity was assessed using the SLEDAI [22] and Physician Global Assessment (PGA) score. The renal biopsy specimens were examined by light microscopy, direct immunofluorescence, and electron microscopy techniques. Daily prednisone intake, concomitant medications, and adverse events (AEs) were regularly collected and updated.

The complete renal response (CRR) was defined as 24-h proteinuria <0.5 g/d, stabilization or improvement in renal function (0 ± 15% of baseline). The partial renal response (PRR) was defined as a reduction in proteinuria at least 50% and to <3 g/d, stabilization or improvement in renal function (0 ± 15% of baseline). No renal response was defined as failure to achieve PRR or CRR [21]. A relapse was defined as follows: (1) nephritic relapse: a recent increase of serum creatinine by >50% with active urinary sediments and (2) proteinuric relapse: development of either a nephrotic syndrome or proteinuria >1.5 g/d without other causes, in an earlier nonproteinuric patient [23].

Patients were considered as in remission if having a clinical SLEDAI score of 0 (serology excluded), PGA score <0.5, and receiving prednisone equivalent dose of ≤5 mg/d with immunosuppressants and antimalarials at a stable dose, according to the recommendations of DORIS Task Force [24]. Lupus Low Disease Activity State (LLDAS) was defined as an SLEDAI ≤4 without activity in major organ systems (renal, central nervous system, cardiopulmonary, vasculitis, fever) and no hemolytic anemia or gastrointestinal activity, PGA score ≤1, a current prednisone dose ≤7.5 mg/d with well-tolerated immunosuppressants and antimalarials according to 2019 EULAR recommendations [25, 26].

Safety and Discontinuation

Discontinuation was defined as an interruption of belimumab for more than 6 months. Among other reasons for discontinuation, inadequate response was defined by the physician judgment as the presence of flares and/or the persistence of moderate/high disease activity. AEs were recorded at each clinical evaluation during the follow-up.

Statistical Analysis

Statistical software SPSS 20.0 (SPSS, Chicago, IL, USA) was employed for statistical analysis. Quantitative data were expressed as mean ± SD or median and range (minimum, maximum). For categorical variables, the χ^2 test was used. A comparison of continuous data with a parametric distribution was performed

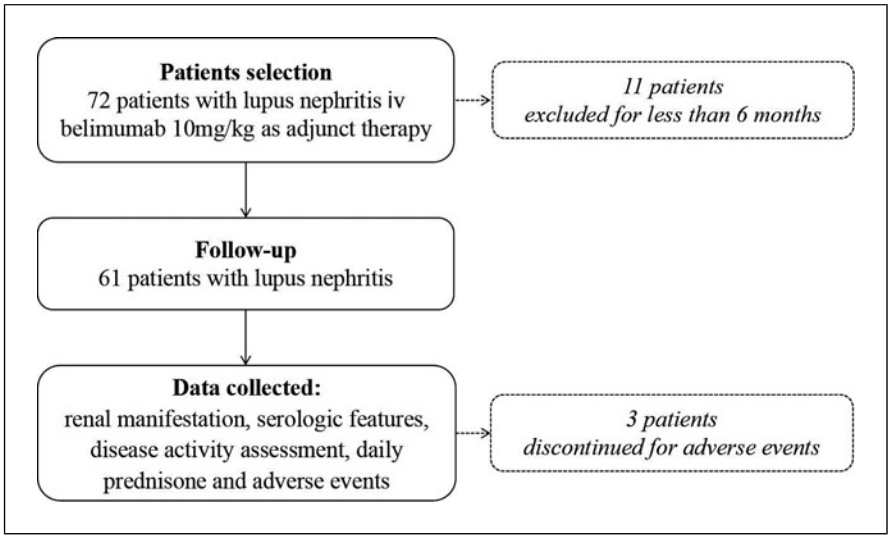

Fig. 1. Flowchart of the study.

using *t* test, *t* test for paired data, and one-way analysis of variance (ANOVA). $p < 0.05$ was considered statistically significant.

Results

Baseline Data of Lupus Nephritis Patients

A total of 61 lupus nephritis patients were included, with a median follow-up period of 9 (6, 19) months. The demographics and clinical characteristics of patients with lupus nephritis at a date of belimumab initiation are listed in Table 1. The average age was 35.0 ± 13.4 years, and the median disease duration at baseline of lupus nephritis was 8.0 (0.2, 24) years.

A total of 93% (57/61) of the cohort had renal biopsy-proven lupus nephritis. By the time of enrollment, the median level of proteinuria was 0.5 (0, 11.3) g/d. Serum creatinine was 72.8 (39.0, 582) μmol/L. Five (8.2%) patients were with eGFR <30 mL/min/1.73 m^2. The SLEDAI score was 6 (0, 19). 37 patients (60.7%) were positive for anti-dsDNA antibody, 21 (32.8%) for low C3, and 25 (41.0%) for low C4.

At baseline, 55 patients (90.2%) were treated with corticosteroids (mean dosage 15.7 mg/d), and 47 patients (77.0%) with hydroxychloroquine. 55 patients (90.2%) were with concomitant immunosuppressants. Eight patients (13.1%) were given multitarget therapeutics (more than one immunosuppressant at the same time). 23 (37.7%) patients were treated with nonstandard of care. The main reasons for belimumab therapy were as follows: active SLE or lupus nephritis with/without previous treatment (60.7%); aim to decrease the use of corticosteroids (29.5%); or aim to prevent disease flare (9.8%).

Clinical Outcomes

Renal Manifestation

In the whole cohort, improvements in renal manifestation were generally occurred from baseline to month 6 and were maintained or continued to improve throughout the study. In all patients, serum creatinine, proteinuria, hematuria, leukocyturia, and cylindruria were measured periodically throughout the study (Table 2). Levels of proteinuria decreased from 0.5 (0, 11.3) g/d to 0.17 (0, 5.4) g/d at month 6 and to 0.13 (0, 5.4) g/d at the last visit ($p = 0.0016$). There was a reduction of patients with proteinuria from 52.5% (32/61) to 29.5% (18/61) and 24.6% (15/61) at month 6 and last visit ($p = 0.007$). Among 21 (33.3%) patients with hematuria, only 9 (14.8%) and 6 (9.8%) patients remained hematuria at month 6 and last visit ($p = 0.0026$). All the 5 (8.2%) patients with leukocyturia and 1 (1.6%) with cylindruria turned negative at month 6 and last visit. The renal function stayed stable with eGFR from 107.1 (7.6, 146.7) mL/min/1.73 m^2 to 96.0 (6.7, 142.0) mL/min/1.73 m^2 and 102 (6.5, 134.1) mL/min/1.73 m^2 at month 6 and last visit (Fig. 2). The eGFR of patients in CKD 4-5 stayed stable without worsened from 17.7 (7.6, 29.0) mL/min/1.73m^2 to 20.0 (6.7, 34.8) mL/min/1.73 m^2 and 19.8 (6.5, 40.0) mL/min/1.73 m^2 at month 6 and last visit.

At baseline, 29 patients (47.5%) already achieved CRR or PRR. At month 6, 43 (70.5%) and 5 (8.2%) of patients achieved CRR and PRR, respectively. Continued

Table 1. Demographics and clinical characteristics of patients with lupus nephritis at the initiation of belimumab

Characteristic	Total (*n* = 61)	Active LN (*n* = 37)	Remission (*n* = 9)
Female sex, number (%)	56 (91.8)	36 (97.3)	7 (77.8)
Age at the first infusion, mean ± SD, years	35.0±13.4	34.1±14.1	34.7±16.0
Follow-up duration, mean ± SD, months	10.3±4.3	9.6±3.8	10.0±5.2
SLE disease activity at baseline			
Disease duration, median (range), years	8 (0.2, 24)	7.5 (0.2, 22)	17 (2, 24)
SLEDAI score, median (range)	6 (0, 19)	10.0 (4, 19)	2 (0, 4)
PGA score, median (range)	1 (0.1, 2.8)	1.2 (0.6, 2.8)	0.1 (0.1, 0.4)
Anti-dsDNA antibody positive, *n* (%)	37 (60.7)	24 (64.9)	6 (66.7)
Low C3, *n* (%)	21 (32.8)	18 (48.6)	1 (11.1)
Low C4, *n* (%)	25 (41.0)	19 (51.4)	1 (11.1)
Renal manifestation at baseline			
SCR, median (range)	72.8 (39, 582)	75 (41.5,582)	82 (58, 291)
Acute kidney injury, *n* (%)	5 (8.2)	5 (13.5)	0
Chronic kidney disease, *n* (%)			
Stage 1	36 (59.0)	21 (56.8)	5 (55.6)
Stage 2	6 (9.8)	3 (8.1)	1 (11.1)
Stage 3	9 (14.8)	4 (10.8)	2 (22.2)
Stage 4	4 (6.6)	2 (5.4)	1 (11.1)
Stage 5	1 (1.6)	1 (2.7)	0
Proteinuria	32 (52.5)	32 (86.5)	0
Hematuria	21 (33.3)	21 (56.8)	0
Leukocyturia	5 (8.2)	5 (21.6)	0
Cylindruria	1 (1.6)	1 (2.7)	0
Histopathologic classification of lupus nephritis, *n* (%)			
Type II	2 (3.3)	0	2 (22.2)
Pure III	5 (8.2)	3 (8.1)	0
Pure IV	31 (50.8)	17 (45.9)	5 (55.6)
Pure V	6 (9.8)	5 (13.5)	0
III and V or IV and V	13 (21.3)	11 (29.7)	0
Unknown	4 (6.6)	1 (2.7)	2 (22.2)
Concomitant treatment, *n* (%)			
Oral corticosteroid	55 (90.2)	34 (91.9)	5 (55.6)
Antimalarials	47 (77.0)	29 (78.4)	6 (66.7)
Immunosuppressants	55 (90.2)	36 (97.3)	8 (88.9)
CYC sequential to MMF	6 (9.8)	6 (16.2)	0
Mycophenolate mofetil	26 (42.6)	14 (37.8)	7 (77.8)
Cyclosporine A	8 (13.1)	5 (13.5)	0
Leflunomide	4 (6.6)	1 (2.7)	1 (11.1)
Tacrolimus	2 (3.3)	3 (8.1)	0
Rituximab	1 (1.6)	1 (2.7)	0
Multi-target therapeutics	8 (13.1)	6 (16.2)	0
Mycophenolate mofetil plus tacrolimus, *n* (%)	4 (6.6)	3 (8.1)	0
Mycophenolate mofetil plus cyclosporine A, *n* (%)	2 (3.3)	1 (2.7)	0
Cyclosporine A plus leflunomide, *n* (%)	2 (3.3)	2 (5.4)	0
Main reasons for belimumab initiation, *n* (%)			
Active SLE/LN	37 (60.7)	37 (100)	0
Decreased use of steroids)	18 (29.5)	0	5 (55.6)
Flare prevention	6 (9.8)	0	4 (44.4)

SD, standard deviation; SLEDAI, SLE Disease Activity Index; PGA, Physician's Global Assessment; LN, lupus nephritis; CYC, cyclophosphamide; MMF, mycophenolate mofetil.

Table 2. Serologic and renal improvement in lupus nephritis at month 6 and the last visit

Category	Baseline	Month 6	Last visit	*p* value (baseline vs. last visit)
Renal manifestation				
Proteinuria, *n* (%)	32 (52.5)	18 (29.5)	15 (24.6)	0.0016
24-h UTP, median (range) (g/d)	0.50 (0, 11.3)	0.17 (0, 5.4)	0.13 (0, 5.4)	0.007
<0.5, *n* = 29	0 (0, 0.50)	0 (0, 0.43)	0 (0, 0.43)	0.067
>0.5, *n* = 32	0.53 (0.52, 11.3)	0.2 (0, 5.4)	0.13 (0, 5.4)	0.004
Hematuria, *n* (%)	21 (33.3)	9 (14.8)	7 (11.5)	0.0026
Leukocyturia, *n* (%)	5 (8.2)	0	0	0.022
Cylindruria, number (%)	1 (1.6)	0	0	0.32
SCR median (range), μmol/L	72.8 (39, 582)	71.0 (42, 593)	69.0 (39.6, 602)	0.85
Normal at baseline, *n* = 52	63.7 (39, 126.7)	69.5 (42, 163.3)	66.5 (39.6, 163.3)	0.62
High at baseline, *n* = 9	185 (153, 582)	242 (124, 593)	242 (119, 602)	0.67
eGFR median (range), mL/min/ 1.73 m^2	107.1 (7.6, 146.7)	96.0 (6.7, 142.0)	102.0 (6.5, 134.1)	0.83
eGFR ≥30 at baseline, *n* = 56	107.9 (31.4, 146.7)	100.5 (23.0, 142.0)	104.5 (16.1, 134.1)	0.88
eGFR <30 at baseline, *n* = 5	17.7 (7.6, 29.0)	20.0 (6.7, 34.8)	19.8 (6.5, 40.0)	0.66
Serologic features				
Anti-dsDNA positive, *n* (%)	37 (60.7)	23 (37.7)	19 (31.1)	0.0011
Low C3, *n* (%)	21 (32.8)	9 (14.8)	8 (16.4)	0.0057
C3 level, mean ± SD, g/L	0.68±0.26	0.79±0.21	0.80±0.21	<0.001
Low at baseline, *n* = 21	0.41±0.123	0.65±0.14	0.65±0.12	<0.001
Normal at baseline, *n* = 40	0.82±0.20	0.86±0.20	0.86±0.20	0.114
Low C4, *n* (%)	25 (41.0)	11 (13.1)	7 (13.0)	<0.001
C4 level (0.12), mean ± SD, g/L	0.14±0.074	0.18±0.064	0.18±0.059	<0.001
Low at baseline, *n* = 25	0.074±0.033	0.14±0.043	0.14±0.042	<0.001
Normal at baseline, *n* = 36	0.19±0.053	0.21±0.054	0.21±0.054	0.001
Steroid dose				
Steroid dose, median (range), mg/d	10 (0, 50)	5 (0, 20)	5 (0, 20)	<0.001
Oral steroids, *n* (%)	55 (90.2)	52 (85.2)	50 (82.0)	0.19
Daily dose >7.5 mg, number (%)	32 (52.5)	22 (36.1)	14 (23.0)	<0.001
Daily dose >5 mg, *n* (%)	39 (63.9)	25 (41.0)	18 (29.5)	<0.001
Disease activity assessment				
SLEDAI score, median (range)	6 (0, 19)	2 (0, 10)	2 (0, 12)	<0.001
PGA score, median (range)	1 (0.1, 2.8)	0.5 (0.1, 2)	0.4 (0.1, 1.5)	<0.001
Remission, *n* (%)	9 (14.8)	21 (34.4)	31 (50.8)	<0.001
LLDAS, *n* (%)	17 (27.9)	28 (45.9)	33 (54.1)	0.0032

UTP, urine total protein; SCR, serum creatinine; eGFR, estimated glomerular filtration rate; SD, standard deviation; SLEDAI, SLE Disease Activity Index; PGA, Physician's Global Assessment; LLDAS, Lupus Low Disease Activity State.

improvements were observed with 45 (73.8%a) and 3 (4.9%) of patients demonstrating CRR and PRR, between baseline and last visit (Fig. 3). No renal flare was observed throughout the study.

Serologic Features

Of the 33 patients with anti-dsDNA-antibody-positive, 14 (22.9%) and 18 (29.5%) patients turned negative at 6 months and last visit. There was a reduction in low-C3-level patients from 21 (32.8%) to 9 (14.8%) and 8 (13.1%) at month 6 and last visit. Similarly, the number of 25 (41.0%) with low-C4-level patients decreased to 11 (18.0%) and 7 (11.5%) at month 6 and last visit. Among patients with anti-dsDNA-antibody-negative and no hypocomplementemia at baseline, the mean levels of serologic features remained normal throughout the study (Table 2).

Steroid Dose

At baseline, 55 (90.2%) patients received steroids with a median prednisone-equivalent dose of 10 (0, 50) mg/d. After 6-month therapy, 3 patients (5.0%) discontinued steroids and 44 patients (72.1%) reduced steroids dose; the median dose reduced to 5 (0, 20) mg/d ($p < 0.001$).

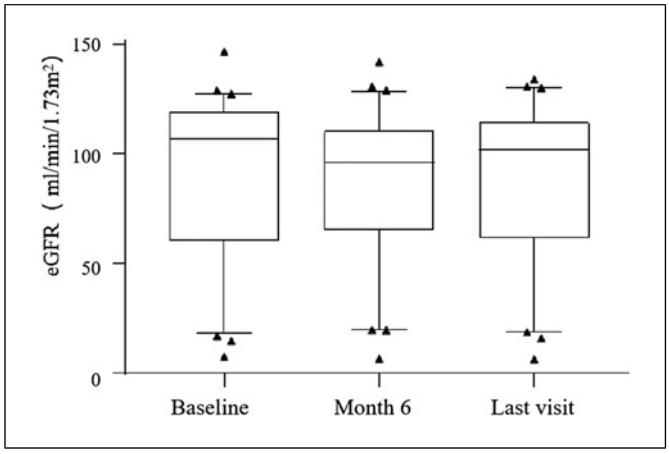

Fig. 2. eGFR fluctuation during belimumab treatment. eGFR, estimated glomerular filtration rate.

The percentage of patients prescribed steroids continued to reduce to last visit (50/61, 82.0%). At last visit, 5 patients (8.2%) had discontinued steroids, 47 patients (77.0%) reduced dose, 14 patients (23.0%) had no change in dose, and no one had a dose increase, and the median dose reduced to 5 (0, 20) mg/d, a decrease from the date of belimumab initiation of 5 mg/d.

The proportion of patients receiving >7.5 mg/d steroids reduced from 32 (52.5%) to 22 (36.1%) at months 6 and 14 (23.0%) at last visit. Meanwhile, 39 (63.9%) patients were prescribed steroids for more than 5 mg daily, which decreased to 25 (41.0%) and 18 (29.5%) at month 6 and last visit (Fig. 4).

Overall Clinical Response and Disease Activity Assessment

Median PGA score decreased from 1.0 (0.1, 2.8) to 0.5 (0.1, 2) at months 6 and 0.4 (0.1, 1.5) at last visit, respectively ($p < 0.001$). Based on PGA score, the majority patients (46/61, 75.4%) showed an overall clinical improvement at last visit. At month 6, 68.9% (42/61) and 31.1% (19/61) of patients achieved ≥20% and ≥50% improvement in overall clinical response to belimumab relative to baseline (Fig. 5a). Continued improvements were observed at last visit with 72.1% (44/61) and 44.3% (27/61) of patients demonstrating ≥20% and ≥50% relative interval improvement.

Median SLEDAI score decreased from 6 (0, 19) at baseline to 2 (0, 10) at months 6 and 2 (0, 12) at last visit, respectively ($p < 0.001$). The disease severity subgroups based on SLEDAI score were divided into mild (scores 0–6), moderate (scores 7–12), and severe (score >12) in our study [27, 28]. 9 patients (14.8%) were in severe subgroup and 16 patients (25.2%) in moderate subgroup (Fig. 5b) at beginning. At last visit, the majority patients ($n = 40$, 63.9%) showed improvements in SLEDAI score. Only 1 patient (1.6%) showed worsened SLEDAI score for a slight decrease of serum C3 level.

The number of patients in remission was 9 (14.8%) at baseline. At month 6 and last visit, it had increased to 21 (34.4%) and 31 (50.8%). Then, there was also an increase in patient number of LLDAS from 17 (27.9%) to 28 (45.9%) at months 6 and 33 (54.1%) at last visit (Fig. 5c).

Clinical Outcomes among Patient with Active Lupus Nephritis at Baseline

At baseline, 37 patients with proteinuria and/or hematuria and/or noninfectious leukocyturia and/or cylindruria and/or suffering AKI were classified as active lupus nephritis. From baseline to month 6 and last visit, there was a decrease in prevalence of patients in active lupus nephritis from 100% (37/37) to 64.9% (24/37) and 56.8% (21/37), respectively ($p < 0.001$). The prevalence of patients with proteinuria decreased from 86.5% (32/37) to 48.6% (18/37) and 40.5% (15/37), respectively ($p < 0.001$). Patients with hematuria showed a similar decrease, from 56.8% (21/37) to 24.3% (9/37) and 11.5% (7/37), respectively ($p < 0.001$). 13.5% (5/37) of patients with leukocyturia and 2.7% (1/37) with cylindruria at baseline turned negative at month 6 and last visit. Median levels of proteinuria were decreased from 1.5 (0.06, 11.3) g/d at baseline decreased to 0.42 (0, 5.4) g/d at month 6 and 0.28 (0, 5.4) g/d at last visit ($p = 0.004$). The median levels of serum creatinine were 77.0 (41.5, 582) μmol/L at baseline, which decreased slightly to 71.0 (42.0, 593.0) μmol/L at month 6 and to 69.0 (39.6, 602.0) μmol/L at last visit ($p = 0.77$). All 5 patients suffering AKI at baseline recovered at month 6 and last visit with a decrease of median serum creatinine from 119.8 (83.9, 126.7) μmol/L to 71.7 (56.0, 127.4) μmol/L and 74 (51.4, 83.4) μmol/L. None of the patients reported onset of AKI throughout the study.

Reductions in steroid dose were achieved in active lupus nephritis ($n = 37$) from 15 (0, 50) mg/d reduced to 10 (0, 20) mg/d at months 6 and 5 (0, 20) mg/d at last visit. 30 patients were receiving a reduced dose. The proportion of patients receiving >7.5 mg/d steroids reduced from 67.6% (25/37) at baseline to 54.1% (20/37) at month 6 and 32.4% (12/37) at last visit. Meanwhile, the proportion of patients receiving >5 mg/d steroids reduced from 78.4% (29/37) at baseline to 59.5% (22/37) at month 6 and 43.2% (16/37) at last visit.

Among this subgroup, 51.4% (19/37) and 13.5% (5/37) demonstrated CRR and PRR at month 6, and 56.8% (21/37) and 8.1% (3/37) demonstrated CRR and PRR at last visit. Because most patients (36/37) received renal biopsy among

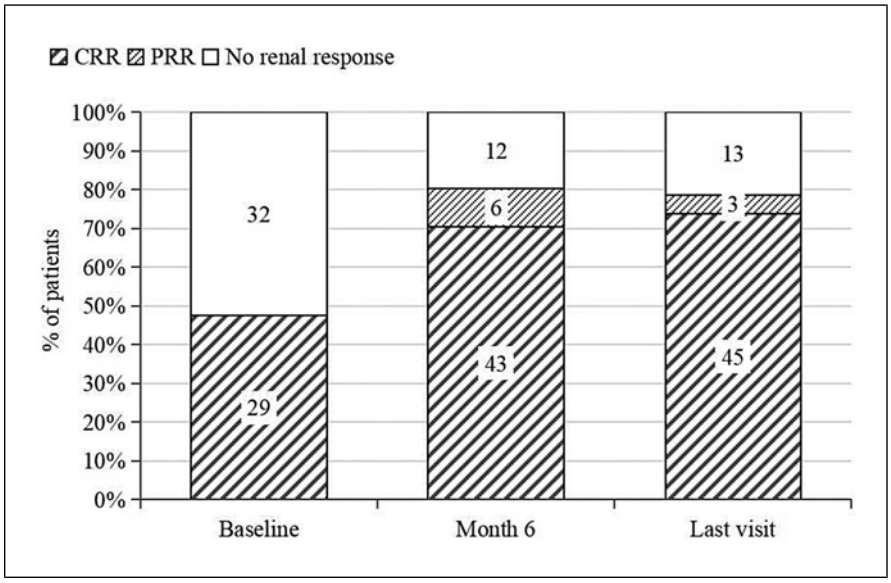

Fig. 3. Renal response during belimumab treatment.

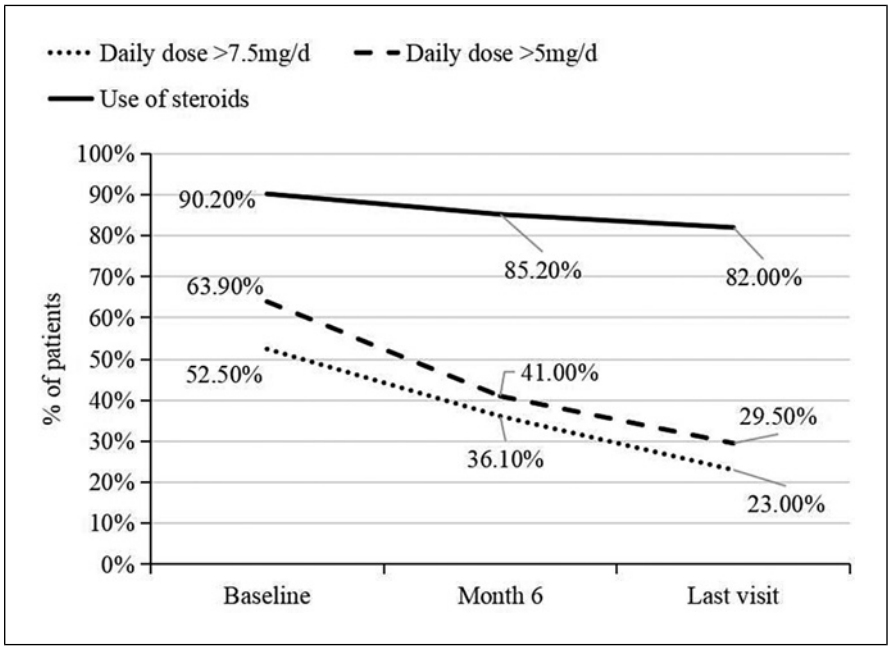

Fig. 4. Steroid dose (prednisone equivalent) during belimumab treatment. CRR, complete renal response; PRR, partial renal response.

this subgroup, an analysis was performed to evaluate whether response to therapy is differed by histologic classification. At last visit, 75% (15/20) patients with class III or IV achieved CRR/PRR, and 50% (8/16) patients with class V (pure or III/IV + V) could demonstrate CRR/PRR ($p = 0.12$).

Clinical Outcomes among Patients in Remission

Four (4/9), five (5/9), and six (6/9) patients discontinued steroids at beginning, month 6, and last visit of belimumab treatment. The median steroid dose decreased from 1.25 (0, 5) mg/d at baseline to 0 (0, 5) mg/d at month 6 and 0 (0, 1) mg/d at last visit. None of these patients received new concomitant immunosuppressants throughout the study. None of them reported disease flare at month 6 and last visit.

Adverse Events

AEs were reported in 25 patients (25/61, 41%) and 27 AEs in total; those that occurred in >1 patient were mild infection

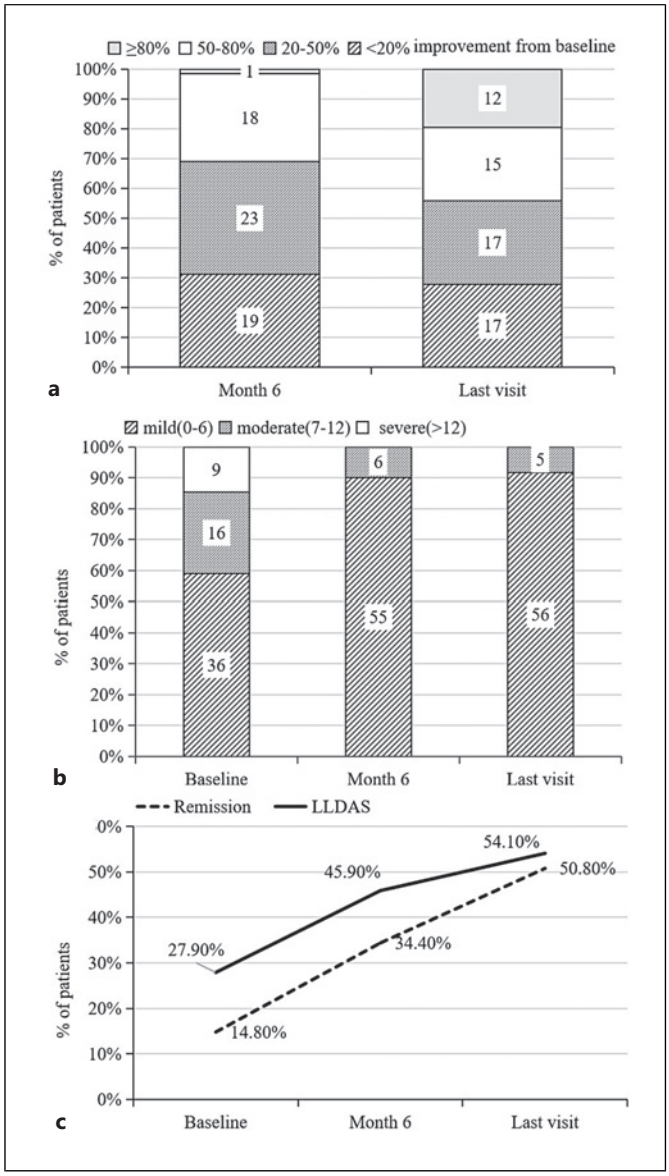

Fig. 5. a Overall clinical improvement from baseline to 6 months and the last visit based on PGA score in the cohort. **b** Disease severity subgroups based on SLEDAI score in the cohort. **c** Treatment targets attained in our cohort. LLDAS, Lupus Low Disease Activity State.

(n = 13), fatigue (n = 4), and sleep disorder (n = 2). Three patients discontinued belimumab because of AEs during the study period, including: drug-induced fever (n = 1), hyperthyroidism (n = 1), and uveitis (n = 1). Only 1 patient was admitted to hospital for severe pneumonia during belimumab treatment, and the severe pneumonia was considered unrelated to belimumab and continued after recovery. No deaths were reported (Table 3).

There were no differences between patients with standard therapies and nonstandard therapies in proportion of AEs (36.8 vs. 56.5%, p = 0.133) in our study. Meanwhile, there were only 2 AEs in 1 patient with recurrent urinary tract infection and colpitis in patients with eGFR <30 mL/min/1.73 m^2 (n = 5) (Table 3).

Discussion

This was an observational cohort study collecting data on belimumab therapy in the management of lupus nephritis patients after its approval in China 2019. It included patients with lupus nephritis and designed to reflect the real-world effectiveness and tolerability of belimumab in addition to standard therapies. After more than 6-month treatment, patients had an overall improvement in the renal response and disease activity. Also, the number of patients receiving steroids and the steroids dose decreased. Furthermore, our results confirmed the safety of belimumab in lupus nephritis [11–15].

In our study, we observed a significant decrease in proportion of proteinuria, hematuria, leukocyturia, and cylindruria with stable renal function. 78.7% of patients were able to achieve CRR/PRR at last visit. In active lupus nephritis subgroup, similar manifestation was noticed. Notably, all 5 lupus nephritis patients suffering acute kidney injury at baseline had renal response with creatinine decreased. No renal flares were observed in our study. The analysis of the previous clinical trials has suggested that patients with active lupus nephritis who received belimumab had the decreased level of proteinuria and stable serum creatinine compared with patients receiving placebo [17, 29]. In the secondary analysis of BLSS-LN, belimumab reduced the eGFR decline versus standard therapies alone [30]. The present study also supports the findings as fewer renal flares with belimumab [31]. As a supplement of RCT trials, our real-life study included a broader spectrum of patients with lupus nephritis, including patients with eGFR <30 mL/minute/1.73 m^2, patients on dialysis, pathological type II, nonstandard therapies, and receipt of B cell-targeted therapy (rituximab).

Also, we found some important biomarkers of active nephritis, like hematuria, leukocyturia, and cylindruria improved during the treatment. The post hoc analysis of BLISS-52 also showed decreased hematuria and leukocyturia in lupus nephritis with belimumab [16]. However, those biomarkers were associated with renal activity in lupus nephritis, which further confirmed the effectiveness of belimumab.

Table 3. AEs in patients with standard therapies and nonstandard therapies

AEs	Total patients (n = 61)	Patients with standard therapies (n = 38)	Patients with nonstandard therapies (n = 23)
AEs in total	27	14	13
AEs related with hospitalization	1	0	1
Severe pneumonia	1	0	1
AEs related to belimumab discontinued	3	2	1
Hyperthyroidism	1	0	1
Uveitis	1	1	0
Drug-induced fever	1	1	0
Nonsevere AEs	23	12	11
Infectious AEs	13	8	5
Urinary tract infections	6	3	3
Upper respiratory tract infections	4	2	2
Gynecological infections	2	2	0
Cutaneous herpes zoster/HSV	1	1	0
Noninfectious AEs	10	4	6
Fatigue	4	2	2
Insomnia	2	0	2
Headache	1	1	0
Diarrhea	1	0	1
Abdominal pain	1	0	1
Elevation of serum CA125	1	1	0

AE, adverse events; CA125, carbohydrate antigen 125.

Moreover, we observed that the proportion of CRR/PRR in patients with proliferative lupus nephritis was higher than those with membranous lupus nephritis (75 vs.50%). Similar results were observed in secondary analysis of BLISS-LN study that patients with proliferative lupus nephritis were benefitted from belimumab therapy in CRR/PRR [30]. Though the patients number were limited, it was a real-world data which need further study to identify who may be more likely to benefit from the targeted therapeutic agents.

Other serologic features generally demonstrated that patients who had abnormal levels at baseline improved toward normal levels and the improvements have continued throughout the whole therapy, including anti-dsDNA antibodies, C3 and C4. In addition, the improvement of majority patients with high SLEDAI score, positive anti-dsDNA antibodies, and low C3 and C4 lasted throughout the study. Meanwhile, the majority of patients with normal serologic features have not worsened throughout the study, suggesting the vital role of belimumab in prevention of flares, which were consistent with those in other observational studies [11–15].

Our study further demonstrated that belimumab has a steroid-sparing effect among lupus nephritis patients, with a reduction in both the number of patients receiving steroids and the mean dose, like studies in SLE patients before [9–16]. Reducing the use of steroid was important, as a prolonged use of high-dose steroids was associated with severe adverse effects, long-term organ damage, and morbidity [32].

The overall clinical response and disease activity significantly improved, which indicated similar findings in Chinese patients compared to other ethnic groups [11–15]. Similar improvements were observed that the proportion of remission and LLDAS, as meaningful treat-to-target outcome in SLE, reached 50.8% and 54.1% at last.

In nine lupus nephritis patients in remission, belimumab was seemed to be good for preventing lupus nephritis recurrence with parallel reductions in steroids. None flares were observed in the subgroup. In recent studies, the risk of a severe flare was also reduced in the belimumab group, especially after the full belimumab effect was observed [33]. These might suggest that belimumab could help to capture even minor signs of disease reactivation, thereby exerting a further protective effect against organ damage.

More importantly, we also observed a good safety profile of belimumab with a relatively low frequency of AEs (41%, *n* of patients%) in our study compared with other studies (33–96%) [10–14, 16]. Considering the concomitant immunosuppressants and steroids, the most frequent infectious AEs might not be entirely due to belimumab. The safety profile for belimumab plus standard therapies had no difference to that of nonstandard therapies in the proportion of AEs. Meanwhile, patients in CKD stage 4–5 including the one with regular dialysis in our study seemed to be a good tolerance of belimumab.

Our study has some limitations owing to retrospective analysis of the small sample size, the short-time follow-up, and lacking of a control group for comparison. Nevertheless, the study did provide some objective data considering the short time after the approval of belimumab for the treatment of lupus nephritis in China. More data should be collected and a longer follow-up would conduct in the future.

In conclusion, it was the first real-life setting of belimumab in lupus nephritis patients in China. The study provided novel evidence to confirm that belimumab improved renal manifestations, decreased disease activity, and reduced steroid dose in patients with lupus nephritis. Then, its efficacy and safety on lupus nephritis need more observational studies and clinical trials.

Statement of Ethics

The research complied with the Declaration of Helsinki and was approved by the Local Ethical Committees of Peking University First Hospital (No. 2017 [1333]) and Peking University International Hospital (No. 2022-KY-0028-01). All patients gave their written informed consent to participate.

Conflict of Interest Statement

The authors declare that they have no competing interests.

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Author Contributions

Meng Tan collected the general and follow-up data, analyzed the statistics, and drafted the manuscript; Jing Xu collected the general and follow-up data of the patients; Ying Tan designed the study and revised the manuscript; Zhen Qu designed the study, had full access to all of the data, and provided final approval of the submitted manuscript; Feng Yu provided intellectual content of importance to this work; and Minghui Zhao reviewed the manuscript. All authors read and approved the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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