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Original Article

ORIGINAL ARTICLE

Efficacy and safety of belimumab in refractory and newly diagnosed active lupus nephritis patients: a real-world observational study

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ABSTRACT

Background. Lupus nephritis (LN), one of the common manifestations of systemic lupus erythematosus, continues to be a principal cause of morbidity and mortality. According to the 2024 Kidney Disease: Improving Global Outcomes guidelines, belimumab has been recommended as adjunct therapy for active LN. However, the differences in its efficacy and safety between refractory and newly diagnosed active LN are unknown. This study aimed to evaluate them in a real-world clinical setting in China.

Methods. We enrolled active LN patients who initiated belimumab as adjunct therapy in our centre between June 2021 and January 2024 and divided them into a refractory group and a newly diagnosed group according to previous immunosuppressive therapy. They were followed up for ≥3 months. Renal manifestations, serologic features, Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score and steroids dosage were recorded. We used generalized estimating equations to compare time series data for each group and analyse the change tendency of variables over time. Efficacy endpoints were complete renal response (CRR) and primary efficacy renal response (PERR). Logistic regression models were used to analyse factors associated with renal response.

Results. Of 116 LN patients receiving belimumab in our centre, a total of 89 active LN patients were included in the analysis, with a median treatment duration of 13 months (range 7–22). Among them 47 were in the newly diagnosed group and 42 were in refractory group. At the initiation of belimumab there is no statistical difference in age, gender, SLEDAI-2K score, renal-related markers (proteinuria, serum albumin, estimated glomerular filtration rate and renal histological classification) and serologic features (positive anti-double-stranded DNA, C3, C4) between the two groups. Compared with refractory patients, newly diagnosed patients had significantly shorter LN duration ($P < .001$) and a larger dosage of steroids ($P < .01$). During the follow-up period, proteinuria, SLEDAI-2K score and dosage of steroids decreased overall and in each group. The decrease was significantly more pronounced in the newly diagnosed group ($P < 0.01$, $P < 0.001$, $P < 0.001$). For the refractory active LN patients, the estimated probability of CRR and PERR at 12 months was 58.3% and 65.4%, respectively, which was comparable to newly diagnosed patients by logrank test ($P = .10$, $P = .51$). No difference was found in adverse event rates ($P = .08$), time to first renal flare ($P = .79$) or renal-related events ($P = .77$). Proteinuria levels at belimumab initiation [odds ratio (OR) 1.306, $P = .02$] and belimumab treatment duration (OR 0.896, $P = .01$) were independently associated with renal response.

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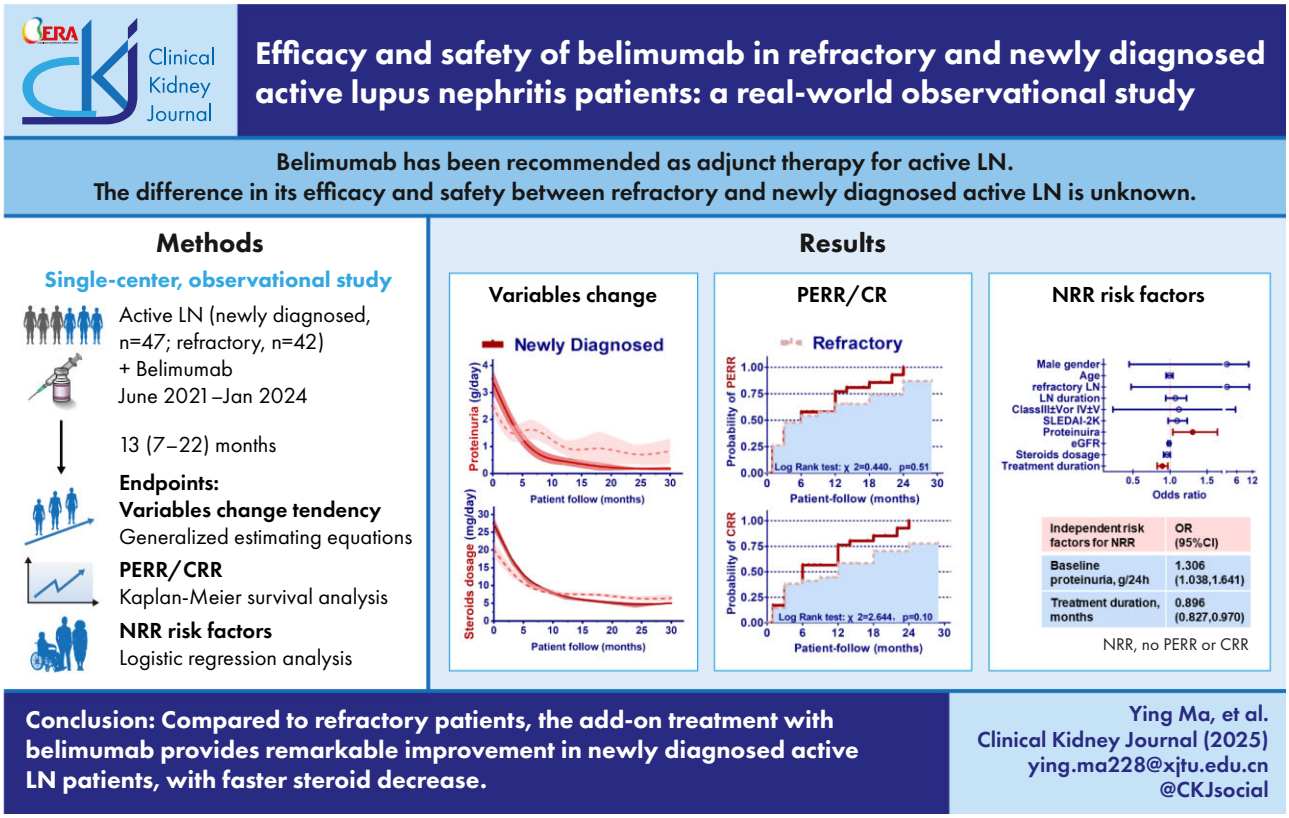
Conclusion. Compared with refractory LN patients, the add-on treatment with belimumab provides remarkable improvement in newly diagnosed active LN patients, with faster steroids decrease. Our data support the efficacy of early introduction of belimumab in Chinese active LN patients in a real-life setting.

GRAPHICAL ABSTRACT



Keywords: belimumab, efficacy, lupus nephritis, safety, steroid sparing

KEY LEARNING POINTS

What was known:

- Belimumab has been recommended as adjunct therapy for active LN, but the difference in its efficacy and safety between refractory and newly diagnosed active LN is unknown.

This study adds:

- Compared with refractory patients, belimumab provides remarkable disease improvement and faster steroids decrease in newly diagnosed active LN patients, with no difference in adverse events.

Potential impact:

- Our data preliminarily support the early introduction of belimumab as adjunct therapy in active LN patients.

INTRODUCTION

Lupus nephritis (LN), with a reported lifetime incidence of 20–60% [1] among patients with systemic lupus erythematosus (SLE), constitutes a principal cause of disease progression and mortality in SLE patients [2, 3]. Over the years the standard therapy for LN has been steroids combined with immunosuppressive agents such as cyclophosphamide (CTX) or mycophenolate mofetil (MMF). Although the prognosis of LN patients has improved over the past decades [4], LN remains difficult to treat, with short-term complete renal response (CRR) rates of ≈10–40% at 12 months [5]. Studies have shown that 13–37% of patients experienced renal flare within 3–5 years of standard therapy [6, 7] and the occurrence of end-stage kidney disease (ESKD) is as high as 10–20% [8, 9]. Together with the fact that patients with

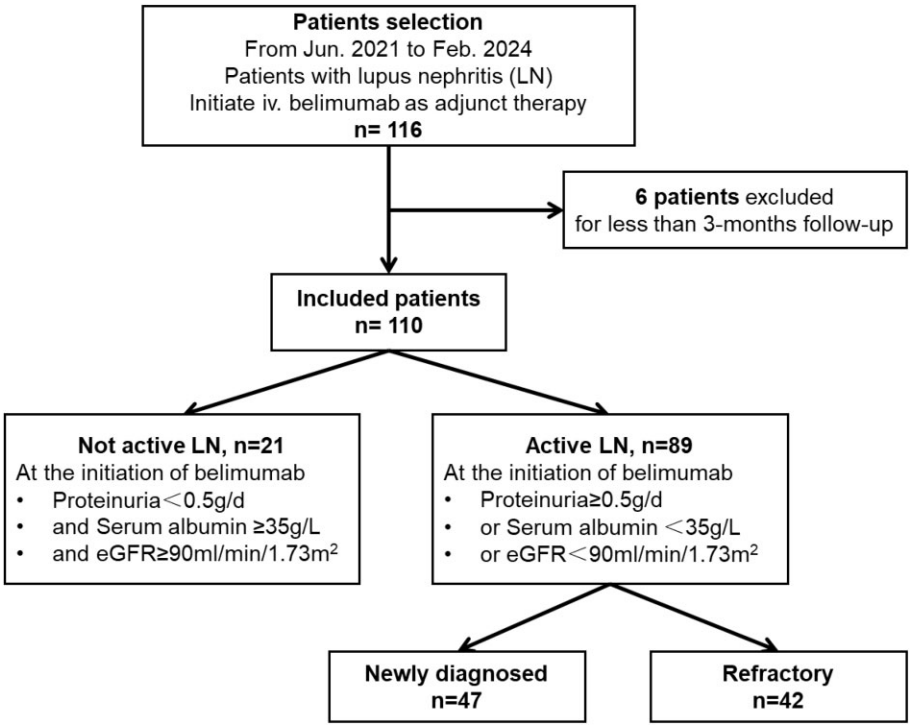


Figure 1: Flow chart of the study.

refractory LN receive high cumulative dosages of steroids and toxic immunosuppressants, exploration of new therapeutic options is important [10].

Belimumab is a recombinant human immunoglobulin G1 λ (IgG1-λ) monoclonal antibody that binds to the soluble B lymphocyte stimulator protein (BLyS), blocking the binding of BLyS to its receptor on B lymphocytes, inhibiting the growth of B lymphocytes and decreasing its growth, differentiation and subsequent immunoglobin production. The phase 3 BLISS-LN study (NCT01639339) [11] and its post hoc analysis [12] showed the addition of belimumab to standard therapy improved renal outcomes in active LN patients, with a reduction of LN flare risk and better preservation of kidney function. In the BElimumab in Real LIfe Setting Study (BeRLiSS-LN), belimumab led to durable renal response in patients with LN [13]. In the current LN guidelines, belimumab has been recommend as an initial therapy for active LN, and for LN patients refractory to first-line treatment regimens, biologic therapies may be beneficial [1, 14]. Recently, more and more real-world studies have confirmed the efficacy and safety of belimumab for the treatment of refractory LN. Case series have reported the use of belimumab in refractory LN and in two of three cases achieved partial remission [15]. Zhang *et al.* [16] observed the overall renal response rate of belimumab among a multicentre refractory LN cohort was 55.6%, with only three adverse events reported. Another single-centre retrospective study of refractory child-onset SLE cohort revealed a significant decrease in urine protein at 24 weeks of belimumab treatment [17]. Now the question is: should belimumab be used early in the disease course or just in refractory patients [18]? Up to now there have been few data directly regarding how the efficacy of belimumab in the treatment of refractory active LN differs from that of newly diagnosed active LN. Herein we aim to compare the efficacy and safety of belimumab in refractory active LN patients versus newly diagnosed active LN patients in a real-world clinical setting in China.

MATERIALS AND METHODS

Study population

Active LN patients treated with belimumab were enrolled in the Nephrology Department of the First Affiliated Hospital of Xi'an Jiaotong University between June 2021 and January 2024. The study flow chart is shown in Fig. 1. Inclusion criteria were as follows: fulfilment of the European League Against Rheumatism/American College of Rheumatology 2019 classification criteria for SLE [19]; diagnosed LN by renal biopsy and confirmed by persistent positive urinalysis according to the 2021 Kidney Disease: Improving Global Outcomes (KDIGO) recommendations [20]; belimumab as adjunct therapy was administered by intravenous infusion with a standard dosing regimen of 10 mg/kg every 2 weeks for the first three doses and every 4 weeks thereafter; active LN patients, which referred to patients who had not achieved complete remission (proteinuria <0.5 g/day, serum albumin ≥35 g/l and estimated glomerular filtration rate (eGFR) ≥90 ml/min/1.73 m^2, according to the KDIGO [1] and a national guideline from China [21]) and needed to initiate immunosuppressive therapy. Newly diagnosed active LN included active LN patients who had not received any immunosuppressive therapy before or under the initial induction treatment for ≤3 months. Refractory active LN was defined as active LN despite previously conventional standard immunosuppressive treatments [10] by steroids in combination with at least one kind of immunosuppressant including CTX, MMF or calcineurin inhibitors (CNIs). Specifically, patients fulfilled the active LN definition at the time of inclusion and failure of initial induction immunosuppressive therapy at 3 months and for which a switch to another induction

therapy regimen had already been carried out or experienced no less than one LN flare after the start of initial immunosuppressive therapy were enrolled in the refractory LN group [22–24]. The baseline time was defined as the time of belimumab initiation. Exclusion criteria were missing clinical data or follow-up time <3 months, age <18 years at baseline, received long-term renal replacement therapy or kidney transplant before baseline, pregnancy or anti-malignant therapy at baseline and during follow-up.

Data collection

The patients were followed up by the LN management group in the outpatient clinics of the First Affiliated Hospital of Xi'an Jiaotong University. Baseline and follow-up data were collected, including age, gender, body mass index (BMI), blood pressure (BP), SLE Disease Activity Index 2000 (SLEDAI-2K) and laboratory examination including 24-h urine protein (24hUP), haematuria, leukocyturia, cylindruria, serum albumin, serum creatinine, eGFR (calculated by the 2021 Chronic Kidney Disease Epidemiology Collaboration formula), serum complement factor 3 (C3), serum complement factor 4 (C4), serum anti-double-stranded DNA (dsDNA)/anti-Smith/anti-SSA/anti-SSB antibody, IgG, IgM and IgA. Blood B lymphocytes ($CD3^-CD19^+$) and T lymphocytes ($CD3^+$) and T cell clusters including $CD4^+$ T lymphocytes and $CD8^+$ lymphocytes counted by flow cytometry. The renal biopsy specimens were examined by light microscopy, direct immunofluorescence and electron microscopy techniques. For those who had a rebiopsy of the kidney before inclusion in the study, we collected the renal pathological diagnosis at the time closest to belimumab initiation. Daily steroids dosage (prednisone equivalent dose), concomitant medications including hydroxychloroquine (HCQ), MMF, CTX, CNIs such as tacrolimus and cyclosporine A, azathioprine and renin–angiotensin–aldosterone system inhibitors were recorded. Adverse events (AEs) were regularly collected and updated. Severe AEs (SAE) were defined as AEs related with hospitalization. Discontinuation was defined as an interruption of belimumab for >3 months. Data collection was stopped in patients who had belimumab discontinuation.

Endpoints and clinical outcome assessments

The primary endpoint was the renal response to belimumab treatment, including CRR and primary efficacy renal response (PERR). The definitions of renal response mainly referred to BLISS-LN [11]: CRR was defined as an eGFR not worse than 10% below the baseline value or ≥90 ml/min/1.73 m^2 and 24hUP <0.5 g/day and inactive urinary sediment [<5 red blood cells (RBCs)/high-power field (HPF) and <5 white blood cells (WBCs)/HPF and no cellular casts (no RBC or WBC casts). PERR was defined as 24hUP <0.7 g/day and an eGFR that was no worse than 20% below the baseline value or at least 60 ml/min/1.73 m^2. Failure to reach CRR or PERR was considered no renal response (NRR). Renal flare was defined as follows: (1) if baseline 24hUP was <0.5 g, an increase to 1 g; if baseline 24hUP was 0.5–1.0 g, an increase to 2 g; and if the baseline 24hUP >1.0 g, double; (2) if baseline serum creatinine <2.0 mg/dl, an increase ≥0.2 mg/dl; and if baseline serum creatinine ≥2.0 mg/dl, increase ≥0.4 mg/dl [3, 25]. Renal-related events (RREs) was defined as doubling of serum creatinine, a decrease in eGFR of >30%, or increased proteinuria or both, ESKD or the need for renal replacement treatment or kidney disease–related treatment failure.

Statistical analyses

Results were expressed as frequencies and percentages for categorical variables, mean ± standard deviation (SD) for normally distributed continuous variables and median values with their interquartile range (IQR; 25th–75th percentile) for non-normally distributed continuous variables. Differences between groups were analysed using the χ^2 test and Wilcoxon rank-sum test or Student's *t*-test as appropriate. Kaplan–Meier curves (logrank test) were used to demonstrate the disease endpoint. Generalized estimating equations (GEEs) were built by R software (version 4.4; R Foundation for Statistical Computing, Vienna, Austria) and the R package geeglm to compare time series data for each group and analyse the change tendency of variables over time. Other statistical analysis was performed using SPSS for Windows (version 20.0; IBM, Armonk, NY, USA). A two-sided *P*-value <.05 was considered statistically significant.

RESULTS

Baseline data of active LN patients

A total of 116 LN patients had been receiving belimumab in our centre (Fig. 1). There were 21 not active LN patients who received belimumab therapy, aiming to decrease the use of steroids (76.2%) or to prevent disease flare (23.8%).

A total of 89 active LN patients were included in the analysis. As shown in Table 1, their average age was 36.1 ± 12.9 years and 76 (85.4%) were women. Among all the enrolled active LN patients, 42 patients were enrolled in the refractory group, with a median number of LN flares of 2 (IQR 2–3). For the previous immunosuppressive therapy, MMF was most frequently used [$n = 33$ (78.6%)], followed by CTX (61.9%) and CNIs (45.2%). There was one patient who received rituximab with an interval of >3 years before belimumab initiation.

At the initiation of belimumab for all enrolled patients, the average SLEDAI-2K score was 13.9 ± 6.0. The most common clinical SLEDAI manifestation was immunologic involvement [79 (88.8%)], followed by haematological [39 (43.8%)] and dermal [19 (21.3%)] involvement. The frequency of hypocomplementemia was 79.8%. A total of 61 patients (68.5%) were positive for anti-dsDNA antibody. Their median LN duration was 18.0 months (IQR 2.0–81.0). The median level of proteinuria was 2.2 g/day (IQR 1.1–4.7). The baseline eGFR was 101.5 ml/min/1.73 m^2 (IQR 51.2–123.5), with 25 patients (28.1%) with an eGFR <60 ml/min/1.73 m^2 and 3 patients with an eGFR <15 ml/min/1.73 m^2. All patients of the cohort had renal biopsy–proven LN, among which 14 patients had a rebiopsy before belimumab initiation (11 histopathologic class transformations and 3 with the original histopathologic class), and they were all recorded in the refractory group. The median time interval between renal biopsy and belimumab initiation was 38.0 days (IQR 6.0–320.0). The leading class was class III or IV, with/without class V [$n = 66$ (74.2%)]. The major concomitant therapy was steroids (98.9%), followed by MMF (52.8%, including three patients who received CTX sequential to MMF) and CNIs (22.5%). There were four patients who received concomitant rituximab therapy, among which one was recorded in the refractory group. In the newly diagnosed group, three patients received rituximab due to a relative contraindication for high-dose steroids (two osteoporosis cases and one symptomatic epilepsy) and their pathological diagnoses were all class IV + V LN.

Table 1 showed the comparison of baseline characteristics between the two groups. At the initiation there is no statistical difference in age, gender, SLEDAI-2K score, serologic features

Table 1: Comparison of clinical parameters and drug between refractory and newly diagnosed active lupus nephritis patients at the initiation of belimumab.

Factors	Total ($N = 89$)	Newly diagnosed active LN ($n = 47$)	Refractory active LN ($n = 42$)	*P*-value
Female, *n* (%)	76 (85.4)	39(83.0)	37(90.2)	.32
Age at first infusion (years)	36.1 ± 12.9	34.9 ± 13.6	37.4 ± 12.1	.35
BMI	22.2 ± 3.1	21.9 ± 2.9	22.6 ± 3.4	.15
Systolic BP (mmHg)	127.0 ± 21.1	124.6 ± 19.6	130.7 ± 23.1	.36
Diastolic BP (mmHg)	87.3 ± 14.7	86.0 ± 14.4	89.2 ± 15.1	.93
Pathoglycaemia, *n* (%)	11 (12.4)	6 (12.8)	5 (11.9)	.90
LN duration (months), median (IQR)	18.0 (2.0–81.0)	2.0 (1.0–15.0)	60.0 (36.0–144.0)	<.001
Time to renal biopsy (days), median (IQR)	38.0 (6.0–320.0)	14.0 (5.0–73.0)	161.0 (8.0–1199.3)	<.01
SLEDAI-2K score, mean ± SD	13.9 ± 6.0	14.6 ± 5.9	13.0 ± 6.0	.22
Laboratory examination, median (IQR)				
Proteinuria (g/24 h)	2.2 (1.1–4.7)	2.3 (1.2–5.2)	2.2 (0.7–4.2)	.14
Urine RBC (RBCs/HPF)	8.5 (1.9–25.4)	14.4 (3.3–36.7)	3.8 (1.6–13.3)	.02
Urine WBC (WBCs/HPF)	4.8 (2.3–15.9)	4.8 (2.6–15.0)	5.1 (1.5–19.9)	.66
Urine cast (cast/LP)	2.8 (0.3–9.4)	4.6 (0.3–16.3)	1.6 (0.3–6.4)	.21
Serum albumin (g/l), mean ± SD	27.5 ± 7.3	26.9 ± 8.1	28.2 ± 6.3	.41
eGFR (ml/min/1.73 m^2)	101.5 (51.2–123.5)	99.0 (39.0–108.9)	112.6 (65.8–128.6)	.07
Acute kidney injury, *n* (%)	9 (10.1)	9 (19.1)	0	<.001
Pathology, *n* (%)				.25
I or II	6 (6.7)	5 (10.6)	1 (2.4)	
III	8 (9.0)	6 (12.8)	2 (4.8)	
IV	26 (29.2)	14 (29.8)	12 (28.6)	
III/IV + V	32 (36.0)	14 (29.8)	18 (42.9)	
V	17 (19.1)	8 (17.0)	9 (21.4)	
AI	6.0 (2.0–8.0)	6.0 (4.0–8.0)	5.0 (2.0–7.5)	.20
CI	1.0 (0.0–1.0)	0.0 (0.0–1.0)	1.0 (0.0–2.0)	.13
C3 (g/l)	0.61 ± 0.26	0.60 ± 0.29	0.62 ± 0.22	.73
C4 (g/l)	0.10 (0.06–0.20)	0.11 (0.06–0.20)	0.10 (0.07–0.20)	.95
Hypocomplementaemia, *n* (%)	71 (79.8)	35 (74.5)	36 (85.7)	.19
Positive anti-dsDNA, *n* (%)	61 (68.5)	30 (63.8)	31 (73.8)	.31
Positive anti-Sm, *n* (%)	17 (28.8), $n = 59$	10 (30.3), $n = 33$	7 (26.9), $n = 26$	.78
Positive anti-SSA, *n* (%)	32 (54.2), $n = 59$	17 (51.5), $n = 33$	15 (57.7), $n = 26$	.64
Positive anti-SSB, *n* (%)	5 (8.5), $n = 59$	2 (6.1), $n = 33$	3 (11.5), $n = 26$	.46
IgG (g/l), median (IQR)	10.6 (7.1–14.8)	10.6 (7.1–15.3)	10.8 (6.9–14.0)	.50
IgM (g/l), mean ± SD	1.0 ± 0.8	1.2 ± 0.9	0.9 ± 0.5	.08
IgA (g/l), mean ± SD	2.4 ± 1.2	2.5 ± 1.2	2.3 ± 1.2	.66
Concomitant therapy				
Oral steroid, *n* (%)	88 (98.9)	46 (97.9)	42 (100)	.26
Dosage of steroid (mg/day), median (IQR)	25.0 (10.0–30.0)	30.0 (18.8–31.3)	15.0 (9.4–30.0)	<.01
Daily dose >7.5 mg, *n* (%)	77 (86.5)	45 (95.7)	32 (76.2)	<.01
Hydroxychloroquine, *n* (%)	58 (65.2)	28 (59.6)	30 (71.4)	0.24
MMF, *n* (%)	47 (52.8)	26 (55.3)	21 (50.0)	0.62
CNIs, *n* (%)	20 (22.5)	6 (12.8)	14 (33.3)	0.02
Multitarget therapeutics, *n* (%)	11 (12.4)	3 (6.4)	8 (19.0)	0.07
Renin–angiotensin system inhibitor, *n* (%)	33 (37.1)	14 (29.8)	19 (45.2)	.13
Sodium–glucose co-transporter 2 inhibitor, *n* (%)	3 (3.4)	1 (2.1)	2 (4.8)	.49
Rituximab, *n* (%)	4 (4.5)	3 (6.4)	1 (2.4)	.35

Pathoglycaemia including impaired fasting glucose, abnormal glucose tolerance and diabetes mellitus.
eGFR calculated by the 2021 Chronic Kidney Disease Epidemiology Collaboration formula.

(positive anti-dsDNA, C3, C4 or hypocomplementaemia) between the two groups. As for renal-related markers, haematuria was more prominent in the newly diagnosed group ($P = .02$), whereas the level of proteinuria, serum albumin and eGFR were comparable, as well as renal histological classification. Compared with the refractory group, the newly diagnosed group had significantly shorter LN duration ($P < .001$), a shorter time interval to renal biopsy ($P < .01$) and a higher proportion of acute kidney injury ($P < .001$). A significantly larger dosage of steroid intake was observed in newly diagnosed active LN patients ($P < .01$), accompanied by less CNI usage ($P = .02$).

Efficacy (treatments response)

Effect on renal parameters and serologic features

The follow-up of all enrolled patients is reported in Fig. 2A. During a median treatment duration of 13 months (range 7–22), the overall proteinuria and eGFR improved over time (Fig. 2B). The average SLEDAI-2K score decreased from 13.9 to 4.0.

GEE analysis showed that proteinuria (Fig. 3A) decreased and serum albumin (Fig. 3B) increased significantly in both groups of active LN patients during belimumab treatment ($P < .001$, $P < .001$). The decrease in proteinuria was more significantly

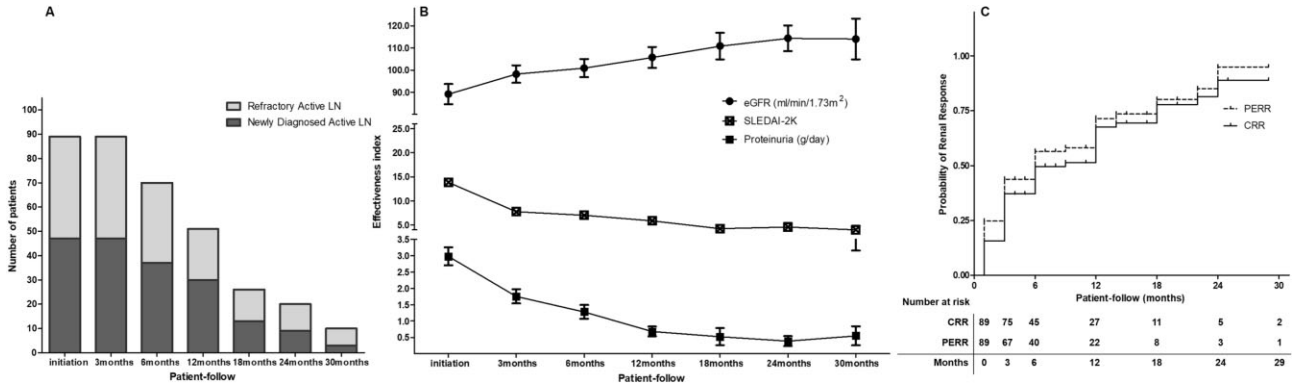


Figure 2: Follow-up of enrolled patients and their effectiveness and response rates during belimumab treatment. **(A)** Numbers of patients included in the analysis at each given time point according to the follow-up schedule. **(B)** Changes in effectiveness indexes during belimumab treatment. **(C)** Renal response during belimumab treatment.

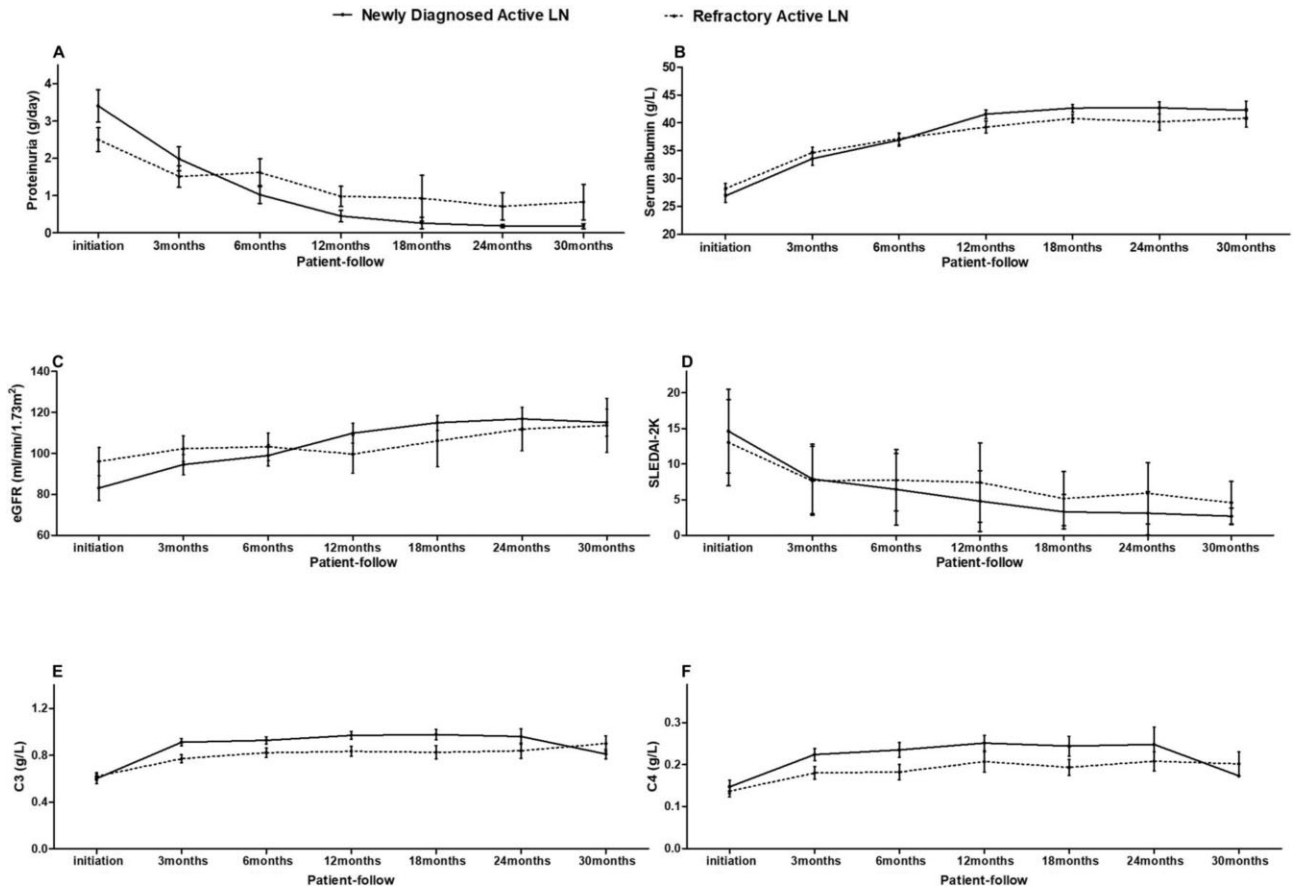


Figure 3: Comparison of efficacy between newly diagnosed and refractory active LN patients. Estimated marginal means and corresponding standard errors of **(A)** proteinuria, **(B)** serum albumin, **(C)** eGFR, **(D)** SLEDAI-2K, **(E)** C3 and **(F)** in newly diagnosed and refractory active LN groups using GEEs.

observed in the newly diagnosed group ($P < .01$). The level of proteinuria of newly diagnosed active LN patients was comparable to that of refractory patients at month 3, while significantly lower ($P = .03$) at the last visit (Table 2).

Two patients developed ESKD. These two kidney biopsies were identified as class IV >10 years ago. They were recorded in the refractory group and experienced no less than three LN flares, resulting in a gradual decrease or frequent fluctuation in kidney function, finally progressing to ESKD. Fig. 3C showed greater improvement of eGFR over time in the newly diagnosed group than the refractory group, confirmed by GEE analysis ($P < .01$).

A decrease in the SLEDAI-2K score was observed in both groups during the follow-up (Fig. 3D; $P < .001$), but the decrease was more significant in the newly diagnosed group ($P < .001$). Of the 30 patients with positive anti-dsDNA antibody in the newly

Table 2: Comparison of clinical parameters between refractory and newly diagnosed active LN patients treated with belimumab at month 3 and the last visit.

	Month 3			Last visit		
Factors	Newly diagnosed active LN ($n = 47$)	Refractory active LN ($n = 42$)	*P*-value	Newly diagnosed active LN ($n = 47$)	Refractory active LN ($n = 42$)	*P*-value
Treatment duration				13.0 (8.0–21.0)	12.0 (6.0–24.3)	.91
SLEDAI-2K score, mean ± SD	7.9 ± 4.9	7.6 ± 4.8	.82	4.0 (2.0–8.0)	4.5 (4.0–9.8)	.22
Proteinuria (g/24 h), median (IQR)	1.2 (0.3–3.9)	0.9 (0.4–2.1)	.61	0.3 (0.1–0.9)	0.6 (0.2–2.2)	.03
Urine RBC (RBCs/HPF), median (IQR)	3.9 (1.9–18.0)	2.4 (0.7–7.2)	.07	3.7 (0.8–11.3)	2.5 (0.6–7.0)	.56
Urine WBC (WBCs/HPF), median (IQR)	2.9 (1.2–10.4)	2.8 (0.7–6.7)	.43	2.3 (0.5–11.8)	2.6 (0.7–6.7)	.85
Urine cast (cast/LP), median (IQR)	0.5 (0.0–2.4)	0.9 (0.1–2.8)	.74	0.4 (0.1–1.7)	0.4 (0.0–2.1)	.83
Serum albumin (g/l), mean ± SD	33.6 ± 8.3	34.6 ± 6.4	.52	38.6 ± 7.6	38.0 ± 6.5	.23
eGFR (ml/min/1.73 m^2)	94.5 ± 33.6	102.3 ± 39.8	.33	111.0 (85.6–121.6)	116.4 (66.5–127.7)	.45
C3 (g/l), mean ± SD	0.91 ± 0.20	0.77 ± 0.21	<.01	0.93 ± 0.19	0.84 ± 0.19	.03
C4 (g/l), mean ± SD	0.22 ± 0.09	0.18 ± 0.10	.04	0.24 ± 0.09	0.20 ± 0.09	.10
Hypocomplementaemia, *n* (%)	16 (34.0)	27 (64.3)	<.01	16 (34.0)	22 (52.4)	.08
Positive anti-dsDNA, *n* (%)	18 (38.3)	26(61.9)	.03	13 (27.7)	25 (59.5)	<.01
Oral steroids, *n* (%)	46 (97.9)	42 (100)	.26	46 (97.9)	40 (95.2)	.49
Dosage of steroids (mg/day)	17.0 ± 6.9	13.8 ± 7.8	.04	7.5 (5.0–10.0)	7.5 (5.0–10.0)	.46
Daily dose >7.5 mg, *n* (%)	42 (89.4)	31 (73.8)	.06	16 (34.0)	18 (42.9)	.39

Table 3: Lymphocyte subset counts at baseline and at month 3.

	Newly diagnosed active LN ($n = 30$)			Refractory active LN ($n = 28$)				
Lymphocyte subset counts	Baseline	Month 3	P1 value	Baseline	Month 3	P1 value	***p2 value***	***p3 value***
B cell count (/μl)	166.0 (91.4–307.0)	154.7 (102.7–360.3)	.88	64.4 (42.7–110.4)	47.3 (29.9–86.6)	.24	<0.001	<0.001
T cell count (/μl)	909.1 (567.2–1177.1)	1630.0 (1160.3–2007.2)	<.001	668.3 (459.8–1099.4)	941.6 (667.0–1472.8)	.01	0.31	<0.01
$CD4^+$ count (/μl)	325.0 (266.0–544.0)	655.5 (522.0–912.0)	<.001	350.5 (224.3–598.6)	464.3 (285.0–608.0)	.08	0.70	<0.01
$CD8^+$ count (/μl)	437.2 (219.3–570.5)	760.5 (549.4–1049.4)	<.001	351.9 (192.8–448.2)	447.0 (329.6–858.0)	<.01	0.39	0.02

p1 value: baseline versus month 3; p2 value: newly diagnosed group versus refractory group at baseline; p3 value: newly diagnosed group versus refractory group at month 3.

diagnosed group, 12 (40.0%) and 17 (56.7%) patients turned negative at 3 months and the last visit, respectively. The proportion of anti-dsDNA antibody–positive patients was significantly higher in the refractory group at month 3 and the last visit (Table 2). C3 and C4 increased gradually over time (Fig. 3E and F), but there was no statistical difference between the two groups by GEE analysis. Table 2 shows that C3 ($P < .01$) and C4 ($P < .05$) were significantly higher in the newly diagnosed group compared with the refractory group at 3 months of follow-up, and C3 was still higher than in the refractory group at the last follow-up ($P = .03$).

There were 62 patients with full records of lymphocyte subset counts. After excluding 4 patients who received rituximab as concomitant therapy, the analysis of the remaining 58 patients showed that the B cell count was significantly higher in newly diagnosed patients both at baseline ($P < .001$) and at month 3 ($P < .001$) (Table 3). Comparing the B cell level between baseline and month 3, no difference was found in either group ($P = .88$, $P = .24$; Fig. 4A). GEE analysis also found no obvious change in the B cell count during the 3 months of follow-up ($P = .55$). As for the T cell count, there was no statistical difference between the two groups at baseline (Table 3, P2 value), then it increased during the first 3 months in each group (Table 3, P1 value; Fig. 4B). Compared with the refractory group, the increase was more prominent in the newly diagnosed group by GEE analysis ($P < .01$), resulting in a higher T cell count, including both $CD4^+$ and $CD8^+$ T cells of newly diagnosed patients at month 3 of follow-up (Table 3, P3 value).

Steroid dosage

The overall proportion of patients receiving >7.5 mg/day (prednisone equivalent dose) of steroids decreased from 86.5% (77/89) at initiation to 38.2% (34/89) at the last visit. An obvious reduction of steroid dose was achieved overall (Fig. 5A). Following a significantly higher baseline dosage of steroid, the newly diagnosed active LN patients still received a higher steroid dose ($P = .04$) at month 3, while it decreased to a comparable dose to that of refractory active LN patients at last visit (Table 2). GEE analysis also showed that during the follow-up period, the decrease in steroid dosage was more significant in the newly diagnosed group ($P < .001$) (Fig. 5B).

Clinical outcome

The estimated overall CRR at 12 months was 67.6% and PERR at 12 months was 71.5% (Fig. 2C). For the newly diagnosed active LN patients, the estimated probability of CRR and PERR at 12 months was 76.3% and 77.0%, respectively, which was higher than that of refractory patients (58.3% and 65.4%, respectively), although without statistical difference ($P = .10$, $P = .51$;

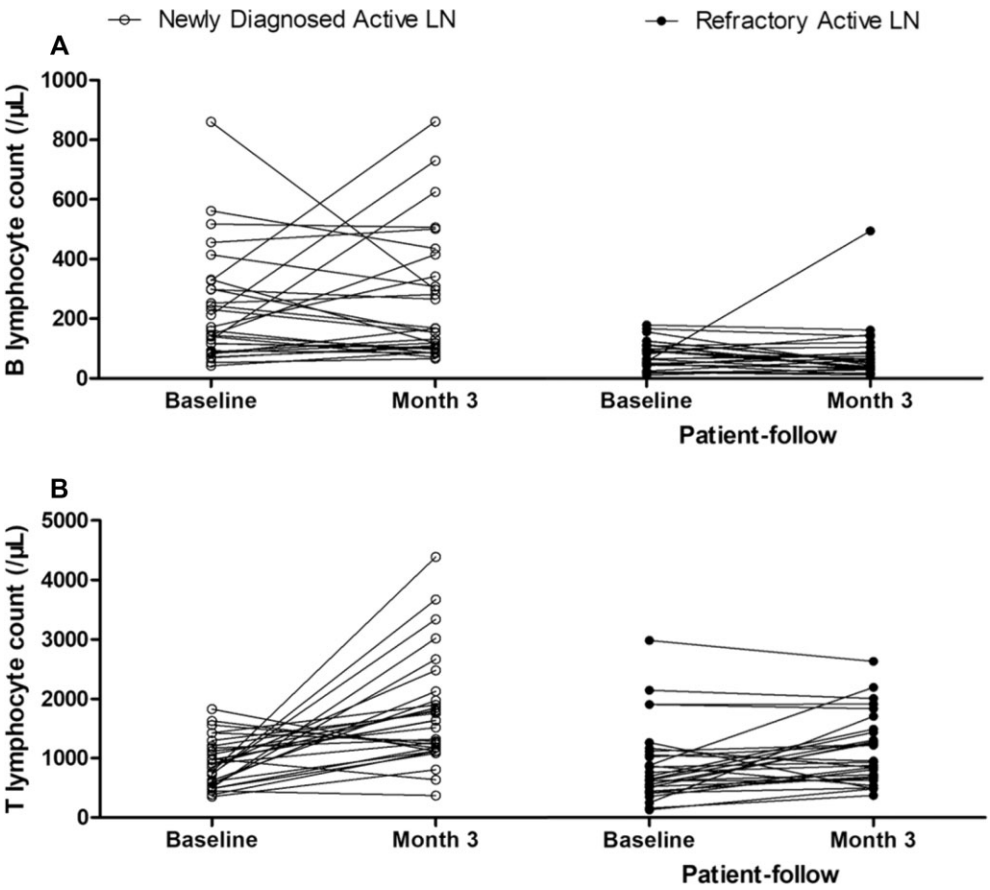


Figure 4: Lymphocyte subset counts at baseline and month 3.

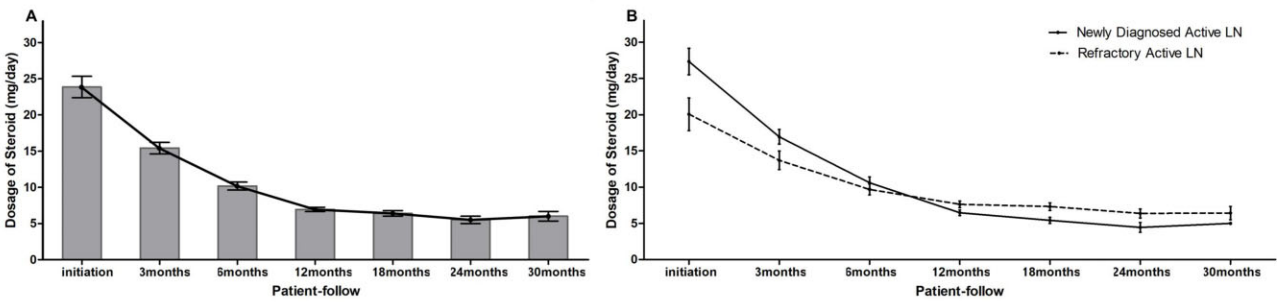


Figure 5: Dosage of steroid (prednisone equivalent) during belimumab treatment.

Fig. 6A and B). During the follow-up there was no significant difference in the risk of renal flare or the RRE between the two groups (Fig. 6C and D).

The results of univariate and multivariate logistic regression models verified that gender, age at belimumab initiation, refractory active LN, pathological class III ± V or IV ± V, baseline SLEDAI-2K score and baseline dosage of steroids were not predictive factors for NRR. In contrast, higher baseline proteinuria could independently predict NRR. According to the multivariate logistic regression model, increasing baseline proteinuria levels was associated with a 30.6% relative increment in the risk of NRR (95% CI 1.038–1.641) and longer belimumab treatment duration was independently associated with a lower risk of NRR [OR 0.896 (95% CI 0.827–0.970)] (Fig. 7).

Safety

Although the total number of AEs and the incidence rate of herpes virus infection in the newly diagnosed group were numerically higher, the incidence rate of common AEs was not statistically different between the two groups (Table 4).

DISCUSSION

This observational cohort study included patients with active LN and was designed to reflect the real-world effectiveness and tolerability of belimumab in addition to standard therapies. These analyses are among the first to assess outcomes of patients based on whether they were newly diagnosed or had refractory

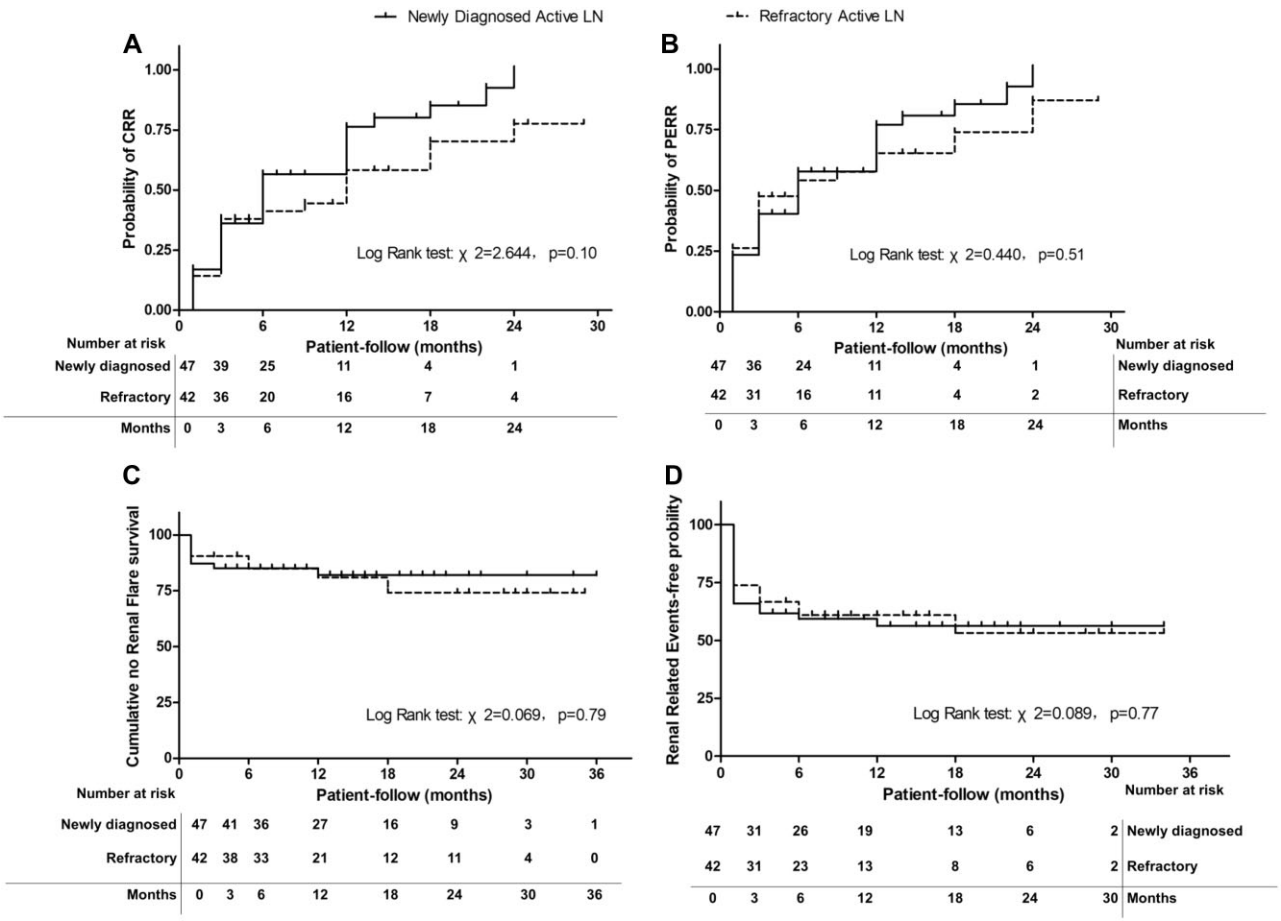


Figure 6: Comparison of efficacy endpoints between the newly diagnosed group and refractory group. **(A)** Time to first CRR and **(B)** time to first PERR. Cumulative rate of **(C)** no renal flare survival and **(D)** no renal-related event.

active LN. After ≥3 months of treatment, patients had improvement in renal parameters and disease activity, accompanied by a decrease in steroid dose.

We observed a significant decrease in proteinuria in all enrolled patients, especially newly diagnosed active LN patients treated with belimumab, which was in line with the post hoc analysis of clinical trials [26] and analysis of BLISS-LN [11]. As for renal function, the median eGFR improved from 101.5 ml/min/1.73 m^2 at baseline to 112.0 ml/min/1.73 m^2 at the last visit, similar to the variation trend of the mean observed eGFR values in the belimumab group of BLISS-LN [11]. Although the comparison of eGFR showed no significant difference between the two groups no matter at month 3 or the last visit, GEE analysis showed better renal function improvement in the newly diagnosed group. Subgroup analysis showed that for those 25 patients with baseline kidney injury (defined as eGFR <60 ml/min/1.73 m^2), 16 patients were in the newly diagnosed group, of which 10 patients had renal function recovery (improved to eGFR ≥60 ml/min/1.73 m^2) at the last visit, while the other 9 kidney injury patients in the refractory group showed only 2 patients who had renal function recovery. The acute kidney injury (AKI) proportion was significantly higher in the newly diagnosed group. Six of nine AKI patients had renal function recovery, which may contribute to the better renal function preservation of the newly diagnosed group. Similarly, an observational cohort study of Chinese LN patients with belimumab also reported all five AKI patients at baseline had renal response with eGFR increased [27].

The LN duration was significantly shorter in the newly diagnosed group. Early use of belimumab treatment would have generated an extra anti-inflammatory response inducing an early complete sustained histologic remission, slowing the progression of fibrosis and preserving glomerular structures and function [28]. However, we cannot identify it because none of our participants repeated the renal biopsy after belimumab initiation. Meanwhile, it has been demonstrated that a progressive number of LN flares was associated with a lower complete and partial response to therapy and an adverse prognosis for kidney function [29]. And recent clinical trials have reported a differential effect of the study treatments in patients with and without previous exposure to immunosuppressants. For our refractory LN patients, the median number of LN flares was two, and all of them had previous exposure to immunosuppressants. These variables together show a negative effect on the treatment response of refractory LN patients.

Moreover, serologic features generally improved overall throughout the therapy. We observed a decrease in the number of hypocomplementaemia patients, as well as the prevalence of anti-dsDNA antibody, especially in the newly diagnosed group. Meanwhile, the majority of patients with normal serologic features did not worsen throughout the study, which is consistent with other studies of LN [3, 16, 27] and SLE [17, 30, 31].

There was no observed belimumab treatment difference in CRR or PERR in patients with refractory and newly diagnosed active LN. The estimated CRRs and PERRs at 12 months in the overall study population were all >60%, which was higher than

Factors	Univariate logistic regression		Multivariate logistic regression	
	Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value
Male gender	1.753(0.502,6.120)	0.38	2.171(0.447,10.538)	0.34
Age at initiation	1.013(0.978,1.049)	0.47	0.992(0.946,1.039)	0.73
Refractory active LN	1.620(0.652,4.026)	0.30	2.257(0.473,10.778)	0.31
LN duration (adjusted per 12months)	1.086(1.002,1.177)	<0.05	1.073(0.942,1.224)	0.29
Class III±V or IV±V	1.800(0.590,5.490)	0.30	1.120(0.227,5.519)	0.89
SLEDAI-2K score	1.077(0.994,1.167)	0.07	1.096(0.975,1.232)	0.13
Baseline proteinuria (g/24h)	1.293(1.055,1.583)	0.01	1.306(1.038,1.641)	0.02
Baseline eGFR (ml/min/1.73m²)	0.984(0.973,0.995)	<0.01	0.987(0.972,1.003)	0.12
Baseline dosage of steroids	1.003(0.971,1.036)	0.86	0.958(0.913,1.004)	0.07
Treatment duration, months	0.887(0.825,0.954)	<0.01	0.896(0.827,0.970)	0.01

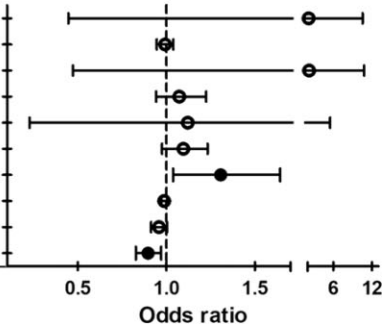


Figure 7: Risk factors for NRR by logistic regression analysis. eGFR calculated by the 2021 Chronic Kidney Disease Epidemiology Collaboration formula. Factors thought to be related to clinical outcomes of peritonitis were entered in a multivariate logistic regression model.

Table 4: AEs in refractory and newly diagnosed active LN patients treated with belimumab.

AEs	Newly diagnosed active LN ($n = 47$), n (%)	Refractory active LN ($n = 42$), n (%)	P-value
SAEs	4 (8.5)	2 (4.8)	.48
AEs in total	11 (23.4)	4 (9.5)	.08
Herpes virus infection	6 (12.8)	1 (2.4)	.06
Respiratory infection	3 (6.4)	1 (2.4)	.35
Digestive system infection	0 (0.0)	1 (2.4)	.28
Urinary system infection	1 (2.1)	1 (2.4)	.94
Infusion reaction	1 (2.1)	0 (0.0)	.26

in BLISS-LN [11]. The distinction might be related to the difference in baseline proteinuria. Our baseline median proteinuria was 2.2 g/day, while the baseline urine protein:creatinine ratio (UPCR) of the belimumab group in BLISS-LN was 3.2 ± 2.7. A secondary analysis of BLISS-LN suggested that belimumab was found to be most effective in improving the PERR and CRR in patients with a baseline UPCR <3 g/g and there was no observed improvement in kidney response in patients with a baseline UPCR ≥3 g/g. Our multivariate logistic regression model also confirmed the predictive value of high baseline urine protein for NRR. The post hoc subgroup analyses of the BLISS-LN trial support the use of belimumab in clinical practice for all patients with LN, whether newly diagnosed or relapsed [32]. Malaweera *et al.* [15] reported experience using belimumab in three cases of refractory LN, and two of the three cases achieved partial remission and improvement in serological markers of SLE and disease activity. However, no study compared the efficacy and safety of belimumab between newly diagnosed and refractory active LN patients. In our study, CRR and PERR in refractory active LN patients were comparable to those in newly diagnosed active LN patients, and refractory active LN was not a predictor of NRR, although the proportion was numerously low in refractory group.

Our study further demonstrated that belimumab has a steroid-sparing effect among active LN patients, with a reduction in the steroid dose, as in other reports in LN patients [3, 15, 27]. There is a wide consensus that steroids are a main cause of toxicity in SLE due to a number of serious complications, including osteonecrosis, osteoporosis, cardiovascular disease and infection [33]. Large observational studies support that steroid-mediated toxicity is largely dependent on the dose and the time of exposure [34, 35]. Prolonged use of high-dose steroids is associated with SAEs, long-term organ damage and morbidity [36]. Reducing the use of steroids is important, both in newly diagnosed and refractory LN patients. More and more studies support that SLE, including severe forms such as LN, can be successfully treated with regimens including lower doses of oral prednisone, with maximum doses ≤30 mg/day followed by a rapid reduction [37–41]. The latest KDIGO LN guidelines [1] recommend intravenous methylprednisolone then oral prednisolone 0.35–1.0 mg/kg/day and a taper to ≤7.5 mg/day by the end of 3 months as initial therapy of active LN. In our study, the baseline oral prednisolone was 30.0 mg/day (IQR 18.8–31.3) in the newly diagnosed group. The reason why it was higher than in the refractory group might be the relatively higher serum creatinine, urine RBC counts and hypocomplementaemia prevalence, as well as lower proportions of concomitant immunosuppressive drugs such as HCQ, CNIs and multitarget therapeutics in newly diagnosed patients, while the steroid dosage of newly diagnosed active LN patients decreased more rapidly and became equivalent to that of refractory patients at last visit.

We also briefly describe the changes in circulating B cells and T cells during 3-month belimumab treatment. The B cell count did not change over time in all enrolled LN patients, and this might be the result of opposite dynamic changes in the B cell subset. Utilizing longitudinal single-cell transcriptome data [42] and high-sensitivity flow cytometry [43], researchers observed initial decreases in naïve and transitional B cells followed by an increase at 3 months, contrasted by an initial increase at week 2 and a subsequent decrease in memory B cells by month 3. The B cell count of refractory active LN patients was consistently lower than that of newly diagnosed patients and may be correlated with multiple factors including disease stage and activity and the impact of concomitant immunosuppressants. We found a sharp increase in T cells (both $CD4^+$ and $CD8^+$) in the overall study population, and the increase was more significant in newly diagnosed patients. Maeda *et al.* [44] also found an association between belimumab treatment and an increase in regulatory T cells. Combining the vital role of T cells [45] and B cells [46, 47] in the pathogenesis of SLE and lymphocyte dynamics provided insights into immunological mechanisms underlying the therapeutic effect of belimumab, underscoring the need for research in predicting drug responses based on immune profiling.

This study had several limitations. First, the relatively small cohort size meant that the study was open to both type 1 and

type 2 statistical errors. The lack of records of some markers and the fact that some patients were lost to follow-up had an impact on the study results. Second, due to the retrospective observational nature of the study design, we could not preclude unrecognized factors that confounded the results, and we were unable to gather full information on self-management (such as diet, change in BMI and BP fluctuation) and adherence to treatment, which may be important factors in our population and assessment. We acknowledge all limitations and risk of bias inherent in the study design. Third, the follow-up period was too short and the power of the study was not sufficient for definite conclusions. Fourth, the lack of a control group without belimumab had impact on efficiency and safety assessment and it needs to be further studied in the future. Additionally, active LN patients enrolled in the study were documented by urine and serum markers instead of renal biopsy–confirmed active lesions, together with a longer time interval between the renal biopsy and inclusion in the refractory group, unavoidably confounding assessment of treatment effects. Lastly, we were unable to generalize the findings to different populations. Nevertheless, the study did provide some preliminary data from a real-world cohort and was the first to assess belimumab efficacy in active LN patients based on whether they were newly diagnosed or refractory patients.

In summary, our study provides evidence to confirm that belimumab improved renal parameters and serological features and decreased disease activity and steroid dose in active LN patients in a real-world clinical setting in China. The more prominent efficacy in newly diagnosed patients might support belimumab as an early treatment option before conventional immunosuppressants.

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AUTHORS' CONTRIBUTIONS

Y.M. was responsible for patients' follow-up, data collection, statistical analysis and manuscript writing. X.L. supervised the statistical analysis. X.Y. and Y.L. were responsible for patients' follow-up and data collection. P.L. was responsible for pathology classification. J.S. designed and supervised the study and revised it critically. W.L. and J.S. was responsible for manuscript review. All authors provided final manuscript approval.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared upon reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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