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Use of belimumab in treating patients with systemic lupus erythematosus: a single-center, real-world retrospective study

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Abstract

Objective To investigate the efficacy and safety of belimumab in the treatment of systemic lupus erythematosus (SLE) in a real-world setting and provide a valuable reference for clinical treatment.

Methods In this retrospective study, 101 patients with SLE who came to our hospital from March 2020 to September 2022, 56 of whom with lupus nephritis (LN), were selected. All patients received belimumab in combination with standard of care(SoC)therapy regimen for more than 52 weeks and their clinical/laboratory data, assessment of disease activity, glucocorticoids dosage and occurrence of adverse events were recorded. Lupus Low Disease Activity State (LLDAS) and DORIS remission as a primary goal in the treatment of SLE. The groups were classified according to the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2 K): SLEDAI-2 K < 6 was categorized as the mild group (mild activity) and SLEDAI-2 K ≥ 6 was categorized as the active group (moderate-severe activity). The disease of the two groups mentioned above were assessed using the SELENA-SLEDAI Flare Index (SFI) and the SLE Responder Index-4 (SRI-4), respectively. Furthermore, we used complete remission (CR) and partial remission (PR) in the kidney as the standard for efficacy evaluation for LN patients.

Results After 52 weeks of treatment with belimumab, patients' complement levels increased significantly ($p < 0.05$); Other indicators such as 24-hour urine protein quantification and daily glucocorticoids dose decreased compared to pretreatment ($p < 0.05$). At 52 weeks, (i) after evaluation, the whole group of patients showed significant improvement in their condition; (ii) 55.4% of patients achieved LLDAS and 23.8% achieved DORIS remission; (iii) 73.2% of patients with LN achieved CR, 16.1% achieved PR. Adverse reactions were observed in 15 patients (14.9%), all of which normalized after symptomatic treatment.

Conclusions In general, during treatment with belimumab, immunological and biochemical indices improved in SLE patients, urinary protein levels were reduced in LN patients, and the rate of renal function remission was effectively increased; At the same time, the use of belimumab is associated with a low frequency of side effects, good overall tolerability and a favorable safety profile.

Keywords SLE, Belimumab, DORIS remission, LLDAS, Complete remission, Partial remission, Safety

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Background

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by immune deficiency and systemic inflammation, the pathogenesis of which is not yet fully understood and which can lead to progressive and irreversible systemic multisystem and multiorgan damage [1]. In recent years, with the deepening research on the pathogenesis of SLE and the emergence of targeted biological therapies, some biologics such as belimumab have been used to treat SLE. Studies have shown that abnormal B cell activation plays an important role in the pathogenesis of SLE [2] and that B lymphocyte stimulator (BLyS) is abnormally overexpressed in SLE. Belimumab was successfully approved by the Food and Drug Administration (FDA) in 2011 as the first biologic drug for the treatment of SLE and approved for marketing and clinical use in China in 2019.It is a human monoclonal immunoglobulin antibody against BLyS, binds to soluble BLyS and inhibits its activity [3] and achieves the purpose of treating SLE. The 2023 EULAR update on recommendations for the treatment of SLE states that in patients who do not respond to hydroxychloroquine alone (or in combination with glucocorticoids) or who are unable to keep their glucocorticoids below a chronically acceptable dose (≤5 mg/day), addition of immunomodulating/immunosuppressive agents (e.g. methotrexate or mycophenolate) and/or biological agents (e.g. belimumab) should be considered [4].

Although belimumab is approved for the treatment of SLE, there are still problems such as organ damage in SLE patients [5], so further evaluation of the effectiveness and safety of belimumab is still needed. In this retrospective study, we observed the physiological indices, therapeutic effects and side effects of belimumab in the process of remission induction of SLE and provided a reference for clinical practice application of belimumab in the treatment from SLE.

Materials and methods

Research subjects

This study was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University (Approval number:2023-KY-0184). All patients were treated with belimumab combined with SoC in the Department of Rheumatology of the First Affiliated Hospital of Zhengzhou University from March 2020 to September 2022. Main inclusion criteria: Meeting European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) diagnostic criteria for SLE 2019; and on the basis of SLE, LN meets the classification criteria recommended by the ACR 1997 (24 h urine protein > 0.5 g; or the presence of a cellular tubular pattern in the urine, including tubular patterns formed by erythrocytes, haemoglobin, granulocytes, and tubular epithelial cells of the renal tubule, or a mixed tubular patterns). Main exclusion criteria: (i) comorbidities with other immune system diseases, such as rheumatoid arthritis, dermatomyositis, etc.; (ii) previous biologic-directed therapy, such as: Rituximab, within the last year; (iii) comorbidities with severe/active infections or malignancies. According to the instructions for use of belimumab, the mode of administration is intravenous drip, and it was given at the dose of 10 mg/kg on weeks 0, 2, and 4, and then every 4 weeks. (At present, there is no subcutaneous injection type of belimumab in China.) Furthermore, the standard of care was unchanged during treatment.

Data collection

Basic information about patients at baseline was collected, including age, gender, and disease duration etc.; medication use, including glucocorticoids, hydroxychloroquine, and immunosuppressive agents; clinical symptoms including rash, alopecia, mucosal ulcers and arthritis Basic information about patients at baseline was collected, including age, gender, and disease duration etc.; laboratory indicators including white blood cells, platelets, anti-double-stranded DNA antibody (anti-dsDNA) positivity rate, complement 3(C3), complement 4(C4), and 24-hour urine protein quantification in patients with LN etc.; and disease activity indicators, including SLEDAI-2 K and Physician Global Assessment (PGA). LLDAS [6] was defined as: (i) SLEDAI-2 K≤4; (ii) no activity in major organ systems and no new features of activity compared to previous assessment; (iii) PGA score≤1; (iv) current glucocorticoids dose≤7.5 mg/day; and (v) use of immunosuppressive agents or biologics at standard maintenance doses. Remission is currently defined by the widely adopted Definition Of Remission In SLE (DORIS) criteria. DORIS remission [7] could be considered: (i) SLEDAI-2 K=0; (ii) PGA<0.5; and (iii) glucocorticoids dose≤5 mg/day and stabilized and maintained with antimalarials, immunosuppressants, and/or biologic agents. The SELENA-SLEDAI Flare Index (SFI) was selected as an assessment tool for clinical relapse in the mild group [8]; the SLE Responder Index-4 (SRI-4) was selected in the active group as an assessment tool for the degree of disease control [9]. Criteria for evaluating the efficacy of patients with LN: Complete remission was defined as normal urine protein [urine protein quantification < 0.5 g/24 h or urine protein creatinine ratio (UPCR) < 500 mg/g], no active urinary sediment, serum albumin ≥ 35 g/L and serum creatinine was normal or increased no more than 10% of baseline; Partial remission was defined as a decrease in urine protein of more than 50% from baseline and a urine protein quantification of < 3.0 g/24 hours, serum albumin > 30 g/L, and an increase in serum creatinine of no more than 10% of

baseline; Nonresponse to treatment was defined as failure to achieve complete or partial remission after treatment [10, 11]. Finally, adverse events during treatment were recorded.

Statistical analysis

Measurements conforming to normal distribution were expressed as mean±standard deviation, and comparisons between multiple groups were statistically analyzed by one-way ANOVA, and two-by-two comparisons were statistically analyzed by repeated-measures ANOVA; Measurements that did not conform to normal distribution were analyzed by a nonparametric rank sum test. Count data were expressed as percentages (n [%]). Differences between the two groups were compared using the chi-square test or Fisher's exact test. Statistical analysis was performed using GraphPad Prism (9.0.0) software. $P<0.05$ was considered statistically significant.

Table 1 Baseline information of SLE patients

Characteristic	SLE patients($n=101$)
Age(years)	27.54±10.68
Disease duration(months)	44.74±47.84
Gender	
Female	93(92.1%)
Male	8(7.9%)
Immunological indicators	
Anti-dsDNA positivity rate	74(73.3%)
Hypocomplementemia	90(89.1%)
Clinical manifestation	
Leucopenia	38(37.6%)
Thrombocytopenia	17(16.8%)
Rash	71(70.3%)
Alopecia	35(34.7%)
Mucosal ulcers	24(23.8%)
Arthritis	66(65.3%)
Serositis	22(21.8%)
Neurological/psychiatric symptoms	7(6.9%)
Lupus nephritis	56(55.4%)
Disease assessment indicators	
SLEDAI-2k	12.5±3.9
PGA	1.7±0.3
Use of antimalarials (hydroxychloroquine)	96(95.0%)
Use of immunosuppressive agents	
Mycophenolate mofetil	54(53.5%)
Cyclophosphamide	5(5.0%)
Tacrolimus	17(16.8%)
Mycophenolate mofetil＋Tacrolimus	6(6.0%)
Cyclosporine A	4(4.0%)
Methotrexate	3(3.0%)
Leflunomide	8(7.9%)
Prednisone dosage(mg/d)	33.57±15.13

Results

Baseline information of SLE patients

A total of 101 SLE patients treated with belimumab in combination with SoC for more than 52 weeks were included in this study. The clinical manifestation of patients at baseline: there were 38 patients (37.6%) with leukopenia, 17 patients (16.8%) with thrombocytopenia, 71 patients (70.3%) with rash, 35 patients (34.7%) with alopecia, 24 patients (23.8%) with mucosal ulcers, 66 patients (65.3%) with arthritis, 22 patients (21.8%) with serositis (including pericardial effusion or pleural effusion), 7 patients (6.9%) with neurological or psychiatric symptoms and 56 patients (55.4%) with LN (Table 1). The mean daily prednisone dosage in 101 SLE patients was 33.57±15.13 mg/d, with 81 active SLE patients were on >0.5 mg/kg/day of prednisolone (PSL) at the time of belimumab induction. In immunosuppressive agents, although azathioprine is also used for SLE in China, it's not available in our hospital (there's no channel to supply the drug).Other basic information is also listed in Table 1.

Changes in the proportion of disease activity states

LLDAS and DORIS remission have been used as the primary goal in the treatment of SLE. The percentage of LLDAS and DORIS remission at baseline was 6.9% and 0, respectively (The glucocorticoid dosage for these 7 patients who achieved LLDAS was 7.5 mg/d, they were used belimumab to try to discontinue glucocorticoids and decrease the accumulation of organ damage); while after 52 weeks of treatment with belimumab therapy it reached 55.4% and 23.8%, respectively (Fig. 1). At 52 weeks, 56 patients achieved LLDAS (their SLEDAI-2 K score at baseline was 11.9±4.2), and another 45 patients did not achieve LLDAS (their SLEDAI-2 K score at baseline was 13.7±3.1). Comparing the SLEDAI-2 K scores at baseline between the two groups, the results were significantly different ($P<0.05$).

Assessment of indicators related to disease activity

Patients were assessed for disease activity using SLEDAI-2 K and PGA: SLEDAI-2 K was 12.5±3.9 at baseline and decreased to 4.2±3.5 at 52 weeks of treatment (Fig. 2A); PGA decreased from 1.7±0.3 to 0.6±0.2 (Fig. 2B). The SRI-4 was selected as an assessment tool for the degree of disease control in the active group($n=94$). 79.8% of patients in the active group had a significant decrease in disease activity at week 52 compared to baseline. (Fig. 2C).

Changes in biochemical/immunological parameters and prednisone dosage before and after treatment with belimumab

C3 levels were 0.63±0.26 g/L at baseline and increased to 0.87±0.21, 0.93±0.20 and 0.94±0.21 g/L at weeks 12, 24

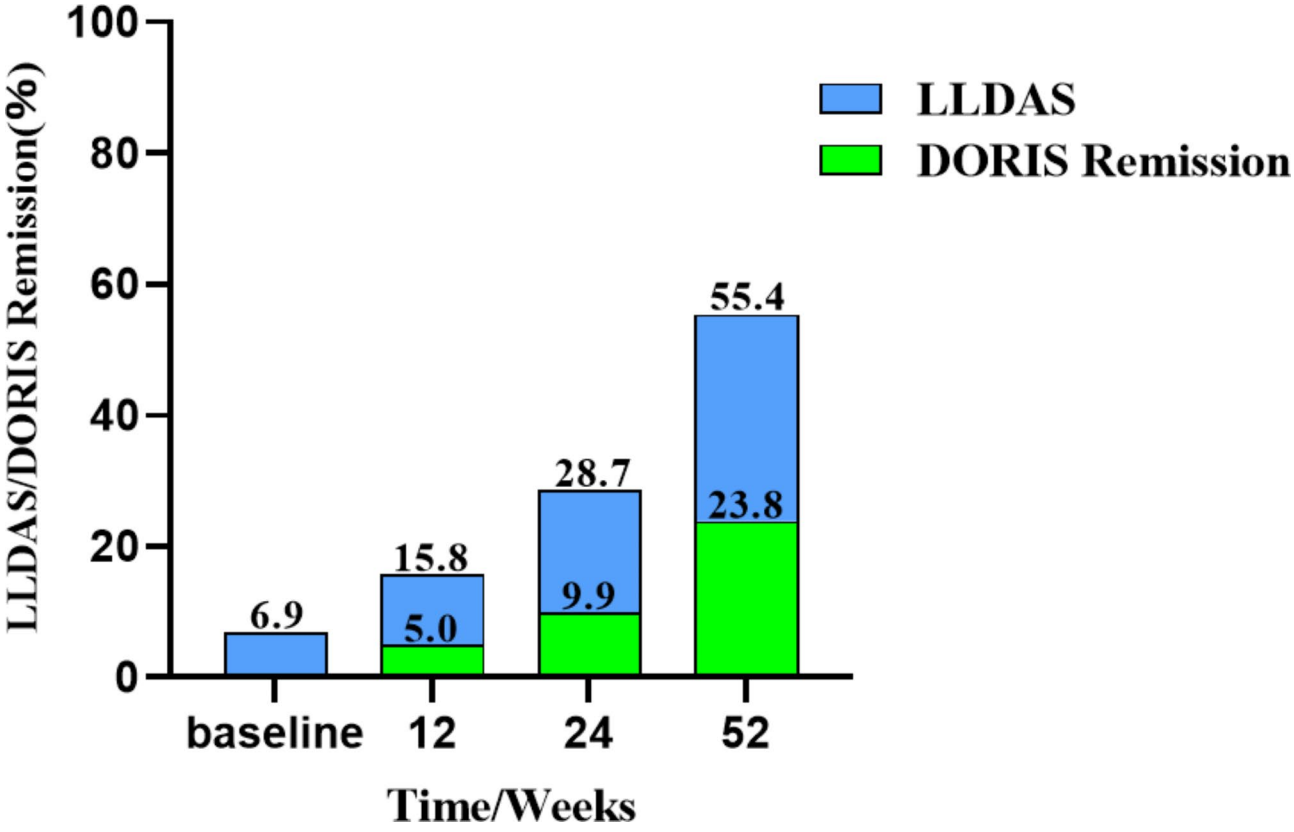

Fig. 1 Changes in the proportion of LLDAS and DORIS remission achieved

and 52 after belimumab treatment, respectively (Fig. 3A). The C4 level was 0.11±0.07 g/L at baseline and increased to 0.18±0.08, 0.19±0.08 and 0.20±0.08 g/L at weeks 12, 24 and 52, respectively (Fig. 3B); the anti-dsDNA positivity rate was 73.3% at baseline and decreased to 57.4%, 51.5% and 43.5% with increasing complement levels at weeks 12, 24 and 52, respectively (Fig. 3C). The prednisone dosage was counted for all patients on belimumab and the daily prednisone dosage was 33.57±15.13, 13.91±7.37, 8.34±3.70 and 5.82±2.83 mg/day at baseline, 12 weeks, 24 weeks, and 52 weeks, respectively (Fig. 3D).

The change in disease activity in patients with LN

There were 56 patients with LN in this study. Their baseline data, including the type of renal biopsy pathology, are shown in Table 2.

The 24-hour urine protein quantification in LN patients was 2.15±1.94 g/d at baseline, which decreased to 0.89±0.81, 0.46±0.38 and 0.30±0.25 g/d at weeks 12, 24 and 52, respectively (Fig. 4A); serum albumin was 34.76±7.07 g/L at baseline, which increased to 39.29±6.02, 41.45±5.30 and 42.73±5.12 g/L, respectively; serum creatinine did not change significantly and was 68.8±30.8, 69.3±30.7, 68.4±30.6, and 68.0±32.3 μmol/L at baseline, week 12, week 24, and week 52, respectively. Complete and partial remission (Fig. 4B) are now widely used in clinical practice.

Adverse events

Fifteen patients (14.9%) experienced adverse reactions during belimumab treatment, as shown in Table 3. During the treatment period, five patients had one suspension of belimumab due to moderate symptoms of infection. Patients with mild symptoms of infection and others who experienced mild adverse reactions returned to normal after symptomatic treatment and did not discontinue belimumab.

Discussion

In this study, we recorded the changes of various indices before and after the use of belimumab in SLE patients, including the improvement of serological indices and disease activity and the reduction of urinary protein levels. This is consistent with the results of some previously published literature from abroad [12, 13]. In recent years, the concept of "Treat to Target" (T2T) [14, 15] has become established in the clinical treatment of SLE. Greater adoption of DORIS remission and LLDAS as T2T targets may help to overcome barriers to achieving T2T and lead to better clinical outcomes for more patients. Although DORIS remission is the recommended therapy goal for

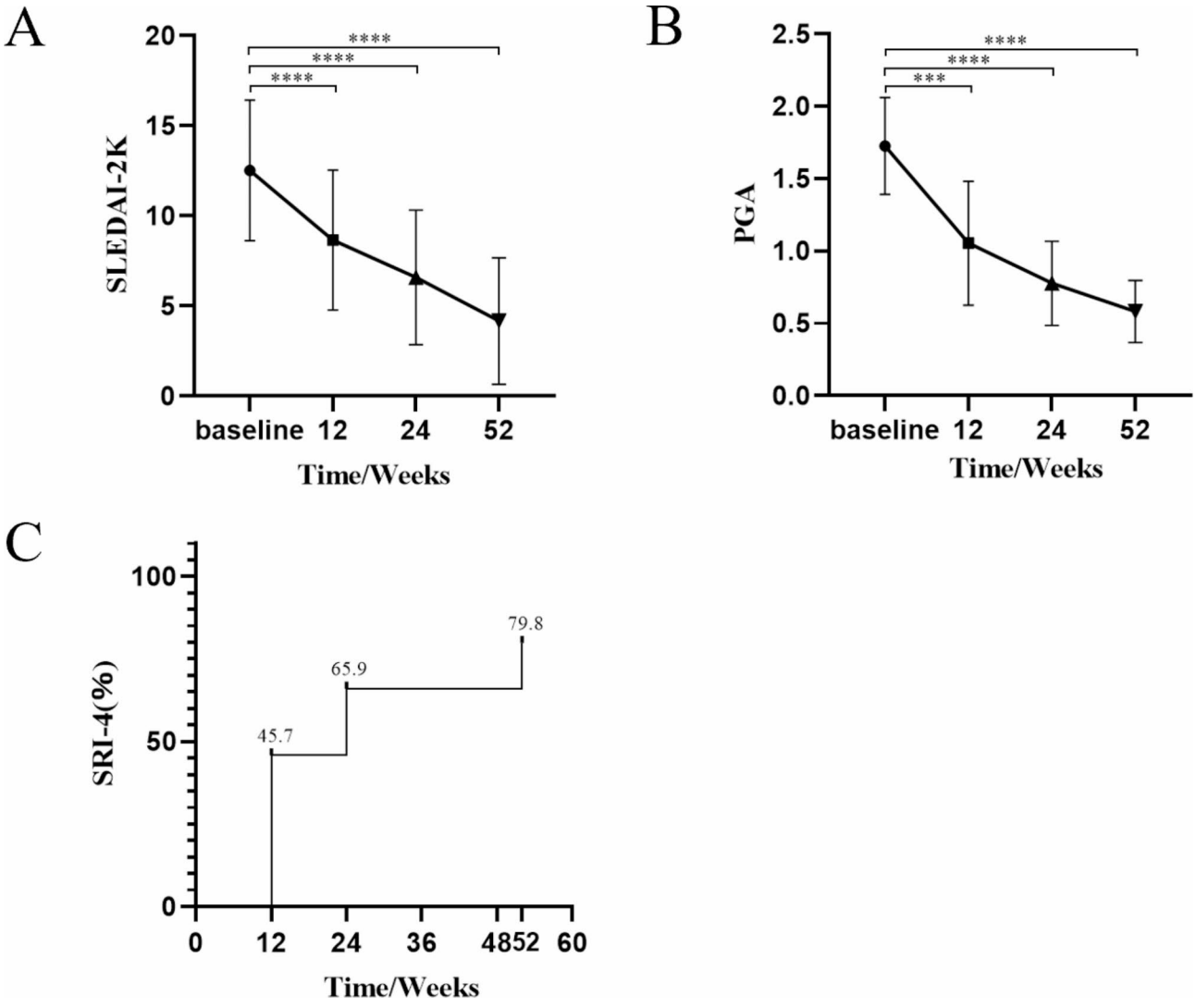

Fig. 2 (**A**) SLEDAI-2 K. (**B**) Physician Global Assessment. (**C**) SLE responder index-4. *** $p < 0.001$; **** $p < 0.0001$

SLE, LLDAS is a more clinically achievable treatment goal with similar clinical efficacy to DORIS remission [14, 16]. The Asia Pacific Lupus Collaboration (APLC) proposed LLDAS as the minimum attainment status for SLE in 2016. In addition, after achieving LLDAS, patients should continue to receive treatment to maximize clinical benefit, and a study [17] also showed that achieving LLDAS and maintaining it for at least 2 years can significantly reduce the degree of organ damage. LLDAS and DORIS remissions are associated with slowing disease progression and a reduction in mortality. For example, Ugarte-Gil [18] et al. found a direct association between the proportion achieving DORIS remission or LLDAS and a reduction in disease damage accumulation. Data from this study showed that after 52 weeks of belimumab treatment, 55.4% of patients achieved LLDAS and 23.8% achieved DORIS remission. Of note, we found that patients who did not achieve LLDAS had a more active disease state at baseline and had a higher SLEDAI-2 K. Our results suggest that belimumab could play a role in helping patients achieve LLDAS and DORIS remission, slowing disease progression, and optimizing quality of life.

SLE is a chronic progressive disease, and assessment of disease activity is needed to guide clinical treatment in clinical work. SRI-4 can more sensitively reflect the treatment effect and disease change of patients [19, 20] and respond to the degree of disease control, and is particularly suitable for assessing the effect of drug treatment in SLE. Two multicenter, randomized, controlled trials (BLISS-52 and BLISS-76) showed that treatment with belimumab in combination with SoC significantly increased the SRI-4 response rate, reduced disease activity and severe relapses in SLE, and improved the quality of life of SLE patients [12, 21]. In our study, the SRI-4 response rate of patients in the active group increased

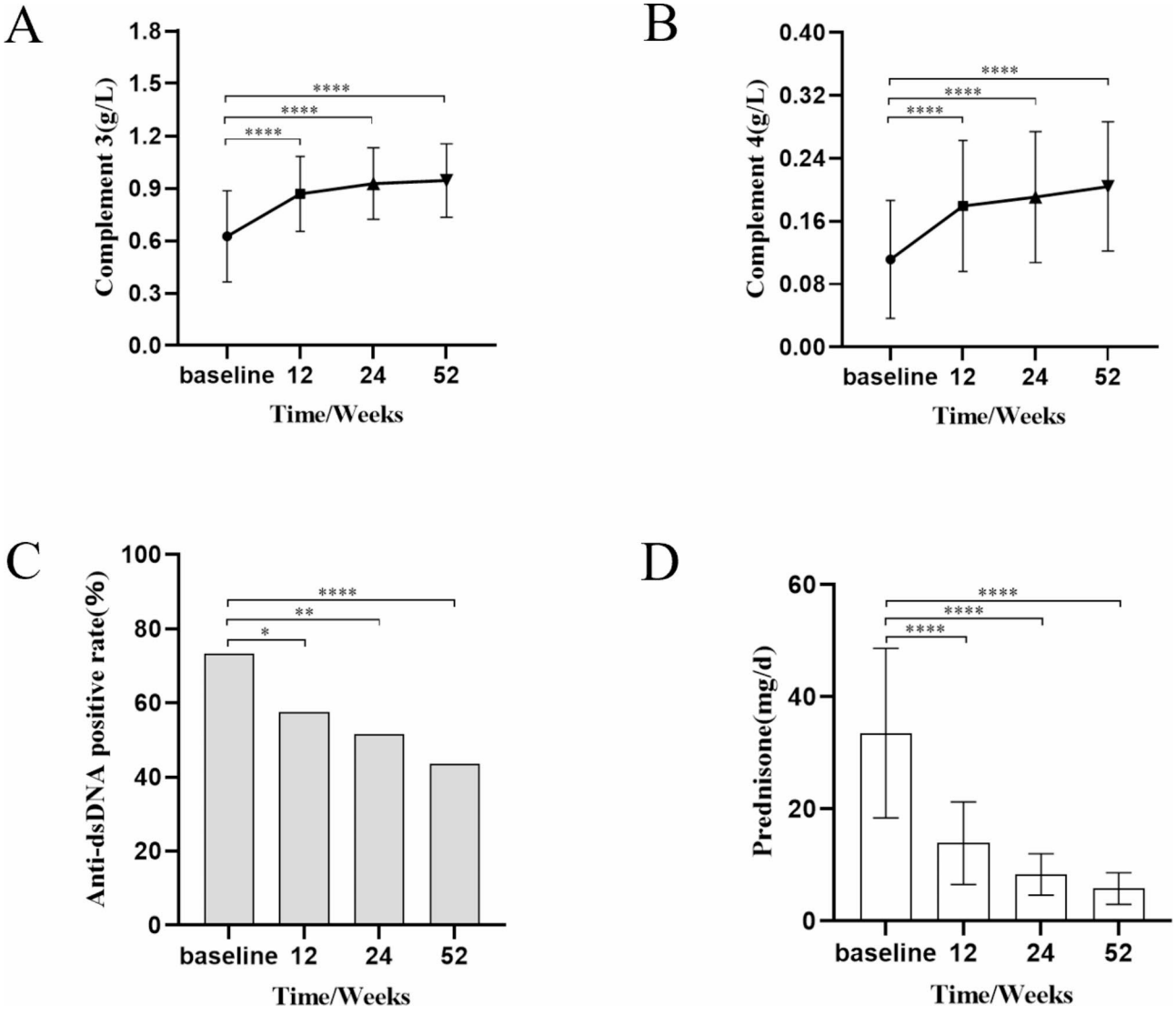

Fig. 3 (**A**) Complement 3(g/L). (**B**) Complement 4(g/L). (**C**) Anti-dsDNA positive rate (%). (**D**) Daily prednisone dosage(mg/d). * $p<0.05$; ** $p<0.01$; **** $p<0.0001$

Table 2 Basic information about patients with LN

Characteristic	SLE-LN patients($n=56$)
24-hour urine protein quantification(g/d)	2.15 ± 1.94
Serum albumin(g/L)	34.76 ± 7.07
Serum creatinine(μmol/L)	68.8 ± 30.8
Renal biopsy pathology($n=47$)	
III	6/47(12.8%)
IV	18/47(38.3%)
V	8/47(17.0%)
IV+V	15/47(31.9%)

to 79.8% at week 52 and disease activity was significantly reduced. Since SRI-4 is not applicable to patients with low disease activity, we chose SFI as an indicator of clinical relapse in the mild group. At week 52, 71.4% of patients in the mild group had no relapses, and the two patients who did relapse had a new rash and alopecia, respectively. However, the sample size of the mild group was too small, which is a limitation of this study and more data are required to validate our conclusions in the future.

LN, as a serious complication of SLE [22, 23], can cause kidney damage with different protein content in urine, edema and even kidney failure, which seriously endangers the health of patients. Some studies have shown that autoantibodies produced by B lymphocytes can form immune complexes, which in turn can lead to glomerulosclerosis and interstitial fibrosis. Sciascia et al. analyzed data from a large clinical trial and some case reports, suggesting that belimumab may play an effective role in the treatment of LN [24]. Of the 56 patients with LN, 47 had complete kidney biopsies data, with the most common

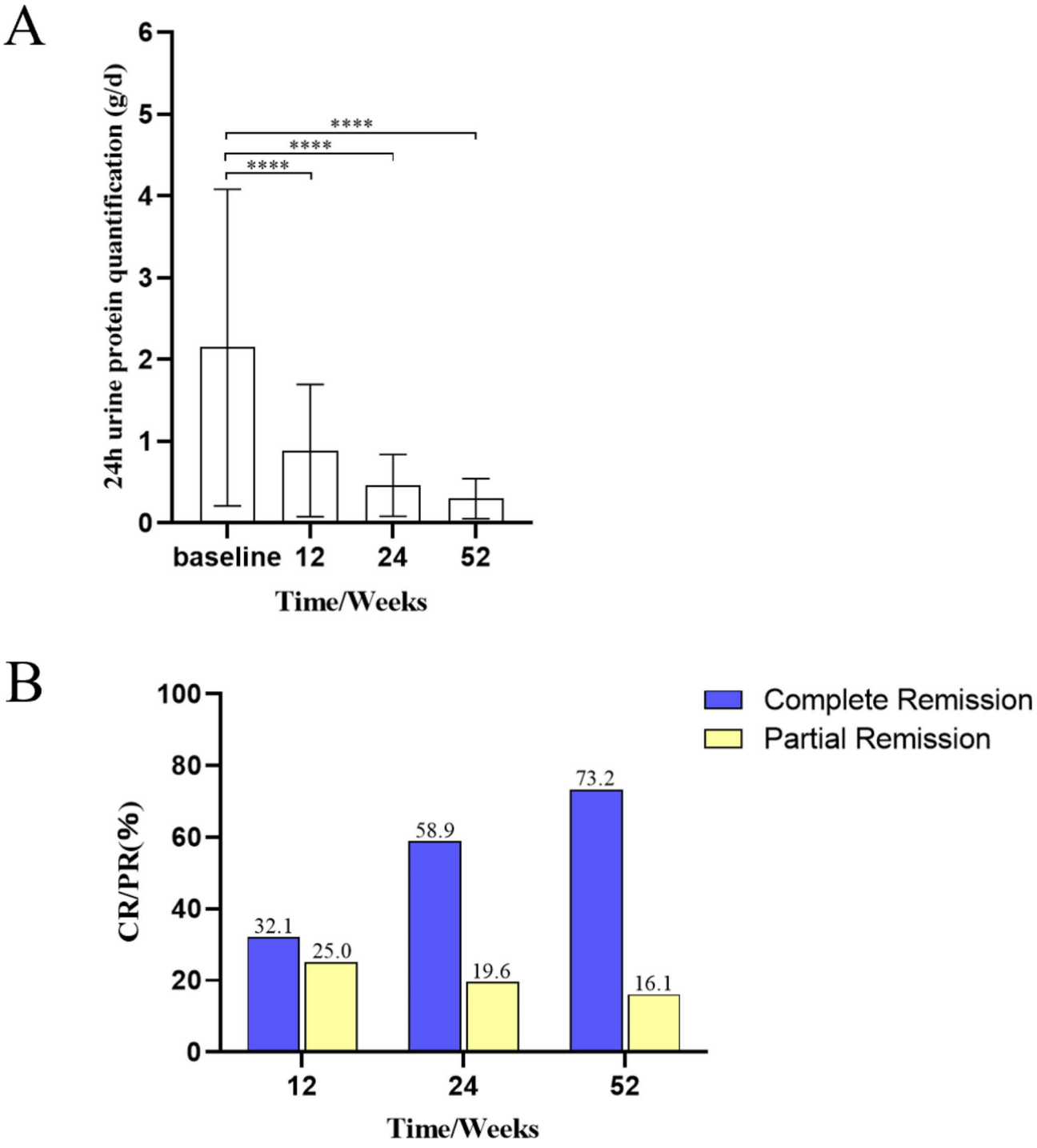

Fig. 4 (**A**) 24 h urine protein quantification (g/d). (**B**) Changes in the proportion of complete and partial remission. **** $p < 0.0001$

pathologic type being LN type IV (38.3%), followed by type IV+V (31.9%), type V (17.0%) %) and type III LN (12.8%). We found that patients with LN treated with belimumab showed a significant reduction in 24-hour urine protein levels, an increase in albumin levels, and no significant change in serum creatinine levels compared to baseline, consistent with the results of a previous study agrees [25]. A retrospective study showed that belimumab combined with SoC treatment could significantly alleviate kidney damage and improve kidney function in patients with LN [26]. In this study, complete and partial renal remission were used as criteria for evaluating LN patients. At 52 weeks, the complete remission rate in LN patients was 73.2%, the partial remission rate was 16.1%,

Table 3 Adverse events

Adverse events *n*(%)	*n*(%)
upper respiratory tract infection	7(6.9%)
bacterial pneumonia	2(2.0%)
fungal pneumonia	1(1.0%)
gastrointestinal infection	2(2.0%)
urinary tract infection	1(1.0%)
herpes zoster	1(1.0%)
allergic reaction to the infusion	1(1.0%)

and in one case no response to treatment (did not achieve complete or partial response). After treatment with belimumab, the overall renal remission rate of patients was significantly higher, indicating that belimumab combined with SoC treatment can improve the degree of kidney injury in patients with LN.

The safety of belimumab in combination with SoC for the treatment of SLE has been demonstrated in many studies, with the probability of various adverse reactions being comparable to that of the placebo group [27, 28]. In our study, the incidence of adverse events was 14.9%. After symptomatic treatment, all patients returned to normal, showing that overall the use of belimumab treatment is well tolerated, but it is still necessary to focus on the occurrence of side effects (e.g. infections) and treat them in a timely manner treat. Furthermore, our study also documented the reasons for discontinuation in 18 patients treated with belimumab for less than 52 weeks (these patients were not counted in the 101 patients in the study): 6 patients were discontinued due to the COVID-19, 4 were lost to follow-up, 3 were discontinued due to ineffectiveness, 2 were discontinued due to pregnancy as well as 3 were discontinued due to financial burden.

However, this study still has some limitations that need to be addressed. First, this study is a single-center retrospective study with a small sample size and some orientations in patient enrollment, which may bias the results. Second, the follow-up period is short, which requires greater attention to the patient's organ damage and treatment progress. Third, placebo-controlled trials are still needed, such as a comparison between patients treated with belimumab+SoC and those treated with SoC alone is necessary to adequately demonstrate its efficacy of the former. Therefore, multicenter clinical trials with a larger sample size and a longer follow-up period are needed to further validate the results. Moreover, we did not documented suicidal and depressive side effects of treatment with belimumab, which also needed special attention.

Conclusions

In summary, during treatment with belimumab, immunological and biochemical indices improved in SLE patients, urinary protein levels were reduced in LN patients, and the rate of renal function remission was effectively increased; At the same time, the use of belimumab is associated with a low incidence of adverse events, is well tolerated overall and has a good safety profile.

Abbreviations

SLE	Systemic lupus erythematosus
LN	Lupus nephritis
SoC	standard of care
LLDAS	Lupus Low Disease Activity State
DORIS	Definition Of Remission In SLE
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SFI	SELENA-SLEDAI Flare Index
SRI-4	SLE Responder Index-4
CR	complete remission
PR	partial remission
BLyS	B lymphocyte stimulator
EULAR	European League Against Rheumatism
PSL	prednisolone
ACR	American College of Rheumatology
C3	complement 3
C4	complement 4
PGA	Physician Global Assessment
UPCR	urine protein creatinine ratio
FDA	Food and Drug Administration
T2T	Treat to Target
APLC	Asia Pacific Lupus Collaboration

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13075-024-03389-4.

Supplementary Material 1

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Author contributions

ZS and CZ designed the study and collected the original data and finished the analysis. ZS, CL and RL drafted the initial manuscript. ZZ, CG and CZ helped revised the manuscript. CG and ZZ provided the funding and supervised the study. The final manuscript was read and approved by all authors. All authors contributed to the article and approved the submitted version.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University (Approval number:2023-KY-0184).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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