Efficacy and safety of telitacicept in patients with lupus nephritis

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Abstract. Although telitacicept is a promising drug for treating systemic lupus erythematosus, there are limited studies on its efficacy and safety in patients with lupus nephritis in China. This lack of research data restricts its potential for broader application and acceptance on a global scale. The present study aimed to determine the efficacy and safety of telitacicept in patients with lupus nephritis (LN) in China. Using a self-controlled before-after comparison method, patients with LN were recruited at Lishui Central Hospital between February 2022 and April 2023, who received telitacicept weekly as part of the standard treatment. Data on the systemic lupus erythematosus disease activity index 2000 (SLEDAI-2K), glucocorticoid dosing and the quantity of immunosuppressive medicines prescribed was collected. Additionally, serum complements, erythrocyte sedimentation rate (ESR), urinary protein levels, immunoglobulin concentrations, serum creatinine levels, plasma albumin concentrations, platelet counts and renal function parameters were documented throughout the study. A total of 13 patients were enrolled in the trial, comprising 11 women and two men. Following 12-48 weeks of treatment with telitacicept (80 or 160 mg per week), 84.6% (n=11) of all patients experienced symptom relief and their SLEDAI-2K score was reduced by more than four points. By the observation endpoint, the median glucocorticoid dosage of the 13 patients was decreased from 15 to 2.5 mg/d, and six patients discontinued their glucocorticoids. Furthermore, 46.1% of patients (n=6) reduced their dose and number of immunosuppressive medicines, while 15.4% (n=2) stopped their immunosuppressive medicines. Minimal changes were observed in serum creatinine, platelet count, C3 levels and C4 levels among patients. Immunoglobulin levels (IgG, IgA and IgM) remained stable or showed an upward trend. Plasma albumin levels remained within the normal range in three patients and increased in ten patients. It increased to the normal range in three of these ten patients. At the endpoint, ESR levels decreased in all patients. Additionally, three patients displayed varying degrees of renal function improvement, and their estimated glomerular filtration rate (ml/min/l.73 m^2) increased from 127.8 to 134.2, 95.1 to 123.1 and 61.5 to 67.3, respectively. Urinary protein levels decreased in all patients. It decreased >0.5 g/l in seven patients and reached the normal levels in three patients. The adverse events of telitacicept were manageable. Among the patients infected with COVID-19, three patients had fever, 10 patients remained asymptomatic and none of them exhibited severe respiratory syndromes. In this study, telitacicept effectively stabilized LN activity and alleviated the clinical symptoms of most patients. Furthermore, it reduced the dose of glucocorticoid and immunosuppressive medicines. Therefore, telitacicept may be a promising treatment option for individuals with lupus nephritis.

Introduction

Systemic lupus erythematosus (SLE) is a chronic multisystemic autoimmune disease, characterized clinically by multi-organ damage and the existence of elevated levels of autoantibodies (1). Lupus nephritis (LN) is one of the most severe organ manifestations of SLE, occurring in 35 to 60% of SLE patients (2). Currently, end-stage renal disease (ESRD) remains an inevitable outcome for patients with LN (3). Within 5 years of an initial lupus nephritis diagnosis, 10-30% of patients with LN developed kidney failure requiring kidney replacement therapy (4). Treatment of lupus nephritis typically involves immunosuppressive and glucocorticoid therapy, although these treatments may not be effective (5). Therefore, the management of LN has been proven challenging over the past three decades, with limited improvements observed in patients' outcomes.

B cells play a pivotal role in autoantibody generation, cytokine secretion and antigen presentation in SLE (6). Belimumab, a B cell-targeted therapy approved for patients with SLE aged ≥5 years (7), has been used for the treatment of LN in studies such as the international Belimumab in LN (Bliss-LN) trial. The Bliss-LN trial revealed that belimumab, combined with standard treatment, reduces the risks associated with LN (8).

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Abbreviations: SLE, systemic lupus erythematosus; LN, lupus nephritis; ESRD, end-stage renal disease; eGFR, estimated glomerular filtration rate; ALB, albumin; ESR, erythrocyte sedimentation rate; SLEDAI-2K, systemic lupus erythematosus disease activity index 2000; MMF, mycophenolate mofetil; CsA, cyclosporine A; FK, tacrolimus; BLyS, B-lymphocyte stimulator; APRIL, a proliferation inducing ligand

Key words: lupus nephritis, systemic lupus erythematosus, telitacicept, safety, efficacy

B lymphocyte stimulator (BLyS) and a proliferation-inducing ligand (APRIL) are members of the tumor necrosis factor family and play significant roles in B cell proliferation and differentiation (9). Telitacicept is the first dual inhibitor of BLys/APRIL, serving as a new recombinant fusion protein binding to both the ligand-binding domain of the TACI receptor and the Fc component of human IgG (10). By binding and neutralizing BLys and APRIL, telitacicept suppresses various stages of development, thereby targeting plasma cells and mature B cells (11). Given its specific molecular mechanisms, telitacicept is anticipated to effectively treat autoimmune diseases (12). It was approved for patients with SLE in China in March 2021 (11) and has verified effectiveness in both children (13) and adults with SLE (14).

Although it is a promising drug for systemic lupus erythematosus, there are few studies on telitacicept in patients with LN in China, which limits its broad application across the world. Therefore, based on specific molecular mechanisms and the results of previous studies, the present study assessed the effectiveness and safety of telitacicept in patients with LN. To the best of our knowledge, the present trial was the first study assessing the efficacy of telitacicept in patients with LN amidst the COVID-19 pandemic.

Materials and methods

Patients. Following the diagnosis criteria for SLE established by the American College of Rheumatology (15), the present study identified patients with active LN, confirmed by kidney biopsy results at Lishui Central Hospital (Lishui, China). Patients (14-85 years old and unable to tolerate the side effects of immunosuppressive medicines or glucocorticoids) receiving standard treatment in conjunction with telitacicept were included in this trial, while individuals allergic to human-sourced biological products, such as telitacicept, or presenting with LN-induced organ damage and severe or chronic infections, were excluded from this trial. Finally, 13 patients (14-85 years old; 11 female and 2 male) meeting the inclusion criteria were enrolled from February 2022 to April 2023. All patients whose data were not previously documented in any publications provided written informed consent to utilize their medical records. This trial was approved by the Ethics Committee of Lishui Central Hospital and was also part of the Pioneer and Leading Project of Zhejiang Province (project no. 2022C03172). In addition, the present study was reviewed and approved by the Ethical Committee of the Lishui Central Hospital (approval no. 2022-278).

Treatment protocol. Considering the disease progression, therapeutic efficacy, patient tolerance and economic considerations, different doses of telitacicept were administered to different patients. All patients received standard therapy in addition to subcutaneous injections of either 80 or 160 mg of telitacicept per week (median duration of treatment, 36 weeks; range, 12-48 weeks), based on the condition of each patient and their laboratory test results. As disease control was achieved during the trial, the dosage of glucocorticoids and immunosuppressive agents was gradually tapered.

Primary outcome measures and assessment. The systemic lupus erythematosus disease activity index 2000 (SLEDAI-2K) score was considered the primary outcome to evaluate the clinical remission status and categorize disease activity (16). This index was assessed at the beginning of the study and monthly following the first dose of telitacicept. A reduction of more than four points in the SLEDAI-2K score was considered satisfactory alleviation of the disease activity Furthermore, changes in dosages of glucocorticoids and immunosuppressive medicines, levels of complement proteins (C3 and C4), immunoglobulins (IgA, IgM and IgG), urinary protein (in consideration of the economic burden on patients, we collected urinary protein concentration data rather than 24-h urinary protein measurements) and erythrocyte sedimentation rate were recorded monthly as primary outcomes.

Secondary outcome measures and assessment. Secondary outcome measures included serum creatinine levels, estimated glomerular filtration rate (eGFR), plasma albumin concentrations, platelet counts and treatment-emergent adverse events, with data collected from medical histories and laboratory test results. Although patients were enrolled at different time points, all shared the same endpoint on April 30, 2023.

Statistical analysis. Statistical analyses were conducted using R (version 4.2.2) (17) and GraphPad Prism 9 (Dotmatics). Counting data are expressed as percentages [n (%)], and measurement data are expressed as mean ± standard deviation or median (range). The Shapiro-Wilk normality test was applied

Table I. Baseline conditions of the 13 patients with LN treated with telitacicept.

Characteristic	Value
Females, n (%)	11 (84.6)
Mean age ± SD, years	39.6±20.0
SLE duration, months[a]	36 (8, 212)
LN duration, months[a]	35 (8, 212)
Organ manifestation before the first dose with telitacicept, n (%)	
Erythema	3 (23.1)
Pneumonia	1 (7.7)
Thrombotic microangiopathy	1 (7.7)
Previous therapies before telitacicept, n (%)	
Hydroxychloroquine	12 (92.3)
Cyclophosphamide	1 (7.7)
Mycophenolate mofetil	7 (53.8)
Biologics used before	0 (0.0)
Multi-targeting MMF + CsA/FK	2 (15.4)
Glucocorticoids + immunosuppressive medicines	12 (92.3)
Reason for using telitacicept, n (%)	
Glucocorticoids side effects	11 (84.6)
Immunosuppressive medicines' side effects	13 (100.0)
Non-remission/disease recurrence	7 (53.8)

[a]Median (range). SLE, system lupus erythematosus; LN, lupus nephritis; MMF, mycophenolate mofetil; CsA, cyclosporine A; FK, tacrolimus; SD, standard deviation.

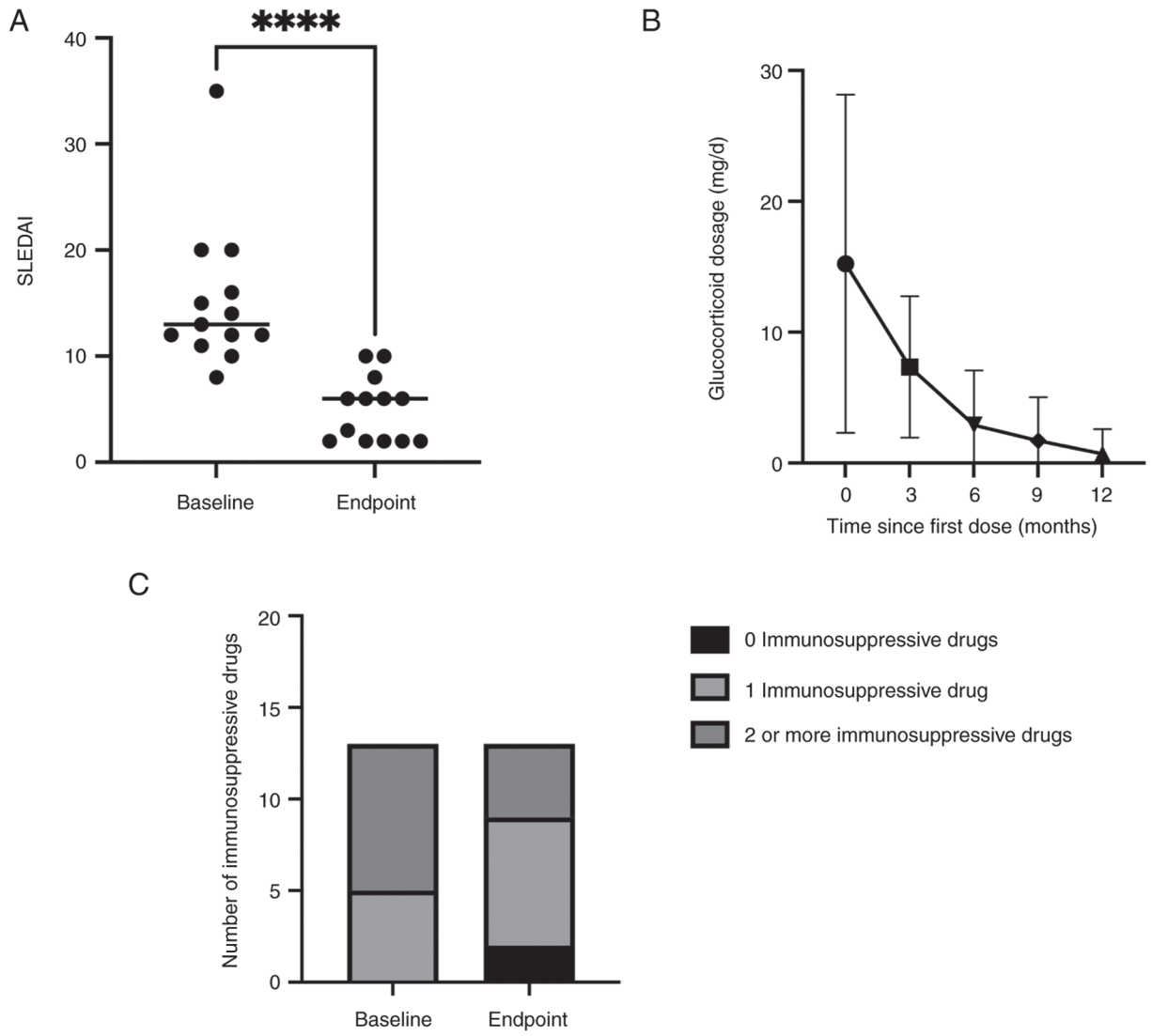

Figure 1. Results of the primary outcome. (A) During the trial, changes in the SLEDAI-2K score in the 13 patients with LN at the beginning and endpoint. (B) Changes in glucocorticoid doses during the trial in 13 patients with LN. (C) Immunosuppressive medicines adjustment of patients with LN at the baseline and the endpoint under treatment with telitacicept. ****P<0.0001. SLEDAI-2K, systemic lupus erythematosus disease activity index 2000; LN, lupus nephritis.

to conduct normal tests on the data. Pre- and post-treatment data were compared using paired students' t-tests (in the presence of normal distribution) or Wilcoxon signed-rank tests (in the absence of abnormal distribution). P<0.05 was considered to indicate a statistically significant difference.

Results

Patients' general information. Based on the inclusion and exclusion criteria, 13 patients with active LN were included in the present trial from February 2022 to April 2023. The trial duration ranged from 12 to 48 weeks. No patients withdrew telitacicept treatment. There were two males and 11 females (84.6%) in this study, with a median age of 39.6±20.0 years. According to the ISN/RPS classification for LN, six patients were classified as class IV+V, two as class III+V, two as class IV, one as class III and two as class V. The median duration of suffering from LN was 35 weeks (range, 8-212 weeks), with a median SLEDAI-2K score of 13 (range, 8-35) at the baseline. Before treatment with telitacicept, all patients received glucocorticoid and immunosuppressive medicines, with eight patients receiving more than two immunosuppressive agents (Table SI). These immunosuppressive medicines included mycophenolate mofetil (n=7), hydroxychloroquine (n=12), cyclosporine (n=1), amethopterin (n=1), tacrolimus (n=1) and cyclophosphamide (n=1). For the 13 patients, telitacicept was administered due to intolerance to side effects associated with immunosuppressive medicines or glucocorticoid, or disease recurrence (Table I). None of the patients showed contraindications to the immunosuppressive therapies.

Efficacy and safety

Primary outcome measures. All patients in the present trial received telitacicept for a minimum of 12 weeks. At the endpoint, the median duration of treatment with telitacicept was 36 weeks (range, 12-48 weeks) and the median SLEDAI-2K score was 6 (range, 2-10) (Table SII). Furthermore, compared with the baseline, 11 patients (84.6%) experienced a reduction in their SLEDAI-2K score by more than four points with telitacicept treatment (P<0.0001; Fig. 1A; Table SIII). The median

Table II. Outcomes of telitacicept in lupus nephritis.

Case	Age, years	SLEDAI-2K (score)		eGFR, ml/min/1.73 m^2		Glucocorticoid reduction[a]	Plasma albumin (change trend)	Urinary protein (change trend)[b]
		Pre-therapy	Post-therapy	Pre-therapy	Post-therapy			
1	31	11	8	45.6	26.8	YES	Rise	NO/descend
2	18	10	10	127.8	134.2	NO/increase	Rise to normal	YES/descend to normal
3	14	35	10	10.1	9.5	YES	Rise to normal	YES/descend
4	23	20	2	95.1	123.1	YES/discontinued	Rise	YES/descend
5	42	12	2	110.5	112.6	YES/discontinued	Rise	N
6	24	20	6	120.3	118	YES/discontinued	Rise	YES/descend to normal
7	83	12	2	81.2	74.8	YES/discontinued	N	N
8	47	12	3	97.3	79.8	YES/discontinued	N	N
9	41	15	2	110.7	109.2	YES/discontinued	N	N
10	72	16	6	61.5	67.3	YES	Rise	YES/descend
11	36	8	2	119.9	119	YES	Rise	YES/descend to normal
12	45	13	6	116.8	113.9	YES	Rise	N
13	48	14	6	103	102.2	YES	Rise to normal	N

[a]Prednisone dose reduced ≥25% compared to baseline; [b]urinary protein is <0.5g. N, normal; SLEDAI-2K, systemic lupus erythematosus disease activity index 2000; eGFR, estimated glomerular filtration rate.

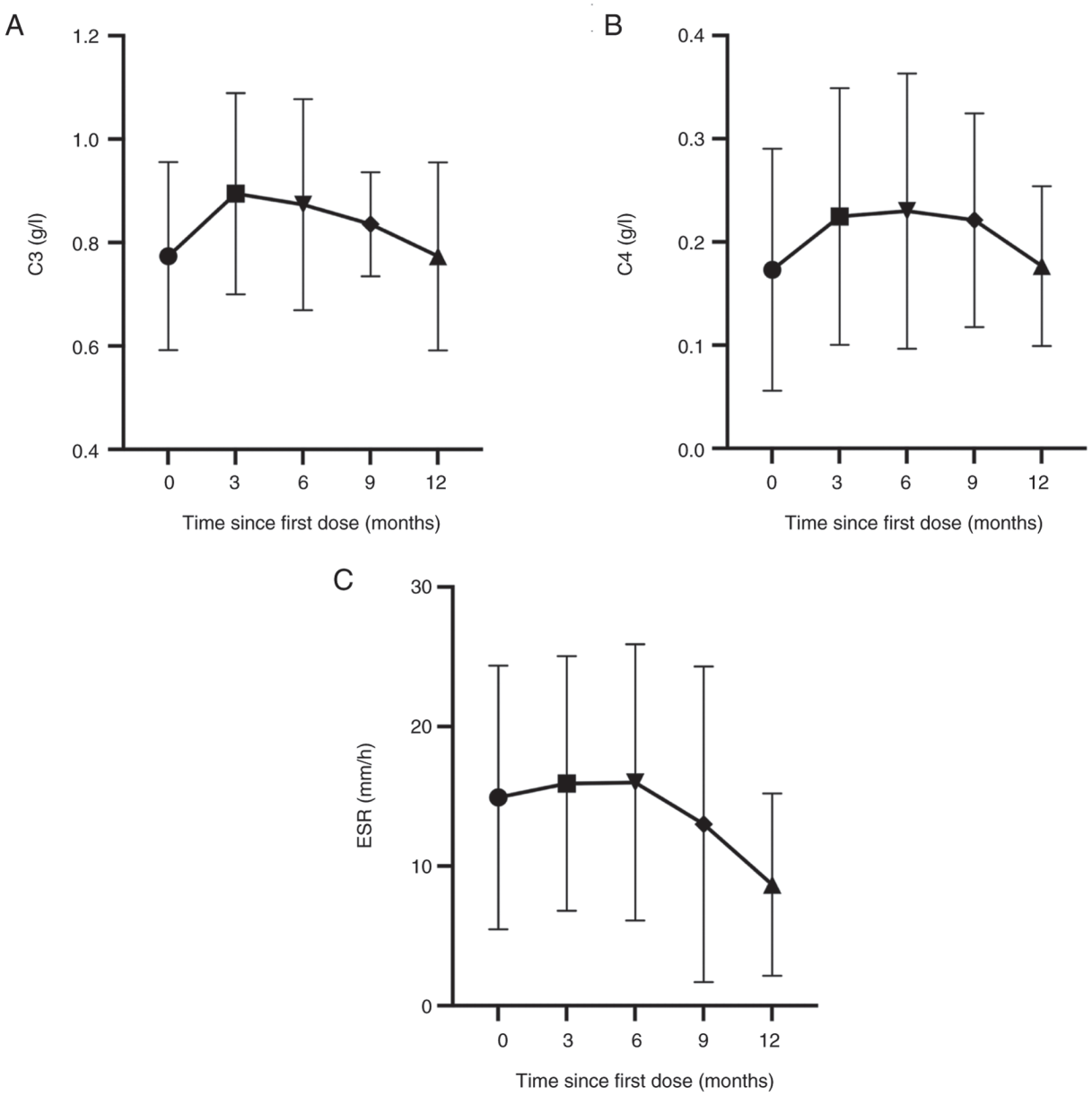

Figure 2. Complement level and erythrocyte sedimentation rate during telitacicept treatment in the 13 patients. Levels of (A) C3, (B) C4 and (C) erythrocyte sedimentation rate of 13 patients with lupus nephritis who received telitacicept treatments. ESR, erythrocyte sedimentation rate.

dosage of glucocorticoids decreased from 15 mg/d before treatment with telitacicept to 2.5 mg/d after treatment (Fig. 1B). The daily glucocorticoid dosage of all patients remained below 10 mg. The glucocorticoid dosage of 12 patients reduced by >25%, and six of these 12 patients discontinued treatment with glucocorticoids. Before discontinuing them, the conditions of the 6 patients were observed and blood test outcomes, including C3, C4 and ESR levels, were monitored. Additionally, the present study re-evaluated the SLEDAI-2K scores of the six patients. Based on these assessments, the doctors made decisions regarding discontinuation of glucocorticoids.

Prednisone dosage increased in 1 out of the 13 patients due to a relapse of LN during the trial (Table II). Meanwhile, the dosage of immunosuppressive medicines decreased in six out of the 13 patients, requiring fewer types of immunosuppressive medicines. Two patients discontinued their immunosuppressive drugs at the endpoint (Fig. 1C; Table SII).

C3, C4 and erythrocyte sedimentation rate (ESR) were reassessed for all patients at the endpoint, with all patients showing a downward trend in ESR levels (Fig. 2). In addition, ten patients (76.9%) showed a stable or increasing trend in C3 and C4 levels (Fig. 2). All patients had stable levels of IgG, IgA and IgM, displaying a trend characterized by an initial decline followed by subsequent elevation (Fig. 3). A total of 12 patients exhibited a decrease in urinary protein at the endpoint compared to before treatment with telitacicept. Seven patients exhibited a decline of >0.5 g/l in urinary protein, and urinary protein levels were normalized in three patients (Fig. 3 and Table II).

Secondary outcome measures. At the endpoint, few patients exhibited changes in the eGFR (ml/min/1.73 m^2). Notably, three patients displayed improvement in renal function, and their eGFR increased from 127.8 to 134.2, 95.1 to 123.1 and

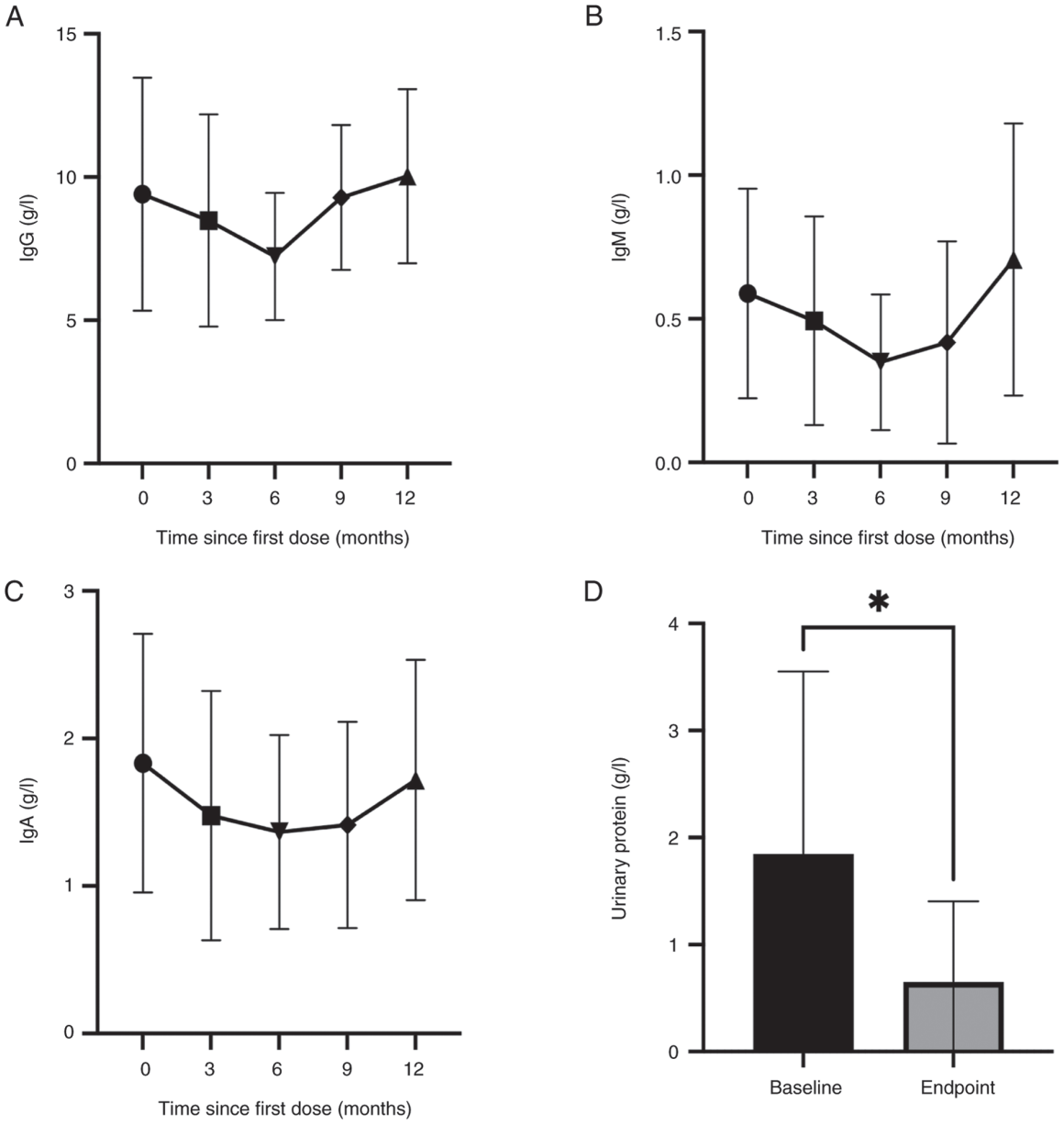

Figure 3. Changes in immunoglobulin and urinary protein for all patients with LN during telitacicept treatment. (A) IgG, (B) IgM and (C) IgA levels of 13 cases who received telitacicept treatments. (D) Changes in urinary protein at baseline and endpoint during the trial of 13 with patients. *P<0.05. LN. LN, lupus nephritis.

61.5 to 67.3, respectively (Fig. 4A and Table II). Renal function remained largely unaffected in seven patients, while the eGFR of three patients decreased during treatment with telitacicept (Table II). Serum creatinine levels of all patients remained generally stable during the treatment period, with slight elevation in three patients (Fig. 4A). After treatment with telitacicept, plasma albumin levels remained normal in three patients and increased in 10 patients. Plasma albumin levels were normalized in three patients (Fig. 4C and Table II). Additionally, all patients showed stable platelet levels during treatment (Fig. 4D).

Drug adverse events. Telitacicept has been reported to cause adverse events, such as infections and herpes zoster (12). However, none of the patients in the present study experienced these symptoms. During treatment, seven patients achieved disease activity control, and their telitacicept dosage was reduced. One patient experienced a urinary tract infection, and another suffered from a lower respiratory tract infection. All these adverse events were mild to moderate and relieved after treatment with systemic medications.

Effect of COVID-19 pandemic on patients with LN. All the 13 patients were affected by COVID-19 during the observation period. Among them, three patients developed fever, and 10 patients remained asymptomatic (Table SIII).

Discussion

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disorder that affects most organs, especially the kidney (18,19). LN is a significant complication of SLE, with the primary treatment goal being the prevention of progressive renal damage and subsequent renal failure (5,20). The

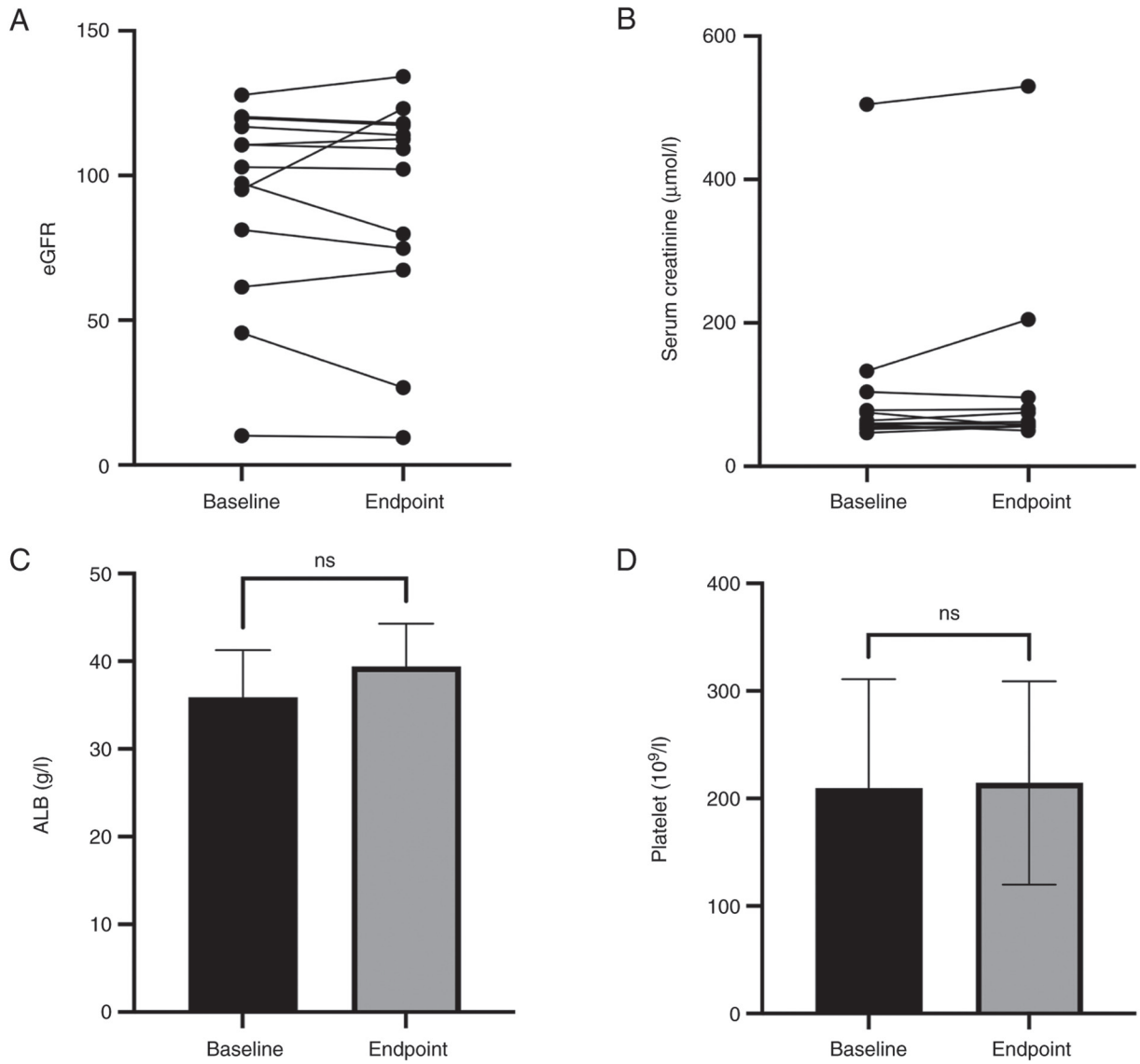

Figure 4. Results of eGFR, serum creatinine, plasma albumin and platelet analyses. Changes in (A) eGFR, (B) serum creatinine, (C) plasma albumin and (D) platelets at baseline and endpoint during the trial of 13 cases with treatment. Values are the mean and standard. eGFR, estimated glomerular filtration rate; ALB, albumin; ns, not significant.

chronicity of LN and its recurrent flares correlate with disease progression (4).

The prescribed immunosuppressive medicines typically include mycophenolate mofetil, hydroxychloroquine, cyclosporine, tacrolimus and cyclophosphamide, all of which lead to serious adverse events (21,22). Hydroxychloroquine, for instance, is excreted by the kidneys, which can increase renal burden and cause pigment changes in the retinal macula, potentially leading to vision loss in the absence of timely treatment (23). A number of recommendations suggest that patients with LN and an eGFR <30 ml/min/1.7 m^2 should receive lower doses of hydroxychloroquine to prevent toxic adverse events (24,25). Cyclophosphamide leads to ovarian failure, making it unsuitable for young women (26). Patients using mycophenolate mofetil are highly likely to discontinue treatment due to gastrointestinal toxicity (27). Although glucocorticoids effectively control inflammation, their long-term use is associated with chronic side effects, such as osteoporosis and glaucoma (28). Complete withdrawal from corticosteroids is the therapeutic objective for all patients with a clinical response.

The patients in the present study received at least one immunosuppressive medicine. Based on the profile of the patients, the current study aimed to substitute these agents with telitacicept at doses of 80 or 160 mg.

Telitacicept is the first 'dual-target' biological agent that can effectively treat patients with SLE (14). A phase 3 study proved that it is effective and well-tolerated by patients with SLE (29), even among pediatric patients (13). It has been considered a potential medicine for treating LN.

However, due to a supply chain shortage, all patients in the trial discontinued treatment with telitacicept at the endpoints. Nonetheless, the study continued to record and analyze their medical data for 4 months after the endpoints.

During the 4-month follow-up period, three patients receiving standard treatment needed a higher dose of mycophenolate mofetil, hydroxychloroquine and cyclophosphamide. Follow-up data revealed that the symptoms of the remaining

patients [10 (76.9%)] were under control, despite giving them the same doses of immunosuppressive medicines and glucocorticoids. The combination of telitacicept and standard treatment controlled their active LNs. According to the guidelines, the 10 patients received their usual doses of immunosuppressive medicines and glucocorticoids (30). However, dose escalation was necessary for all 13 patients. Further studies may be needed to provide a more detailed explanation for this discrepancy. No deaths were recorded during this study. Two patients (15.4%) experienced mild to moderate adverse events, all of whom recovered after receiving systemic treatment.

All patients enrolled in this study were infected by COVID-19 at different times, but none of them exhibited serious complications, such as pneumonia. Further studies are needed to unravel the potential effectiveness of telitacicept for respiratory system-related diseases.

Compared with other studies on telitacicept (31-33), the present study did not include a large number of patients to establish a control group. As previously mentioned, due to the shortage of the supply chain, the duration of treatment with telitacicept was not long.

Telitacicept, a novel biological agent, introduces a new therapeutic paradigm, offering alternatives to glucocorticoid therapy. Telitacicept, a new class of biological agents, was effective in SLE. To the best of our knowledge, the present study analyzed the efficacy and safety of telitacicept in Chinese patients with LN during the COVID-19 pandemic for the first time. Telitacicept may allow reducing the dosage of immunosuppressive agents and glucocorticoids in patients with LN.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

HZ made substantial contributions to the conception of the study and drafted the manuscript. HQH and HLW collected patient data. DXZ and HY analyzed the data. QKZ was responsible for the interpretation of the data and ethical approval. LJ designed the research. LJ and QKZ confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was reviewed and approved by the Ethical Committee of the Lishui Central Hospital (approval no. 2022-278). All patients whose data were not previously documented in any publications provided written informed consent to utilize their medical records.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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