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Effect of *Tripterygium* glycosides combined with belimumab on the efficacy and serum immune indices in patients with lupus nephritis

QIONG LIU, NAN DING, ZHIJUAN HU

Hebei General Hospital, China

Abstract

Introduction: *Lupus nephritis (LN) is an autoimmune disease with challenging clinical management. This study aimed to evaluate the efficacy of Tripterygium glycosides combined with belimumab in LN treatment and its effects on serum immune indices.*

Material and methods: *In a randomized, open-label trial, 172 LN patients from Hebei General Hospital (June 2019-June 2022) were assigned to a control group (belimumab alone) or a study group (belimumab + Tripterygium glycosides). Primary outcomes included serum inflammatory factors, immunoglobulins (IgA, IgG, IgM), T lymphocyte subsets ($CD4^+$, $CD8^+$, $CD4^+/CD8^+$), complement C3 and C4, and renal function indices (24 h urinary protein, urinary microalbumin, urinary NAG). Secondary outcomes included Traditional Chinese Medicine Symptoms (TCMS) score, lupus activity (Systemic Lupus Erythematosus Disease Activity Index [SLEDAI]), clinical efficacy, and adverse reactions.*

Results: *After exclusions, 85 patients were included in the study group and 68 in the control group. Following treatment, both groups showed significant reductions in inflammatory factors, IgA, IgM, IgG, $CD8^+$ T cells, renal function indices, TCMS score, and SLEDAI score, alongside increases in $CD4^+$ T cells, $CD4^+/CD8^+$ ratio, and complement C3 and C4 ($p < 0.05$). Improvements were significantly greater in the study group ($p < 0.05$). The study group also showed higher clinical efficacy and fewer adverse reactions than the control group ($p < 0.05$).*

Conclusions: *Tripterygium glycosides combined with belimumab effectively improves inflammation, immune function, and renal function in LN patients, supporting its clinical application.*

Key words: *Tripterygium glycosides, belimumab, lupus nephritis, inflammatory factors, immune function.*

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Introduction

Systemic lupus erythematosus (SLE) is characterized by abnormal immune cell function and the production of anti-nuclear autoantibodies, which seriously affect health. The risk of its onset is driven by both genetic and non-genetic factors, and the two interact with each other. Genetically, susceptible genes such as complement genes (e.g. C1q deficiency) determine susceptibility to disease and organ involvement, increasing the risk of lupus nephritis and other conditions. Non-genetic factors such as ultraviolet radiation, chemical infections, and fluctuations in female estrogen levels may trigger or worsen the condition [1]. SLE involves multiple organ lesions and induces the occurrence of lupus nephritis (LN) without efficient or targeted treatment [2]. LN is an autoimmune disease, which is mainly manifested by zygomatic erythema, intermittent fever, oral ulcers, etc., and glomerular and tubular hypoplasia, proteinuria, haematuria, and interstitial renal lesions. LN is prone to relapse, and prolonged treatment can lead to the development of uremia, which can seriously damage the health of patients [3]. In one study, about half of the patients with severe LN achieved clinical remission after immunosuppressive therapy, while the other patients with LN had some degree of renal damage [4]. High doses or long-term use of immunosuppressive drugs in clinical practice may cause adverse events, including the risk of serious infections, bone marrow suppression, and increased incidence of malignant tumors. Early recognition and active intervention are crucial in treatment of this disease, which is conducive to increasing renal survival and im-

Correspondence: Qiong Liu, Hebei General Hospital, China, e-mail: lq800813@163.com
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proving disease prognosis [5]. Therefore, there is a need for research or discovery of novel treatments for LN that are targeted, accurate, or efficient.

At present, the pathogenesis of LN is relatively complex. Based on this characteristic, a multi-target treatment plan is recommended and adopted in clinical practice, with the core treatment goal of helping patients achieve clinical remission or maintaining the degree of disease activation at a low level. In current clinical practice, commonly used therapeutic drugs mainly include steroid drugs and biologics [6]. Corticosteroids mainly bind to glucocorticoid receptors in the cytoplasm to exert inhibitory effects on cellular immunity, and have been widely used as effective anti-inflammatory and immunosuppressive agents in clinical practice. In the treatment of autoimmune diseases, this drug can significantly improve patient prognosis. In SLE patients, standardized use of glucocorticoids can reduce the 5-year mortality rate by 20-30% compared to non-use patients, and the disability rate caused by organ damage (such as kidney failure and joint deformity related disability) can be reduced by 15-25%, fully reflecting its effect on improving the quality of life of patients [7]. Traditional biological therapy still has significant limitations in the treatment of LN, manifested by low clinical remission rates, frequent disease relapse, and persistent risk of organ damage in some patients after treatment. At the same time, patients who use glucocorticoids (in combination with immunosuppressants) long term also face the challenge of drug-related adverse reactions, such as liver injury and Cushing's syndrome, which are common toxic side effects [8]. B-cell hyperfunction is currently recognized as the immunopathogenesis of LN, and CD20 plays an important role in B-cell proliferation and differentiation. Biological agents targeting B cells include belimumab and CD20 monoclonal antibodies (rituximab, ocrelizumab, obinutuzumab) [9]. Belimumab is currently the first biological agent approved for the treatment of LN in China. It can block the binding of soluble B-lymphocyte stimulating factor and its receptor on B-cells, inhibit B-cell activation, and induce auto-reactive B-cell apoptosis [10]. Clinical studies have shown significant and sustained reductions in IgG and autoantibodies in belimumab-treated patients, with improvements in C3 and C4, and higher rates of negative conversions for ds-DNA antibodies, anticardiolipin antibodies, and anti-ribosomal P antibodies [11]. A retrospective analysis of studies has shown that belimumab-treated patients achieved dose reductions of glucocorticoids and other baseline medications [12]. This suggests that belimumab in combination with conventional therapy can more significantly control LN disease activity, reduce the risk of severe relapse, and result in higher complement levels, as well as significantly reducing hormone dosage and patient dependence on hormones [13].

According to traditional Chinese medicine, this disease belongs to the categories of "kidney obstruction" and "edema disease". The disease is considered to involve a deficiency of the root (*ben*) and the excess of the branch (*biao*). The main cause of this deficiency is spleen and kidney deficiency, which is manifested by pathogenic heat, blood stasis, phlegm dampness, and other internal and external factors [14]. The *Su Wen – Six Sections of the Theory of Hidden Images* states: "The kidneys are the main pillar, the foundation of storage and concealment, and the residence of essence". The kidney yin forms the foundation of the body's yin. As stated, "The yin of the five zang organs cannot be nourished without it". Kidney essence is stored in the kidneys; if kidney yin is insufficient, fire becomes overactive, and the body's ability to consolidate is weakened. Excessive stimulation can lead to leakage of essence, which may manifest as urinary protein and related symptoms [15]. Therefore, traditional Chinese medicine treatment for LN emphasizes the combination of tonifying the kidneys, promoting blood circulation, removing blood stasis, and eliminating turbidity and toxins. This not only alleviates clinical symptoms but also enhances immunity, thereby delaying the progression of LN [16].

Herbal medicines act as unique agents in the treatment of LN, such as *Tripterygium wilfordii*. *Tripterygium*, a type of vine plant, has medicinal value mainly concentrated in its roots and flesh. Multiple compounds with clear therapeutic activity can be extracted from it, including terpenes (such as *Tripterygium* glycoside A and lactones), alkaloids (such as *Tripterygium* glycoside alkaloids), and flavonoids. These components participate in the pathological regulation of LN through synergistic effects [17]. Terpenoids are the main active components of *Tripterygium* glycosides in exerting immunomodulatory effects. *Tripterygium* glycoside A can reduce the production of pro-inflammatory cytokines by inhibiting the nuclear factor kappa B signaling pathway required for T cell activation, while regulating the distribution of T lymphocyte subsets and correcting cellular immune imbalances [18]. Alkaloids can further enhance anti-inflammatory effects by downregulating the expression of inflammatory cytokines and reducing systemic and renal local inflammatory responses in LN patients. Although flavonoids have a low content, they can clear oxygen free radicals through antioxidant effects, assist in protecting renal parenchymal cells, and reduce secondary damage to the kidneys caused by oxidative stress [19]. In traditional Chinese medicine theory, the synergistic effect of *Tripterygium* glycosides, as mentioned above, corresponds to its efficacy of "clearing heat and removing blood stasis, promoting diuresis and reducing swelling, and dispelling wind and dampness", which can simultaneously improve the condition of LN from both pathological mechanisms and traditional Chinese medicine syndromes [20]. In recent years, numerous studies have indicated that the active ingredients of *Tripterygium wilfordii* and its preparations improved lymph node LN patients' symptoms, reduce the levels of urinary protein, blood urea

nitrogen and blood creatinine, improve the antibodies to complement and ds-DNA, and alleviate renal damage. Their efficacy is further improved when combined with glucocorticoids or other immunosuppressants, which has led to widespread clinical use [21-24].

To the best of our knowledge, no other study has investigated this combination. Therefore, this study mainly observed the clinical efficacy of *Tripterygium* glycosides combined with belimumab in LN patients, and analyzed their effect on the improvement of serum inflammatory factor expression and immune function indices, with a view to providing a new scientific evidence of the clinical treatment of LN patients.

Material and methods

Study design

This study is a systematic evaluation and integration aimed at comparatively analyzing the clinical efficacy of *Tripterygium* glycosides in combination with belimumab in patients with LN, and further evaluating their impact on patients' serum inflammatory factor expression and immune function indices. This study was conducted at Hebei General Hospital. A total of 172 LN patients admitted to Hebei General Hospital between June 2019 and June 2022 were enrolled and assigned to the study group and control group depending the intervention. The study flow chart is illustrated in Figure 1.

Inclusion and exclusion criteria

Inclusion criteria: 1) Meets the diagnostic criteria of the LN Diagnosis and Treatment Guidelines, and has not received treatment with glucocorticoids or immunosuppressive drugs within one week prior to enrollment [25]; 2) Age 30-65 years; 3) The patient and their family members have been informed of the relevant information regarding the study. With the patient signing a written informed consent form, family members are encouraged to participate in protocol communication to ensure cooperation in subsequent treatment.

Exclusion criteria: 1) Patients with cardiovascular disease, neurological or other serious organ function damage; 2) Patients with a history of malignant tumor; 3) Patients with chronic diseases; 4) Patients with serious infections or rheumatic diseases; 5) Patients in pregnancy or breastfeeding; 6) Allergy to the drug ingredients involved in this experiment.

Ethical statement

The study was performed in compliance with the Declaration of Helsinki and the ethical guideline of the hospital, and was approval by the hospital's ethical committee.

Interventions

All patients were given glucocorticoids and other basic treatments (including blood pressure control therapy, such as the use of angiotensin-converting enzyme inhib-

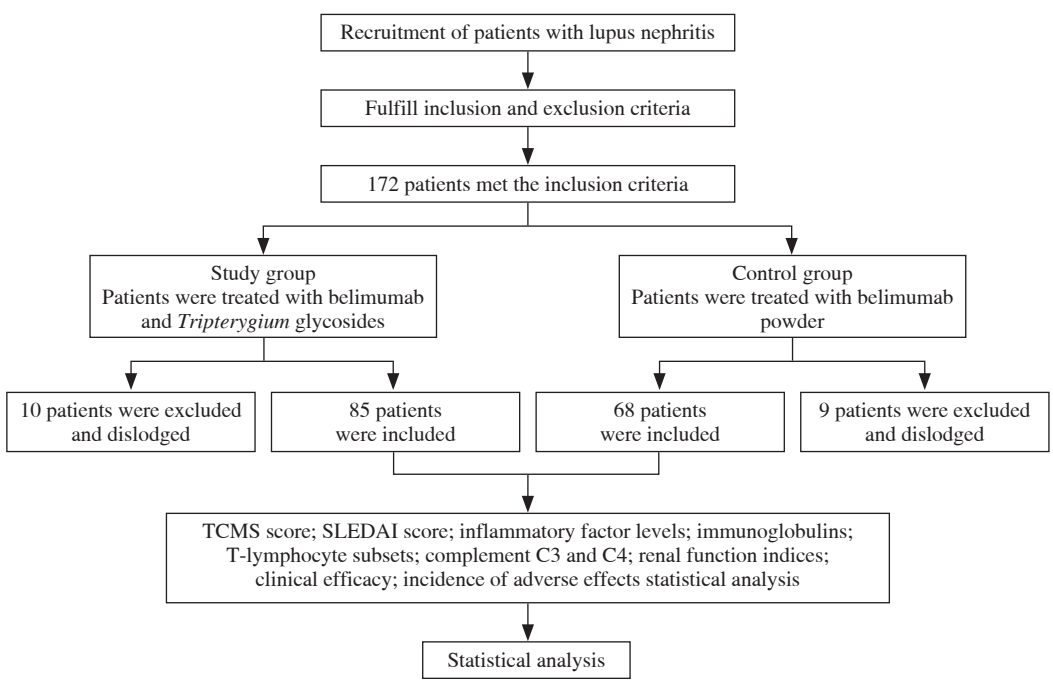

Fig. 1. Flowchart

itors; lipid regulation therapy, such as statins; and symptomatic supportive therapy, such as correcting anemia, electrolyte imbalances, maintaining water and sodium balance, etc.). In addition, patients were treated with mycophenolate mofetil (10-30 mg/kg, State Pharmaceutical Code H20080016, Warner Pharmaceuticals) and hydroxychloroquine (5 mg/kg, State Pharmaceutical Code No. H19990263, Shanghai Shangyi Pharmaceuticals Chinese and Western Pharmaceuticals Ltd.) treatment.

In the control group, belimumab (Specification: 120 mg, Registration No. S20190032, GlaxoSmithKline Manufacturing SPA, Italy) was added to the treatment with 10 mg/kg intravenously for the first 3 times every 2 weeks, and every 4 weeks thereafter for 6 consecutive months.

The study group was treated with *Tripterygium* glycosides (1.5 mg/kg, orally, 3 times/day, State Pharmaceutical Code Z31020415, Shanghai Fudan Fuhua Pharmaceutical Co., Ltd.) in addition to the treatments given to the control group for 3 continuous months. The interventions in the 3rd-6th months were consistent with the control group.

Main results

Serum inflammatory factors

Referring to the ELISA detection process for serum inflammatory factors reported by Kanlioglu *et al*. (including sample centrifugation conditions, reagent incubation parameters, and quality control standards) [26], inflammatory factor indices were observed in the two groups of patients. In the morning, a 5 ml specimen of elbow venous blood was drawn on an empty stomach, centrifuged at 3000 r/min for 10 min, and the supernatant was taken after serum separation. The serum specimen was analyzed by the ELISA method uniformly by the laboratory department of our hospital, and the levels of serum inflammatory markers of the patients were recorded postoperatively. Serum levels of C-reactive protein (CRP), tumor necrosis factor α (TNF-α), interleukin (IL)-6, IL-8 and IL-18 were analyzed using a human CRP ELISA kit (PC190, Shanghai Beyotime Biotechnology Co., Ltd.), human TNF-α ELISA kit (97072ES96, Shanghai Yeasen Biotechnology Co., Ltd.), human IL-6 ELISA kit (PI325, Shanghai Beyotime Biotechnology Co., Ltd.), human IL-8 ELISA kit (PI641, Shanghai Beyotime Biotechnology Co., Ltd.), and human IL-18 ELISA kit (PI558, Shanghai Beyotime Biotechnology Co., Ltd.).

Immunological functions

Serum levels of IgA, IgM, and IgG were detected using a fully automatic biochemical analyzer (AU5841, Beckman Coulter, Inc.) [27].

Percentages of $CD4^+$ and $CD8^+$ T cells in peripheral blood mononuclear cell samples were detected using a human $CD4^+$ T cell ELISA kit (JKbio 14552, Shanghai Jingkang Bioengineering Co., Ltd.) and a human $CD8^+$ T cell ELISA kit (JKbio 14553, Shanghai Jingkang Bioengineering Co., Ltd.) [28].

Complement C3 and C4 levels

Immunoturbidimetric assay was used to detect complement C3 and C4 levels in serum using a complement 3 assay kit (SNM253, Beijing Biolab Tech Co., Ltd.) and complement 4 assay kit (SNM252, Beijing Biolab Tech Co., Ltd.) [29].

Renal function indices

Urine was collected from both groups before and after treatment, and 24-h urine protein quantification, urine microalbumin, and urinary N-acetyl-β-D-glucosaminidase (NAG) levels were detected using a fully automatic biochemical analyzer (AU5841, Beckman Coulter, Inc.) [30].

Secondary results

Traditional Chinese Medicine Symptoms (TCMS) score

Fever, rash, ulcer, fatigue, and weakness were selected for TCMS assessment with reference to the *Guidelines for Clinical Research on Traditional Chinese Medicine* [31], and the range of the scores for each item was 0-3. The TCMS score was a composite of all the symptom scores, with higher scores indicating greater severity according to TCM.

Disease activity

Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) was used to evaluate and compare the disease activity of the two groups [32]. Scores of 0-4 indicate basically inactive disease, 10-14 indicate moderate activity, and ≥ 15 indicate severe activity.

Clinical efficacy

Referring to the *Guidelines for Diagnosis and Treatment of Lupus Nephritis in China* and relevant clinical research efficacy evaluation standards [33], combined with the observation indicators of this study, the following criteria were formulated: a significant effect (complete remission) refers to a decrease of ≥ 70% in TCMS score compared to baseline, SLEDAI score drops to 0-4 points (basically no activity), serum inflammatory factors and immunoglobulin levels return to the normal reference range in the laboratory, complement C3 and C4 levels return to the normal range, 24-hour urine protein quantification < 0.5 g, and urine microalbumin and urinary NAG levels are normal. Effective (partial relief) refers to a decrease of 30-69% in TCMS score compared to baseline, a decrease of ≥ 4 points in SLEDAI score compared to baseline but below 14 points, a decrease of ≥ 50% in serum inflammatory factors and immunoglobulin levels compared to baseline, an increase of ≥ 30% in complement C3 and C4 levels compared to baseline, a decrease of ≥ 50%

and < 3.0 g in 24-hour urine protein quantification compared to baseline, and a decrease of ≥ 50% in urinary microalbumin and urinary NAG levels compared to baseline. Ineffective refers to failure to meet the above effective standards, or no significant improvement or even aggravation in TCMS score, SLEDAI score, and laboratory indicators. Total effective rate = (number of significantly effective cases + number of effective cases)/total cases × 100%.

Adverse reactions

The incidence of adverse reactions (including nausea, dizziness, diarrhea, and drug-induced rash) was monitored and documented in both patient groups throughout the treatment period.

Follow-up visits

This study was primarily scheduled for a 6-month post-treatment follow-up to assess the durability of the effects and to address any potential complications or problems.

Sample size calculations

As of March 2020, the number of LN patients in the belimumab post-market monitoring study is estimated to be approximately 250 out of 1024 SLE patients [34]. Based on the BLISS-52 trial (GSK study BEL110752; NCT00424476) and epidemiological data [35], the rate of renal episodes per patient is estimated to be 0.05 per year, and belimumab protects about 1/3 of patients. This sample size provided 80% of the target power at the 5% significance level.

Statistical methods

SPSS 27.0 statistical software was used for data analysis. The normality of the quantitative data was evaluated through the Shapiro Wilk test. Quantitative data that conform to the normal distribution were presented as mean ± standard deviation ($\bar{x} \pm s$), and the independent sample *t*-test was used for inter-group comparison. The count data are expressed as rate (%), and comparisons between groups were conducted using the χ^2 test. The level of statistical significance was set at $p < 0.05$.

Results

Basic information

After applying the exclusion criteria, a total of 85 patients were included in the study group and 68 in the control group. The baseline demographic characteristics and baseline status of the patients randomly assigned to the control and study groups are indicated in Table 1; no significant differences were observed between the groups

Table 1. Patient demographics and baseline disease characteristics

Parameter	Control group (*n* = 68)	Study group (*n* = 85)	t/χ^2	*p*
Age (years)	50.03 ±7.34	49.92 ±7.58	–0.091	0.928
Sex (male/female)/ (percentage of women, %)	20/48 (70.59)	24/61 (71.76)	0.025	0.876
Disease duration (years)	13.83 ±3.12	13.69 ±2.90	–0.287	0.775
Body surface area (m^2)	1.65 ±0.17	1.68 ±0.17	1.085	0.280
Body mass index (kg/m^2)	22.24 ±2.26	22.46 ±2.18	0.610	0.543
Alcohol consumption (Yes/no) Percentage (%)	31/37 (45.59)	38/47 (44.71)	0.020	0.887
Hypertension (Yes/no) Percentage (%)	33/35 (48.53)	43/42 (50.59)	0.080	0.777
Diabetes (Yes/no) Percentage (%)	40/28 (58.82)	51/34 (60.00)	0.021	0.885
SLEDAI score (score)	12.22 ±0.23	12.18 ±0.19	–1.178	0.241
ESR (ms/h)	33.27 ±0.47	33.13 ±0.51	–1.747	0.083
Anti-dsDNA antibody (IU/ml)	285.12 ±4.63	284.48 ±4.97	–0.816	0.416
C3 (g/l)	0.60 ±0.18	0.62 ±0.18	0.683	0.496
C4 (g/l)	0.14 ±0.07	0.12 ±0.07	–1.756	0.081
Renal biopsy activity index score (score)	7.74 ±0.51	7.69 ±0.52	–0.596	0.552
Renal biopsy chronicity index score (score)	2.53 ±0.51	2.49 ±0.44	–0.521	0.604
24 h urine protein (mg)	5548.86 ±41.10	5541.56 ±36.11	–1.168	0.245
Serum albumin (g/dl)	2.28 ±0.41	2.33 ±0.42	0.739	0.461
Serum creatinine (μmol/l)	73.47 ±2.71	73.11 ±2.42	–0.867	0.387

Table 2. Comparisons of serum inflammatory factor indices

Norm	Time	Control group	Study group	*t*	*p*
CRP (mg/l)	Pre-treatment	7.20 ±1.22	7.06 ±0.99	–0.784	0.435
	Post-treatment	4.15 ±0.98*	3.40 ±0.77*#	–5.302	< 0.001
TNF-α (pg/ml)	Pre-treatment	14.98 ±3.58	14.42 ±3.73	–0.939	0.349
	Post-treatment	6.44 ±1.51*	4.11 ±1.04*#	–11.275	< 0.001
IL-6 (ng/l)	Pre-treatment	51.06 ±9.33	51.59 ±8.61	0.365	0.716
	Post-treatment	38.99 ±6.14*	26.33 ±4.52*#	–14.681	< 0.001
IL-8 (ng/l)	Pre-treatment	6.55 ±1.96	6.38 ±1.56	–0.597	0.551
	Post-treatment	4.06 ±0.78*	3.22 ±0.84*#	–6.343	< 0.001
IL-18 (pg/ml)	Pre-treatment	520.33 ±37.90	524.72 ±36.48	0.727	0.468
	Post-treatment	391.12 ±28.04*	228.60 ±20.15*#	–41.667	< 0.001

** Indicates significant difference versus pre-treatment, $p < 0.05$; # represents the comparison between the study group and the control group after treatment, $p < 0.05$*

Table 3. Indicators of immune function

Norm	Time	Control group	Study group	*t*	*p*
IgA (g/l)	Pre-treatment	3.62 ±0.36	3.67 ±0.33	0.894	0.373
	Post-treatment	2.74 ±0.40*	2.30 ±0.41*#	–7.456	< 0.001
IgM (g/l)	Pre-treatment	2.59 ±0.57	2.48 ±0.70	–1.047	0.297
	Post-treatment	1.94 ±0.55*	1.54 ±0.50*#	–4.703	< 0.001
IgG (g/l)	Pre-treatment	22.23 ±3.22	22.46 ±3.19	0.441	0.660
	Post-treatment	17.51 ±3.67*	13.41 ±3.15*#	–7.432	< 0.001
$CD4^+$ T cells (%)	Pre-treatment	29.41 ±8.83	29.23 ±8.07	–0.131	0.896
	Post-treatment	33.68 ±8.07*	39.37 ±8.60*#	4.179	< 0.001
$CD8^+$ T cells (%)	Pre-treatment	39.02 ±5.55	39.73 ±5.60	0.782	0.435
	Post-treatment	36.48 ±4.47*	30.25 ±5.11*#	–7.917	< 0.001
$CD4^+/CD8^+$	Pre-treatment	0.67 ±0.21	0.70 ±0.21	0.878	0.381
	Post-treatment	1.06 ±0.31*	1.26 ±0.30*#	4.037	< 0.001

** Indicates significant difference versus pre-treatment, $p < 0.05$; # represents the comparison between the study group and the control group after treatment, $p < 0.05$*

in demographic variables/instruments/status ($p > 0.05$). Thus, the randomization process achieved the important goal of evenly assigning participants to the two groups, the two groups were comparable at the pre-treatment level, and confounding by demographic/clinical factors did not affect the analysis of treatment outcomes.

Main results

Serum inflammatory factors

Detection of serum inflammatory factors in patients with nephritis helps to assess the effectiveness of patient treatment, and the results of the comparison of serum inflammatory factor levels between the groups are presented in Table 2. Before treatment, no significant differences were observed in the levels of CRP, TNF-α, IL-6, IL-8, and IL-18 between the groups ($p > 0.05$). After treatment, the inflammatory factor levels in the control group patients were 4.15 ±0.98 mg/l, 6.44 ±1.51 pg/ml, 38.99 ±6.14 ng/l, 4.06 ±0.78 ng/l, and 391.12 ±28.04 pg/ml, respectively, and in the study group were 3.40 ±0.77 mg/l, 4.11 ±1.04 pg/ml, 26.33 ±4.52 ng/l, 3.22 ±0.84 ng/l, and 228.60 ±20.15 pg/ml, respectively, which were significantly below pre-treatment levels, and the study group was significantly below the control group ($p < 0.05$). These results indicated that inflammatory factor levels were significantly reduced in both groups after treatment, and the study group showed a significantly better improvement in the blood inflammatory response.

Immune function

Lupus nephritis is an autoimmune disease, and the assessment of its immune indicators facilitates the analysis of the active state of the body's immune system. The results of our analysis and comparisons of the immune function indicators for both groups are presented in Table 3. Before treatment, the comparisons of results for immune function indices between the groups showed no significant differ-

Table 4. Complement C3 and C4 levels

Norm	Time	Control group	Study group	*t*	*p*
C3 (g/l)	Pre-treatment	0.83 ±0.08	0.82 ±0.10	–0.671	0.504
	Post-treatment	0.90 ±0.09*	1.00 ±0.08*#	7.267	< 0.001
C4 (g/l)	Pre-treatment	0.17 ±0.03	0.16 ±0.05	–1.453	0.148
	Post-treatment	0.29 ±0.08*	0.40 ±0.10*#	7.376	< 0.001

** Indicates significant difference versus pre-treatment, p < 0.05; # represents the comparison between the study group and the control group after treatment, p < 0.05*

Table 5. Comparisons of renal function indices

Norm	Time	Control group	Study group	*t*	*p*
24 h urine protein quantification (g)	Pre-treatment	3.98 ±0.60	3.99 ±0.62	0.101	0.920
	Post-treatment	2.35 ±0.41*	1.13 ±0.48*#	–16.653	< 0.001
Urine microalbumin (μg/l)	Pre-treatment	15.16 ±3.29	15.05 ±3.09	–0.213	0.832
	Post-treatment	11.11 ±2.05*	9.07 ±1.39*#	–7.313	< 0.001
Urine NAG level (U/l)	Pre-treatment	20.94 ±4.43	20.61 ±3.80	–0.496	0.621
	Post-treatment	13.36 ±4.29*	9.04 ±3.24*#	–7.095	< 0.001

** indicates significant difference versus pre-treatment, p < 0.05; # represents the comparison between the study group and the control group after treatment, p < 0.05.*

ence ($p > 0.05$). After treatment, the IgA, IgM and IgG levels, and the percentage of $CD8^+$ T cells in the control group were 2.74 ±0.40 g/l, 1.94 ±0.55 g/l, 17.51 ±3.67 g/l, and 36.48 ±4.47%, and in the study group were 2.30 ±0.41 g/l, 1.54 ±0.50 g/l, 13.41 ±3.15 g/l, 30.25 ±5.11%, and 1.26 ±0.30, which were significantly below the pre-treatment levels ($p < 0.05$). The $CD4^+$ T cell percentage and $CD4^+/CD8^+$ were 33.68 ±8.07% and 1.06 ±0.31 in the control group and 39.37 ±8.60% and 1.26 ±0.30 in the study group, respectively, which were significantly above the pre-treatment levels ($p < 0.05$). The changes in immune indices in the study group were superior to the control group ($p < 0.05$). This indicates that the immunotherapy in both groups improved significantly after treatment, and the immune function in the study group improved more markedly.

Complement C3 and C4

C3 and C4 are often reduced in patients with LN, and their deposition in the kidney is one of the main causes of nephritis. Therefore, we further evaluated the C3 and C4 levels of both groups of patients, and their comparative results are presented in Table 4. Before treatment, the complement C3 and C4 levels were 0.83 ±0.08 g/l and 0.17 ±0.03 g/l in the control group patients and 0.82 ±0.10 g/l and 0.16 ±0.05 g/l in the study group patients, respectively, with no significant difference between the groups ($p > 0.05$). After treatment, the C3 and C4 levels in the control group were 0.90 ±0.09 g/l and 0.29 ±0.08 g/l, respectively, while levels in the study group were 1.00 ±0.08 g/l and 0.40 ±0.10 g/l, respectively, which were significantly above the pre-treatment level, and the study group was above the control group ($p < 0.05$). It indicates that the immune status of the patients' organism was improved after treatment, the complement level was significantly increased, and the degree of improvement in the study group was superior to the control group.

Renal function indicators

Renal function indices are of great significance in assessing renal health status and disease progression. The comparison of renal function indicators between the groups of patients is displayed in Table 5. Before treatment, the 24 h urinary protein quantification, urinary microalbumin, and urinary NAG levels of patients in the control group were not significantly different from the study group patients ($p > 0.05$). After treatment, the renal function indicators of patients in the control group were 2.35 ±0.41 g, 11.11 ±2.05 μg/l, and 13.36 ±4.29 U/l, while those of patients in the study group were 1.13 ±0.48 g, 9.07 ±1.39 μg/l, and 9.04 ±3.24 U/l, respectively, which were significantly below the pre-treatment level ($p < 0.05$). All values in the study group were significantly below those of the control group ($p < 0.001$). It indicated that the renal injury of the patients was significantly improved after treatment, and the improvement of the study group was superior to the control group.

Secondary results

TCMS

We analyzed TCMS scores for both groups of patients, and the results of the comparison between the groups are presented in Table 6. Before treatment, the TCMS scores of the patients in the control group and the study group were 13.29 ±1.99 and 13.39 ±2.08, respectively, and no

Table 6. Comparisons of TCMS scores ($\bar{x}$ ±s, score)

	Control group	Study group	*t*	*p*
Pre-treatment	13.29 ±1.99	13.39 ±2.08	0.301	0.764
Post-treatment	9.39 ±1.56	7.55 ±1.46	–7.514	< 0.001
t	–12.719	–21.187		
p	< 0.001	< 0.001		

Table 7. Comparison of SLEDAI scores ($\bar{x}$ ±s, score)

	Control group	Study group	*t*	*p*
Pre-treatment	10.99 ±3.35	10.76 ±3.13	–0.438	0.662
Post-treatment	4.42 ±1.40	3.32 ±1.23	–5.168	< 0.001
t	–14.922	–20.396		
p	< 0.001	< 0.001		

Table 8. Clinical efficacy analysis

Group	Significant effect (*n*)	Effective (*n*)	Ineffective (*n*)	Total effective rate (*n*, %)
Control group	27	30	11	57 (83.82)
Study group	35	46	4	81 (95.29)
χ^2		6.438		
p		< 0.05		

Table 9. Incidence of adverse reactions

Variable	Control group, *n* (%)	Study group, *n* (%)	χ^2	*p*
Nausea	1 (1.47)	0 (0.00)	1.005	0.316
Dizziness	0 (0.00)	1 (1.18)	1.005	0.316
Diarrhea	1 (1.47)	0 (0.00)	1.005	0.316
Drug rash	2 (2.94)	1 (1.18)	1.020	0.312
Hyperuricaemia	1 (1.47)	0 (0.00)	1.005	0.316
Abnormal liver function	1 (1.47)	1 (1.18)	0.000	1.000
Urinary tract infection	1 (1.47)	1 (1.18)	0.000	1.000
Gastrointestinal disorders	1 (1.47)	1 (1.18)	0.000	1.000
Fever	1 (1.47)	0 (0.00)	1.005	0.316
Pneumonia	1 (1.47)	0 (0.00)	1.005	0.316
Overall response rate	10 (14.71)	5 (5.88)	4.310	< 0.05

The total incidence of adverse reactions is calculated as the number of patients with adverse events divided by the total number of observed cases multiplied by 100%. When multiple adverse events occur in the same patient, it is counted as one case

significant difference was found between the groups ($p > 0.05$). After treatment, the TCMS scores in both groups were 9.39 ±1.56 and 7.55 ±1.46, respectively, which were below the pre-treatment scores ($p < 0.001$), and the TCMS scores in the study group were significantly lower than those in the control group ($p < 0.001$). These results indicated that the TCM symptoms in both groups showed improvement after treatment, and the study group displayed better symptom improvement.

Disease activity

The assessment of the degree of disease activity in LN patients was mainly analyzed using the SLEDAI score, and the results of SLEDAI score comparison between the groups of patients are illustrated in Table 7. Before treatment, the results of SLEDAI scores in the control group and study group were 10.99 ±3.35 and 10.76 ±3.13, respectively, with no significant difference between the groups ($p > 0.05$). After treatment, the SLEDAI scores in the two groups were 4.42 ±1.40 and 3.32 ±1.23, respectively, which were below the pre-treatment scores, and the scores in the study group were significantly lower compared to the control group ($p < 0.001$). It indicates that the disease activity status of both groups of patients improved markedly after treatment, with the study group achieving greater remission of lupus activity.

Clinical efficacy

We analyzed the clinical efficacy of the two groups of patients by combining the effects of drug treatment in both groups, and the results of the analysis are illustrated in Table 8. The total efficacy rate in the control group was 83.82% (57/68), and in the study group it was 95.29% (81/85), which was a statistically significant difference ($p < 0.05$). The results showed that the patients in the study group had better efficacy, indicating that the clinical efficacy of *Tripterygium* glycosides combined with belimumab was better than that of belimumab alone in patients with LN.

Adverse reactions

We followed up the patients to observe the adverse reactions. Patients in both groups experienced adverse reactions such as nausea and headache of varying degrees during treatment, as shown in Table 9. The occurrence of adverse reactions such as nausea and dizziness was

not statistically significantly different between the groups ($p > 0.05$). The total incidences of adverse reactions in patients of the control group was 14.71% (10/68), and the total incidence of adverse reactions in patients of the study group was 5.88% (5/85), which was statistically significantly different between the groups ($p < 0.05$). This indicates that the treatment method used for the patients in the study group was more effective and safer.

Discussion

Lupus nephritis is a chronic inflammatory disease that frequently recurs and is a mortality risk factor. The pathogenesis of LN has not been fully elucidated, but researchers believe that it is closely related to the immune function, inflammatory response, and the severity of SLE [36]. There have been many studies on the treatment of LN with TCM, but the use of TCM as a booster agent has limited clinical efficacy and adverse effects [37]. *Tripterygium* glycosides are widely used in the treatment of diseases such as glomerulonephritis and immune nephritis with better anti-inflammatory and immunosuppressive effects [38]. Hence, in this study, the combination of *Tripterygium* glycosides with belimumab was analyzed in comparison with belimumab alone to explore potentially more viable therapeutic options for LN therapy.

Lupus nephritis is classified as "kidney paralysis" and "erythroderma" in traditional Chinese medicine. It is thought to result from congenital deficiency of kidney qi, emotional and emotional trauma, and impaired circulation of qi and blood, which prevents proper nourishment of the skin, leading to skin damage and gradual penetration of the disease into the internal organs [39]. *Tripterygium* glycosides are a potent bioactive compounds obtained from the traditional Chinese medicine *Tripterygium wilfordii*, which has the effects of inhibiting humoral immunity, cellular immunity, regulating renal function, and anti-inflammation [40]. In this study, LN patients were treated with *Tripterygium* glycosides combined with belimumab, and the results showed that the TCMS and SLEDAI scores of both groups were below pre-treatment levels, and the scores in the study group were significantly lower than the control group ($p < 0.05$). It showed that the TCMS of both groups improved markedly after treatment, the degree of disease activity was reduced, the clinical symptoms were alleviated, and the patients in the study group displayed a better improvement effect, which indicated that maintenance therapy with *Tripterygium* glycoside tablets could achieve good efficacy in both alleviating LN symptoms and controlling SLE activity.

Patients with LN often have varying degrees of renal injury and inflammatory responses. CRP is a non-specific marker of inflammation and tissue injury with good stability and accuracy. When inflammation or tissue damage occurs in the body, CRP is produced by liver cells and undergoes changes in levels under the regulation of cytokines such as TNF-α and IL-6. If the level of inflammatory factors does not decrease after treatment, it indicates that there is still damage in the body. Therefore, in this study, the levels of relevant inflammatory factors were detected [41]. The results showed that, after treatment, the levels of blood inflammatory factors in both groups were significantly lower than those before treatment, and the levels in the study group were significantly lower than those in the control group ($p < 0.05$). This indicated that the blood inflammatory response of patients in the study group was significantly improved after treatment, with lower levels of inflammatory factors than the control group, suggesting that this treatment could effectively alleviate the body's inflammatory response. In a study on peripheral blood inflammatory factor levels and clinical value in LN patients, Ye *et al*. also reported that combined Chinese and Western medicine treatment could reduce patients' serum inflammatory factor levels [42]. Similar findings were observed in the current research.

In general, modulation of the body's immune response to reduce the degree of renal injury in the pathological state of patients with LN is the key to pharmacological treatment. Common indicators of immune function in LN are IgA, IgM, IgG, $CD4^+$, and $CD8^+$ T cell percentages, and $CD4^+/CD8^+$ [43-45]. Complement C3 and C4 belong to the same complement system and have various roles such as bactericidal, regulatory, immunological, and inflammatory mediators [46]. The results of the study showed that after treatment, the IgA, IgM, and IgG levels, and the percentage of $CD8^+$ T cells in both groups were significantly reduced, the $CD4^+$ T cell percentage and $CD4^+/CD8^+$ ratio were significantly increased, and the changes in immune indices in the study group were superior to the control group ($p < 0.05$). Complement C3 and C4 levels were significantly elevated in both groups, and the study group levels were higher than the control group ($p < 0.05$). This might be related to the anti-inflammatory and renal function regulating the effects of *Tripterygium* glycosides. *Tripterygium* glycoside tablets, as a complex of active ingredients extracted from the traditional herb *Tripterygium wilfordii*, contain core active substances such as *Tripterygium* glycoside A, erythropoietin, and lactones. *Tripterygium* glycoside A can directly regulate cellular immune balance by inhibiting T cell activation and proliferation, reducing the release of pro-inflammatory cytokines such as IL-2 and IFN-γ. *Tripterygium* glycosides can inhibit excessive activation of B cells, reduce the production of immunoglobulins (IgA, IgM, IgG), and thus improve humoral immune disorders. *Tripterygium* glycoside lactones can also alleviate complement mediated inflammatory damage by inhibiting excessive consumption of complement C3 and C4. It is the synergistic effect of these components that endows *Tripterygium* glycosides with the comprehensive immune regulatory ability to simultaneously regulate cellular immunity, humoral immunity, and the complement

system [47]. This is similar to the findings reported by Jiang *et al*. in the study of IFN-γ and IL-4 expression and its efficacy prediction before and after LN treatment with TCM combined with cyclophosphamide [48]. It suggests that *Tripterygium* glycosides and belimumab may exert a better synergistic effect to markedly improve the humoral and cellular immune functions and alleviate the symptoms of patients.

Due to the specific characteristics of the structure of the kidney itself and its strong compensatory function, early clinical symptoms of kidney disease are not obvious, and whether kidney disease can be recognized and diagnosed at an early stage is the key to the treatment of this disease [49]. Therefore, this study analyzed urine protein and urine NAG levels, and the results showed that the relevant indicators were markedly reduced in both groups, with the study group results being below those of the control group ($p < 0.05$). It showed that the renal injury was remarkably improved after treatment, and the study group showed superior improvement to the control group. In the systematic review and meta-analysis by Li *et al*. of the Shenqi Dihuang decoction for the treatment of LN, the efficacy of the combination of Chinese and Western medicines was reported to be superior to the use of Western medicines alone [50]. This is consistent with the findings of the present study. The findings of the study revealed that the clinical efficacy of this study group was superior to the control group and the incidence of adverse reactions was lower than that of the control group. The findings of the present study indicated that the combination of *Tripterygium* glycosides with belimumab in the therapy of LN was highly effective, improving inflammatory factor levels, immune function, disease activity, and renal function, highlighting its significant clinical value.

There are some limitations to this study. Sample sizes are relatively small, which can lead to biased findings and affect the extrapolation and reliability of the conclusions. The limitation of the single-center study design is that there are differences in the patients' own underlying conditions, which may affect the generalisability of the findings. Chinese medicine has a lengthy history of evidence-based therapy of LN, and the forms of treatment are rich and varied. In this study, the therapeutic effect was demonstrated only from single herbs, so the herbal soup formula was not fully represented. In addition, only the short-term therapeutic effect was observed, failing to estimate the long-term effectiveness of *Tripterygium* glycosides combined with belimumab in patients, while the long-term effect is crucial for a comprehensive understanding of the therapeutic effect and the development of a scientific therapeutic strategy.

Conclusions

In this study, we analyzed the effectiveness of *Tripterygium* glycosides in combination with belimumab in the therapy of LN in order to provide a drug pathway for the therapy of this disease. The results showed that after treatment, the TCMS score, SLEDAI score, inflammatory factor levels, IgA, IgM, and IgG levels, and $CD8^+$ T cell percentage and renal function indices of patients in both groups were significantly reduced, and $CD4^+$ T cell percentage, $CD4^+/CD8^+$ ratio, and complement C3 and C4 levels were significantly increased. The improvement of all indicators in the study group was superior to the control group. The clinical efficacy of the study group was superior to the control group, and the incidence of adverse reactions was below the control group. This indicates that *Tripterygium* glycosides combined with belimumab has significant efficacy in the treatment of LN, which can effectively improve the disease activity and renal function, reduce the inflammatory response, and improve the immune function, providing a new reference method for the clinical treatment of LN patients. However, due to the small sample size and short clinical treatment duration of this study, the long-term effectiveness of this treatment method cannot be observed. In the future, multicenter, large-sample, high-quality clinical studies should be conducted to corroborate these findings by incorporating more specific clinical indicators.

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Disclosures

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The authors declare no conflict of interest.

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