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RESEARCH

Evaluation of the efficacy and safety of belimumab and telitacicept in patients with systemic lupus erythematosus: results from a retrospective, observational study

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Abstract

This investigation aimed to evaluate the efficacy and safety of belimumab and telitacicept in active systemic lupus erythematosus (SLE) and to explore potential predictors within a treat-to-target paradigm. 101 individuals were retrospectively enrolled at Guangdong Provincial People's Hospital between January 2021 and December 2023, receiving either belimumab (n = 50) or telitacicept (n = 51) in conjunction with standard therapy for more than 24 weeks. Key clinical endpoints were evaluated, with lupus low disease activity state (LLDAS) as the primary outcome. Multivariate analysis was employed to investigate factors associated with failure to attain LLDAS. Baseline characteristics were balanced in both groups after propensity score-based inverse probability of treatment weighting. At 24 weeks, the rates of attainment of LLDAS were 54.86% in the telitacicept group and 33.13% in patients receiving belimumab ($p = 0.048$). A larger proportion of patients receiving telitacicept attained prednisone dosages of ≤ 7.5 mg/day ($p = 0.012$). Improvements in complement C4 levels and the occurrence of severe hypogammaglobulinemia were more pronounced among patients receiving telitacicept, with no differences in SLE Responder Index 4, DORIS remission, and renal response. Treatment with telitacicept (OR = 0.80, $p = 0.032$) and elevated levels of complement C3 (OR = 0.63, $p = 0.003$) were associated with a decreased risk of failing to achieve LLDAS. No severe adverse events were documented in both groups. Both belimumab and telitacicept displayed satisfactory effectiveness and safety profiles. Our findings imply telitacicept may offer potential benefits associated with the early attainment of LLDAS and reduced glucocorticoid exposure. Restricted by the observational design, the findings require further validation in prospective studies.

Keywords Systemic lupus erythematosus · Belimumab · Telitacicept · LLDAS · IPTW

Introduction

Systemic lupus erythematosus (SLE) is a persistent autoimmune disorder characterized by aberrant immunological regulation and the production of numerous autoantibodies. This ultimately results in inflammation and dysfunction in multiple organ systems [1]. Diverse mechanisms involved in SLE lead to significant variations in clinical presentation and often complicated treatment efficacy and long-term prognosis, especially in individuals undergoing conventional management with corticosteroids and immunosuppressive agents [2].

B-cell abnormalities, particularly those involving excessive proliferation and maturation fueled by B-cell activating factor (BAFF) and proliferation-inducing ligand (APRIL), are regarded as important contributors to the pathophysiology of SLE [3, 4]. This has paved the way for targeted

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therapeutic approaches directed against B-cell signaling pathways. Belimumab, a monoclonal antibody that neutralizes soluble BAFF, was officially approved by the FDA in 2012 as the first biological agent specifically indicated for treating active SLE [5]. In contrast, telitacicept is a recombinant fusion protein designed to interfere with signaling through BAFF/APRIL by binding to a transmembrane activator, calcium modulator, and cyclophilin ligand interactor (TACI). It demonstrated promising SLE Responder Index 4 (SRI-4) results in a Phase IIb clinical investigation and has been conditionally approved for SLE in China since March 2021 [6]. Various randomized controlled trials (RCTs) and observational studies have shown the effectiveness of both belimumab and telitacicept in Chinese populations with lupus [7, 8].

Recently, the treat-to-target framework in SLE management has been endorsed worldwide, with target endpoints including lupus low-disease activity state (LLDAS) and definition of remission in SLE (DORIS) [9, 10]. Evidence suggests that early attainment of LLDAS correlates with lower risks of early irreversible organ injury and aids in sustained disease control [11, 12]. Meanwhile, maintaining LLDAS or remission over prolonged durations confers beneficial outcomes in mitigating further disease progression and improving the quality of life [13]. Retrospective and post-hoc analyses of clinical trials and large-scale real-world datasets highlight the role of belimumab in facilitating LLDAS and DORIS remission [14, 15]. However, because telitacicept is relatively new, clinical data remains sparse regarding its capacity to help individuals achieve LLDAS, particularly within the treat-to-target approach framework. Moreover, few observational studies have demonstrated the differences in the efficacy of belimumab and telitacicept, as direct head-to-head randomized trials are still lacking. Additional comparative data are necessary to identify factors related to clinical outcomes and optimize treatment decisions when choosing among BAFF/APRIL inhibitors.

Against this background, we conducted a single-center observational study to evaluate the clinical outcomes and safety parameters of belimumab and telitacicept in active SLE. Another objective was to identify potentially relevant predictors of failing to achieve treat-to-target goals when applying these BAFF/APRIL-targeted biological therapies.

Methods

Participants and study design

An observational, retrospective study design was used, as illustrated in Fig. 1. The Institutional Review Board of the Guangdong Academy of Medical Sciences granted its approval (ID: S2024-170-02). From January 2021 to December 2023, participants diagnosed with SLE who had started either belimumab or telitacicept at the Department of Rheumatology and Immunology of Guangdong Provincial People's Hospital were included. Each participant was assigned to the belimumab or telitacicept group based on the chosen biological therapy. All individuals fulfilled the 1997 American College of Rheumatology (ACR) and 2019 EULAR/ACR classification criteria for SLE. Participants were administered with belimumab intravenously (10 mg/kg at 0, 2, and 4 weeks, every 4 weeks thereafter) or telitacicept subcutaneously (160 mg every week).

Key eligibility requirements for inclusion were as follows: (1) a minimum of six months of continuous belimumab or telitacicept therapy in conjunction with standard treatment; (2) an active SLE status with systemic lupus erythematosus disease activity index 2000 (SLEDAI-2 K) score ≥ 6 at baseline; and (3) consistent follow-up visits permitting ongoing evaluation. The exclusion criteria were as follows: (1) concomitant serious infections or malignancies; (2) prior use of any other B-cell-targeted biologics within three months preceding baseline; and (3) pregnancy or lactation at any point during the study timeframe. The proportion of participants with medication discontinuation within 24 weeks and associated reasons for exclusion were illustrated in Supplementary Table S1.

Data collection and study outcomes

Patient data were extracted from medical charts, including demographic variables (e.g., age, gender, and disease duration), treatment exposures (e.g., concurrent medications and dosages), and relevant clinical findings. Records of serological parameters (e.g., complement levels, immunoglobulin concentrations, and anti-dsDNA titers), daily glucocorticoid dosages, and other clinical manifestations were evaluated at baseline and throughout the scheduled monitoring intervals. SLEDAI-2 K and Physician's Global Assessment (PGA) were recorded to assess the disease activity. Adverse events (AEs) and reasons for discontinuing the biologic therapy were documented.

Achieving LLDAS was pre-defined as the primary efficacy outcome and re-evaluated at weeks 4, 12, 24, and 52. LLDAS consisted of the following criteria: (1) SLEDAI ≤ 4 without involvement of major organ systems, (2) absence of any new clinical disease manifestations, (3) PGA ≤ 1, (4) daily prednisone (or equivalent) dosage ≤ 7.5 mg/day, and (5) maintenance of standard therapy. The secondary objectives included the frequency of participants reaching DORIS remission or obtaining SRI-4 responses, changes in SLEDAI-2 K and PGA evaluations over time, reductions in daily glucocorticoid doses, and improvements in serological measures. DORIS was defined as clinical SLEDAI $= 0$,

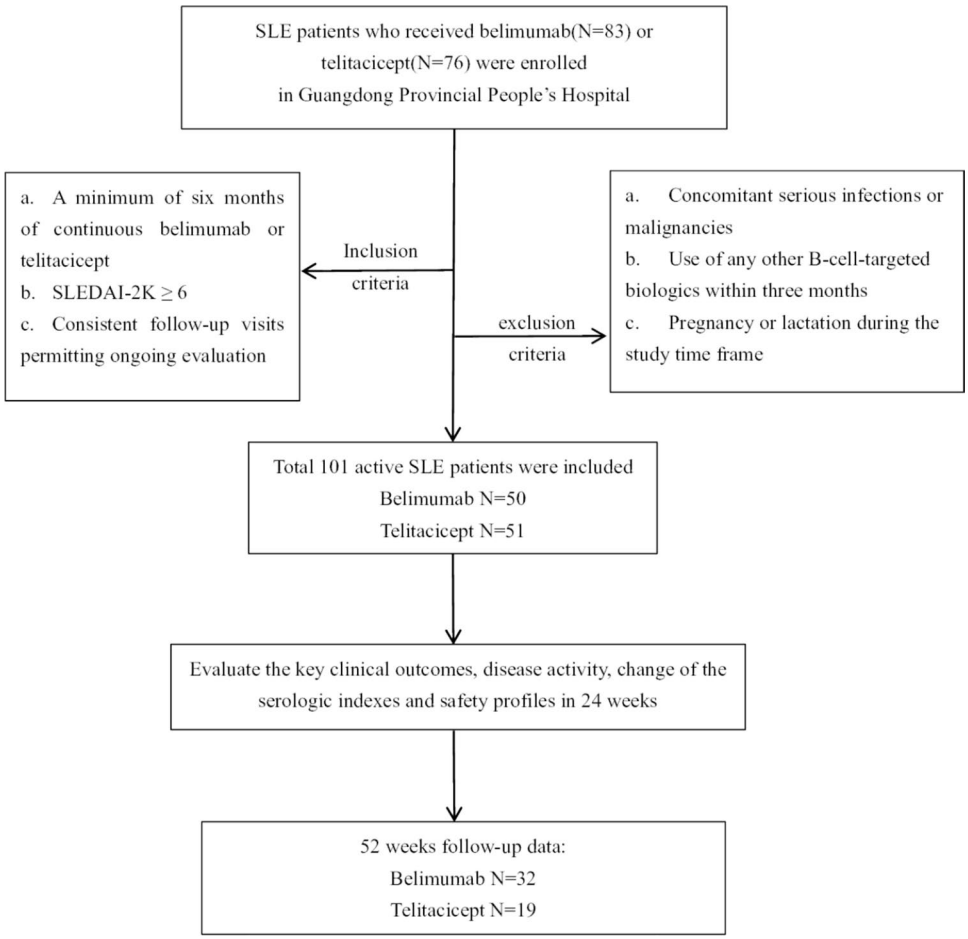

Fig. 1 Protocol flowchart of the study design

PGA < 0.5, and prednisone dosage ≤ 5 mg/day with standard maintenance therapy.

Urinary protein to creatinine ratio (UPCR), serum albumin, and creatinine were also recorded. Attainment of renal partial response (PR), complete response (CR), and primary efficacy renal response (PERR) were utilized for renal assessment of patients with lupus nephritis. PR was defined as UPCR < 3000 mg/g with a decrease of more than 50% from baseline. CR was defined as UPCR < 500 mg/g, with an estimated glomerular filtration rate (eGFR) ≥ 90 mL/min/1.73 m^2, or a reduction of less than 10% from baseline. PERR was defined as UPCR ≤ 700 mg/g, eGFR ≥ 60 mL/min/1.73 m^2, or a decrease of less than 20% from baseline, without rescue therapy [16].

Statistical methods

Descriptive statistics for categorical data were reported with frequencies and percentages. Clinical characteristics were compared between the two treatment groups with the Chi-square test or Fisher's exact test for categorical variables. Meanwhile, continuous data were reported with median (IQR) or mean values ± standard deviation (SD), detected with Student's independent t-test and Mann–Whitney U test.

Propensity scores (PS) were calculated using multivariable logistic regression analysis, which included age, disease duration, system involvements, immunological indicators, disease activity, daily prednisone dosage, and the use of immunosuppressants. Inverse probability of treatment weighting (IPTW) was employed to minimize the impact of potential confounding between the two treatment groups. The PSs were weighted by the ratio of patients treated with telitacicept to all patients/PS in the telitacicept group and the ratio of patients treated with belimumab to all patients/1-PS in the belimumab group. Standardized mean differences (SMD) were estimated to assess the balance of baseline covariates before and after IPTW adjustment.

Univariate and multivariate logistic regression models were applied to identify factors correlated with failure to achieve LLDAS at 24 weeks. The independent variables identified in univariate analysis would be integrated into a multivariate logistic regression model. Additionally, another multivariate model (forward method, Wald test) was also utilized with independent variables selected by an automatic algorithm to enhance explanatory efficacy. Statistical

analyses were completed with R software (version 4.4.2) and SPSS software (version 27.0). The statistical significance level was set at a *P*-value < 0.05, two-tailed. The production of all statistical plots was performed using GraphPad Prism (version 10).

Result

Baseline characteristics before and after adjustment with PS-based IPTW

101 SLE patients were retrospectively identified in this single-center cohort, with 50 individuals receiving belimumab and 51 individuals receiving telitacicept for at least 24 weeks. 92.08% of individuals were female, and the median age was 28 years (IQR: 21, 38). The most frequent clinical presentations were mucocutaneous (67.33%), renal (40.59%), and hematological (39.6%) involvements in our cohort.

To further mitigate selection bias, we conducted PS-based IPTW to balance baseline characteristics across the two treatment arms. Table 1 illustrated a comparison of various clinical manifestations before and after IPTW. Baseline characteristics were similar between the two treatment groups, with no significant variations. The SMDs were less than 0.10 for all characteristics after IPTW, indicating a balanced distribution of covariates (Fig. 2).

Key endpoints and clinical outcomes after adjustment with PS-based IPTW

We performed an evaluation of clinical outcomes between the belimumab and telitacicept groups after adjustment with PS-based IPTW. At 24 weeks, the SRI-4 response rate was 71.36% in the telitacicept group and 57.16% in the belimumab group without statistically significant variation (Fig. 3A). The percentages of patients achieving LLDAS were observed to be 3.27%, 7.77%, and 33.13% in the belimumab group, and 8.26%, 20.27%, and 54.86% with telitacicept at 4, 12, and 24 weeks, respectively. A consistently higher proportion of patients attained LLDAS was noted in the telitacicept group, with a significant difference recorded at 24 weeks (54.86% vs. 33.13%, $p = 0.048$), as shown in Fig. 3B. For those patients (N = 51) who completed 52 weeks of follow-up, 66.46% of those receiving telitacicept achieved LLDAS and 50.40% in the belimumab arm. Furthermore, an analysis of the specific reasons contributing to failure to attain LLDAS at 24 weeks indicated a larger percentage of patients observed in the belimumab group who failed to satisfy criterion 4 (prednisone dosage ≤ 7.5 mg/day) in contrast to those receiving telitacicept (64.34% vs. 36.78%, $p = 0.014$), as depicted in Fig. 3C.

As an additional therapeutic goal within the treat-to-target framework, the results demonstrated a gradual upward trend in attaining DORIS remission across both treatment groups (Fig. 3D). After 24 weeks of BAFF/APRIL inhibitor treatment, the DORIS remission rate was recorded at 23.74% in the telitacicept group and 12.19% of those receiving belimumab, with no significant difference. Additionally, it showed similar trends in declines of SLEDAI-2 K and PGA scores over time in two groups (Fig. 3E, F).

Following the initiation of treatment, there was a significant reduction in the daily dosage of prednisone from the baseline over time in both groups. Lower prednisone daily dosages were observed in the telitacicept group at week 24 (7.98 ± 3.09 mg/day vs. 10.58 ± 5.93 mg/day, $p = 0.013$) (Fig. 4A). We further assessed the attainment of low glucocorticoid dosages of ≤ 7.5 mg/day and ≤ 5 mg/day at 24 weeks. As shown in Fig. 4B, a greater proportion of patients with prednisone dosages of ≤ 7.5 mg/day were noted in patients treated with telitacicept (63.22% vs. 35.3%, $p = 0.012$), with no significant difference in attaining prednisone dosages of ≤ 5 mg/d in both treatment groups (28.46% vs. 18.69%, $p = 0.292$).

Sustained improvements in serological indicators were observed throughout the treatment period in both the belimumab and telitacicept groups. Decreased anti-dsDNA antibodies concentrations were observed, alongside increased complement C3 levels during the initial 12 weeks, remaining stable thereafter (Fig. 4C, D). However, no significant differences were noted across both treatment groups for both indices. Furthermore, higher levels of complement C4 were observed in the telitacicept group throughout the 24-week follow-up duration (all $p < 0.05$) (Fig. 4E). Serum IgG levels in both treatment groups exhibited a decline over time, stabilizing after 12 weeks, with no significant differences in mean values at any time point (Fig. 4F). We further investigated the incidence rates of hypogammaglobulinemia associated with BAFF/APRIL inhibitors treatment (Fig. 4G). The telitacicept group demonstrated a relatively higher frequency of hypogammaglobulinemia with proportions of serum IgG < 5 g/L (10.83% vs. 0%, $p = 0.031$) or IgG < 7 g/L (25% vs. 8.4%, $p = 0.055$).

The rates of attaining LLDAS and improvements in other secondary endpoints among SLE patients treated with belimumab and telitacicept before IPTW adjustment were illustrated in Supplementary Fig. S1. At 24 weeks, 54.9% of the patients receiving telitacicept achieved LLDAS, with the 34.0% rate in the belimumab group ($p = 0.035$) (Supplement Fig. S1B). A greater proportion of patients receiving telitacicept achieved prednisone dosages of ≤ 7.5 mg/day at 24 weeks (64.71% vs. 36%, $p = 0.004$) (Supplement Fig. S1H). Similar trends in the attainment of LLDAS and the administration of low-dose daily prednisone were observed in the telitacicept group before IPTW.

Table 1 Baseline characteristics of patients in belimumab and telitacicept treatment groups before and after IPTW

Characteristics	Before IPTW			After IPTW		
	Belimumab	Telitacicept	*P*-value	Belimumab	Telitacicept	*P*-value
	n = 50	n = 51		n = 53[a]	n = 49[a]	
Age, year	27 (19.8, 35.5)	29 (21, 38)	0.455	27.4 (23, 35.1)	29 (20.8, 38)	0.921
Disease duration, month	51.14 ± 70.96	64.33 ± 56.42	0.303	61.34 ± 81.86	58.24 ± 54.76	0.856
Sex			0.487			0.962
Male	5 (10.0%)	3 (5.9%)		4 (7.9%)	4 (8.2%)	
Female	45 (90.0%)	48 (94.1%)		49 (92.1%)	45 (91.8%)	
System involved						
Mucocutaneous	33 (66.0%)	35 (68.6%)	0.778	37 (70.5%)	32 (66.2%)	0.658
Musculoskeletal	17 (34.0%)	19 (37.3%)	0.733	20 (38.2%)	19 (38.6%)	0.970
Renal	22 (44.0%)	19 (37.3%)	0.490	19 (35.8%)	18 (37.8%)	0.846
Hematological	20 (40.0%)	20 (39.2%)	0.936	19 (35.3%)	19 (38.2%)	0.774
Serositis	6 (12.0%)	5 (9.8%)	0.723	5 (9.2%)	5 (10.4%)	0.839
Immunological indicators						
Anti-dsDNA positive	39(78.0%)	38 (74.5%)	0.680	39 (73.4%)	37 (75.5%)	0.837
Anti-dsDNA, IU/mL	151 (34.63, 264.20)	111.30 (13, 500)	0.370	150.61 (18.44, 261.29)	116.57 (14.88, 439.20)	0.783
Anti-SSA	33 (66.0%)	40 (78.4%)	0.163	39 (74.0%)	36 (73.4%)	0.956
IgG, g/L	13.58 (10.16, 17.47)	15.41 (13.31, 18.68)	0.157	13.49 (10.36, 21.88)	15.43 (13.41, 18.34)	0.428
IgA, g/L	2.33 (1.55, 3.46)	2.36 (1.84, 3.28)	0.913	2.29 (1.52, 3.26)	2.39 (1.87, 3.28)	0.517
IgM, g/L	0.94 (0.55, 1.38)	0.81 (0.48, 1.24)	0.354	0.95 (0.52, 1.48)	0.80 (0.48, 1.24)	0.282
Hypocomplementemia	38 (76.0%)	36 (70.6%)	0.539	37 (70.7%)	36 (73.3%)	0.799
C3, g/L	0.67 (0.47, 0.92)	0.72 (0.52, 0.97)	0.499	0.67 (0.47, 1.05)	0.71 (0.50, 0.95)	0.940
C4, g/L	0.08 (0.04, 0.15)	0.13 (0.04, 0.21)	0.189	0.09 (0.04, 0.16)	0.12 (0.04, 0.19)	0.480
Lymphocyte counts, $\times 10^9$ /L	1.05 (0.61, 1.68)	0.93 (0.67, 1.41)	0.580	0.92 (0.60, 1.47)	0.94 (0.67, 1.43)	0.928
Disease activity						
SLEDAI-2 K	10 (6, 14.25)	8 (6, 13)	0.385	8 (6, 13.81)	8 (6, 12.74)	0.734
PGA	1.75 (1.40, 2)	1.70 (1.40, 2)	0.756	1.60 (1.40, 2)	1.70 (1.49, 2)	0.920
Glucocorticoid use						
Prednisone at baseline, mg/day	29.70 ± 15.74	26.67 ± 18.54	0.378	28.12 ± 15.04	28.35 ± 19.26	0.949
Immunosuppressants						
HCQ	48 (96.00%)	50 (98.04%)	0.617	52 (97.6%)	48 (98.3%)	0.789
MMF	33 (66.00%)	30 (58.82%)	0.457	31 (59.3%)	29 (59.4%)	0.993
CYC	5 (10.00%)	6 (11.76%)	0.776	8 (15.8%)	7 (14.5%)	0.886
FK506	8 (16.00%)	9 (17.65%)	0.825	7 (13.4%)	8 (15.4%)	0.764

IPTW, inverse probability of treatment weighting; C3, complement C3; C4, complement C4; SLEDAI-2 K, systemic lupus erythematosus disease activity index 2000; PGA, physician's global assessment; HCQ, hydroxychloroquine; MMF, mycophenolate mofetil; CYC, cyclophosphamide; FK506, tacrolimus

[a]The number of subjects changed after IPTW in the calculation; however, the actual number of subjects did not change

Therapeutic outcomes for lupus nephritis

Forty-one participants diagnosed with LN were enrolled in this cohort, treated with either belimumab (N = 22) or telitacicept (N = 19). Among these patients, 17 individuals underwent renal biopsy procedures, with the histopathological classification detailed in Supplementary Table S2. After IPTW, the mean urinary protein to creatinine ratio exhibited a significant reduction of more than 50% over time; however, no significant differences were observed across both treatment groups (Fig. 5A). As illustrated in Fig. 5B–D, 43.94% and 60.22% of patients receiving belimumab achieved CR and PERR at 12 weeks, compared to 43.13% and 60.30% in the telitacicept group, respectively. With continuous improvements by 24 weeks, 68.26% and 71.87% of patients achieved CR and PERR in the belimumab group, and 74.90% and 78.67% in the telitacicept group. There were no statistical differences in achieving CR, PR, and PERR

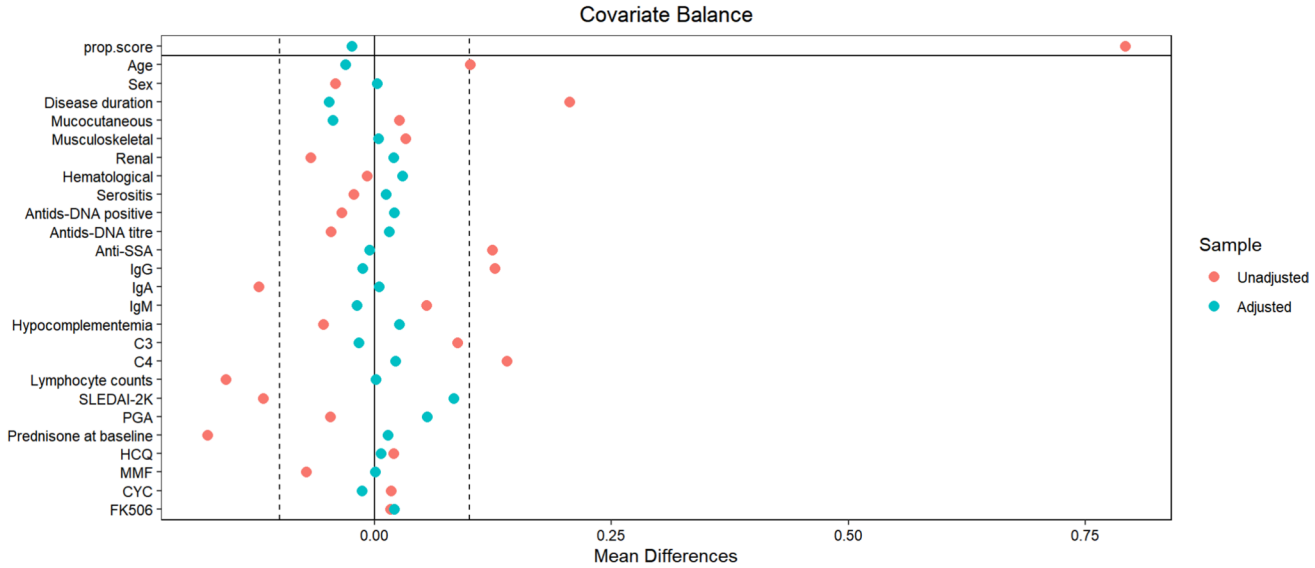

Fig. 2 The standardized mean differences before and after propensity score-based inverse probability of treatment weighting

between two treatment groups (all $p > 0.05$). No instances of renal function deterioration or renal flares were recorded.

Factors associated with failing to attain LLDAS

The findings of univariate logistic regression analysis before IPTW were depicted in Table 2, which described the relation between baseline characteristics and the risk of failure to LLDAS at 24 weeks. It appeared that treatment with telitacicept (OR = 0.42), anti-SSA positive status (OR = 0.39), and higher levels of complement C3 (OR = 0.12) were correlated with the reduced risk of failure to attain LLDAS. By contrast, elevated levels of PGA (OR = 3.79) and higher daily dosages of prednisone at baseline (OR = 1.03) increased the risk. Conversely, the multivariate logistic regression results after IPTW, employing the enter method (shown in Table 3), indicated that only the use of telitacicept (OR = 0.35, $p = 0.025$) reached statistical significance, potentially owing to the limited sample size. However, further application of the forward method (Wald statistic) in the multivariate analysis identified two variables, the use of telitacicept (OR = 0.80, $p = 0.032$) and elevated complement C3 (OR = 0.63, $p = 0.003$), both of which were associated with a a lower likelihood of failure to achieve LLDAS.

Safety profiles

Table 4 exhibited the adverse events during the 24-week observation period. After initiating treatment, 24% of patients receiving belimumab and 25.49% of those treated with telitacicept experienced adverse events in total, with no serious adverse events documented. Injection site reactions were observed in two patients. Notably, infections emerged as the most frequent adverse reactions, reported in nine patients receiving belimumab and eleven patients in the telitacicept group. Among the broad spectrum of infections, upper respiratory tract infections (N = 10) were the predominant observed events, followed by herpes zoster (N = 5) and urinary tract infections (N = 3). All infection cases recovered following appropriate anti-infection and supportive treatment. In addition, it was identified that those suffering from hypogammaglobulinemia had elevated infection risks, with no significant correlations between the concomitant use of MMF and increased infection risks (Supplementary Table S3). Three patients experienced delays or reductions in telitacicept dosage due to infections and severe hypogammaglobulinemia (serum IgG < 5 g/L), with improvement following the administration of anti-infection and immunoglobulin replacement therapy.

Discussion

In this observational study, we assessed the efficacy and safety of belimumab and telitacicept in active SLE, aiming to complement the current knowledge on their therapeutic potential. Our data indicated that at the 24-week milestone, 54.86% of the patients on telitacicept reached LLDAS, compared to the 33.13% rate observed in those receiving belimumab. This difference aligned with a previous Chinese real-world study in which telitacicept appeared to encourage more rapid disease control [17]. Although a similar tendency was noted regarding DORIS remission, statistical significance was not consistently achieved, potentially

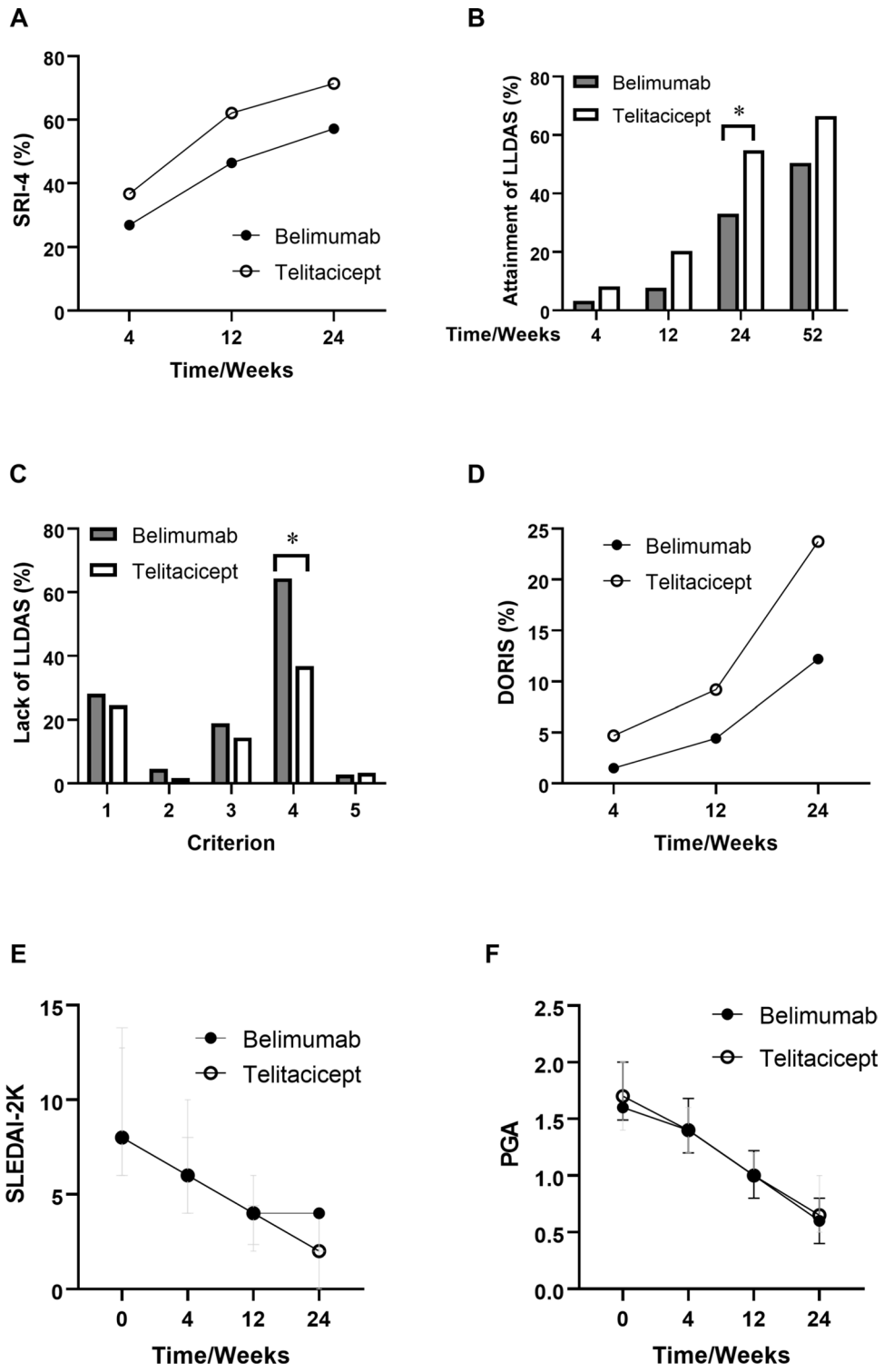

Fig. 3 Clinical outcomes between belimumab and telitacicept treatment after IPTW. **A** SRI-4 response at 4, 12, and 24 weeks. **B** Attainment of LLDAS at 4, 12, 24, and 52 weeks. **C** Analysis of lack of LLDAS attainment at 24 weeks. **D** Attainment of DORIS remission at 4, 12, and 24 weeks. **E** Changes in SLEDAI-2 K scores from baseline to 24 weeks. **F** Changes in PGA from baseline to 24 weeks. (*$p < 0.05$, **$p < 0.01$) IPTW, inverse probability of treatment weighting; SRI-4, systemic lupus erythematosus responder index; LLDAS, lupus low disease activity state; DORIS, definition of remission in SLE; SLEDAI-2 K, systemic lupus erythematosus disease activity index 2000; PGA, physician's global assessment

due to sample size constraints. In terms of extended therapy beyond the early treatment phase, the cumulative attainment of LLDAS and DORIS remission increased in patients who completed 52 weeks of follow-up in both groups. Additionally, previous work suggested that telitacicept provided more robust SRI-4 responses than belimumab in certain cohorts [18]. Nonetheless, our study did not detect a major difference in SRI-4 achievement between the two groups, perhaps reflecting the higher disease activity levels in our study population at baseline or other confounders associated with clinical practice. Moreover, we noted an elevation in complement C4 levels in individuals receiving telitacicept.

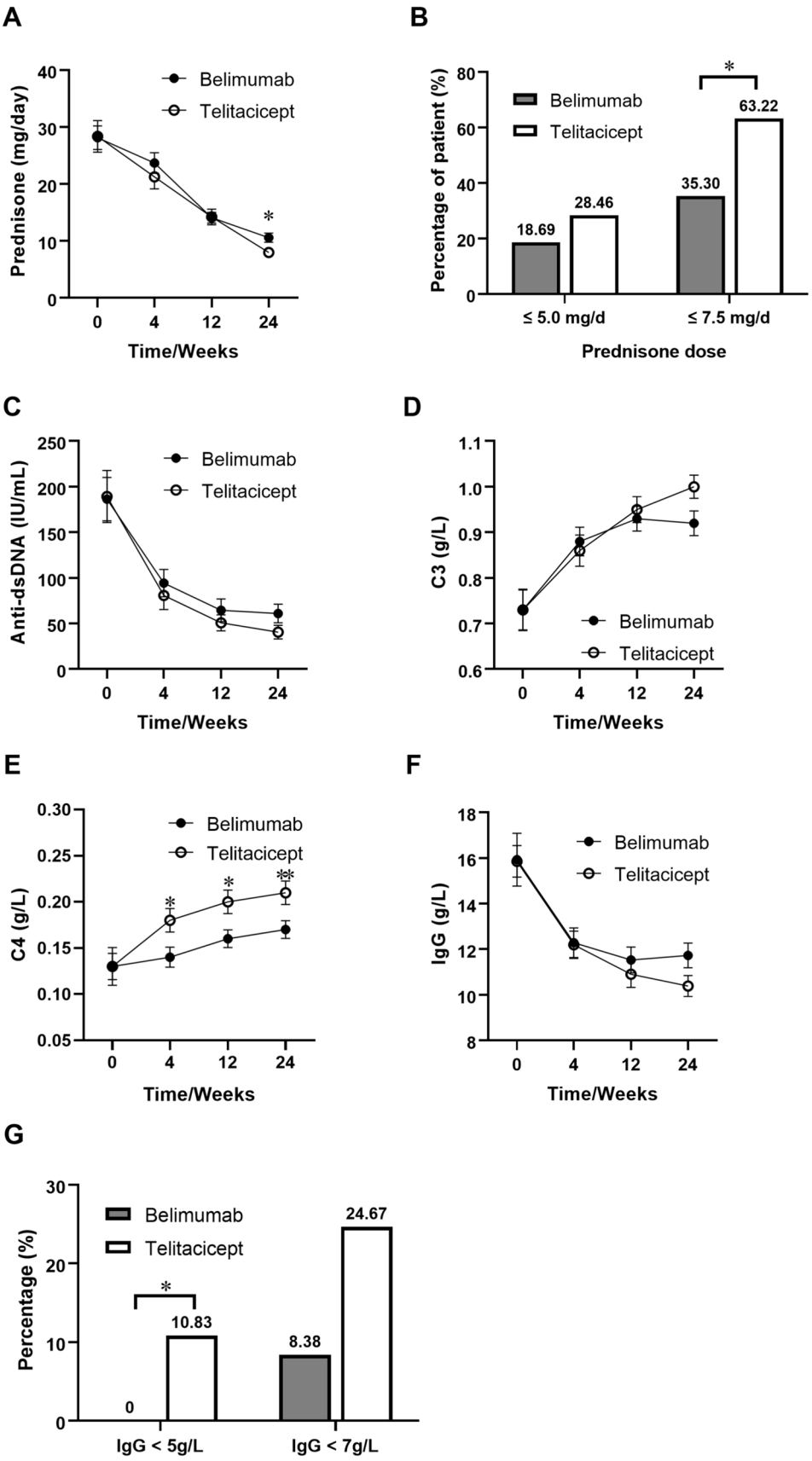

Fig. 4 Glucocorticoid dosages and serological indicators changes from baseline after IPTW **A** Changes in glucocorticoid dosages from baseline to 24 weeks after IPTW. **B** Attainment of low glucocorticoid dosages of ≤ 5 mg/day or ≤ 7.5 mg/day at week 24 after IPTW. **C**–**F** Changes in levels of anti-dsDNA, C3, C4, and serum IgG from baseline to 24 weeks after IPTW. **G** Frequency of hypogammaglobulinemia between belimumab and telitacicept treatment after IPTW. (*$p < 0.05$, **$p < 0.01$) C3, complement C3; C4, complement C4; IgG Immunoglobulin G

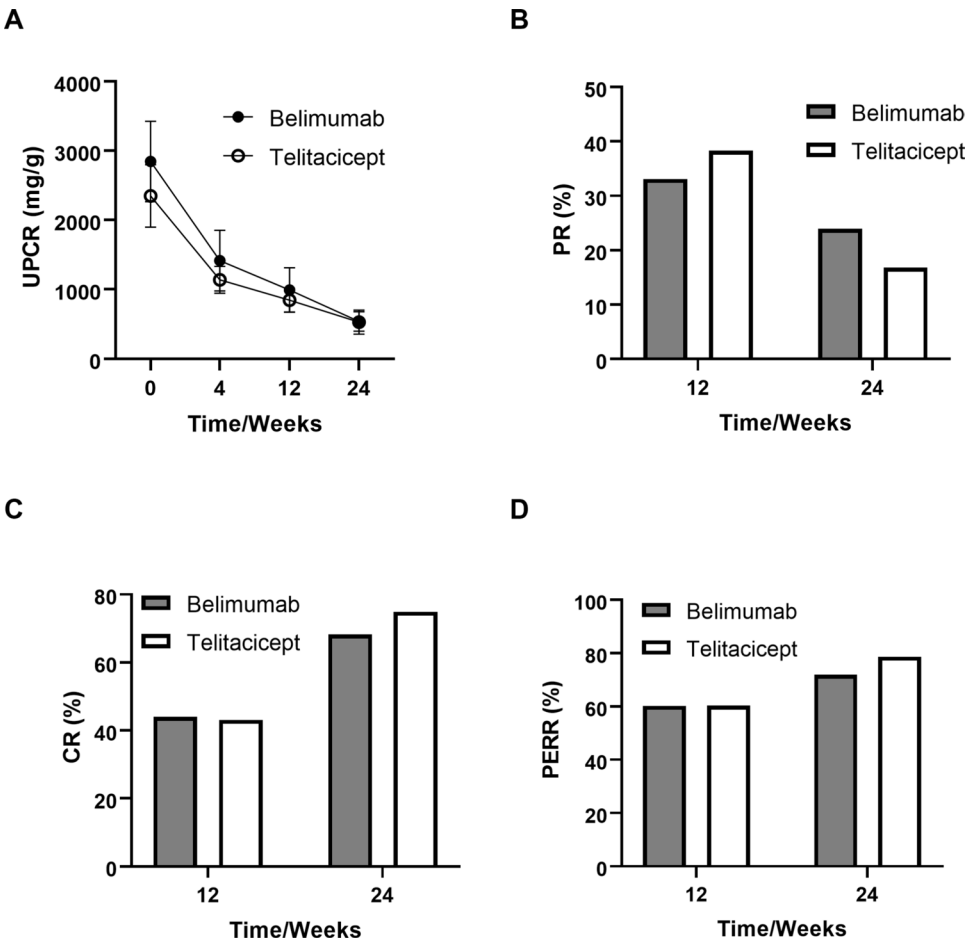

Fig. 5 Treatment outcomes in lupus nephritis between belimumab and telitacicept treatment after IPTW. **A** Changes in UPCR from baseline to 24 weeks after IPTW. **B**–**D** PR, CR, and PERR at 12 and 24 weeks between belimumab and telitacicept treatment groups after IPTW. UPCR, urinary protein to creatinine ratio; PR, partial response; CR, complete response; PERR, primary efficacy renal response

Improvements in SLEDAI-2 K, complement C3, anti-dsDNA antibodies, and PGA values were broadly comparable between both treatment arms. Altogether, our findings hinted at the potential benefits of telitacicept associated with the attainment of LLDAS and complement normalization in active SLE.

One substantial goal of SLE therapy, reiterated in emerging guidelines, is to reduce the glucocorticoid use whenever feasible, which served as "bridge therapy" [19]. Chronic high-dose steroid treatment exacerbates the likelihood of complications such as osteoporosis, vascular calcification, diabetes, and weight gain [20]. Prior clinical investigations and observational reports indicated that both belimumab and telitacicept helped lower the daily doses of corticosteroids [6, 14]. However, minimal research simultaneously examines the capacity of these two biologics to facilitate significant steroid-sparing. In our study, patients from both treatment groups were monitored by physicians from the same medical team, employing standardized criteria for disease evaluation and glucocorticoid dosage modification in accordance with clinical guidelines. A higher proportion of patients were observed to attain prednisone doses ≤ 7.5 mg/day in the telitacicept group before and after IPTW adjustment. Furthermore, 25 participants were able to decrease glucocorticoid dosages to 5 mg/day or less (15 individuals treated with telitacicept), and a single patient on telitacicept successfully discontinued steroids altogether under close supervision. Our study indicated that telitacicept might be associated with lower glucocorticoid dosages. These steroid-sparing patterns may explain the higher attainment rates of LLDAS and DORIS remission observed in the telitacicept subgroup. Similar trends in the attainment of LLDAS and low-dose daily prednisone were observed in the telitacicept group before and after IPTW, which supported the robustness of our findings. Considering that the administration of glucocorticoid may be affected by the prescribing practices of physicians, it is imperative that our findings should undergo additional validation through randomized studies.

Kidney involvement is a frequent and severe manifestation of SLE, and renal failure significantly contributes to morbidity and mortality rates [21]. Studies have shown that adding biological agents, such as belimumab or telitacicept, may improve renal function outcomes [16, 22]. In the present cohort, 41 individuals (40.59%) experienced LN, most with a histopathological pattern of Class IV + V. More than 50% of LN patients did not undergo renal puncture

Table 2 Univariate analysis of risk factors with failure to attain LLDAS at week 24 before IPTW

Parameters	Univariate	
	OR (95% CI)	*P*
Treatment		
Belimumab	1	–
Telitacicept	0.42 (0.19–0.95)	*0.036*
Age	0.97 (0.93–1.01)	0.098
Disease duration, year	1.00 (0.99–1.00)	0.485
Sex		
Male	1	–
Female	0.39 (0.07–2.02)	0.261
System involved		
Mucocutaneous	1.52 (0.66–3.50)	0.328
Musculoskeletal	0.85 (0.37–1.92)	0.688
Renal	1.46 (0.65–3.27)	0.356
Hematological	1.61 (0.72–3.64)	0.249
Serosa	1.46 (0.40–5.35)	0.564
Immunological indicators		
Anti-dsDNA, IU/mL	1.00 (1.00–1.00)	0.222
Anti-SSA	0.39 (0.15–1.00)	*0.049*
IgG, g/L	1.01 (0.95–1.08)	0.668
IgA, g/L	1.16 (0.89–1.52)	0.274
IgM, g/L	0.80 (0.51–1.27)	0.349
C3, g/L	0.12 (0.03–0.47)	*0.003*
C4, g/L	0.14 (0.00–4.28)	0.259
Lymphocyte counts, $\times 10^9$ /L	0.95 (0.53–1.72)	0.867
Disease activity		
SLEDAI-2 K	1.05 (0.96–1.13)	0.287
PGA	3.79 (1.01–14.19)	*0.048*
Prednisone at baseline	1.03 (1.01–1.06)	*0.009*
Immunosuppressants		
HCQ	Failed estimation	–
MMF	0.72 (0.32–1.62)	0.426
CYC	4.12 (0.84–20.13)	0.081
FK506	1.18 (0.41–3.40)	0.759

Italic values are statistically significant difference

OR, odds ratio; CI,confidence interval

Table 3 Multivariate analysis of risk factors with failure to attain LLDAS at week 24 after IPTW

Variable	Multivariate (enter)		Multivariate (forward: Wald)	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Treatment				
Belimumab	1	–	1	–
Telitacicept	0.35 (0.14–0.86)	*0.025*	0.80 (0.66–0.98)	*0.032*
Anti-SSA	0.44 (0.14–1.35)	0.154		
C3	0.24 (0.05–1.25)	0.093	0.63 (0.47–0.85)	*0.003*
PGA	1.79 (0.36–9.09)	0.482		
Prednisone at baseline	1.01 (0.98–1.04)	0.551		

Italic values are statistically significant difference

OR, odds ratio; CI, confidence interval

biopsy, suggesting these diagnoses could not be completely validated. The specific reasons included the patients' preferences and the presence of contraindications related to renal puncture. After 24 weeks of BAFF/APRIL inhibitor treatment, the telitacicept and belimumab cohorts demonstrated clinically relevant decreases in proteinuria and improved overall kidney function. According to our analyses, approximately 70.73% of LN-affected subjects achieved CR, and nearly 75.61% achieved PERR without renal flares at the 24-week checkpoint. Hematological manifestations, including hemolytic anemia, leukopenia and thrombocytopenia, occur frequently in SLE [23]. In our study population, 40 individuals (39.6%) showed hematological anomalies, of whom 13 patients achieved LLDAS within the 24-week treatment. Both belimumab and telitacicept produced notable improvements in these parameters, which were in line with previous observational data [24, 25].

Through multivariable analysis, the selection of BAFF/APRIL inhibitors and complement C3 levels were recognized as predictive factors associated with failing to attain LLDAS at the 24-week time point. It appeared that treatment with telitacicept was an independent positive predictor for LLDAS, while lower complement C3 levels had a negative impact. In our cohort, telitacicept showed a significant steroid-sparing effect to facilitate the attainment of LLDAS. Meanwhile, lower complement C3 levels indicated serologic activity, which suggested higher disease activity and risk of flare even in clinically quiescent status [26]. Due to the limitations of observational design and relatively small sample size, this association between the selection of BAFF/APRIL and attainment of LLDAS should be interpreted with caution. Investigating other precise predictors was beyond the scope of this project, such as disease duration and organ involvements, highlighting the need for future larger-scale trials.

Recent therapeutic guidance, such as the 2023 EULAR recommendations, suggests the early introduction of biologics in cases of active lupus to facilitate efficient disease activity control. In particular, belimumab is recommended for the management of moderate-to-severe SLE and LN [19]. Updated kidney-focused guidelines (Kidney Disease: Improving Global Outcomes, 2024) further suggest that belimumab, when used alongside immunosuppressants, may be viable as part of frontline LN therapy for class III/IV [27]. Other B cell-directed therapies, such as rituximab, have not consistently improved major clinical endpoints in rigorous trials, limiting their use mostly to

Table 4 Adverse events after 24-week follow up

	Belimumab (N = 50)	Telitacicept (N = 51)
Any adverse event, n (%)	12 (24%)	13 (25.49%)
Serious adverse events, n (%)	0 (0)	0 (0)
Infection, n (%)	9 (18%)	11 (21.57%)
Upper respiratory tract infections, n (%)	5 (10%)	5 (9.80%)
Urinary tract infections, n (%)	1 (2%)	2 (3.92%)
Herpes zoster, n (%)	2 (4%)	3 (5.88%)
Pneumonia, n (n)	1 (2%)	0 (0)
COVID-19 infection, n (%)	1 (2%)	0 (0)
Skin and Soft Tissue Infections, n (%)	0 (0)	1 (1.96%)
Cholecystitis, n (%)	1 (2%)	0 (0)
Injection Reactions, n (%)	1 (2%)	1 (1.96%)
Leucopenia, n (%)	1 (2%)	0 (0)

refractory SLE or when other biologics cannot be administered [28]. There is also atacicept, a BAFF/APRIL dual inhibitor that underwent early termination in certain LN trials after serious infection events were encountered [29]. In contrast, telitacicept, a similar dual-targeting drug, has demonstrated a more favorable safety profile in phase II/III evaluations in China, broadening its clinical utility [6]. Additionally, recent reports indicate the potential efficacy of telitacicept, even in individuals who have experienced suboptimal responses to belimumab [30].

The overall safety and tolerability of belimumab and telitacicept in our cohort were acceptable, with an aggregate AE incidence of 24.8%. Infections were the main adverse events and were typically resolved upon administration of anti-infective agents. The most frequently reported infections involved the respiratory system, the urinary system, and herpes zoster infections. Interestingly, while the mean decrease in serum IgG was similar across both subgroups, there appeared to be a slight tendency toward more frequent severe hypogammaglobulinemia (IgG < 5 g/L) in participants receiving telitacicept. Four noteworthy low IgG levels were observed in patients treated with telitacicept, whereas none were documented in the belimumab group. Of those four patients, three experienced infections and had to pause or reduce telitacicept, accompanied by intravenous immunoglobulin replacement in some instances. This phenomenon might reflect the dual blockade of BAFF and APRIL, given the role of APRIL in supporting plasma cell maturation and immunoglobulin secretion. Other studies have reported similar accelerated declines in immunoglobulin levels among telitacicept recipients [8], which suggested the potential application for other autoimmune disorders, for instance, Sjögren's syndrome characterized by high immunoglobulin levels [31]. Consequently, serum IgG levels should be carefully monitored throughout therapy, especially when patients begin to have lower IgG levels. Strategies such as dose adjustments or immunoglobulin infusions may be warranted in cases of hypogammaglobulinemia associated with telitacicept.

The study had several limitations. Firstly, the non-randomized design of the observational study inevitably introduced confounding by indication. In our study, the treatment decisions regarding belimumab and telitacicept were collaboratively made by physicians and patients, based on a comprehensive evaluation of individual disease characteristics, drug availability, and preferences for administration routes. This approach further complicated the direct comparison of therapeutic effects and challenged the establishment of causal relationships. Even with statistical adjustment using PS-based IPTW to mitigate selection bias, unmeasured variables would still influence the treatment assignment and clinical outcomes. This highlighted the cautious interpretation of the findings. Second, telitacicept is relatively new in clinical practice, limiting the sample size for a single-center study. Our study excluded participants who discontinued treatment within 24 weeks due to inadequate efficacy. This exclusion may further increase selection bias and potentially overestimate the effectiveness of the treatments. Therefore, the results may not be applicable to the entire population with active SLE. In addition, due to the constraints of the retrospective study, we encountered challenges in handling with missing data and ensuring consistent follow-up evaluations. This limitations hindered the use of specific statistical techniques, such as hazard analysis, and complicated the accurate assessment of time-dependent variables. As a result, identifying a comprehensive range of potential risk factors for the attainment of LLDAS remains challenging. Based on these limitations, well-structured, prospective RCTs with larger sample sizes featuring head-to-head comparisons of belimumab and telitacicept are essential for verifying these results and refining SLE treatment algorithms. However, in the real-world context, there are ethical and practical limitations to conducting an RCT for this specific comparison. Nonetheless, we hope this observational study

could offer insights into the clinical experiences related to the treatments of belimumab and telitacicept.

In conclusion, both belimumab and telitacicept displayed satisfactory effectiveness and safety profiles in active SLE. Our findings implied telitacicept may offer potential benefits associated with the early attainment of LLDAS and reduced glucocorticoid exposure. Given its dual blockade mechanism, monitoring serum immunoglobulin concentrations is prudent when using telitacicept. Limited by the nature of the observational study, the findings require further validation in prospective evaluation.

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Data availability The data that support the results of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval The study was carried out in accordance with the Declaration of Helsinki and was approved by the Institutional Review Boards of Guangdong Academy of Medical Sciences (ID: S2024-170-02). Written informed consent was obtained from all participants.

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