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ORIGINAL ARTICLE

Early effectiveness and safety analysis of belimumab in addition to standard treatment in patients with systemic lupus erythematosus

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ABSTRACT

Objectives: This study aimed to evaluate the early effectiveness and safety of belimumab in addition to standard therapy in patients with systemic lupus erythematosus (SLE) for 24 weeks.

Patients and methods: This retrospective study was conducted with 60 adult patients with active SLE between June 2020 and August 2022. The patients either received intravenous belimumab in addition to standard therapy (n=31; 24 females, 7 males; mean age: 33.7±14.1 years; range, 18 to 52 years) or only standard therapy (n=29; 22 females, 7 males; mean age: 34.1±13.4 years; range, 19 to 66 years) for 24 weeks. Outcome measures, including safety and effectiveness (Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index [SELENA-SLEDAI]), changes in biomarkers (double-stranded DNA [deoxyribonucleic acid]), serum complement levels, and immunoglobin G (IgG) were recorded. Adverse events were recorded.

Results: Baseline demographic and clinical characteristics were similar between the two groups. More patients in the belimumab group achieved a reduction of ≥4 points in SELENA-SLEDAI at weeks 12 and 24 (week 12, 77.4% *vs.* 41.4%, p=0.008; week 24, 87.1% *vs.* 48.3%, p=0.002). The mean score of SELENA-SLEDAI was significantly lower in the belimumab group compared to the standard therapy group at week 12. However, a significant difference was not reached at week 24. Moreover, mean levels of serum C3 and C4 in the belimumab group were significantly higher than those in the standard therapy group at weeks 12 and 24. A higher proportion of patients in the belimumab group had a normal C3 level than in the standard therapy group. In addition, belimumab treatment resulted in a significant decrease in IgG levels at both weeks 12 and 24. At week 24, the belimumab group had a higher reduction in prednisone dose than the standard therapy group. Furthermore, the percentages of patients with more than 50% reduction in prednisone over baseline were significantly greater for belimumab versus standard therapy at week 12 (p=0.002). The occurrence of adverse events was similar between the two groups (standard therapy group, 44.8%; belimumab group, 51.6%).

Conclusion: Intravenous belimumab was well tolerated and significantly improved disease activity in Chinese patients with SLE at the early stage of treatment. More importantly, belimumab treatment could result in a rapid reduction in prednisone dose as early as week 12.

Keywords: Belimumab, clinical improvement, early effectiveness, prednisone, safety, systemic lupus erythematosus.

Systemic lupus erythematosus (SLE) is an organ- and life-threatening systemic autoimmune disease characterized by the presence of various autoantibodies. B cells have an important role in the progression and induction of SLE.[1] B cell-activating factor, also called B lymphocyte stimulator (BLyS), has been established to play an essential role in promoting B cell survival, differentiation, and activity via its interactions with BLyS receptor 3.[1] Forced overexpression of BLyS would drive SLE-like disease in mice models.[2] In contrast, targeting BLyS with pharmacological blockade or genetic deletion can successfully alleviate and protect murine models from SLE-induced manifestation.[3,4] Moreover, the serum level of BLyS is positively associated with SLE activity and anti-double-stranded deoxyribonucleic acid (dsDNA) antibody titers, further supporting the clinical significance of BLyS in SLE pathogenesis.[5]

Currently, the recommended first-line treatment for SLE includes glucocorticoids, hydroxychloroquine, and immunosuppressive

drugs (mycophenolate mofetil or cyclophosphamide), which is undoubtedly effective in protecting organs and reducing mortality, but no drug is specific for SLE.[6] Thus, there is a need to develop a warranted drug that is more specific to SLE and has more effective and less toxic modes. Belimumab is a fully humanized immunoglobulin (Ig) G1λ, a monoclonal antibody that targets BLyS, that induces B cell apoptosis and modulates B cell activation. As the first biological drug licensed and approved by the United States Food and Drug Administration and the European Medicines Agency, belimumab is recommended to be combined with the standard of care for patients with autoantibody-positive systemic SLE.[6]

Numerous reports, including the latest two well-designed phase 3 trials BLISS-52 and BLISS-76, mainly focus on the long-time therapeutic effect of belimumab on SLE patients for more than one year.[7,8] Whether belimumab combined with standard care in SLE patients for a short term would still achieve clinical improvement remains elusive. In this study, the clinical outcomes of SLE patients managed with standard therapy plus belimumab were compared with standard therapy alone for 24 weeks to investigate the effectiveness and safety of short-term use of belimumab with standard treatment in SLE. This study aimed to present the fast-acting remission of belimumab plus standard treatment in the clinical and serological index, as well as the fast reduction of steroid dosage.

PATIENTS AND METHODS

This retrospective study was conducted with 60 adult patients with active SLE followed at the University of South China Affiliated Changsha Central Hospital, Department of Rheumatology and Immunology between June 2020 and August 2022. At screening, enrolled patients were at least ≥18 years of age and had autoantibody-positive SLE (antinuclear antibody titers >1:100, anti-dsDNA positivity, or low complement components of C3 and C4 or twice), which fulfilled the 1982 American College of Rheumatology classification criteria for SLE, which was updated in 1997. Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score was >8 for all patients regardless of the initiation of induction therapy. The exclusion criteria were as follows: active severe central nervous system SLE, acute severe lupus nephritis, or systemic prednisone (or equivalent) >1.5 mg/kg/day; B cell-targeted therapy within one year or prior belimumab use. The patients either received intravenous belimumab in addition to standard therapy (belimumab group, n=31; 24 females, 7 males; mean age: 33.7±14.1 years; range, 18 to 52 years) or only standard therapy (standard therapy group, n=29; 22 females, 7 males; mean age: 34.1±13.4 years; range, 19 to 66 years) for 24 weeks. The standard therapy, included corticosteroids, hydroxychloroquine, or immunosuppressants. Intravenous belimumab 10 mg/kg on days 1 (baseline), 15, and 29 and every 28 days thereafter was administered to the belimumab group until week 24.

The baseline characteristics for 60 patients were reviewed, including age, sex, course of the disease, SELENA-SLEDAI score, percentage of patients with progressive organ dysfunction, laboratory data, and the standard therapeutic drugs. Laboratory data included hemoglobin, white blood cells, platelet count, serum creatinine, antinuclear antibodies, anti-dsDNA, C3, C4, and IgG (Table 1). The activity of the disease and the dosage of corticosteroids, which was used in 60 patients, at week 12 and week 24 were also analyzed. Safety assessments, including cancer, postinjection systemic reactions, and infections, were analyzed.

Statistical analysis

GraphPad Prism version 8.0.2 (GraphPad Software Inc., San Diego, CA, USA) was used for statistical analyses. Variables were displayed as mean ± standard deviation or median (25^{th}-75^{th} percentile). Student's t-test was used for two-group comparisons. The two-way analysis of variance was performed for comparisons of repeated measures at weeks 12 and 24. The statistical difference in categorical data was analyzed using Fisher exact test. A value of $p<0.05$ was considered statistically significant.

Table 1. Baseline patients demographics and clinical characteristics

	Without belimumab (n=29)				With belimumab (n=31)				
Week characteristics	n	%	Mean±SD	Mean	n	%	Mean±SD	Mean	*p*
Age at treatment (year)				34.1				33.7	
Sex Female Male	 22 7				 24 7				0.89*
SELENA-SLEDAI			13.16±4.4				15.00±4.8		0.13#
Organ involvement									
Mucocutaneous	6	20.7			7	22.6			>0.99*
Hydrohymenitis	8	27.6			15	48.4			0.77*
Haematologica	10	34.5			15	48.4			0.31*
Renal	16	55.2			14	45.2			0.61*
Joint	6	20.7			12	38.7			0.16*
CNS	1	3.4			2	6.5			>0.99*
Anti-dsDNA antibody positive (≥10 IU/mL)	24				25				
Low C3 serum levels (<0.09 g/L)	29				31				
Low C4 serum levels (<0.01 g/L)	28				29				
Ig G serum levels (g/L)			17.30±4.2				18.68±5.9		0.30#
The dose of prednisone at baseline			48.62±8.3				49.35±96		0.75#
Prednisone and HCQ only (%)	1	3.4			3	9.7			
Prednisone and immunosuppressant only	6	20.7			8	25.8			

SD: Standard deviation; SELENA-SLEDAI: Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index; CNS: Central nervous system; dsDNA: Anti-double-stranded deoxyribonucleic acid; IgG: Immunoglobulin G; HCQ: Hydroxychloroquine; * Fisher exact test; # Independent sample t test.

RESULTS

Baseline demographics and clinical characteristics of the patients were similar between the two treatment groups (Table 1). SELENA-SLEDAI scores in the standard therapy group were 13.16±4.4, which were also comparable with that in the belimumab group with 15.0±4.8.

The two groups did not differ in baseline biomarker characteristics. Twenty-four and 25 patients were associated with anti-dsDNA at high titer in the standard therapy group and the belimumab group, respectively. Before belimumab treatment, all patients had low C3 serum levels. There were 28 patients in the standard therapy group and 29 patients in the belimumab group who had low C4 serum levels. The mean IgG serum levels were 17.3 g/L and 18.7 g/L in the standard therapy and belimumab groups, respectively, without significant differences.

In addition, the use of immunosuppressive/immunomodulatory agents and antimalarials was similar between the two groups at baseline. The mean dose of prednisone medication in the standard therapy group was 48.62±8.3 mg/day at baseline, which was comparable with the belimumab group (49.35±96 mg/day, p=0.75).

Clinical and serological improvements during belimumab treatment at weeks 12 and 24 were described (Figure 1). The mean SELENA-SLEDAI score declined from 15.0±4.8 to 11.7±6.0 at week 12 and to 8.9±6.4 at week 24 in the standard therapy group, and it decreased from 13.16±4.4 to 6.4±3.7 at week 12 and to 4.3±3.2 at week 24 in the belimumab group (Figure 1a).

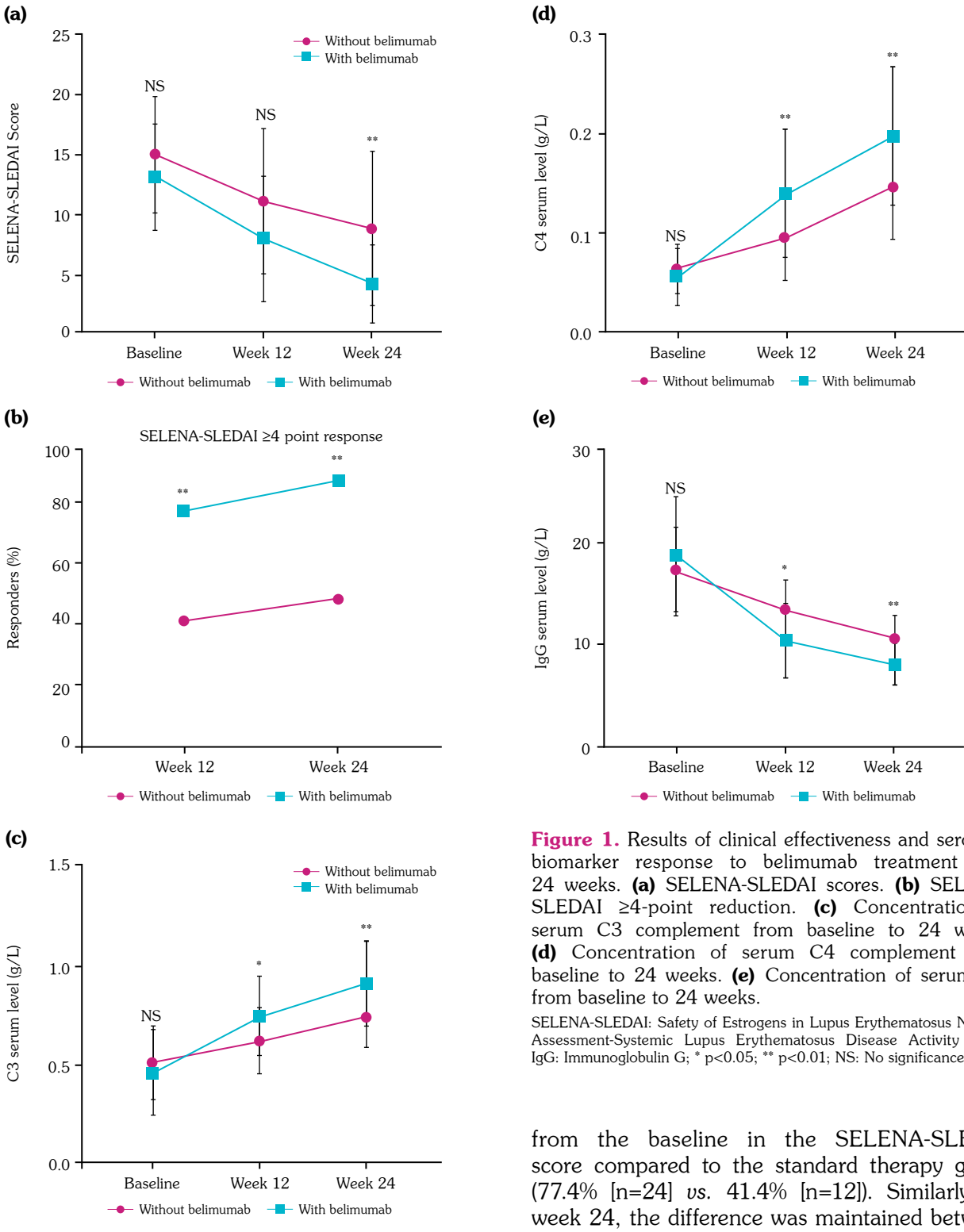

Figure 1. Results of clinical effectiveness and serologic biomarker response to belimumab treatment over 24 weeks. **(a)** SELENA-SLEDAI scores. **(b)** SELENA-SLEDAI ≥4-point reduction. **(c)** Concentration of serum C3 complement from baseline to 24 weeks. **(d)** Concentration of serum C4 complement from baseline to 24 weeks. **(e)** Concentration of serum IgG from baseline to 24 weeks.

SELENA-SLEDAI: Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index; IgG: Immunoglobulin G; * p<0.05; ** p<0.01; NS: No significance.

Significant improvements were observed in the SELENA-SLEDAI score. At week 12, a remarkably greater proportion of patients in the belimumab group had a ≥4-point reduction from the baseline in the SELENA-SLEDAI score compared to the standard therapy group (77.4% [n=24] *vs.* 41.4% [n=12]). Similarly, by week 24, the difference was maintained between the two groups (87.1% [n=27] *vs.* 48.0% [n=14]). Moreover, the belimumab addition resulted in a greater mean absolute reduction in the SELENA-SLEDAI score compared to standard therapy at week 24 (p=0.003, Figure 1b).

Table 2. Changes in biomarker measures and prednisone use from baseline at weeks 12 and 24

	Week 12					Week 24				
	Without belimumab		With belimumab			Without belimumab		With belimumab		
Biomarker	n	%	n	%	*p**	n	%	n	%	*p**
Anti-dsDNA antibody level										
Shift from positive[a] to negative (%)	2/26	7.7	4/24	16.7	0.4	7/26	26.9	9/24	37.5	0.54
C3										
Low[b] to normal/high[c] (%)	0/29	0	8/31	25.8	0.005	4/29	13.8	14/31	45.2	0.001
C4										
Low[d] to normal/high[e] (%)	11/28	39.3	19/29	65.5	0.06	25/28	89.3	25/29	86.2	>0.99
Prednisone dose reduction by ≥50% over baseline	6/29	20.7	19/31	61.3	0.0018	29/29	100	31/31	100	>0.99

dsDNA: Anti-double-stranded deoxyribonucleic acid; [a]: ≥30 IU/Ml; [b]: <0.09 g/L; [c]: ≥0.09 g/L; [d]: <0.01 g/L; [e]: ≥0.01 g/L; * Fisher exact test.

Among patients with anti-dsDNA antibody values ≥10 IU/mL at baseline, the median reduction was –72.8% (70.3-65.9%) in the standard therapy group and –50.8% (54.3-40.3%) in the belimumab group at week 12. At week 24, the decreases in median values continued, with –85.4% (88.8-83.4%) in the standard therapy group and –83.4% (93.8-78.4%) in the belimumab group. Moreover, of patients with anti-dsDNA antibody positive at baseline, 7.7% (n=2) in the standard therapy group and 16.7% (n=4) in the belimumab group shifted into negative anti-dsDNA antibodies at week 12. At week 24, the anti-dsDNA antibody levels returned to normal in seven (26.9%) patients in the standard therapy group and in nine (37.5%) patients in the belimumab group (Table 2).

The mean levels of C3 in the belimumab group were significantly higher compared to those in the standard therapy group at weeks 12 and 24 (p=0.03 and p=0.002, respectively; Figure 1c). In addition, at weeks 12 and 24, significantly more patients returned to normal for serum C3 levels in the belimumab group than in the standard therapy group (p=0.005 and p=0.001, respectively; Table 2). Similarly, there was also a greater increase in serum C4 levels in the belimumab group than in the standard therapy group at weeks 12 and 24 (p=0.008 and p=0.006, respectively; Figure 1d). Among patients with low C4 levels (<0.01 g/L) at baseline, 39.3% (n=11) in the standard therapy group and 65.5% (n=19) in the belimumab group shifted into a normal C4 level at week 12. At week 24, the C4 levels normalized in 25 (89.3%) patients in the standard therapy group and 25 (86.2%) patients in the belimumab group, without significant differences (Table 2). Furthermore, belimumab treatment also resulted in a marked decrease in IgG levels at weeks 12 and 24 (p=0.003 and p=0.0002, respectively; Figure 1e).

Due to the clinical improvement, the dose of prednisone could be reduced in all patients in disease remission within six months after belimumab infusion. At week 24, the mean

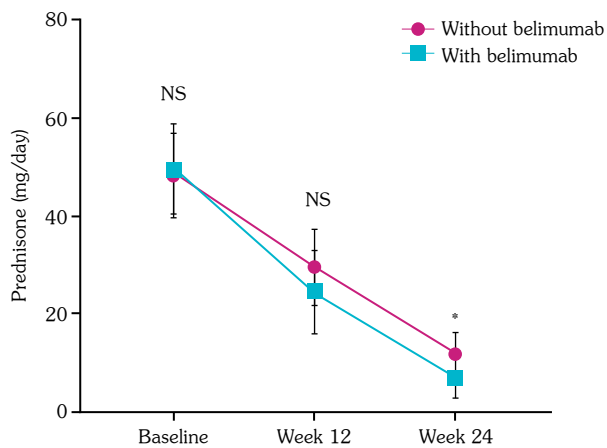

Figure 2. The steroid sparing effect of belimumab at baseline, 12 weeks, and 24 weeks.
* p<0.05; NS: No significance.

Table 3. Summary of adverse events

	Without belimumab		With belimumab		
Adverse events	n	%	n	%	*p*
Any event	13	44.8	16	51.6	0.62*
Pneumonia	2	6.9	3	9.7	
Herpes zoster virus	2	6.9	1	3.2	
Upper respiratory tract infection	7	24.1	8	25.8	
Adolescent fibroadenoma of breast	0	0	1	3.2	
Urinary tract infection bacterial	1	3.4	2	6.5	
Cytomegalovirus infection	1	3.4	2	6.5	

change of prednisone use from baseline to week 24 was significantly higher in the belimumab group than that in the standard therapy group (mean difference: 4.8; confidence interval 2.1-7.5; p=0.0002). However, there was no significant difference in the mean change of prednisone dose between the two groups (Figure 2) at week 12. In addition, compared to the standard therapy group, the proportion of patients in the belimumab group with at least a 50% reduction in prednisone dose over baseline was significantly greater at week 12 (p=0.0018). At week 24, all patients included had a prednisone dose reduction ≥50% (Table 2).

During the 24 weeks of treatment, the incidences of adverse events (AEs) of belimumab infusion were similar between the two groups (Table 3). The majority of AEs were mild to moderate. The most common AEs reported in standard therapy and belimumab groups were upper respiratory tract infections (24.1% *vs.* 25.8%, respectively). Two patients in the standard therapy group and three patients in the belimumab group experienced pneumonia. Herpes zoster virus infection occurred in two patients in the standard therapy group and one patient in the belimumab group. An adolescent fibroadenoma of the breast was reported in one patient receiving belimumab and cured by surgical management. Cytomegalovirus infection was reported in one patient in the standard therapy group and two patients in the belimumab group. Two patients receiving belimumab and one patient treated with standard care were diagnosed with bacterial urinary tract infections. No patient had discontinuation of belimumab infusion due to AEs and postinjection systemic reactions in the belimumab group.

DISCUSSION

This 24-week retrospective study reported the effectiveness of belimumab treatment in patients as early as 12 weeks with safety and tolerability in our department. The findings reveal that the use of belimumab produces early improvement in disease activity with decreasing prednisone dose, consistent with previous studies.[7,8]

One of the most prominent features of our study is the early effectiveness benefit of belimumab for decreasing disease activity in SLE patients. More patients in the belimumab group achieved an SLE Responder Index 4 (assessed with >4-point reduction from baseline in SELENA-SLEDAI) response as early as week 12 compared to the standard therapy group, and this clinical improvement continued at week 24. A phase 3 clinical trial with the largest number of SLE patients to date enrolled reported that clinical improvement was observed at week 16 after initiation of belimumab at 10 mg/kg.[7] Anjo et al.[9] also reported that significant improvements in disease and serological activity were achieved as early as six months after belimumab use. As a specific monoclonal antibody targeting BLyS, belimumab is effective in inducing autoimmune B-cell apoptosis, which contributes to the early effectiveness in our report. In addition, the

standard care with the full dose of prednisone and immunosuppressants in our study should be another essential contributor to the early onset of clinical improvement with belimumab treatment. Therefore, belimumab combined with standard care could be effective in reducing the disease activity at an early stage, which significantly decreases organ damage, morbidity, and mortality in SLE patients.

Rapidly reduction in prednisone dose has always been the primary goal for SLE patients to prevent side effects and long-term damage, particularly the decrease in the risk of infection and occurrence rate of fragility fracture. A previous study has confirmed the steroid-sparing effect of belimumab for a long duration.[7] Of note, a reduction in prednisone dose at the early stage of treatment would have clinical significance for decreasing risks of infection and improvement of general health in patients with SLE. Our study showed that belimumab had steroid-sparing effects. As early as week 12, our study revealed that the proportion of patients with a reduction of more than 50% over baseline in the dose of prednisone was significantly higher in the belimumab group than in the standard group, which was consistent with Navarra et al.'s[7] finding that belimumab treatment reduced the dose of prednisone as early as eight weeks. In addition, the average prednisone dose in the belimumab group was lower than in the standard group at week 24. A prolonged high dose of prednisone was confirmed to be the primary cause of long-term damage and mortality in SLE patients. Therefore, reduction in corticosteroid use at the early stage by belimumab treatment provides benefits for improvement of the general health of patients with SLE.

Belimumab treatment led to a rapid improvement in serological activity. As early as 12 weeks after starting belimumab exposure, significantly higher proportions of patients in the belimumab group had the normal serum complement and Ig concentration than in the standard therapy group. Moreover, these improvements were sustained at week 24. These findings are consistent with the phase 3 clinical trial that included the largest number of SLE patients treated with belimumab.[7] It is well known that systemic complement activation results in widespread tissue damage and prolonged inflammation, which is the hallmark of SLE. Belimumab can effectively inhibit systemic complement activation at an early stage by making low complement concentrations return to normal. In our study, eight (25.8%) patients with low serum C3 levels and 19 (65.5%) patients with low serum C4 levels returned to normal as early as week 12. Consistently, Frieri et al.[10] verified that belimumab suppressed the function of B cells effectively as early as eight weeks, and clinical effectiveness was noted at 16 weeks.

In this study, belimumab was well-tolerated over 24 weeks of treatment, and the overall incidence rate of AEs reached 51.6%, which was similar to the standard therapy group ($p=0.62$, Table 3). The percentage of patients with AEs in our study was lower than those from two phase 3 randomized, double-blind, placebo-controlled trials.[7,8] The small sample and short duration of our study are partly responsible for this discrepancy. The most common types of AEs were bacterial and viral infections. However, no infusion reactions including hypersensitivity reactions and postinjection systemic reactions were reported in our study. Interestingly, one patient in week 16 treatment of belimumab experienced adolescent fibroadenoma of the breast but fully recovered with surgical management. As the breast was not routinely inspected before belimumab infusion, whether this AE was related to belimumab management is not clear. As belimumab only targets the active B cells and plasma cells by neutralizing BLyS, it had no effect on memory B cells and T cells that survive independence on BLyS. Therefore, the preservation of memory B cells and T cells makes the immune system respond to infection, which mainly accounts for the good safety of belimumab.[11]

This study has several limitations. First, the study may present with some subjective bias as there was no blinding. Second, the dose of prednisone and the type of immunosuppressants varied, leading to difficulty in comparison between baseline, week 12, and week 24. Lastly, a small data set, loss to follow-up, and incomplete data points due to the retrospective design should also be mentioned.

In conclusion, this study described the fast-acting remission and well tolerability of intravenous

belimumab combined with standard therapy in Chinese patients with SLE. Both disease activity and the serological index were effectively relieved. More importantly, the rapid reduction in prednisone use in patients at an early stage provided encouraging results for the prognosis of SLE patients. Together with the ease of use, time-saving clinical improvement, and slight side effects, the results of this study further provide convincing evidence that intravenous belimumab plus standard treatment is a desirable therapeutic option for SLE management.

Ethics Committee Approval: The study protocol was approved by the Institutional Review Board of our institution.

Patient Consent for Publication: Written informed consent for publication of the clinical details and clinical images was obtained from the patients.

Data Sharing Statement: All data generated or analyzed during this study are included in this published article.

Author Contributions: Wrote the initial draft of the manuscript: L.Y.H., M.M.Y.; Collected and analyzed the data: R.W.; Supervised the project from initiation and revised the manuscript: J.L.L.

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