

A modified regimen of low-dose rituximab therapy for patients with refractory immune thrombocytopenia associated with systemic lupus erythematosus

Shuo Zhang* , Nan Jiang*, Li Wang , Li Zhang, Hua Chen, Mengtao Li and Xiaofeng Zeng

Abstract

Background: Severe and refractory immune thrombocytopenia (ITP) affects the life expectancy of patients with systemic lupus erythematosus (SLE) and poses a challenge in their clinical management. This intervention study employed a small sample size to evaluate the efficacy and safety of a modified low-dose rituximab (RTX) regimen in patients with SLE-associated refractory ITP.

Methods: Eight patients with severe SLE-associated refractory ITP were enrolled in this intervention study. They received an infusion of intravenous RTX (200 mg) on days 1 and 15. The dose of corticosteroids (prescribed previously) was gradually tapered, and immunosuppressants were withdrawn. Patients were followed up at 1, 3, 6, and 12 months; platelet counts, other laboratory indicators, and side effects were recorded. We used intention-to-treat analysis to calculate the response rate.

Results: Seven participants (87.5%) completed the study. At 1 month, two patients (25.0%) achieved partial response (PR); the PR rate increased to 87.5% at 3 months. At 6 months, three patients (37.5%) achieved complete response (CR). However, the CR rate dropped to 25.0% at 12 months. The overall responses (ORs) were 25.0% (2/8), 87.5% (7/8), 75.0% (6/8), and 75.0% (6/8) at 1, 3, 6, and 12 months, respectively. Two patients developed a mild infusion reaction and one discontinued the study due to herpes zoster virus infection and an allergic reaction 2 weeks after the first dose of RTX.

Conclusion: Modified low-dose RTX therapy (two infusions of 200 mg every 2 weeks) could be a promising new option for patients with SLE-associated refractory ITP with a satisfactory response rate.

Keywords: immune thrombocytopenia, low-dose regimen, rituximab, safety, systemic lupus erythematosus

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by autoantibody-induced systemic inflammation, immune complex formation, and complement activation. As a hematological manifestation of SLE, thrombocytopenia is present in 10–40% of patients.^{1–5} The severity of thrombocytopenia in SLE patients can be a useful independent prognostic factor for

predicting survival.¹ Severe and refractory immune thrombocytopenia (ITP) affects SLE patients' life expectancy and poses a challenge in their clinical management.¹

As a monoclonal antibody against positive CD20 cells, rituximab (RTX) has been widely used in some autoimmune diseases including SLE and ITP. In patients with SLE, a systematic review

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Correspondence to:

Li Wang

Department of
Rheumatology and
Clinical Immunology,
Peking Union Medical
College Hospital, Peking
Union Medical College
and Chinese Academy of
Medical Sciences, No. 1
Shuaifuyuan, Dongcheng
District, Beijing 100730,
China.
wangli2221@sina.com

Shuo Zhang

Nan Jiang

Li Zhang

Hua Chen

Mengtao Li

Xiaofeng Zeng

Department of
Rheumatology and Clinical
Immunology, Peking Union
Medical College Hospital,
Peking Union Medical
College and Chinese
Academy of Medical
Sciences, Beijing, China

*These authors contribute
equally.

recommended RTX as a treatment option for organ-specific manifestations such as arthritis and thrombocytopenia, with good safety and effectiveness in terms of disease activity, immunologic parameters, and steroid-sparing effects.⁶ RTX is also recommended either as a monotherapy or as an add-on therapy to immunosuppressants in the guidelines.⁷ In adult patients with ITP, RTX is considered an off-label second-line option in most guidelines, with a 60% rate of initial response in ITP.^{8,9}

However, the optimal dosage for SLE-associated ITP is still under investigation. Although the intravenous (IV) dosage of 375 mg/m² per week for four consecutive weeks in patients with ITP or refractory SLE associated with major organ involvement showed satisfactory responses in previous studies,¹⁰ a low-dose regimen (100 mg IV per week for 4 weeks) has been shown to minimize the side effects and reduce costs.^{11,12} The low-dose RTX regimen in the study by Chen *et al.* is associated with a good response rate (as high as 70% at week 24).^{11,12} To find a safer and more economical therapy with similar or better effectiveness, we conducted this exploratory intervention study to test for the efficacy of a modified low-dose RTX regimen in the management of SLE-associated refractory ITP.

Patients and methods

Participants

Eight patients with SLE-associated refractory ITP at Peking Union Medical College Hospital were enrolled in this exploratory intervention study between January 2013 and September 2019. The inclusion criteria were age ≥ 18 years; diagnosis of SLE according to Systemic Lupus International Collaborating Clinics (SLICC)-2012 criteria;¹³ severe ITP [defined as platelet count (PLT) $< 10 \times 10^9/L$ or $< 30 \times 10^9/L$ with bleeding propensity]; and refractory ITP [defined as patients who had received and exhibited treatment failure with at least one course of methylprednisolone pulse therapy (1 g/day for 3 consecutive days), or IV immunoglobulin (IVIG) (20 g/day for 3–5 consecutive days), high-dose glucocorticoid (1 mg/kg/day prednisolone equivalent) in combination with two or more immunosuppressants].¹¹ Patients with drug-induced thrombocytopenia, thrombotic microangiopathy-induced thrombocytopenia, splenomegaly, active

infections, any history of severe drug allergy, or malignant diseases were excluded.

Ethical approval was obtained from the Research Ethics Committee of Peking Union Medical College Hospital (No. S-K1566), and written consent was obtained from each patient.

Treatment regimen

We designed this regimen according to the total dose of a previous low-dose protocol in the study by Chen *et al.*¹¹ RTX (Roche, USA), at a dose of 200 mg, was administered IV once every 2 weeks for a total of two infusions (days 1 and 15). We followed the standard protocol for RTX administration. Patients were administered premedication with antihistamines and antipyretics, but not corticosteroids. The initial infusion rate for the first RTX infusion was 50 mg/h; subsequently, the rate was escalated in increments of 50 mg/h every 30 min to a maximum of 400 mg/h. Intravenous corticosteroids were not administered at the time of RTX infusion. Previous doses of oral corticosteroids (7.5–60 mg q.d.) were continued and gradually tapered to a minimal maintenance dose (5 mg every other day to 7.5 mg q.d.). All previous immunosuppressants were withdrawn. Patients were followed up at 1, 3, 6, and 12 months after the first dose of RTX. The clinical manifestation, laboratory data (complete hemogram, lymphocyte subsets, and serum immunoglobulin), and medication were recorded during follow-up.

Biochemical measurements

The clinical and laboratory data sources were obtained from the medical records of the patients. Enzyme-linked immunosorbent assays were used to detect anti-extractable nuclear antigen (ENA) antibodies, anti-cardiolipin (ACL), and anti- β 2-glycoprotein-I (anti- β 2GPI). Lupus anticoagulant (LAC) was measured using the prothrombin time dilution method (1:500). Antinuclear antibody (ANA) and anti-double-stranded DNA (dsDNA) antibody were measured by an immunofluorescence test. In addition, complement 3 (C3), C4, serum immunoglobulin (IgG, IgA and IgM), erythrocyte sedimentation rate, high-sensitivity C-reactive protein, albumin, urea, serum creatinine, lymphocyte subsets [CD19+ B cells, CD16+ CD56+ natural killer (NK) cells, CD3+ CD4+ Th cells, and CD3+ CD8+ Tc cells], and

a complete hemogram were measured. Serum samples were collected early in the morning after an 8-h fasting period.

Response criteria

Response was evaluated 1, 3, 6, and 12 months after the first dose of RTX. For SLE-associated ITP, the response criteria were the same as those commonly used for primary ITP:¹⁴ complete response (CR) was defined as a PLT level $>100 \times 10^9/L$, partial response (PR) as a PLT level of $30\text{--}100 \times 10^9/L$ with at least a doubling of the initial (i.e. pre-treatment) count, and no response as patients without CR or PR. Patients with CR or PR were regarded as overall response (OR) to the therapy. We used intention-to-treat analysis to calculate the response rate.

Statistical analysis

All statistical analyses were performed using SPSS 20.0 software (SPSS Inc, Chicago, IL, USA) and R statistical software version 3.4.3 (<http://www.R-project.org/>). The data were presented as mean \pm SD for normally distributed continuous variables, mean and interquartile range (IQR) for skewedly distributed continuous variables, and numbers and proportions (%) for categorical variables. Data were compared between groups using the Student's *t* test for continuous variables. Correlation analysis was performed using Pearson's correlation coefficient. A *p* value of <0.05 was considered to indicate statistically significant differences.

Results

Clinical and laboratory characteristics of the participants

The study included eight patients with SLE-associated ITP. The mean age was 31.3 ± 7.2 years, and all participants were women. The SLE disease duration ranged from 0.5 to 15 years (average: 4.9 years, IQR: 1.3–7.0 years), while the mean duration of ITP was 4.1 years (range: 0.5–15 years, IQR: 1.0–4.5 years). The clinical manifestations began with bleeding tendency (including epistaxis, skin purpura, gingivorrhagia, and/or abnormal vaginal bleeding) in seven patients (87.5%). Other symptoms included fever, arthritis, sicca syndrome, malar rash, Raynaud phenomenon, anemia, and so on. Two

of the patients had Evans syndrome. The mean PLT level at baseline was $14.3 \pm 10.1 \times 10^9/L$. All participants tested negative for hepatitis B (HBV) and C viruses (HCV). Participants' baseline characteristics are shown in Table 1.

Response rate to therapy

Seven participants (87.5%) completed the study. At 1 month, two patients (25.0%) achieved PR; the PR rate increased to 87.5% at 3 months. At 6 months, three patients (37.5%) achieved CR; however, the CR rate dropped to 25.0% at 12 months. The OR was 25.0% (2/8), 87.5% (7/8), 75.0% (6/8), and 75.0% (6/8) at 1, 3, 6, and 12 months, respectively (Figure 1).

Monitoring of laboratory parameters

Laboratory parameters were obtained for the seven remaining patients in the study. PLT levels gradually increased from $14.3 \pm 8.9 \times 10^9/L$ at baseline to $91.7 \pm 29.6 \times 10^9/L$ at 6 months, followed by a decrease to $74.4 \pm 30.8 \times 10^9/L$ at 12 months. The PLT levels at 3, 6, and 12 months were significantly higher than that at baseline, which indicates that the time of onset of action of RTX was around 3 months ($p < 0.01$, $p < 0.01$, and $p < 0.01$, respectively). Although peripheral lymphocyte levels were similar at all the observation points ($p = 0.77$), peripheral CD19+ B cells dropped dramatically at 3 months from $437.6 \pm 473.0 \times 10^9/L$ to $5.2 \pm 5.9 \times 10^9/L$, and then gradually increased at 6 and 12 months ($12.2 \pm 13.9 \times 10^9/L$ and $184.7 \pm 174.9 \times 10^9/L$, respectively). Meanwhile, peripheral blood CD3+ CD4+ cells, CD3+ CD8+ cells, and CD16+ CD56+ NK cells remained stable throughout the study ($p = 0.93$, $p = 0.85$, and $p = 0.30$, respectively). Although IgG levels represent another dimension of B-cell function evaluation, no significant differences were observed ($p = 0.34$) (Figure 2). The B-cell counts had a trend of a negative correlation with PLT levels, although without statistical significance ($r = -0.243$, $p = 0.19$).

Safety

Two patients showed a minor infusion reaction during the first RTX infusion [Grade 2, Common Terminology Criteria for Adverse Events (CTCAE) version 5.0]. The symptoms resolved after the infusion rate was adjusted. Furthermore,

Table 1. Basic characteristics, follow-up, and adverse events of modified low-dose RTX regimen for SLE-associated refractory ITP.

No.	Sex	Age, years	Disease duration, years	Manifestations	Auto-antibodies	Previous treatment*	SLEDAI at enrollment	PLT count, $\times 10^9/L$					Adverse events
								Month 0	Month 1	Month 3	Month 6	Month 12	
1	F	30	6	Epistaxis, photosensitivity, fever, Raynaud, arthritis, Evans syndrome, positive Coombs' test, low complements	ANA, anti-RNP, anti-Sm, anti-SSA, AHA, anti-Ro52	IVIg, CS pulse, CSA, FK506, MMF, AZA, HCQ	3	7	21	80	92	41	Infusion reaction
2	F	21	2	Purpura, epistaxis, thrombosis, positive Coombs' test, low complements	ANA, anti-dsDNA, anti-rRNP, anti-SSA, anti-Ro52	IVIg CS pulse, CSA, HCQ, VCR, TPO	5	12	19	56	101	120	Infusion reaction
3	F	35	4	Purpura, Raynaud, dry eyes, flaky tooth loss, low complements	ANA, anti-RNP, anti-SSA, anti-dsDNA	CS pulse, CSA, HCQ, VCR, TPO, danazol	1	1	25	52	108	53	None
4	F	24	8	Fever, dizzy, jaundice, proteinuria, Evans syndrome, positive Coombs' test, low complements	ANA, anti-Ro52, anti-SSA	CS, CTX, CSA, FK506, MMF, AZA, HCQ	3	14	35	68	89	90	None
5	F	38	0.5	Purpura, fatigue, pleuritic, pericarditis, carotid artery occlusion, low complements	ANA, anti-SSA, ACL	IVIg, CS, CSA, HCQ, TPO, danazol	1	30	56	98	35	42	None
6	F	29	3	Purpura, gingival bleeding, fever, Malar rash, low complements	ANA, anti-Ro52, anti-SSA	IVIg, CS, FK506, HCQ, TPO	1	8	24	62	85	73	None
7	F	30	15	Purpura, epistaxis, rash, arthritis, dry eyes and mouth, low complements	ANA, anti-Ro52, anti-SSA, anti-SSB	IVIg, CS, CTX, MMF, AZA, HCQ	1	28	79	84	132	102	None
8	F	43	1	Purpura, vaginal bleeding, alopecia, dry eyes and mouth, positive Coombs' test	ANA, ACL, anti-SSA, anti-Ro52	IVIg, CS, HCQ	5	14	/	/	/	/	Allergy reaction, HZV infection

ACL, anti-cardiolipin; AHA, anti-histone antibody; ANA, antinuclear antigen; AZA, azathioprine; CS, corticosteroids; CSA, cyclosporine; CTX, cyclophosphamide; HCQ, hydroxychloroquine; HZV, herpes zoster virus; ITP, immune thrombocytopenia; IVIg, intravenous immunoglobulin; MMF, mycophenolate mofetil; PLT, platelet; RTX, rituximab; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; TPO, thrombopoietin; VCR, Vincristine.

*The previous treatments were for all the manifestations of SLE, including ITP.

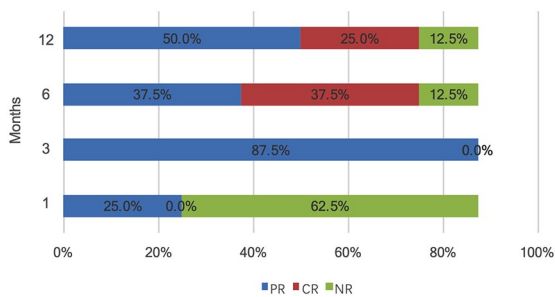


Figure 1. Response rate of the modified low-dose rituximab regimen in patients with refractory SLE-associated immune thrombocytopenia.

another patient developed an allergic reaction during the second infusion, which necessitated termination of the treatment. This patient also developed herpes zoster virus (HZV) infection the day after the second infusion (Grade 3, CTCAE version 5.0) and was discontinued from the study. During the follow-up, all other patients were observed for symptoms and laboratory indicators of infection, especially tuberculosis (TB), HBV, or HCV infection. One of the patients tested low-titer positive in the T-SPOT.TB test at baseline, although no TB flare was observed at follow-up (the patient was not given anti-TB treatment).

Discussion

Severe or refractory thrombocytopenia remains a serious systemic complication of SLE with great challenges in the clinical management. This intervention study recruited eight adults receiving modified low-dose RTX for SLE-associated ITP. The main findings of this study show that the modified regimen has a good response rate.

In patients with SLE, the most common cause of severe thrombocytopenia is ITP. Elimination of the producer of the antigen-specific antibody, B cells, could be a promising treatment option. As a chimeric murine/human monoclonal antibody, RTX targets the B-cell membrane glycoprotein CD20 and leads to B-cell depletion and dysfunction (including autoantibody production, antigen presenting, and cytokine secretion).^{11,15} In the last 20 years, the effectiveness of RTX in ITP and some autoimmune diseases has been proven, and guidelines are progressively considering it a choice of treatment in such diseases.

In this study, 87.5% of the patients responded to the modified low-dose RTX at 3 months, and a

response rate of 75.0% was observed through to 12 months, on intention-to-treat analysis. In patients with ITP who received RTX, a systematic review reported a 64% (95% confidence interval: 58–70%, $n = 1746$) pooled response rate, regardless of the RTX dosage.¹⁶ In patients with SLE-associated ITP, the response rate with the standard dosage (375 mg/m²/week for 4 weeks or 1000 mg on days 1 and 15) was 75.0–90.9%.^{17–19} Data on the effectiveness of low doses of RTX in the treatment of SLE-associated autoimmune thrombocytopenia are limited. Some clinicians have reported several cases of good responses to low-dose RTX in patients with lupus-induced thrombocytopenia.¹² In an earlier study at our center, 70% (7/10) OR was achieved at 24 weeks in SLE-associated thrombocytopenia patients who received RTX at a dose of 100 mg/week for 4 weeks.¹¹ Thus, our modified low-dose RTX regimen achieved a similar response rate compared with previously reported standard-dose (375 mg/m²/week for 4 weeks or 1000 mg on days 1 and 15) and low-dose (100 mg/week for 4 weeks) regimens.

Safety evaluation is an important aspect of developing new regimens. Generally, RTX is well-tolerated with mild and easily manageable side effects, including infections, allergy, infusion reaction, and so on. One patient dropped out of this the study due to HZV infection, although the symptoms were relatively mild and the patient recovered soon after. Thus, screening for latent infections before treatment and prevention of infections after treatment are recommended. Two other patients developed mild infusion reactions that did not affect treatment and subsided after the infusion rate was slowed. Infusion reactions after the first administration of RTX have been reported in 15–60% of patients¹⁵ and are usually mild to moderate; severe (grade 3–4) reactions only occur in around 10% of patients.^{20,21} In previous studies, the occurrence rates of adverse effects were similar among the different dosages of RTX. With the low-dose RTX regimen in the study by Chen *et al.*,¹¹ infection occurred in 10% of the patients, while 20% had an infusion reaction. As for the standard dosage regimen, 9.9% of SLE-associated immune cytopenia patients experienced adverse events, which were mainly mild-to-moderate infusion reactions.¹⁷ In another retrospective cohort, adverse effect manifestations and rates of RTX were as follows: infection 14.3%, allergy 9.5%, gastrointestinal tract reaction 9.5%, and death 9.5%.¹⁸ Although

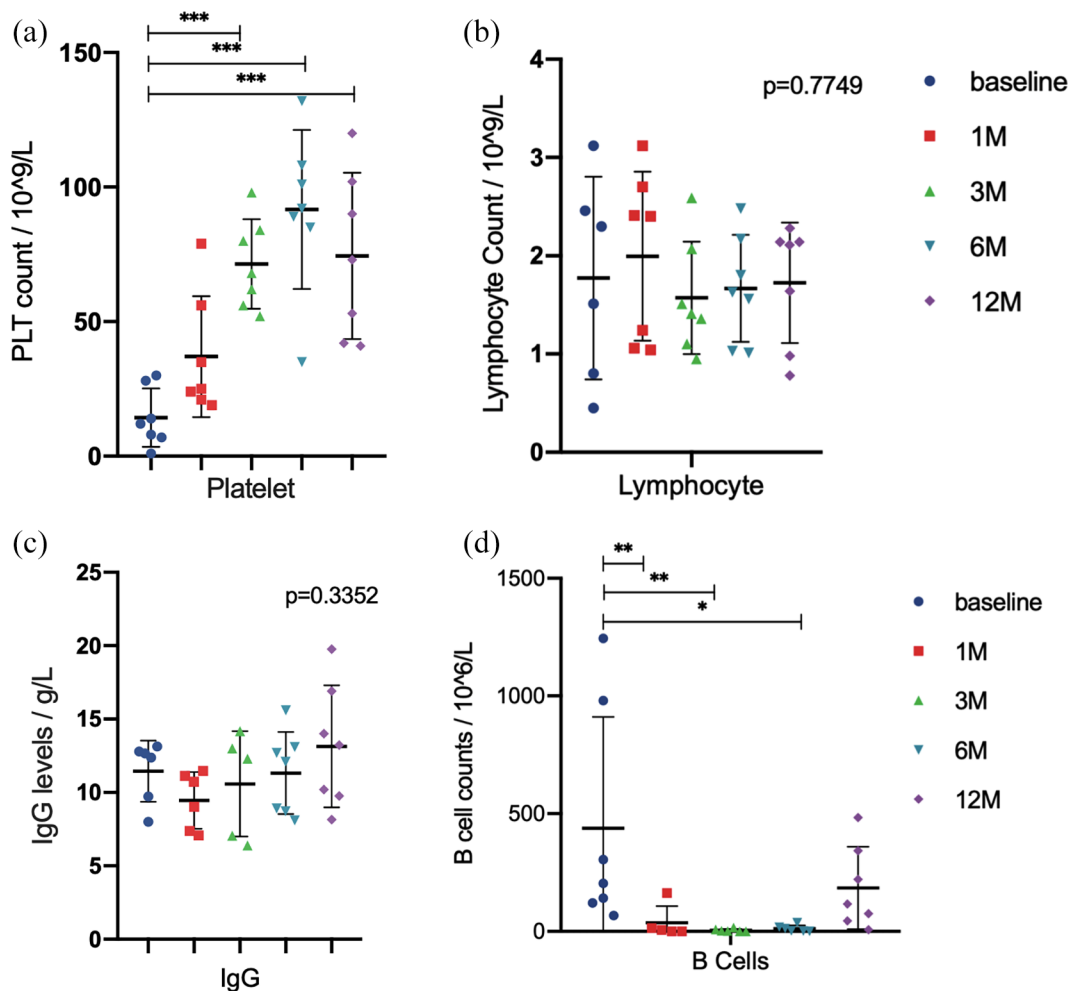


Figure 2. Laboratory parameter changes during follow-up in patients with refractory SLE-associated immune thrombocytopenia who had modified low-dose rituximab regimen. (a) Platelet counts, (b) lymphocyte counts, (c) serum immunoglobulin G (IgG) levels, and (d) B-cell counts.

the incidence of adverse effects was similar to that in previous reports, the safety of the modified low-dose RTX regimen still needs to be further evaluated in a study with a large sample size.

Generally speaking, the modified low-dose RTX regimen is associated with a satisfactory response rate, similar to those reported for previous treatment regimens (RTX at 375 mg/m²/week for 4 weeks, 1000 mg on days 1 and 15, 200 mg or 500 mg/weekly or every 2 weeks 1–3 times, or 100 mg/week for 4 weeks). However, our modified regimen had some unique strengths, including saving time and reducing costs and length of hospital stay.

Meanwhile, we monitored some laboratory indicators to identify factors predictive of response.

The B-cell counts showed a trend of negative correlation with PLT levels; B-cell counts reflect the B-cell depletion effectiveness of RTX. Similar trends were observed in a previous study.¹¹ Owing to the limited number of participants, it was impossible to detect all of the possible predictive factors in this study. Previous studies in patients with ITP revealed that women, young patients, and patients with a duration of ITP <12–24 months had better responses.^{22–24} Further studies with a larger sample size and control groups are needed.

These findings have practical and clinical implications. To the best of our knowledge, this study is the first in which this modified low-dose RTX regimen was administered to patients with refractory

SLE-associated ITP. However, our analysis may have been limited by several factors. First, as an exploratory intervention study, only eight patients were included without a control group. The imbalance in age and gender might have led to biased research results and even an overestimation of the response rates to this regimen. Further randomized clinical trials are needed to verify these results. One patient withdrew from this study due to HVZ infection. Losing this patient's data might have influenced our results, owing to further reduction in the sample size. This was potentially minimized by conducting an intent-to-treat analysis. Furthermore, we found a trend of decrease in PLT levels at 12 months, which led to the suspicion of potential disease relapse in the future. Thus, a long-term follow-up study is needed. Finally, due to the long study period, there may be some time-dependent variables that affected our findings.

Conclusion

In conclusion, this study shows that a modified low-dose RTX therapy (200 mg every 2 weeks, twice) could be a promising new treatment option for patients with refractory SLE-associated ITP, due to its satisfactory response rate.

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Author contributions

All authors made substantial contributions to this study. NJ, LW, LZ, and HC acquired the data. SZ and LW performed the data analysis and drafted the manuscript. ML and XZ provided critical revisions to the manuscript and valuable feedback. All authors read and approved the final manuscript.

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Conflict of interest statement


The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

The study was approved by the Institutional Review Board of Peking Union Medical College Hospital (approval number: S-K1566). All the patients from our center provided written informed consent in accordance with the Declaration of Helsinki.

ORCID iDs

Shuo Zhang  <https://orcid.org/0000-0001-8171-2779>

Li Wang  <https://orcid.org/0000-0003-0899-5703>

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