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ORIGINAL ARTICLE

Tofacitinib therapy in systemic lupus erythematosus with arthritis: a retrospective study

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Abstract

Objective To estimate the effectiveness and safety of tofacitinib in treating systemic lupus erythematosus (SLE) patients with arthritis.

Methods This research was a retrospective cohort study that focused on SLE patients who had arthritis and were treated with tofacitinib at the Department of Rheumatology and Immunology from January 2020 to January 2022. Clinical outcomes, disease activity, immunological parameters, and adverse events were systematically evaluated pre- and post-treatment at 4, 12, and 24 weeks.

Results Twenty-two patients were analyzed. At the 4-week mark, 5 (22.7%) patients were partially relieved, and 17 (77.3%) unalleviated. By the 12-week assessment, CR off corticosteroids was observed in four patients (18.2%), and CR on corticosteroids was seen in six patients (27.3%), with an additional six (27.3%) maintaining partial remission. At 24 weeks after treatment, three patients (13.6%) achieved CR off corticosteroids, ten patients (45.5%) achieved CR on corticosteroids, and all patients received remission. Compared to before treatment, The SLEDAI and PGA scores significantly improved. The level of C3 was increased significantly, and the absolute $CD3^+$ T cell count, the 28-tender and the 28-swollen joint count, and the levels of serum IL-6 were significantly decreased at 24 weeks after treatment.

Conclusion Tofacitinib demonstrates significant therapeutic potential in SLE patients with arthritis, with a safety profile, and the therapeutic mechanism of tofacitinib may be related to reducing IL-6 expression and inhibiting T cell activation.

Key Points
- *Tofacitinib demonstrates significant therapeutic potential in SLE patients with arthritis*
- *The therapeutic mechanism of tofacitinib may be related to reducing IL-6 expression and inhibiting T cell activation*

Keywords Arthritis · Systemic lupus erythematosus · Tofacitinib

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Introduction

Although abnormal activation of B cells has been considered an important pathogenesis in systemic lupus erythematosus (SLE), the persistence of T cell activation and cytokine secretion also contributed to the SLE development [1, 2]. T lymphocytes in individuals with lupus generate proinflammatory cytokines that have abnormal cell signaling characteristics [3]. Cyclosporine A and tacrolimus, which are traditional immunosuppressive drugs, effectively reduce T cell activation in individuals with lupus, leading to positive treatment outcomes. Nevertheless, the therapeutic use of these substances is restricted due to their evident adverse effects, including nephrotoxicity [4]. Our prior investigation has manifested that tofacitinib may inhibit T cell activation by elevating the TGF-β type I receptor expression in treating lupus mice [5]. Additional clinical evidence is required to elucidate the effectiveness and mechanism of tofacitinib therapy in individuals with SLE.

Janus kinases (JAKs) are involved in the pathways of multiple cytokines that are linked to SLE, encompassing type I interferons (IFNs), interleukin-6 (IL-6), IL-12, and IL-23. The JAKs have crucial implications on the SLE development [6]. Consequently, the suppression of JAK has shown potential as a viable therapeutic approach for SLE. JAK inhibitors (jakinibs) have manifested effectiveness in several murine models of lupus [7]. Clinical studies with jakinibs have shown clinical effectiveness in treating arthritis in individuals with mild-to-moderate SLE [8]. Three multicenter randomized controlled trials (RCTs) have recently examined the effectiveness and safety of baricitinib in individuals with SLE. Nevertheless, their outcomes have proven contradictory. The available data pertaining to this topic are inadequate, and many investigations have shown inconsistent results [9–11]. Thus, this investigation investigated the effectiveness and possible mechanisms of tofacitinib in treating SLE in conjunction with arthritis.

Materials and methods

Patient screening process

The ethical council of Fujian Provincial Hospital (Fuzhou, China) accepted this retrospective research. Patients who met the diagnostic criteria for SLE as outlined by the American College of Rheumatology (ACR) Revised Criteria were enrolled in the Rheumatology and Immunology department at Fujian Provincial Hospital between January 2020 and January 2022. Initially, patients needed to have arthritis and a clinical SLE Disease Activity Index-2000 (SLEDAI-2 K) score of ≥ 4. SLE patients who had additional connective tissue illnesses, infections, or malignancies were eliminated from the investigation. Typically, 22 SLE patients were chosen to participate in this research. The screening process is illustrated in Fig. 1.

Tofacitinib treatment

Baseline and follow-up assessments were conducted on all patients at 4, 12, and 24 weeks after commencing tofacitinib

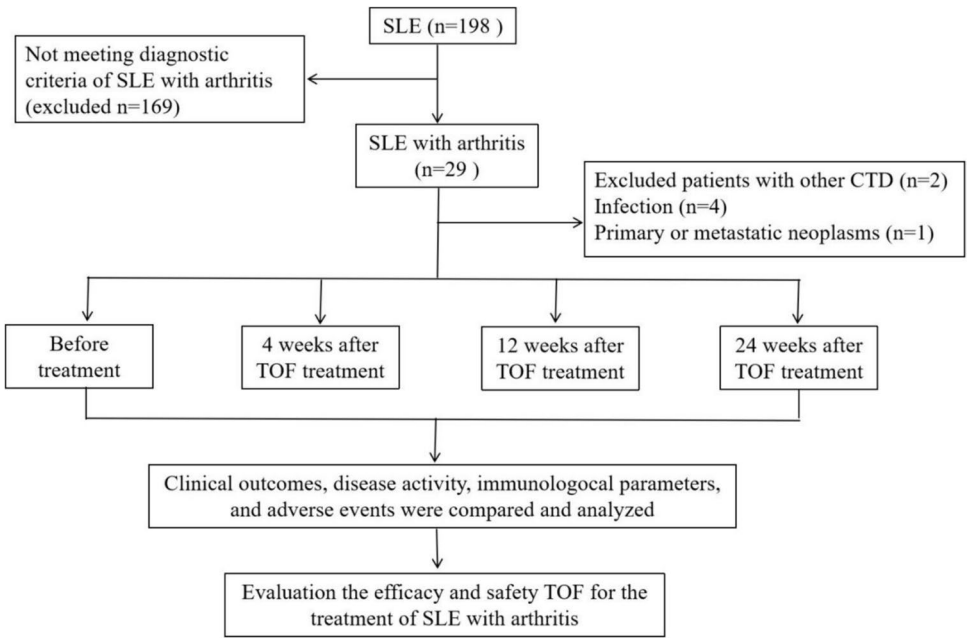

Fig. 1 Flowchart of patients' selection process and study design. SLE, systemic lupus erythematosus; TOF, tofacitinib

therapy. The patient received a 5-mg dose of tofacitinib twice a day. The study medicine was introduced to the current stable background treatment, which may consist of corticosteroids up to a dosage of 20 mg/day of prednisone or an equivalent, a single antimalarial drug, or a single immunosuppressant such as methotrexate or mycophenolate, without immunosuppressant drugs. The dose of oral glucocorticoid was gradually reduced to the minimum maintenance dose. Antimalarials and immunosuppressants were not permitted to be increased at any point.

Definition of disease remission

The Definition of Remission in SLE established three distinct degrees of remission based on guiding principles [12]: (1) complete remission, no disease activity in corticosteroid-free patients; (2) clinical remission (CR) off corticosteroids, serologically active clinical quiescent (SACQ) disease in corticosteroid-free patients; (3) CR on corticosteroids, SACQ disease in patients taking glucocorticoid dose of ≤ 5 mg/day at 6 months.

Clinical and immunological assessments

The clinical effect of tofacitinib treatment for patients was evaluated through the analysis of levels of C3 and anti-dsDNA at baseline and after 4, 8, 12, and 24 weeks of tofacitinib treatment. The SLE disease activity was assessed by SLEDAI-2 K, Physician Global Assessment (PGA), on a Likert scale ranging from 0 to 3 and 28-tender and 28-swollen joint count.

ELISA

A 3-ml sample of venous blood was taken from all patients. Samples were centrifuged for 5 min at 3000 r/min. The upper serum was taken and stored at − 80 ℃. The serum cytokines IL-2, IL-6, and INF-γ were detected by ELISA.

Flow cytometry

Whole blood treated with anticoagulant was exposed to the following fluorescent antibodies at a temperature of 4 °C for a duration of 30 min: CD3-FITC, CD16-PE, CD45-PerCP-Cy5.5, CD4-PC7, CD19-APC, and CD8-APC-Cy7. Next, red blood cells were ruptured using an ammonium chloride potassium buffer, then cleaned, and stabilized for flow cytometry.

Statistical analysis

Data analysis was conducted exclusively using GraphPad Prism 8 software. The data are presented as the mean ± SD. Categorical data is shown in the form of frequencies and percentages. For this investigation, the Wilcoxon signed-rank test, a nonparametric approach, was employed to compare parameters before and after tofacitinib treatment. This decision was taken due to the limited sample size and the uneven distribution of data. A p-value < 0.05 was considered to have significance.

Results

Patient demographics and clinical characteristics

Table 1 shows the patients' main characteristics. Twenty-two SLE patients with rash (18 females and 4 males, aged 18–56 years, mean 28.9 ± 11.2 years) were enrolled and underwent tofacitinib treatment. The mean disease duration was 78 ± 94 months (range 1–400 months), and the follow-up time was 24 weeks. The medication history of the SLE patients with rash who underwent tofacitinib treatment is listed in Table 1.

Tofacitinib treatment response rate

All 22 patients had arthritis at baseline. Five patients were relieved with a mitigated SLEDAI-2 K and PGA score but not CR (alleviated) 4 weeks after the first tofacitinib treatment, and 17 patients did not improve (unalleviated). After 12 weeks of tofacitinib treatment, CR off corticosteroids was seen in four patients (18.2%), and CR on corticosteroids was seen in six patients (27.3%). The number of patients alleviated increased to 6 (27.3%), but two patients experienced a flare. At 24 weeks, all patients were effectively relieved. Three patients (13.6%) achieved CR off corticosteroids, and ten patients (45.5%) achieved CR on corticosteroids (Fig. 2C). The SLEDAI and PGA scores before and after treatment are also shown in Fig. 2A and B.

Clinical and immunological assessments of tofacitinib treatment

As shown in Fig. 2, the laboratory parameters and SLEDAI scores were also evaluated before and after tofacitinib treatment. Compared to before treatment, the levels of C3 increased significantly at 24 weeks (Fig. 3A), whereas there was no significant disparity in the amounts of C4 and anti-dsDNA at the beginning and after 24 weeks (Fig. 3B and C). The absolute number of $CD3^+$ T cells showed a significant drop following 24 weeks (Fig. 3D). Furthermore, the 28-tender and 28-swollen joint count exhibited a significant reduction after 24 weeks (Fig. 3E and F).

Table 1 Patients' demographics and clinical characteristics

No	Sex	Age (y)	Disease duration (m)	Previous-TOF treatment	24 W after TOF treatment	Systemic involvement
1	F	38	1	P20 mg/d, HCQ, MTX	P5 mg/d, HCQ, MTX, JAKi	-
2	F	19	12	HCQ	HCQ, JAKi	Mucocutaneous
3	F	23	36	P10 mg/d, HCQ	HCQ, JAKi	Mucocutaneous
4	F	27	108	MP16 mg/d, HCQ, MTX	HCQ, MTX, JAKi	-
5	F	31	72	P20 mg/d, MMF	P10 mg/d, MMF, JAKi	Hematological, cardiovascular
6	F	31	108	MP8 mg/d, HCQ, MTX	HCQ, MTX, JAKi	-
7	F	18	12	MP16 mg/d, HCQ	MP4 mg/d, HCQ, JAKi	Mucocutaneous
8	F	56	400	MP12 mg/d, HCQ, MTX	MP8 mg/d, HCQ, MTX, JAKi	-
9	F	18	12	MP16 mg/d, MMF	MP6 mg/d, MMF, JAKi	Hematological
10	M	27	120	MP16 mg/d, MMF, HCQ	MP4 mg/d, MMF, HCQ, JAKi	Mucocutaneous, serositis
11	F	47	144	MP8 mg/d, HCQ	MP4 mg/d, HCQ, JAKi	Mucocutaneous
12	F	28	120	HCQ, MTX	HCQ, MTX, JAKi	-
13	F	21	24	HCQ	HCQ, JAKi	Mucocutaneous
14	F	23	120	MP12 mg/d, HCQ	MP4 mg/d, HCQ, JAKi	Hematological
15	F	20	18	HCQ, MMF	HCQ, MMF, JAKi	Mucocutaneous
16	M	19	10	HCQ	HCQ, JAKi	Mucocutaneous
17	M	21	3	MP12 mg/d, HCQ, MTX	MP4 mg/d, HCQ, MTX, JAKi	-
18	F	31	12	P20 mg/d, HCQ, MMF	P7.5 mg/d, HCQ, MMF, JAKi	Hematological, mucocutaneous, serositis
19	F	36	1	P10 mg/d, HCQ, MMF	HCQ, MMF, JAKi	-
20	F	27	108	MP8 mg/d, HCQ, MTX	HCQ, MTX, JAKi	-
21	M	56	240	MP8 mg/d, HCQ	HCQ, JAKi	-
22	F	18	12	P20 mg/d, MMF	P10 mg/d, MMF, JAKi	Hematological, mucocutaneous, serositis

F, female; *M*, male; *P*, prednisone; *MP*, methylprednisolone; *HCQ*, hydroxychloroquine; *MMF*, mycophenolate mofetil; *MTX*, methotrexate; *JAKi*, janus kinase inhibitors

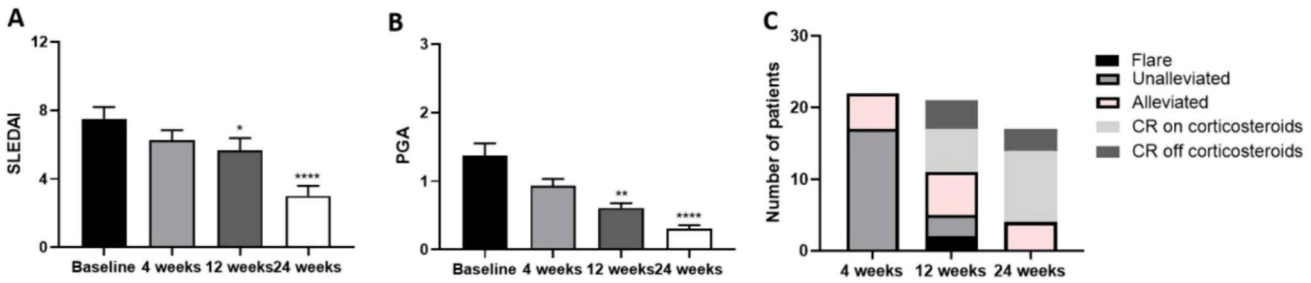

Fig. 2 Improvements in systemic lupus erythematosus disease activity, weeks 4–24 after tofacitinib treatment. **A** The SLEDAI score before and after treatment, compared to the baseline. **B** The PGA score before and after treatment, compared to the baseline. **C** Frequency of disease state and remission in patients with SLE since the treatment of tofacitinib. Data are presented as means ± SEM. $*p < 0.05$; $**p < 0.01$; $***p < 0.001$

Comparison of T cell activation-related cytokines before and after tofacitinib treatment

To clarify the possible mechanism by which tofacitinib therapy has implications for SLE patients, we assessed the cytokine levels linked to T cell activation both before treatment and the following 24 weeks. The outcomes showed that the IL-6 levels were mitigated after 24 weeks, in contrast to those before treatment (Fig. 4A). However, there was no significant change in the IL-2 or INF-γ levels (Fig. 4B and C).

Toxicity and safety

In this study, no severe or significant side effects were recorded. Only one patient suffered a serious upper

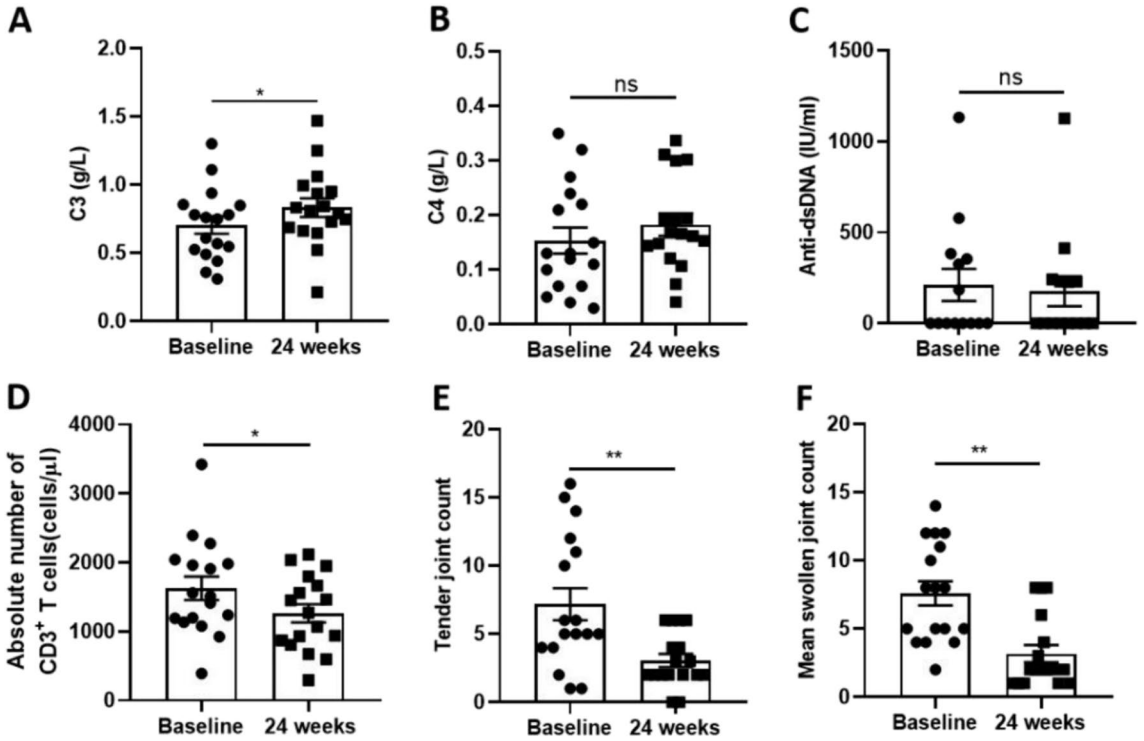

Fig. 3 Laboratory parameters and tender or swollen joint count before and 24 weeks after tofacitinib treatment ($n = 17$). **A**–**C** The levels of C3, C4, anti-dsDNA following tofacitinib treatment. **D** Changes in the absolute count of $CD3^+$T cells following tofacitinib treatment. **E** The tender joint count score before and 24 weeks after tofacitinib treatment. **F** The swollen joint count before and 24 weeks after tofacitinib treatment. Data are presented as means ± SEM. $*p < 0.05$; $**p < 0.01$

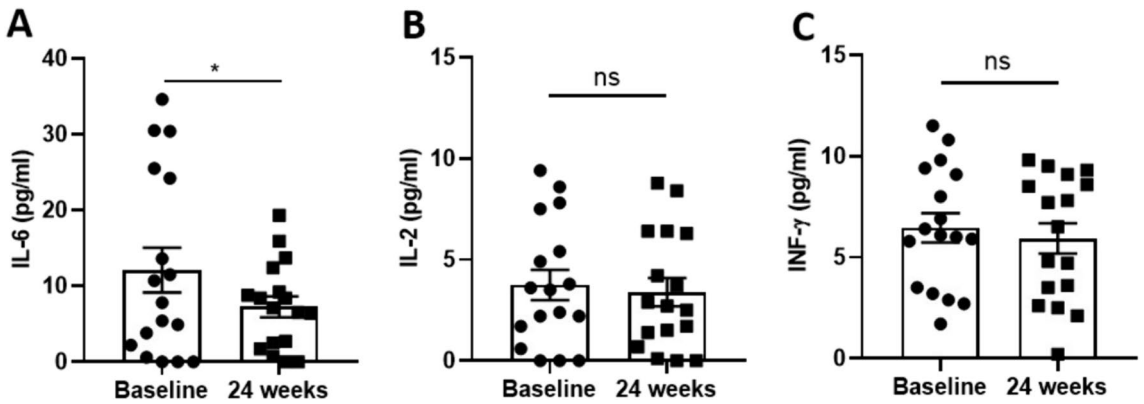

Fig. 4 Comparison of T cell activation-related cytokines before and after tofacitinib treatment ($n = 17$). **A**–**C** The levels of IL-6, IL-2, and IFN-γ before and after tofacitinib treatment. Data are presented as means ± SEM. $*p < 0.05$

respiratory tract infection. The clinical presentation of this patient is a high fever for 1 day and flu-like symptoms, without cough or sputum. After symptomatic treatment such as fever reduction for 1 week, the patient recovered, suggesting a possible viral infection. Neither allergic reactions nor other infections were observed during or after tofacitinib treatment.

Discussion

SLE is an autoimmune disorder marked by an abnormal immune response and the generation of autoantibodies, leading to inflammation and harm to different organs in the body. Although there is a considerable comprehension of

the causes of SLE and several therapy choices are accessible, numerous people continue to suffer from disease activity and its associated repercussions [13, 14]. The management of diseases and the improvement of treatment results remain significant concerns. In light of the present therapy regimens for SLE being ineffective, lacking specificity, and prone to causing various adverse effects, there is a need for new and more effective treatment choices to enhance the survival and well-being of individuals with this condition.

The SLE development includes the disruption of many innate and adaptive immunological pathways [15]. Previous research conducted by our lab and other researchers has shown that the JAK/STAT pathway is now acknowledged as a possible key contributor to the development of SLE. Our earlier findings showed that jakinibs, namely tofacitinib, effectively improved nephritis in MRL/lpr mice. This was confirmed by proteinuria and renal histological evaluations. Additionally, our research revealed that tofacitinib effectively decreased the levels of anti-dsDNA antibodies in the plasma and reduced the deposition of IgG in the kidneys [5]. Previous clinical trials have manifested that baricitinib has a positive safety profile and has the potential to successfully mitigate disease activity in active SLE patients [9, 10]. The encouraging results of a Phase 2 study and a subsequent SLE-BRAVE-I Phase 3 trial prompted further investigation into the possibility of baricitinib as a SLE treatment. Nevertheless, a trial called SLE-BRAVE-II revealed poor results, which have raised doubts about the therapeutic efficacy of baricitinib in treating SLE [9]. Presently, a meta-analysis has performed statistical research on the available clinical trial data and discovered that baricitinib 4 mg may possess the capability to enhance SLE disease activity, especially in those with articular signs [16]. It is possible that the lack of statistical significance is due to the variability observed at the study level or the limited sample size. In order to have a deeper understanding of the potential benefits of baricitinib in attaining complete response in SLE patients, more research investigations with bigger cohorts are necessary.

The major aim chosen for this clinical research is the remission of arthritis by SLEDAI-2 K. This choice was made since arthritis and rash are prevalent symptoms of SLE, and some studies have shown that tofacitinib has limited effectiveness in treating rash in SLE patients. Arthritis and musculoskeletal pain are common complaints in individuals with SLE. Enhancement in quality of life is associated with improvement in musculoskeletal complaints, as assessed by life quality [17–20]. Treatment with tofacitinib manifested enhancement in the percentage of individuals experiencing joint soreness, as assessed using a 28-joint test. Treatment with tofacitinib has shown a significant decrease in the percentage of patients experiencing the most severe joint pain and overall pain. Further evidence corroborating the outcomes for the main objective was the significant enhancements in crucial overall indicators of disease activity, encompassing SLEDAI and PGA, seen in patients following the tofacitinib administration.

JAK inhibitors have the ability to control several types of immune cells, such as T, B, and DC cells. Baricitinib functions by blocking type I interferon to decrease the dendritic cells of the innate immune system [21]. Furthermore, it regulates the activity of B and T cells in the adaptive immune system by inhibiting the signaling of IL-23, IL-2, IL-12, and type I interferon [21]. The latest research has also found that the JAK/STAT pathway can regulate the differentiation of age-associated B cells closely connected with the SLE pathogenesis, and the use of JAK inhibitor tofacitinib in lupus mice can reduce the proportion of age-associated B cells and disease activity [22].

This study mainly focuses on the regulatory effect of JAK inhibitors on T cells in lupus. The previous research findings are as follows: The JAK/STAT signaling pathway has the capacity to alter the expression levels of IFN-regulated factor (IRF)-related genes. These genes were manifested to be elevated in $CD3^+$ T cells in patients with active SLE [23]. Tofacitinib may reduce the survival rate of renal $CD69^+CD103^+$ tissue-resident memory T cells, which are seen in elevated numbers in the kidney tissues of patients with SLE or MRL/lpr mice [24]. Our earlier research manifested that tofacitinib effectively suppressed T cell activation in vitro and in vivo, indicating its promise as a therapeutic treatment for SLE. This clinical study confirms that tofacitinib can reduce T cell activation and related cytokines in lupus patients, thereby confirming our previous research.

In this study, we manifest that tofacitinib is both safe and well-tolerated in individuals with mild-to-moderate SLE. No unanticipated adverse events or exacerbation of SLE disease activity, serious adverse events, opportunistic infections, or thromboembolic events have been seen with the administration of tofacitinib.

As anticipated, there was a higher incidence of infections, mostly upper respiratory tract infections, after the administration of tofacitinib. The infection rate associated with tofacitinib was comparable to the rate reported in earlier studies for baricitinib, which was 6% [25]. The incidence of significant infections may be impacted by the frequent use of potent immune-modifying standard-of-care medication as a concurrent therapy. There were no documented fatalities, malignancies, major adverse cardiovascular events, cases of tuberculosis, or serious cases of herpes zoster.

The present research has limitations in terms of its brief length and a limited number of participants with mild-to-moderate illness. This research has some constraints that restrict the extent to which conclusions may be made. Significantly, this research only assessed a duration of 24 weeks. The specified time span constrained the capacity to evaluate long-term consequences and harm. Additional enhancements in effectiveness may be shown in a 52-week research.

Patients were permitted to maintain their current stable background standard-of-care medication, which included corticosteroids. The inclusion of background therapy had the potential to complicate the interpretation of the data.

In conclusion, our findings indicate that a 24-week course of tofacitinib treatment in SLE patients with arthritis is safe and effective, and the mechanism underlying the effect of tofacitinib in these patients may be related to reducing IL-6 expression and inhibited T cell activation.

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Data Availability The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Declarations

Ethics approval and consent to participate The study was approved by the ethics committee of Fujian Provincial Hospital (No. K2020-03–014). Written informed consent was obtained from all participants.

Disclosures None.

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