Oral tofacitinib citrate for recalcitrant cutaneous lupus

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INTRODUCTION

Cutaneous lupus erythematosus (CLE) is an autoimmune disorder with variable skin manifestations that can occur with or without systemic lupus erythematosus (SLE). While topical agents such as corticosteroids and calcineurin inhibitors for single lesions and systemic agents such as antimalarials, immunomodulators, and immunosuppressants for multiple lesions have demonstrated effectiveness in the treatment of CLE, options are limited when these modalities fail. The limited access to quinacrine in recent years has restricted antimalarial combination use, emphasizing the need for alternative therapies. Recommended second and third-line systemic treatments for CLE include methotrexate, mycophenolate mofetil, dapsone, systemic retinoids, and thalidomide.1 However, the use of thalidomide is limited by cost, the risk of thromboembolic events, and the high incidence of peripheral neuropathy.2 Lenalidomide is not often readily available for non-oncologic use. Therefore, there is an unmet need for novel effective therapies in the treatment of CLE.

Janus kinases (JAKs) are receptor-bound tyrosine kinases that mediate the action of various inflammatory cytokines through intracellular signaling via transducing signal transducer and activator of transcription proteins. Many cytokines implicated in lupus pathogenesis depend on JAK signaling to exert their intracellular action. In particular, interferon-associated JAK activation is thought to play a key role in CLE lesions; a recent study showed a significant upregulation of JAK signaling in cutaneous lesions of lupus.3 Therefore, JAK inhibitors represent a compelling option for the treatment of CLE.

Tofacitinib, a pan-JAK inhibitor with relative selectivity for JAK 1/3, has demonstrated promising results in the treatment of cutaneous features of SLE in a recent study.4 In another study, 67% of patients with SLE showed resolution of their arthritis or rash while on baricitinib 4 mg daily, a JAK 1/2 inhibitor, although improvement was not significant at a dose of 2 mg daily.5 In both studies, the subtype of CLE was not defined, as improvement was measured using the Systemic Lupus Erythematosus Disease Activity Index 2000 scale, which is not specific to skin disease.

In this article, we describe the efficacy of tofacitinib in 3 patients with CLE, using the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI), a scale that has been validated for the assessment of CLE.6

METHODS

We identified all patients with CLE who were prescribed tofacitinib at the Skin Care Center. Improvement was evaluated using the CLASI score and clinical information in the patient’s chart. Other endpoints included adverse events and the need for concurrent therapies. The subtype of CLE was assessed using information available in the charts. The cutaneous involvement in the first and second...
patients was evaluated using photographs and teleconsultation due to restrictions associated with the COVID-19 pandemic. Although in-person visits were offered, both patients declined. Patients were instructed to have a third party take photographs of all skin-involved areas. We ensured that all anatomical locations not included in the photographs were devoid of CLE involvement by questioning the patient. If there was any doubt, the patient was asked to send additional pictures. CLASI score items referring to mucous membrane involvement, dyspigmentation, and alopecia were determined by verbal questioning. It should be noted that the use of photographs to calculate CLASI scores has not yet been validated, thus caution should be exercised when interpreting the results.

RESULTS

The diagnosis of CLE was based on clinical, histopathologic, and laboratory evidence. CLE subtype was assessed clinically, according to Gilliam’s classification.7 Three patients with CLE treated with tofacitinib were identified (Table I). All of them had biopsy-confirmed CLE. They had multiple skin lesions and had failed at least 2 second or third-line systemic agents, in combination with antimalarial therapy and topical therapy, including potent corticosteroids and/or calcineurin inhibitors. The dose of tofacitinib was 5 mg twice daily for all patients. The first patient, a 51-year-old man with rheumatoid arthritis, had severe discoid lupus (Fig 1, upper panel), Raynaud syndrome, and fingertip ulcerations. He had been on hydroxychloroquine 400 mg daily for one year, and mycophenolate mofetil 1 g daily for 6 months for the treatment of his arthritis. Because his cutaneous lupus remained active, tofacitinib was added to the existing treatment. After 4 months, his CLASI score had decreased from 28 to 8, although he had ongoing Raynaud syndrome despite treatment.

Table I. Clinical summaries of patients treated with tofacitinib

| Patient No./Age/sex | Disease duration | Clinical presentation | Previous treatments | Concurrent treatments | Duration of tofacitinib treatment | CLASI activity Before | CLASI activity After | Clinical outcome |
|---------------------|-----------------|----------------------|---------------------|----------------------|-------------------------------|-------------------|-------------------|-----------------|
| 1/50s/M  | 2 years | Discoid lupus Raynaud syndrome and fingertip ulcerations | HCQ                  | MMF 2 g/d                  | 4 months | 28*  | 8* | Improvement in discoid lupus Ongoing Raynaud syndrome despite treatment |
| 2/70s/F  | 8 years | SCLE Sjögren syndrome | HCQ                  | HCC 400 mg/d                 | 7 months | 21*  | 0* | Resolution of all cutaneous lesions of lupus |
| 3/50s/F  | 11 years | Discoid lupus Tumid lupusACLE SLE | HCQ                  | Prednisone 10 mg/d             | 1 month | 23  | 16 | Effectiveness on limbs but ongoing facial involvement, tofacitinib switched to MMF and prednisone 20 mg/d after 1 month |

ACLE, Acute cutaneous lupus erythematosus; AZA, azathioprine; CLASI, cutaneous lupus erythematosus disease area and severity index; CsA, cyclosporine; CQ, chloroquine; HCC, hydroxychloroquine; MTX, methotrexate; MMF, mycophenolate mofetil; SCLE, subacute cutaneous lupus erythematosus; SLE, systemic lupus erythematosus. *CLASI scores from patients 1 and 2 were calculated using patient-supplied pictures.
the first patient had changes in his baseline parameters, his white blood cell count dropping from $4 \times 10^9/L$ to $2.6 \times 10^9/L$, remaining stable afterward.

**DISCUSSION**

Two studies have described the use of JAK inhibitors in the treatment of CLE, using the SLE Disease Activity Index 2000 as the main end point. JAK inhibitors have not specifically been studied for the treatment of skin involvement. In this study, we measured CLASI scores, which monitor skin disease activity on a more continuous scale than the SLE Disease Activity Index 2000. In the 3 patients studied, CLASI improvement was more than 4 points, which is the number required for clinically significant improvement. Reported side effects from tofacitinib include infections, cytopenia, thrombocytosis, and elevated liver enzymes, none of which were observed in the patients presented. Potentially increased rates of venous thromboembolic disease and malignancy are additional concerns. The main limitation of this study is the use of photographs and teledermatology to derive CLASI scores in 2 of the patients, a method that has not been validated and could lead to potential bias. Other limitations include the retrospective design, the small number of patients, the short follow-up, and the concurrent use of other treatments. Although our results are encouraging, larger studies are needed to assess the effectiveness of JAK inhibitors in CLE.

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Conflicts of interest
None disclosed.

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