doi:10.36849/JDD.7098

BRIEF COMMUNICATION Journal of Drugs in Dermatology

Open-Label Phase 2 Pilot Study of Oral Tofacitinib in Adult Subjects With Discoid Lupus Erythematosus (DLE)

Sarah Alsukait MBBS, Christine Learned BA, David Rosmarin MD

Tufts Medical Center Department of Dermatology, Boston, MA

INTRODUCTION

Discoid lupus erythematosus (DLE) is a chronic inflammatory skin disease that occurs with or without systemic lupus erythematosus (SLE). DLE treatment is challenging, and there is paucity of effective therapeutic options for patients with recalcitrance or intolerance to conventional therapies. Interferon-associated Janus Kinase (JAK) activation is considered a key mediator in lupus, highlighting the potential therapeutic role of JAK inhibitors.[1] We evaluated the efficacy and safety of oral tofacitinib, a JAK inhibitor currently approved for the treatment of psoriatic arthritis, rheumatoid arthritis, polyarticular course juvenile idiopathic arthritis, ankylosing spondylitis, ulcerative colitis, in adult patients with active DLE with or without concurrent SLE.

Here, we describe the results of a 24-week, open-label, single-center pilot study of five patients with DLE, including 1 with concurrent SLE treated with 5 mg oral tofacitinib administered twice daily. All had biopsy-proven DLE for > 6 months, DLE covering > 5% of body surface area (BSA) or SLE with DLE covering > 2% of BSA, and Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) score > 8 at baseline. The primary endpoint was an improvement in CLASI activity (CLASI-A) score at week 24, a validated score for cutaneous lupus erythematosus (CLE) severity. A four-point or 20% decrease in CLASI-A score was identified as minimal clinically significant improvement. However, a 6-point decrease or 50% reduction in CLASI-A reflects an important change.[2] Quality of life (QoL) was assessed using Skindex-29, a validated skin-specific QoL survey.[3] Other endpoints are summarized in Table 2. Study visits occurred every 2-4 weeks, during which clinical and safety parameters were evaluated. This study was approved by Tufts Institutional Review Board and registered with ClinicalTrials.gov (NCT03159936).

Patient characteristics are described in Table 1. Five patients (4 females) with a mean age of 47.6 years were enrolled. Three of five patients completed the study. One was lost to follow-up (#2) and one early terminated (#3) due to flaring of established psoriasis. The average disease duration was 7.8 years, and all patients had failed or were intolerant to topical steroids and antimalarials. Three patients received combination therapy with hydroxychloroquine. Assessments and outcomes are described in Table 2. Two patients showed improvement in DLE by week 24 with a 75% reduction in CLASI-A score (#1, #5), and two showed minimal response with a 30% reduction (#2, #4). Patient #3 showed only 13% reduction in CLASI-A, which was assessed at week five due to early termination. Only one patient had concurrent SLE (#1), which was non-responsive based on SLE Responder Index (SRI). Three patients had scalp involvement, and those who completed the study (#1, #5) experienced 100% and 65% hair regrowth, respectively. Three patients (#2, #4, #5) experienced a decrease in their Skindex-29 score with a 22%, 47%, and 38% reduction, respectively whereas two patients had an increase in Skindex-29 scores. None of the subjects achieved a Physician's Global Assessment (PGA) of clear and almost clear (0-1). Mild to moderate adverse events (AEs) occurred in four patients (Table 2). No serious AEs were observed.

To date, no drug has been approved for the treatment of DLE.[1] In a phase II trial, baricitinib, a JAK1/2 inhibitor, improved the proportion of patients with SLE achieving resolution of arthritis or rash; however, this effect was mainly due to joint improvement, whereas skin severity as measured by CLASI did not improve.[4] Recently it was announced that baricitinib development for lupus treatment was discontinued after one phase 3 study met and one phase 3 study did not meet the primary endpoint of SRI-4 response.[5] Tofacitinib has demonstrated promising results in treating cutaneous features of SLE.[6] A recent case series described three patients with recalcitrant CLE who responded to tofacitinib with CLASI improvement of more than 4 points.[7] The improvement observed in two of our participants further supports the role of JAK in CLE pathogenesis. Study limitations include a small sample size, lack of a control group, and concurrent use of other treatments. Randomized, placebo-controlled, dose-ranging trials with a larger number of patients are required to further determine the efficacy of JAK inhibitors in DLE.

TABLE 1.

Baseline Characteristics and Treatment Course of Discoid Lupus Erythematosus Patients Treated With Tofacitinib

Characteristic	Patient No.				
	1	2	3	4	5
Age, y/Gender/Race	48/F/Asian	37/F/Caucasian	39/M/Hispanic	56/F/Caucasian	58/F/Caucasian
Smoking history	No	Yes	No	No	No
Concurrent SLE	Yes with lupus nephritis	No	No	No	No
Disease duration prior to Tofacitinib, y	DLE 1, SLE 14	2	7	17	12
Relevant concurrent therapies	HCQ 400 mg/d	HCQ 400 mg/d	--	HCQ 400 mg/d	--
Prior LE treatments attempted	Topical steroids, HCQ, MMF, dapsone, topical tacrolimus, belimumab, systemic steroids, MTX, AZA	Topical steroids, HCQ, ILT, dapsone, hydroxyzine	Topical steroids, HCQ (discontinued due to drug eruption), MTX, topical tacrolimus	Topical steroids, HCQ, topical pimecrolimus, ILT	Topical steroids, HCQ, topical tacrolimus, prednisone, ILT
ANA, dsDNA, ENA positivity	ANA 1:160, SS-A 40.8	No	No	No	No
Tofacitinib treatment duration, w	24	16	5	24	24

Abbreviations: F, Female; M, Male; y, year; w, weeks; SLE, systemic lupus erythematosus; DLE, discoid lupus erythematosus; HCQ, hydroxychloroquine; MMF, mycophenolate mofetil; MTX, methotrexate; AZA, azathioprine; ILK, intralesional triamcinolone; ANA, antinuclear antibody; dsDNA, double-stranded DNA; ENA, extractable nuclear antigen antibody; LE, lupus erythematosus.

TABLE 2.

Assessments and Treatment Outcomes in Discoid Lupus Erythematosus Patients Treated With Tofacitinib

Characteristic	Patient No.									
	1		2		3		4		5	
Week/Visit	B	W24	B	WK16	B	W5	B	W24	B	W24
CLASI (Activity)	12 (A8)	6 (A2)	56 (A36)	51 (A25)	24 (A15)	22 (A13)	35 (A10)	32 (A7)	22 (A12)	9 (A3)
CLASI activity % change	75%		30.5%		13.3%		30%		75%	
SLEDAI-2K	10	8	2	2	4	4	2	2	4	4
BSA	2%	1%	9%	7%	7%	7%	6.5%	6.9%	5.5%	1%
PGA	2	1.7	3	2.8	1.9	1.8	2.4	1.9	2.3	4
Pain VAS	48	41	100	93	0	94	10	10	14	0
Itch VAS	2.9	5.6	10	6	0	9	3	0.5	6.7	0.5
Patient GA	4.9	5.6	10	8.8	0	0	5	1	3.4	9
Alopecia diameter, mm	10	0.0	--	--	30	30	--	--	20	7
SKINDEX-20a	68	74	143	111	72	96	117	62	59	36
SRI	Non-responder		NA		NA		NA		NA	
Outcome based on CLASI activity	Improved		Minimal response		No response		Minimal response		Improved	
Study status	Completed		Lost to follow-up		Early terminated		Completed		Completed	
Adverse events	Folliculitis, gastroenteritis, scalp pruritus		Secondary bacterial skin infection on existing DLE lesion		Flaring of established psoriasis		None		Acne, paronychia	

Abbreviations: B, Baseline; W24, week 24; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000 score; BSA, body surface area; PGA, physician global assessment; VAS, visual analog scale; GA, global assessment; mm, millimeter; SRI, SLE Responder Index; NA, not applicable.
[a]Linear scale, running from 0 to 100; higher scores indicate a lower level of quality of life.

DISCLOSURES

David Rosmarin has received honoraria as a consultant for AbbVie, Abcuro, AltruBio, Boehringer-Ingelheim, Bristol Meyers Squibb, Celgene, Concert, CSL Behring, Dermavant, Dermira, Incyte, Janssen, Kyowa Kirin, Lilly, Novartis, Pfizer, Regeneron, Sanofi, Sun Pharmaceuticals, UCB, VielaBio; has received research support from AbbVie, Amgen, Bristol Meyers Squibb, Celgene, Dermira, Galderma, Incyte, Janssen, Lilly, Merck, Novartis, Pfizer, and Regeneron Pharmaceuticals Inc; and has served as a paid speaker for AbbVie, Amgen, Celgene, Janssen, Lilly, Novartis, Pfizer, Regeneron Pharmaceuticals Inc., and Sanofi.

Pfizer Inc. is the maker of the drug tofacitinib and has provided funding to conduct this study. Pfizer Inc. also contributed to the study design.

IRB approval: reviewed and approved Tufts Institutional Review Board; approval # 12376

Clinicaltrials.gov listing: NCT03159936

Funding: The sponsor of the study is Tufts Medical Center. Pfizer Inc. is the maker of the drug tofacitinib and has provided funding to conduct this study.

REFERENCES

1. Wenzel J. Cutaneous lupus erythematosus: new insights into pathogenesis and therapeutic strategies. *Nat Rev Rheumatol.* 2019 Sep;15(9):519-532.
2. Chakka S, Krain RL, Concha JSS, Chong BF, Merola JF, Werth VP. The CLASI, a validated tool for the evaluation of skin disease in lupus erythematosus: a narrative review. *Ann Transl Med.* 2021;9(5):431.
3. Klein R, Moghadam-Kia S, Taylor L, Coley C, Okawa J, LoMonico J, Chren MM, Werth VP. Quality of life in cutaneous lupus erythematosus. *J Am Acad Dermatol.* 2011;64(5):849-58.
4. Bruce IN, Gomez E, Carmack T, et al. Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet.* 2018;392(10143):222-231.
5. Lilly. Updates on OLUMIANT® (baricitinib) Phase 3 lupus program and FDA review for atopic dermatitis. Available at: https://investor.lilly.com/news-releases/news-release-details/updates-olumiantr-baricitinib-phase-3-lupus-program-and-fda. Accessed June 05, 2022.
6. You H, Zhang G, Wang Q, Zhang S, Zhao J, Tian X, Li H, Li M, Zeng X. Successful treatment of arthritis and rash with tofacitinib in systemic lupus erythematosus: the experience from a single center. *Ann Rheum Dis.* 2019;78(10):1441-1443.
7. Bonnardeaux E, Dutz JP. Oral tofacitinib citrate for recalcitrant cutaneous lupus. *JAAD Case Rep.* 2021 Oct 2;20:61-64.

AUTHOR CORRESPONDENCE

David Rosmarin MD
E-mail:..... dermrese@iu.edu