

Treatment of cutaneous sarcoidosis with tofacitinib 2% ointment and extra virgin olive oil



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Key words: cutaneous sarcoidosis; JAK inhibitor; JAK-STAT; oleoanthal; olive oil; tofacitinib.

INTRODUCTION

Sarcoidosis is a chronic multisystem inflammatory disorder characterized by granuloma formation. Macrophage accumulation and activation in sarcoidosis is thought to be mediated by CD4+ helper T cells via interferon γ (IFN γ) and other cytokines. IFN γ acts through the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling pathway.¹ Immunosuppressants such as corticosteroids, methotrexate, and tumor necrosis factor- α inhibitors are used to treat sarcoidosis, but these medications may have significant adverse effects and are variably effective. Interruption of JAK-STAT signaling holds promise for treatment. Oral JAK inhibitors have resulted in clinical and histologic resolution of cutaneous sarcoidosis¹⁻³ and other granulomatous diseases such as granuloma annulare¹ and necrobiosis lipoidica.^{4,5} Recently, use of topical tofacitinib, a selective inhibitor of JAK1 and JAK3, has resulted in resolution of localized⁶ and generalized⁷ granuloma annulare. Here, we present a patient with primarily cutaneous sarcoidosis with quiescent lung disease who experienced marked improvement of cutaneous lesions after topical tofacitinib therapy.

CASE REPORT

A 46-year-old man presented for evaluation and management of scaly papules and plaques. Nine years before, he developed nonhealing crusted nodules on his scalp and arms and within multiple tattoos. Skin examination revealed violaceous, atrophic, scaly patches and thin plaques on his scalp and arms with associated cervical and submandibular

Abbreviations used:

EVOO:	extra virgin olive oil
IFN:	interferon
JAK:	Janus kinase
STAT:	signal transducer and activator of transcription

lymphadenopathy (Fig 1). Biopsy of an arm lesion demonstrated sarcoidal granulomatous inflammation with aggregates of histiocytes and giant cells, with minimal surrounding lymphocytic inflammation. Angiotensin-converting enzyme and 1,25-(OH)₂ vitamin D were elevated at 73 pg/dL (normal, 18-72 pg/dL) and 84 U/L (normal, 9-67 U/L), respectively, and the 25-OH vitamin D concentration was 11 ng/mL (normal, 30-100 ng/mL). Evaluation for sarcoidosis revealed subtle fibronodular changes in the right lung and bilateral hilar and mediastinal lymphadenopathy on chest imaging. He had no pulmonary symptoms, and his pulmonary function tests have remained normal. An ophthalmologic examination and electrocardiogram were normal.

The patient was initially treated with intralesional triamcinolone acetonide injection (10 mg/mL) and topical clobetasol propionate 0.05% ointment. He had persistent active cutaneous disease resistant to tacrolimus 0.1% ointment, tretinoin 0.025% cream, adapalene 0.1% gel, pimecrolimus 1% cream, triamcinolone acetonide 0.1% ointment, oral hydroxychloroquine at a dose of 200 mg daily due to transaminitis at higher dose, and oral doxycycline at a dose of 100 mg twice daily. The patient was reluctant to use systemic

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Funding sources: none.

IRB approval status: Not applicable.

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JAAD Case Reports 2021;9:■-■.

2352-5126

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<https://doi.org/10.1016/j.jidcr.2020.12.021>



Fig 1. Scalp at presentation, before treatment. Violaceous, atrophic, scaly patches and thin plaques with crusted nodule at center of scalp.

medications and discontinued hydroxychloroquine and doxycycline. He continued to use triamcinolone acetonide 0.1% ointment as needed. His cutaneous disease progressed with multiple large, scaly, violaceous, atrophic plaques with mild dyspigmentation on his scalp (Fig 2, A) and thick scaling papules on his right forearm and left posterior arm tattoo. He was prescribed compounded tofacitinib 2% ointment twice daily (30-g tube), which he used as prescribed for 2 weeks. He then self-adjusted his regimen to apply tofacitinib every other day in combination with self-initiated extra virgin olive oil (EVOO) to his scalp daily for 2 weeks and intermittently thereafter. The patient was uncertain whether skin changes occurred on this regimen. On repeat assessment by his dermatologist 5 months later, his examination showed significant improvement in erythema, scaling, and induration, and the plaques appeared less violaceous (Fig 2, B). His Cutaneous Sarcoidosis Activity Morphology Instrument disease activity scores on his scalp improved from 9 to 5, and he has described continued improvement beyond that. He experienced no adverse effects during treatment.

DISCUSSION

The JAK-STAT pathway is a critical signaling mechanism for various cytokines, including IFN γ , which plays a central role in inflammatory disorders and granuloma formation. There are 4 JAK proteins and 7 STAT proteins. IFN γ activates JAK1 and JAK2, thereby activating STAT1 with downstream target transcription, while other cytokines act through different JAK-STAT pathways. JAK inhibitors are variably selective for individual JAK proteins. Tofacitinib is thought to primarily act through JAK1 and JAK3 inhibition, while ruxolitinib blocks JAK1 and JAK2.⁸

JAK inhibitors are Food and Drug Administration–approved for a variety of indications and have recently shown promise in treatment of inflammatory skin disorders, including psoriasis, atopic dermatitis, alopecia areata, vitiligo, and granulomatous diseases such as granuloma annulare, necrobiosis lipoidica, and cutaneous sarcoidosis.^{2,4,7} To date, successful treatment of 5 patients with cutaneous sarcoidosis with oral JAK inhibitors has been reported.^{1-3,9}

JAK-STAT pathway activation signatures, especially STAT1- and STAT3-dependent transcripts, are constitutively expressed in cutaneous tissue, plasma, and peripheral blood mononuclear cells in patients with sarcoidosis. Treatment with oral tofacitinib has been shown to eradicate expression of STAT1 and STAT3 signatures on immunohistochemical analysis and normalize IFN γ , IFN α , and interleukin 6-STAT3 on RNA sequencing of lesional tissue in patients with cutaneous sarcoidosis with concomitant clinical improvement.^{1,3} Of note, JAK-STAT–independent pathways are also down-regulated by tofacitinib, suggesting more far-reaching effects of cytokine dysregulation.^{1,3}

We observed clinical improvement of cutaneous sarcoidosis in our patient after treatment with topical tofacitinib. To our knowledge, there are no prior reports of improvement of cutaneous sarcoidosis by topical tofacitinib. Tofacitinib 2% ointment led to near resolution of treated lesions in 1 patient with localized granuloma annulare⁶ and in 1 patient with generalized granuloma annulare with localized application.⁷

Treatment of recalcitrant cutaneous sarcoidosis typically involves systemic medications, which carry significant adverse effects. Some patients, such as ours, are hesitant to use systemic therapy. Our findings suggest that topical tofacitinib may be a viable alternative. Although oral JAK inhibitors have been reported to be well tolerated in patients with cutaneous granulomatous disease thus far,^{1,2,4} risks include infection, particularly viral infection or reactivation, and thrombosis,⁸ and the small sample size of these reports may underestimate the adverse effects of systemic JAK inhibition. Several of these reports have also noted insurance barriers to adherence, and topical tofacitinib could serve as an alternative. However, topical JAK inhibitors are currently not widely available nor covered by insurance and may also incur significant out-of-pocket costs.

Our patient self-administered EVOO to his scalp within the time frame of clinical improvement. EVOO contains oleocanthal, which is thought to have anti-inflammatory properties similar to those of nonsteroidal anti-inflammatory agents via cyclooxygenase 1 and cyclooxygenase 2 inhibition.

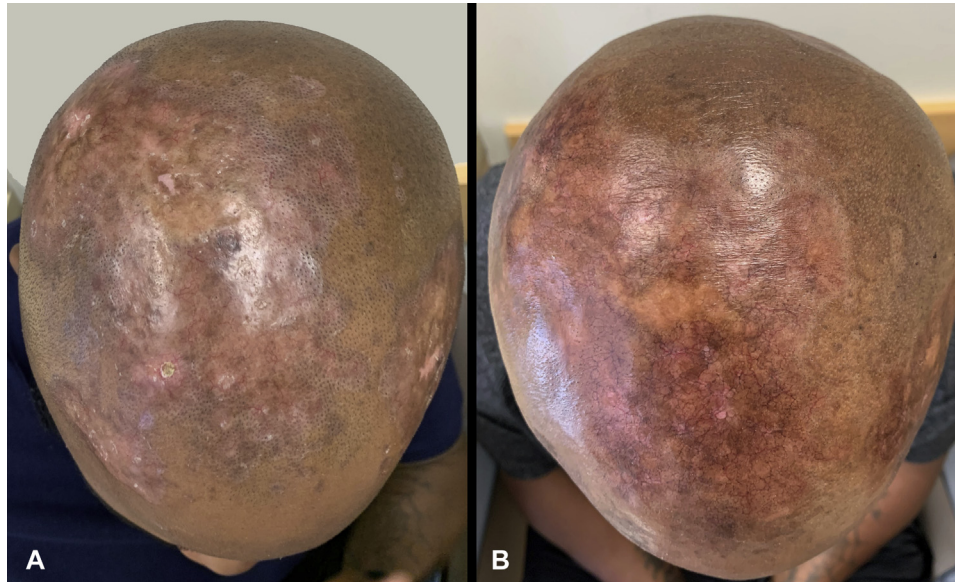


Fig 2. Cutaneous sarcoidosis before and after tofacitinib 2% ointment and extra virgin olive oil applied to the scalp. **A**, Violaceous, scaly plaques on the scalp; Cutaneous Sarcoidosis Activity Morphology Instrument activity score 9: inflammation (3), induration (1), surface change (1), area (4). **B**, Improvement in lesions on the scalp after 5 months of intermittent topical tofacitinib. Cutaneous Sarcoidosis Activity Morphology Instrument activity score 5: inflammation (1), induration (0), surface change (0), area (4).

Intriguingly, oleocanthal also has been shown to block the activity of STAT3 in hepatocellular carcinoma and melanoma. It is possible that oleocanthal contributed to the patient's improvement through these mechanisms, although, notably, oleocanthal comprises only 0.02% of EVOO by weight.¹⁰

We report clinical improvement in cutaneous sarcoidosis with tofacitinib 2% ointment in combination with EVOO. Our case highlights the need for further exploration of topical JAK inhibitors in cutaneous sarcoidosis.

Conflicts of interest

Dr Rosenbach receives research support from Processa and has received consulting fees from Merck, Janssen, and Lilly. Drs Alam and Fang have no conflicts of interest to declare.

REFERENCES

- Damsky W, Thakral D, McGeary MK, Leventhal J, Galan A, King B. Janus kinase inhibition induces disease remission in cutaneous sarcoidosis and granuloma annulare. *J Am Acad Dermatol.* 2020;82(3):612-621.
- Wei JJ, Kallenbach LR, Kreider M, Leung TH, Rosenbach M. Resolution of cutaneous sarcoidosis after Janus kinase inhibitor therapy for concomitant polycythemia vera. *JAAD Case Rep.* 2019;5(4):360-361.
- Damsky W, Thakral D, Emeagwali N, Galan A, King B. Tofacitinib treatment and molecular analysis of cutaneous sarcoidosis. *N Engl J Med.* 2018;379(26):2540-2546.
- Damsky W, Singh K, Galan A, King B. Treatment of necrobiosis lipoidica with combination janus kinase inhibition and intralesional corticosteroid. *JAAD Case Rep.* 2020;6(2):133-135.
- Lee J, English JC. Improvement in ulcerative necrobiosis lipoidica after janus kinase-inhibitor therapy for polycythemia vera. *JAMA Dermatol.* 2018;154(6):733-734.
- Damsky W, King BA. Treatment of granuloma annulare with tofacitinib 2% ointment. *JAAD Case Rep.* 2019;6(1):69-71.
- Durgin JS, Shields BE, Rosenbach M. Generalized granuloma annulare: a widespread response to limited application of compounded 2% topical tofacitinib. *JAAD Case Rep.* 2020;6(10):1113-1115.
- Wang A, Singh K, Ibrahim W, King B, Damsky W. The promise of JAK inhibitors for treatment of sarcoidosis and other inflammatory disorders with macrophage activation: a review of the literature. *Yale J Biol Med.* 2020;93(1):187-195.
- Rotenberg C, Besnard V, Brillet PY, Giraudier S, Nunes H, Valeyre D. Dramatic response of refractory sarcoidosis under ruxolitinib in a patient with associated JAK2-mutated polycythemia. *Eur Respir J.* 2018;52(6):1801482.
- Segura-Carretero A, Curiel JA. Current disease-targets for oleocanthal as promising natural therapeutic agent. *Int J Mol Sci.* 2018;19(10):2899.