Treatment of granuloma annulare with tofacitinib 2% ointment

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Granuloma annulare (GA) is an autoimmune cutaneous disorder characterized by clusters of macrophages and T cells giving rise to pink papules and annular plaques. GA can be challenging to treat, and even localized disease is often unresponsive to topical corticosteroids and calcineurin inhibitors; intralesional triamcinolone can be effective in some cases. Better therapies are needed for GA and other cutaneous granulomatous disorders.

In GA, $CD4^+$ helper T cells with a T_h1 phenotype tend to predominate among the lymphocytic portion of the infiltrate.[1] These T cells produce interferon (IFN)-γ, a cytokine that has a well-characterized role in macrophage activation and granuloma formation.[2] In GA, IFN-γ is likely a key driver of macrophage recruitment, activation, and retention in lesional skin. IFN-γ (and other cytokines) signals through the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway inside target cells. Thus, drugs that inhibit the activity of IFN-γ (and other cytokines) via blocking JAK-STAT signaling, may offer a pathogenesis-directed treatment approach for GA and other granulomatous disorders.

Along these lines, we recently showed that JAK-STAT signaling is constitutively activated in GA (and sarcoidosis) in a pattern consistent with IFN-γ–dependent activation of macrophages.[3,4] We showed that treatment of patients with recalcitrant sarcoidosis and GA with an oral JAK inhibitor, tofacitinib, induced dramatic disease remission in these patients.[3,4]

Abbreviations used:

GA:	Granuloma annulare
IFN:	interferon
JAK:	Janus kinase
JAK-STAT:	Janus kinase signal transducer and activator of transcription

In most patients with localized GA, treatment with an oral JAK inhibitor would be inappropriate. Despite the apparent efficacy of oral tofacitinib in cutaneous granulomatous disorders, it remains unknown whether a topical JAK inhibitor might show similar efficacy. Here we evaluate the efficacy of tofacitinib 2% ointment in a patient with localized GA.

A 69-year-old man with a 1-year history of GA presented for evaluation and treatment. The lesions were asymptomatic. He also had type 2 diabetes and hypertension. Cutaneous examination revealed pink papules and annular plaques without scale on the neck, forehead, arms and hands (Fig 1). A skin biopsy from the forearm showed a perivascular lymphocytic infiltrate associated with a perivascular and interstitial histocytic infiltrate in the dermis, with focal areas of degenerated collagen palisaded by

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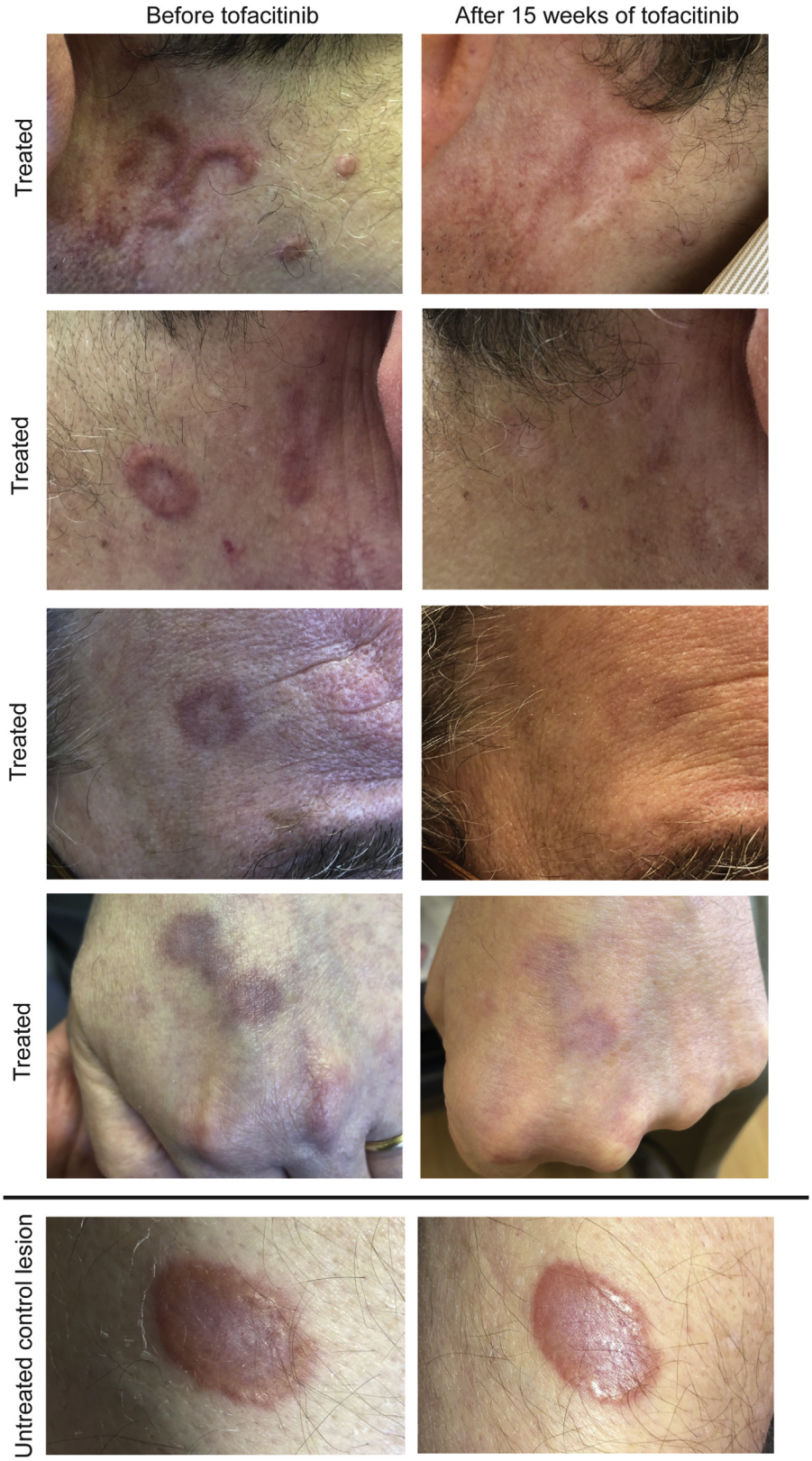

Fig 1. Effect of tofacitinib 2% ointment in GA. **Upper panels**, Clinical images before tofacitinib (**left panels**) and after 15 weeks of tofacitinib 2% ointment twice daily (**right panels**). **Lower panels**, a single lesion was left untreated to control for spontaneous resolution of GA. Clinical image of the untreated lesion before and after treatment of the other lesions.

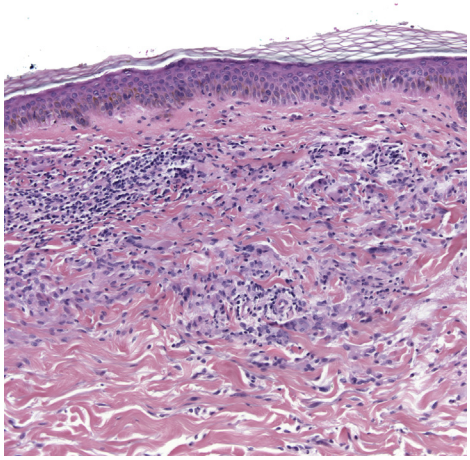

Fig 2. Skin biopsy shows GA. Histocytes and lymphocytes in the dermis, with focal areas of degenerated collagen palisaded by histiocytes, consistent with GA. (Original magnification: ×200.)

histiocytes, consistent with GA (Fig 2). Solar elastosis was minimal, and elastophagocytosis was not observed.

The patient was previously treated with triamcinolone 0.1% ointment without effect. Treatment of a single plaque on the dorsal hand with intralesional triamcinolone led to flattening of that lesion. The patient was offered repeat intralesional triamcinolone and/or oral hydroxychloroquine but declined. Instead, compounded tofacitinib 2% ointment was initiated twice daily. He was instructed to apply the tofacitinib to all but 1 lesion (on the forearm); this lesion was left untreated to control for the observation that localized GA can occasionally undergo spontaneous remission. After 15 weeks, there was marked improvement and near resolution of all treated lesions (Fig 1). The untreated lesion on the forearm persisted. No adverse effects occurred.

JAK inhibition is an emerging, molecularly targeted approach for cutaneous granulomatous disorders. We previously showed that patients with recalcitrant GA and sarcoidosis experienced disease remission on oral tofacitinib.[3,4] Others have reported a similar effect in patients with sarcoidosis treated with oral ruxolitinib (another JAK inhibitor), administered for concomitant myeloproliferative neoplasms.[5,6] Clinical trials are underway to better characterize the role of oral JAK inhibitors in the treatment of severe cutaneous sarcoidosis and GA (NCT03910543, NCT03793439).

We show that tofacitinib 2% ointment was effective in a patient with localized GA. Tofacitinib 2% ointment was chosen because this concentration of tofacitinib has been used in clinical trials. A specific effect of tofacitinib is supported by the observation that a single untreated lesion did not also improve during tofacitinib treatment of the other lesions. Biopsy after clinical improvement of the GA was not pursued; however, in patients treated with oral tofacitinib, histologic clearance of granulomas has been observed.[3,4]

These data suggest that topical JAK inhibitors may be beneficial in patients with cutaneous granulomatous disorders with limited involvement. Larger studies are warranted to better characterize the role of topical JAK inhibitors in treating GA and related disorders.

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