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Treatment of Granuloma Annulare Using Tapinarof Cream 1%

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ABSTRACT

Granuloma annulare (GA) is a benign, non-infectious cutaneous granulomatous disease. Its pathogenesis is not completely elucidated but has recently been thought to involve immunologic and cytokine receptor signaling dysregulation. This includes the involvement of both Th1 and Th2 pathways as well as Th17 and Th22 axes and the Janus kinase/signal transducers and activators of the transcription (JAK-STAT) pathway. First-line treatment is typically intralesional or topical corticosteroids; however, these therapies do not always provide consistent, long-term efficacy for all patients. The successful use of therapies that target the specific inflammatory and immunologic mechanisms that underlie the pathogenesis of GA has been described. Here we describe a case of long-standing GA treated with tapinarof cream 1% applied once daily for 30 days. To our knowledge, this treatment has not yet been adequately described in the literature.

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INTRODUCTION

Granuloma annulare (GA) is a benign, non-infectious cutaneous granulomatous disease with an estimated prevalence of up to 0.06% in the United States.[1] It typically presents as skin colored to erythematous papules or plaques of circinate or annular configuration.[2]There are multiple variants including localized, generalized, perforating, patch, and subcutaneous subtypes.[2] The pathogenesis of the disease remains elusive. Current theories involve immunologic and cytokine receptor signaling responses. Newer research highlights GA as an immunologically driven condition elucidating the involvement of both Th1 and Th2 pathways as well as Th17 and Th22 axes and the Janus kinase/signal transducers and activators of transcription (JAK-STAT) pathway.[3,4] However, it is important to note that emerging studies may not consistently concur, and larger studies are needed to investigate the pathogenic arms involved in the disease process with the ultimate goal of streamlining treatment.

There are currently no Food and Drug Administration (FDA)-approved therapies specifically for GA. Intralesional or topical corticosteroids are considered first-line options.[2] However, even our first-line treatment options do not offer consistent efficacy for all patients, and thus we must turn to second-line and third-line options whose efficacy are typically not supported by large, randomized controlled trials but rather anecdotal reports or trials with small sample sizes. These include, but are not limited to, biologic therapy, phosphodiesterase-4 inhibition, antimalarials, antimicrobials, isotretinoin, methotrexate, pentoxifylline, phototherapy, sulphasalazine, and more recently, JAK inhibitors.[2] Indeed, both oral and topical tofacitinib have recently been reported to be efficacious in treating GA, underscoring the immunologic mechanisms at play in the pathogenesis of the disease.[3,5,6,7] Given the recent evidence implicating these immunologic mechanisms, including Th1, Th2, and Th17 pathways, in the pathogenesis of GA, we hypothesized that treatment with tapinarof cream 1% may improve GA symptoms.

Case Study

A 49-year-old healthy female presented with a long-standing history of GA with concomitant pruritus. The patient reported that the condition had been biopsy-proven in the past and had been present for a few years. Previous treatments included several courses of topical corticosteroids. These treatment courses provided intermittent relief, but she continued to experience frequent flares on the dorsal surface of her hand (Figure 1). She expressed interest in topical non-steroidal treatment due

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FIGURE 1. Granuloma annulare affecting the dorsal surface of the patient's hand.

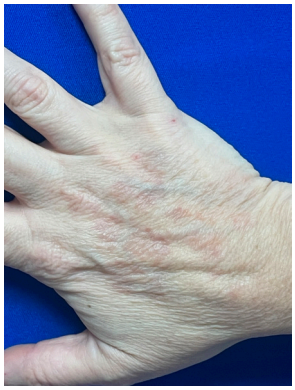
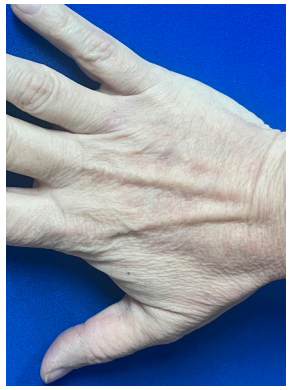


FIGURE 2. Granuloma annulare involved area 30 days after daily application of tapinarof cream 1%.

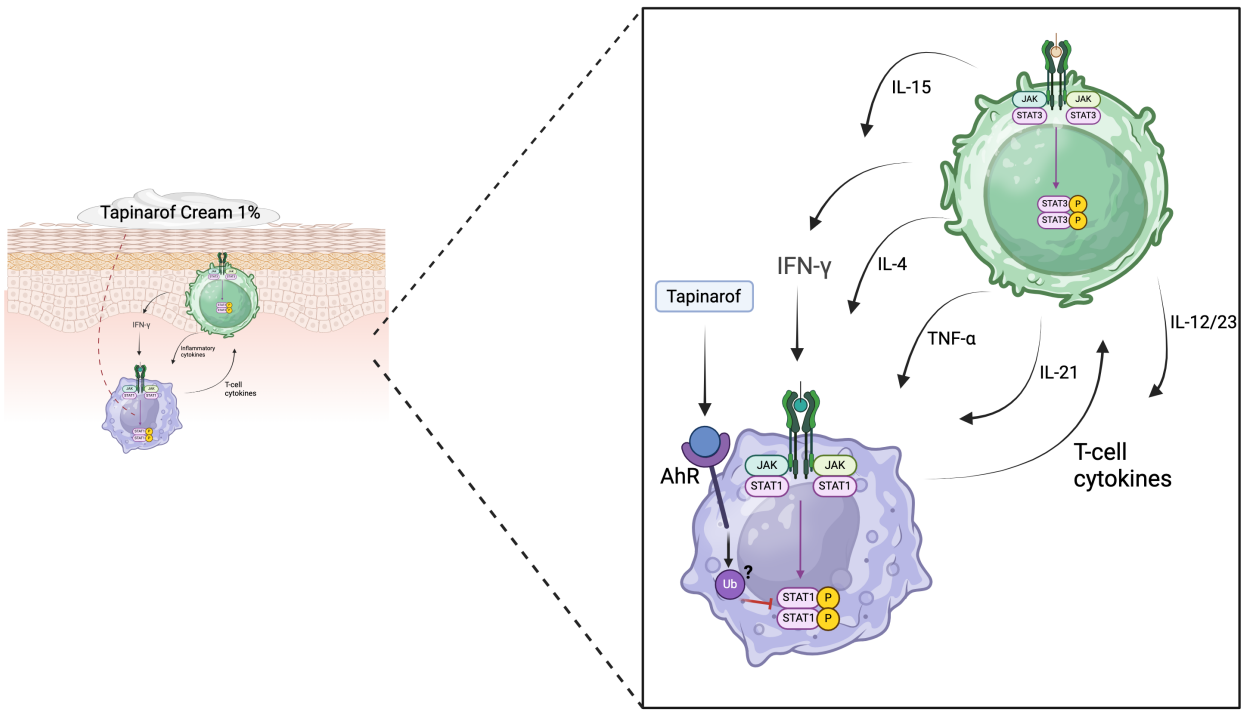


to concerns about adverse effects of corticosteroids. Given the patient's personal decision not to pursue corticosteroid therapy, she opted for off-label topical treatment with tapinarof cream 1%, a first-in-class aryl hydrocarbon receptor (AHR) agonist with cutaneous anti-inflammatory effects currently approved for the treatment of adult plaque psoriasis.[8] The patient was instructed to apply tapinarof cream 1% once daily to the affected areas for 30 days. Clinical follow-up 1 month after treatment initiation showed significant clinical improvement with complete resolution of the GA lesions (Figure 2). The patient was then instructed to use tapinarof as needed at the first sign of, and during, disease flare.

DISCUSSION

Given its unclear etiology, GA treatment has proven to be challenging. Recent evidence highlighting immunologic dysregulation in the pathogenesis of the disease opens the door to exploring emerging therapeutics that are designed to target these pathways. Tapinarof is a novel AHR-modulating agent that downregulates proinflammatory cytokines and balances skin barrier protein dysregulation.[8] The pathogenesis of GA is thought to involve the upregulation of inflammatory cytokines involved in both Th1 and Th2 pathways including but not limited to interferon (IFN)-γ, tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-4, IL-21, IL-31, IL-12/23, IL-15, and IL-6.[3,4,7] Upregulation of

FIGURE 3. Proposed mechanism of tapinarof cream 1% in the treatment of granuloma annulare through the aryl hydrocarbon receptor (AhR) mediated degradation of STAT1. Created with BioRender.com.



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Th17, Th22, and JAK-STAT axes, particularly STAT1 and STAT3, may also contribute to the disease process.[4,7] The reported efficacy of treating GA using therapies that target these cellular pathways strongly reinforces their potential significance in the underlying pathological process. This includes treatment of GA with TNF-inhibition, JAK-inhibition, and IL-4 and IL-13 inhibition.[3,5,6,9,10]

As a granulomatous disorder, GA is also characterized by macrophage accumulation and activation in the skin, similar to other granulomatous diseases such as necrobiosis lipoidica, sarcoidosis, and Crohn's disease. The accumulation of these macrophages and the cytokines they secrete reinforces the upregulation of inflammatory cytokines implicated in the disease process. In fact, a recent report of non-ulcerated necrobiosis lipoidica successfully treated with tapinarof[11] is what led us to believe that tapinarof may also be successful in treating GA in our patients. The authors of this report propose that the downregulation of TNF-α and IL-23, secreted by macrophages upregulated in necrobiosis lipoidica, and deactivation of STAT6, underlies the efficacy of tapinarof for the disease. We suggest a similar mechanism for the utility of tapinarof in the treatment of GA, particularly supported by evidence suggesting AHR regulation of STAT1 activation, a pathway recently implicated in the pathogenesis of GA (Figure 3).[4,7,12] It is hypothesized that AhR may act as a ligand-dependent E3 ubiquitin ligase which catalyzes the attachment of ubiquitin (Ub) to STAT1 thereby targeting it for degradation (Figure 3).[12]

Thus, we present a unique report of tapinarof cream 1% for the treatment of GA. This treatment resulted in rapid (4 weeks) clearance of GA in a middle-aged female patient. We hope this innovative approach to treating GA will refine future therapeutic strategies. We believe that tapinarof may supersede the previously regarded first-line treatments for GA, corticosteroids, given its safety profile and demonstrated efficacy not only in this case, but in other cases of granulomatous inflammatory disease. Our patient benefited immensely in the clearance of her disease as well as amelioration of her itch with the once-daily application of tapinarof cream 1% to affected areas for 30 days. More studies are warranted to investigate the efficacy and mechanism of action of tapinarof in the treatment of GA. This case highlights the potential of AHR agonism in improving GA, thus decreasing the need for frequent use of steroids commonly associated with adverse effects. Furthermore, this case offers support to emerging theories that underscore immunologic and cytokine receptor signaling responses in the pathogenesis of GA.

DISCLOSURES

NTI is a paid consultant and speaker for Dermavant Sciences. The other authors have no conflicts to disclose.

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