

IN-DEPTH REVIEW

Apremilast in the Management of Generalized Granuloma Annulare: A Case Series

Jazmine Nesvik, DO¹, Leslie Marshall, DO², David Cleaver, DO³, Jonathan Cleaver, DO³, Lloyd Cleaver, DO³

¹ Northeast Regional Medical Center, Kirksville, MO

² Ozarks Medical Center, West Plains, MO

³ Cleaver Dermatology, Kirksville, MO

ABSTRACT

Background: Granuloma annulare is a difficult disease to treat and can lead to anxiety and frustration for both patients and providers. The pathogenesis of granuloma annulare is unknown, resulting in few thoroughly studied or consistently effective treatments.

Objective: 1) To discuss whether treatment with apremilast could lead to improvement or resolution of generalized granuloma annulare. 2) To explore the possible pathogenesis of granuloma annulare and the mechanism of apremilast in treating this disease.

Methods: A case series was used to study the clinical response of 6 patients with a history of recalcitrant generalized granuloma annulare taking apremilast 30mg twice daily.

Results: Two patients achieved complete clearance of their disease without recurrence while the remaining 4 patients achieved significant improvement in lesion number, induration, and erythema.

Limitations: This is a small case series and larger, controlled trials with long-term follow-up are needed. There is no objective method for evaluating the extent of disease improvement in granuloma annulare. Furthermore, our patients used concomitant topical and intralesional steroids while on apremilast.

Conclusion: This case series illustrates a novel therapy, apremilast, a phosphodiesterase-4 inhibitor, in the treatment of patients with generalized granuloma annulare and explores possible mechanisms behind the success of this treatment.

INTRODUCTION

Granuloma annulare (GA) is a benign cutaneous disease that appears as erythematous papules coalescing into annular plaques with granulomatous inflammation seen histologically.¹ The most common clinical phenotypes include localized GA, subcutaneous GA, and generalized GA (GGA). Although GA is

commonly self-limited, GGA is diffuse and tends to be the subtype most refractory to treatment with the possibility of persisting for years.² Commonly employed treatment modalities have not been thoroughly studied outside of case studies or series. However, there is strong expert consensus for intralesional triamcinolone as first-line therapy. Other treatment modalities that have shown some efficacy in GA include PUVA, UVA1, narrowband UVB, pulsed-dye laser,

antimalarial drugs such as chloroquine and hydroxychloroquine, TNF-alpha inhibitors, fumaric acid esters, and vitamin E, among others.¹

GA has been associated with several diseases including diabetes, hyperlipidemia, hypothyroidism, systemic lupus erythematosus, rheumatoid arthritis, and hypertension.³ Hypertension, however, may not be independently associated with GA and instead secondarily associated via its association with hyperlipidemia and diabetes. The etiology of GA is unknown; however, several theories have been proposed. Multiple studies support the hypothesis of GA being triggered by a delayed-type IV hypersensitivity.⁴ Low levels of TGF-beta and elevations in IL-1 and IL-2 receptors were identified in one study, leading authors to conclude that collagen synthesis is regulated by helper T cells as a result of a reparative mechanism in GA.⁴ An additional theory is that GA represents an immune-mediated, type III hypersensitivity reaction resulting in a chronic vasculitis.⁵

Apremilast is an oral, small molecule that inhibits phosphodiesterase-4 (PDE4).⁶ Phosphodiesterases typically degrade cAMP intracellularly. Apremilast's inhibition of PDE4 prevents cAMP from being degraded leading to increased levels of cAMP, a second messenger important in regulating inflammation in numerous cell types throughout the body. Side effects from apremilast are very mild and most commonly include diarrhea, nausea, headache, upper respiratory tract infection, and nasopharyngitis.⁷

After exhausting standard treatment options for patient 1's GGA without success, she expressed frustration and embarrassment over her extensive GA lesions. Needing to explore other off-label options for this patient,

it was decided to trial apremilast given its known anti-inflammatory effects and well-studied safety profile with minimal adverse effects. Once success was seen with treating this first patient, we continued to trial apremilast in additional patients experiencing recalcitrant GGA which we discuss in this case series.

CASE REPORT

We report six cases of recalcitrant GGA in five females and one male who experienced improvement in their disease while on apremilast. The time from diagnosis to apremilast initiation ranged from 3 months to 5 years (**Table 1**). The patients had a variety of associated comorbidities, including obesity, diabetes, and hypothyroidism. The diagnosis of GA was made clinically in all 6 patients and was further confirmed with punch biopsy in 4 of the 6 patients. All 6 failed multiple treatments for GA including topical, intralesional, and oral steroids; narrowband UVB; hydroxychloroquine; and minocycline. Given the patients continued pruritus and cosmetic concerns over the lesions, further treatment was desired.

Each patient was initiated on an apremilast starter pack, beginning with 10mg daily on day 1 and titrating up to 30mg twice daily by day 7. Patient responses were assessed by physicians during in-person clinic visits every 1-3 months based upon improvement in number, size, and appearance of lesions including induration and erythema. All patients experienced improvement of their GGA as early as 4 weeks after initiation. Responses varied, ranging from complete clearance without relapses to significant improvement in lesion induration, erythema, and number. A summary of patient responses is shown in **Table 1**. Duration of control on apremilast ranged from 6 months

Table 1. Individual patient characteristics, response to treatment, and treatment status.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age (years)	30	66	61	73	45	67
Sex	F	F	F	F	M	F
Comorbidities	Obesity, HTM	Obesity, seboPsO	Obesity, diabetes	Obesity, HLD, hx breast CA	HLD, HTM	Diabetes, HLD, hx uterine CA
Morphology	Generalized pink papules coalescing into large plaques	Generalized pink annular papules and plaques	Generalized pink papules and plaques	Annular pink papules on arms, neck	Annular pink papules on upper and lower extremities	Generalized pink to orange papules coalescing into large plaques
Time to response on apremilast	3 months	6 weeks	4 weeks	Unknown	3 months	10 weeks
Duration of control on apremilast	47 months	20 months	8 months	10 months	6 months	6 months
Response to apremilast	Mostly clear with rare mild flares	Complete clearance after 6 weeks without relapse	Significant improvement in induration and plaque number	Significant improvement in lesion induration, erythema, and number	Complete clearance without relapse	Significant improvement in lesion induration, erythema, and number
Reason for discontinuing	N/A – still on 30 mg QD	N/A – still on 30 mg BID	Stopped responding after temporarily discontinuing	Stopped responding after temporarily discontinuing	N/A – still on 30 mg BID	Ran out of medication
Biopsy confirmed	Yes	No	Yes	Yes	Yes	No
Adverse effects	None	None	None	None	None	None
Previously failed treatments	Topical, oral, and IL steroids	Topical steroids	Topical steroids, HCQ	HCQ, minocycline, oral steroids	Topical and IL steroids, minocycline	Topical and IL steroids
Concomitant therapies	Topical steroids	Topical steroids	Topical steroids	Topical and IL steroids	IL steroids	Topical steroids



Figure 1. Patient 1 treatment response.



Figure 2. Patient 2 treatment response.



Figure 3. Patient 5 treatment response.

to 47 months and counting. Three patients who are either mostly clear or completely clear still remain on apremilast. Patient 1 has been well-controlled on 30mg daily for 47 months (**Figure 1**). An attempt was recently made to decrease to 30 mg daily instead of twice daily apremilast, but this triggered a flare which resolved when she resumed 30mg twice daily. Patients 2 and 5 are completely clear on 30mg twice daily (**Figures 2 and 3**). Patients 3 and 4 stopped responding after temporary apremilast discontinuation unrelated to medication adverse effects and did not respond when apremilast was reinitiated. Patient 6 self-discontinued after running out of medication although she was improving while taking it. None of the patients experienced any medication-related adverse events.

DISCUSSION

As mentioned above, apremilast is a PDE4 inhibitor that leads to increased cAMP within cells. In diseases with increased expression of PDE4 isoforms, such as psoriasis, decreased intracellular cAMP results in elevated levels of pro-inflammatory mediators and decreased levels of anti-inflammatory mediators.⁶ By inhibiting PDE4 in psoriasis, apremilast leads to increased cAMP and decreased pro-inflammatory mediators, including TNF-alpha, IFN-gamma, and IL-2. Notably, increased IL-2 production has also been identified in GA lesions.⁸

In our patients' cases, we theorize apremilast works mechanistically for GA similarly to how it works for psoriasis. Given that IL-2 production and increased IL-2 receptors have been identified in GA, apremilast may interfere with IL-2 production in T cells. Alternatively, it could interfere with macrophage activation via IFN-gamma receptors on T-cells or tissue destruction by

macrophages via TNF-alpha, all through suppression by cAMP. Furthermore, apremilast may function on a broader level in GA by interfering with the release of proinflammatory cytokines or by increasing the release of anti-inflammatory cytokines via cAMP. We also must consider the possibility that the patients' GGA resolved as part of its natural course in conjunction with the administration of apremilast, although this is unlikely to have happened in all 6 patients shortly after medication initiation after years of recalcitrant disease.

Another limitation of our study is the fact that the study type is a case series. A larger, randomized controlled trial would be beneficial to determine if apremilast is effective for GGA. Additionally, most of our patients were concomitantly treated with intralesional and topical steroids while on apremilast which could have influenced their disease course. Further, a more objective evaluation of disease improvement would be beneficial. Other case studies on this subject mentioned that biopsying the lesions could be a limitation to the study as it may stimulate resolution of the disease. However, only 4 out of 6 of our patients had confirmation biopsies, which makes it less likely that the patients' disease resolved secondary to biopsy trauma.

At the time of writing, four case studies with a cumulative total of 9 patients have been published on the treatment of GGA with apremilast. Our case series adds 6 patients to this total further supporting the use of apremilast as a novel treatment for GGA. It also follows patients over a longer period comparatively. Our study is also differentiated from the four patient case series by Blum and Altman in that our patients continued topical and intralesional steroids during treatment with apremilast while their patients discontinued steroid use.⁹

CONCLUSION

This case series illustrates a novel therapy, apremilast, in the successful treatment of six patients with recalcitrant GGA. PDE4 inhibition in GA may exert its effect by decreasing pro-inflammatory cytokines, decreasing IL-2 production, increasing IFN-gamma stimulation or TNF-alpha release, or increasing anti-inflammatory cytokines, likely through a second messenger pathway involving increased cAMP. Our study further supports prior literature regarding the use of apremilast as a novel treatment for recalcitrant GGA. Larger, controlled trials with long-term follow-up are needed to further evaluate the efficacy of apremilast in the treatment of GGA.

GA = granuloma annulare, GGA = generalized granuloma annulare, PUVA = psoralen plus ultraviolet A phototherapy, UVA1 = ultraviolet A1 phototherapy, UVB = ultraviolet B phototherapy, M = male, F = female, N/A = not applicable, QD = daily, BID = twice daily; HLD = hyperlipidemia; HCQ = hydroxychloroquine; HTM = hypothyroidism; CA = cancer; seboPsO = seborrheic dermatitis; IL = intralesional; hx = history

Conflict of Interest Disclosures: None

Funding: None

Corresponding Author:

Jazmine Nesvik, DO
315 S Osteopathy
Kirksville, MO 63501
Email: jazminenesvik@atsu.edu
Phone: (320) 491-0988

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