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Apremilast for generalized granuloma annulare: a case series of eight patients

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Learning Objectives

1. Define granuloma annulare (GA)
2. Compare local and generalized granuloma annulare (GGA)
3. Define first-line treatment for GGA and describe its limitation
4. Briefly explain the mechanism of action of apremilast
5. List inflammatory skin conditions that apremilast is approved to treat
6. Identify clinical outcomes for the eight cases
7. Identify cases that experienced side-effects and describe

Introduction

Granuloma annulare is a benign inflammatory granulomatous dermopathy characterized clinically by coalescent annular papules and plaques with necrobiotic granulomas on histology. There are multiple clinical and histologic subtypes; generalized GA is widespread and often refractory to treatment. Apremilast, a PDE-4 inhibitor, has been shown in limited case reports and small series to be of potential benefit in GGA.

1. GA presents as reddish-brown papules that coalesce into smooth annular plaques. Histologically, interstitial or palisaded granulomas are present with increased mucin and eosinophils.
2. Localized GA involves only one or a few lesions, and most patients have no extracutaneous associations. GGA involves multiple diffuse lesions and may be associated with underlying hyperlipidemia, diabetes, thyroid disease, lymphoma, malignancy, and viral infections. GGA is less likely than localized GA to remit spontaneously and is often treatment-resistant.
3. First-line treatment with topical and intralesional steroids is often inadequate or contraindicated due to extensive body surface areas involved.
4. Apremilast is a PDE-4 inhibitor, which increases levels of intracellular cAMP and inhibits the production of Th-1 cytokines including TNF-α and INF-γ. Overproduction of these cytokines is suspected to contribute to the pathogenesis of GA.
5. Apremilast is currently approved to treat plaque psoriasis, psoriatic arthritis, and oral ulcerations of Behçet disease.

Methodology

- A retrospective chart review of eight patients with biopsy-proven granuloma annulare was performed.
- Criteria for Cases:
  - Patients who were prescribed apremilast for generalized granuloma annulare were included.
  - Patients whose cases had previously been published in the literature were excluded.
  - Patients had to have failed at least one other therapy prior to initiation of apremilast to be included.
- Treatment:
  - Apremilast was initiated in all eight patients using standard up-titration with eventual dosing of 30mg twice daily except for patient number four who was prescribed 30mg daily due to renal insufficiency.

Figures

Figure 1: Case 6 initial presentation

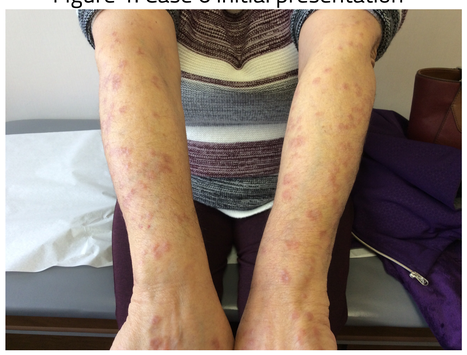

Figure 2: Case 6 after 24 months of treatment

Results

Case #	Age/ Sex	Failed Tx	Location	Duration	Outcome **	Side Effects
1	55F	Methotrexate; Betamethasone 0.05% ointment BID	R elbow; R medial superior chest	3 months	NCR	None
2	75F	Betamethasone 0.05% cream BID	Trunk; extremities	6 months	Improved	Nausea, Diarrhea †
3	66M	Triamcinolone 0.025% cream BID	Chest; Abdomen; Upper back	2 months	None	None
4	52M	Intralesional triamcinolone 2.5 mg/ml	Proximal dorsal forearms	41 months	NCR	Nausea, diarrhea †
5	68F	Clobetasol 0.05% cream BID; Metronidazole 500mg po daily; PUVA (unknown duration)	Trunk; Extremities	1 month	None	Depression, nausea †
6	58F	NBUVB; Excimer laser; Metronidazole 500mg daily, adapalene gel 0.3% daily, crisaborole 2%, halobetasol 0.05%, prednisone 20mg daily	Trunk; Extremities	2 years*	Improved	None
7	70F	Ciprofloxacin 500 mg monthly; Doxycycline 200mg twice monthly; Rifampin 600mg monthly; Clobetasol 0.05% BID	Trunk; Extremities	5 months*	NCR	None
8	66F	Triamcinolone 0.1% cream BID	Face; Trunk; Upper Extremities	3 months*	Improved	None

***Treatment ongoing**
****None, Improved, Near-Complete Resolution (NCR)**
†Patients discontinued therapy secondary to side effects

Conclusions

With this series of eight patients, the author expands upon previously published cases and propose apremilast as an effective and well-tolerated treatment for GGA. These cases had all previously failed numerous treatments for GA. Three patients showed near-complete resolution. Only two of eight patients had no improvement. Three patients discontinued therapy secondary to side effects, and six cases had no reported side effects.

In this review of eight cases, apremilast has considerably improved outcomes of GGA with a very low side effect profile. Currently, there is a paucity of reliable treatment options for GGA and the author supports apremilast as a safe and efficacious treatment option in patients with refractory GGA.

6. Out of eight patients, three patients showed near-complete resolution of GGA. Three additional patients experienced some improvement. Two patients experienced no clinical improvement.
7. Out of eight patients, three experienced side-effects. Two of these patients discontinued therapy due to side-effects that included nausea, diarrhea, and depression.

References

1. Lukács J, Schliemann S, Elsner P. Treatment of generalized granuloma annulare - a systematic review. *J Eur Acad Dermatol Venereol.* 2015;29(8):1467-1480. doi:10.1111/jdv.12976
2. Wang J, Khachemoune A. Granuloma Annulare: A Focused Review of Therapeutic Options. *Am J Clin Dermatol.* 2018;19(3):333-344. doi:10.1007/s40257-017-0334-5
3. Naka F, Strober BE. Methotrexate treatment of generalized granuloma annulare: a retrospective case series. *J Dermatolog Treat.* 2018;29(7):720-724. doi:10.1080/09546634.2018.1447075
4. Fässler M, Schlapbach C. Granuloma annulare arising under systemic psoriasis therapy successfully treated with adalimumab. *JAAD Case Rep.* 2020;6(9):832-834. Published 2020 Jul 15. doi:10.1016/j.jdcr.2020.07.013Danese S, Neurath MF, Kopoń A, et al. Effects of Apremilast, an Oral Inhibitor of Phosphodiesterase 4, in a Randomized Trial of Patients With Active Ulcerative Colitis. *Clin Gastroenterol Hepatol.* 2020;18(11):2526-2534.e9. doi:10.1016/j.cgh.2019.12.032
5. Schafer PH, Parton A, Capone L, et al. Apremilast is a selective PDE4 inhibitor with regulatory effects on innate immunity. *Cell Signal.* 2014;26(9):2016-2029. doi:10.1016/j.cellsig.2014.05.014
6. Danese S, Neurath MF, Kopoń A, et al. Effects of Apremilast, an Oral Inhibitor of Phosphodiesterase 4, in a Randomized Trial of Patients With Active Ulcerative Colitis. *Clin Gastroenterol Hepatol.* 2020;18(11):2526-2534.e9. doi:10.1016/j.cgh.2019.12.032
7. Kaushik A, Raj D, Chatterjee D, Vinay K. Apremilast in orofacial granulomatosis-A report of five cases. *Dermatol Ther.* 2020;33(6):e14345. doi:10.1111/dth.14345
8. Nassim D, Alajmi A, Jfri A, Pehr K. Apremilast in dermatology: A review of literature. *Dermatol Ther.* 2020;33(6):e14261. doi:10.1111/dth.14261

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