Tildrakizumab ineffective in generalized granuloma annulare

Eingun James Song, MD
Mill Creek, Washington

Key words: biologic; granuloma annulare; tildrakizumab; treatment.

INTRODUCTION

Generalized granuloma annulare is a widespread inflammatory condition that can have a significant impact on the quality of life. Treatment remains a challenge, as evidenced by the ever-growing list of therapeutic options. A part of the difficulty in the treatment remains the incomplete understanding of its immunopathogenesis. The effectiveness of the tumor necrosis factor (TNF) alpha inhibitor class has highlighted the role of a T helper (Th)1-mediated delayed-type hypersensitivity reaction, but not all patients are responders, and there are also cases of paradoxical granuloma annulare after starting the treatment.[1,2] Furthermore, there are reports of interleukin (IL) 17 inhibitors actually triggering granuloma annulare, which speaks to the heterogeneous nature of this disease.[3,4]

The development of targeted biologic agents in dermatology has undoubtedly revolutionized treatment outcomes, but their use is restricted to a limited number of Food and Drug Administration-approved indications. Many dermatologic conditions remain orphan diseases, which has led to an increase in off-label biologic use. Herein, we report our experience of treating a case of generalized granuloma annulare with tildrakizumab, an anti—IL-23p19 monoclonal antibody approved for the treatment of plaque psoriasis.

Abbreviations used:

IL:	interleukin
Th:	T helper
TNF:	tumor necrosis factor

CASE REPORT

A 58-year-old woman with a past medical history of hypertension, hyperlipidemia, hypothyroidism, and depression presented with over a 10-year history of widespread annular dermal plaques involving her face, neck, arms, torso, and legs. Histopathology was consistent with granuloma annulare. She had previously failed to show improvement with ultrapotent topical steroids, intralesional steroids, narrowband ultraviolet B phototherapy, oral antibiotics (rifampin, ofloxacin, and minocycline), hydroxychloroquine, methotrexate, and apremilast. The patient's plaques completely cleared with adalimumab, but she had to discontinue the treatment after a lapse in insurance coverage, which led to a relapse of her disease. Based on a case report of ustekinumab, an IL-12/23 inhibitor, successfully treating granulomatous

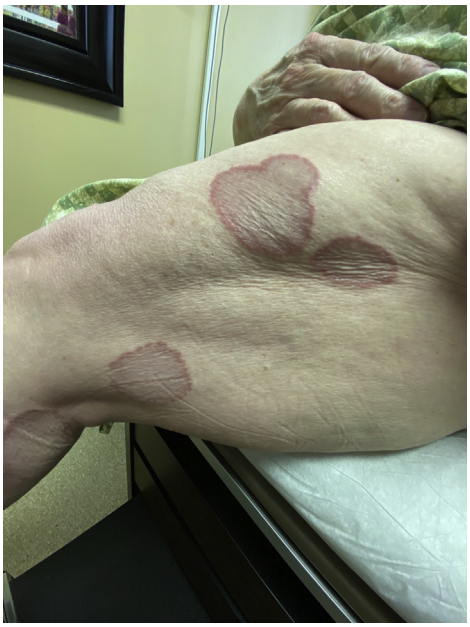

Fig 1. Pretreatment photographs.

From the North Sound Dermatology, Mill Creek, Washington.
Funding sources: None.
Conflicts of interest: None disclosed.
IRB approval status: Not applicable.
Correspondence to: Eingun James Song, MD, North Sound Dermatology, Mill Creek, WA 98012. E-mail: esong812@gmail.com.

JAAD Case Reports 2021;7:3-4.
2352-5126

https://doi.org/10.1016/j.jdcr.2020.10.034

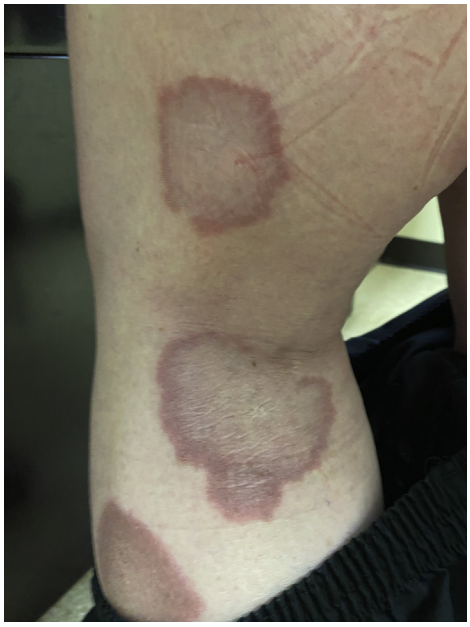

Fig 2. Post-treatment photographs after 28 weeks of tildrakizumab treatment.

dermatitis in a setting of necrobiosis lipodica,[5] it was decided to start treatment with tildrakizumab, a selective IL-23 inhibitor.

One hundred milligram of tildrakizumab was administered subcutaneously at weeks 0 and 4 and then every 12 weeks, consistent with the approved psoriasis dosing (Fig 1). At her 28-week follow-up, the patient did not show any appreciable improvement and chose not to continue with the treatment (Fig 2).

DISCUSSION

The inefficacy of tildrakizumab in this case adds to the growing body of literature that the IL-23/Th17 pathway does not play a central role in the immunopathogenesis of granuloma annulare. In fact, several cases of anti—IL-17 inhibitors causing de novo granuloma annulare have been described.[3,4] More recently, a case of localized granuloma annulare due to apremilast, which is known to inhibit the Th17 pathway, was also reported.[6] Because granuloma formation is mediated primarily by macrophages and Th1 cytokines, such as interferon gamma and TNF-α, the ineffectiveness of selectively targeting the IL-23/Th17 pathway should not be a surprise. This may actually be an instance where less selective inhibition in the form of an IL-12/23 inhibitor may be more beneficial as IL-12 signaling plays a role in the Th1 pathway. Therefore, further studies using ustekinumab in the treatment of granuloma annulare should be performed to see if it may be a treatment alternative to TNF-α inhibition.

REFERENCES

1. Min MS, Lebwohl M. Treatment of recalcitrant granuloma annulare (GA) with adalimumab: a single-center, observational study. *J Am Acad Dermatol*. 2016;74(1):127-133.
2. Voulgari PV, Markatseli TE, Exarchou SA, Zioga A, Drosos AA. Granuloma annulare induced by anti-tumour necrosis factor therapy. *Ann Rheum Dis*. 2008;67(4):567-570.
3. Bonomo L, Ghoneim S, Levitt J. A case of granuloma annulare associated with secukinumab use. *Case Rep Dermatol Med*. 2017;2017:5918708.
4. Clark ML, Tobin CA, Sutton A, Missall TA. Granuloma annulare in the setting of secukinumab. *Case Rep Dermatol Med*. 2018;2018:5175319.
5. Hassoun LA, Sivamani RK, Sharon VR, Silverstein MA, Burrall BA, Tartar DM. Ustekinumab to target granulomatous dermatitis in recalcitrant ulcerative necrobiosis lipoidica: case report and proposed mechanism. *Dermatol Online J*. 2017;23(7):13030/qt3k32k916.
6. Fässler M, Schlapbach C. Granuloma annulare arising under systemic psoriasis therapy successfully treated with adalimumab. *JAAD Case Rep*. 2020;6(9):832-834.