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Ustekinumab to target granulomatous dermatitis in recalcitrant ulcerative necrobiosis lipoidica: case report and proposed mechanism

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Abstract

We present a 42-year-old woman with no history of diabetes or glucose intolerance who had a 5-year history of ulcerative necrobiosis lipoidica (NL). Despite failure of multiple medications, she experienced clearing of her ulcers after her treatment was changed to ustekinumab. We discuss our patient's disease course and elaborate upon mechanistic reasons for her improvement related to ustekinumab therapy.

Keywords: necrobiosis lipoidica, ustekinumab, granulomatous dermatitis, Th1, macrophage, IFNγ

Introduction

Necrobiosis lipoidica (NL) is a rare, chronic granulomatous cutaneous disease that most often affects the lower extremities. The etiology of the condition is unknown but there appears to be some association with diabetes mellitus. Lesions most often begin as asymptomatic papules and nodules that over time can develop into atrophic plaques. Rarely, erosions or ulcerations can also occur, and management of ulcerative NL poses a clinical challenge. There is no cure for NL, but patients with the non-ulcerative form are most often treated with topical and intralesional corticosteroids [1]. Other therapies, including topical tacrolimus, topical psoralen plus ultraviolet A (PUVA) photochemotherapy, and systemic medications (such as tetracycline antibiotics, antimalarials, and immunomodulators) are pursued for more recalcitrant cases [2-4]. If ulcerations do develop, patients require consistent and extensive wound care coupled with the use of adjuvant agents. There is a paucity of evidence supporting efficacy of one treatment over another for ulcerative NL, leaving providers to attempt consecutive trials of different therapies, including biologic agents such as TNF inhibitors [5]. We present a report of a patient with ulcerative NL, who after multiple failed therapies, including TNF inhibitors, experienced significant improvement on ustekinumab. NL is known to be a granulomatous disease process, and both macrophages and the Th1 cytokine IFNγ are required for granuloma formation [6]. We therefore propose that in our patient, ustekinumab may have decreased granuloma formation by targeting IL-12 leading to less IFNγ production from Th1 cells.

Case Synopsis

A 42-year-old woman without diabetes or glucose intolerance presented with a 5-year history of ulcerative necrobiosis lipoidica (NL), with symptoms including both pain and itch. She had tried numerous therapies for NL, but experienced either treatment failure or adverse effects from all agents. At the time of her initial diagnosis, she was started on pentoxifylline without improvement. She was subsequently transitioned to cyclosporine, with some symptomatic relief, but this medication was discontinued secondary to hypertension. Mycophenolate mofetil was then attempted in lieu of cyclosporine, but she continued to experience ulceration, pain, and itch. Etanercept was tried next, which was effective for approximately 6 months, until loss of efficacy with recurrence of ulcerations. She was then transitioned to another TNF inhibitor, adalimumab, but continued to have severe ulcerations necessitating weekly Unna

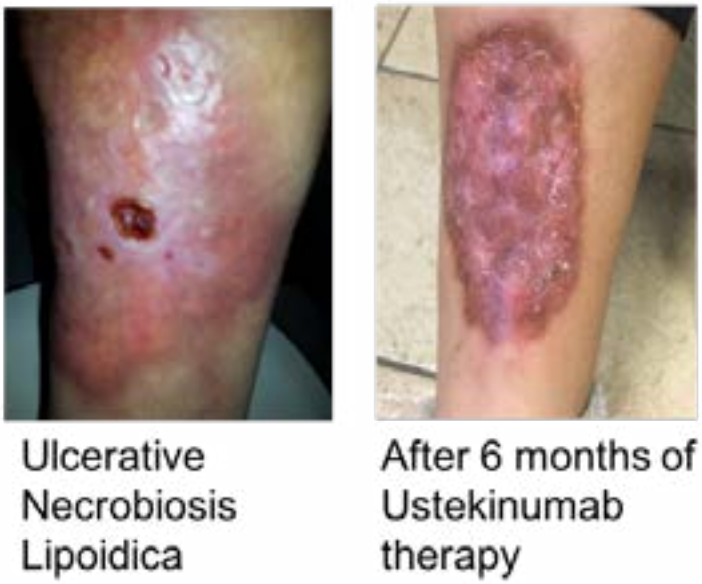

Figure 1. *Ulcerative NL and response to ustekinumab therapy. Left panel: Ulcerative necrobiosis lipoidica on the right shin. Right panel: right shin after 6 months of therapy with ustekinumab 45mg every 9 weeks with no recurrence of ulceration.*

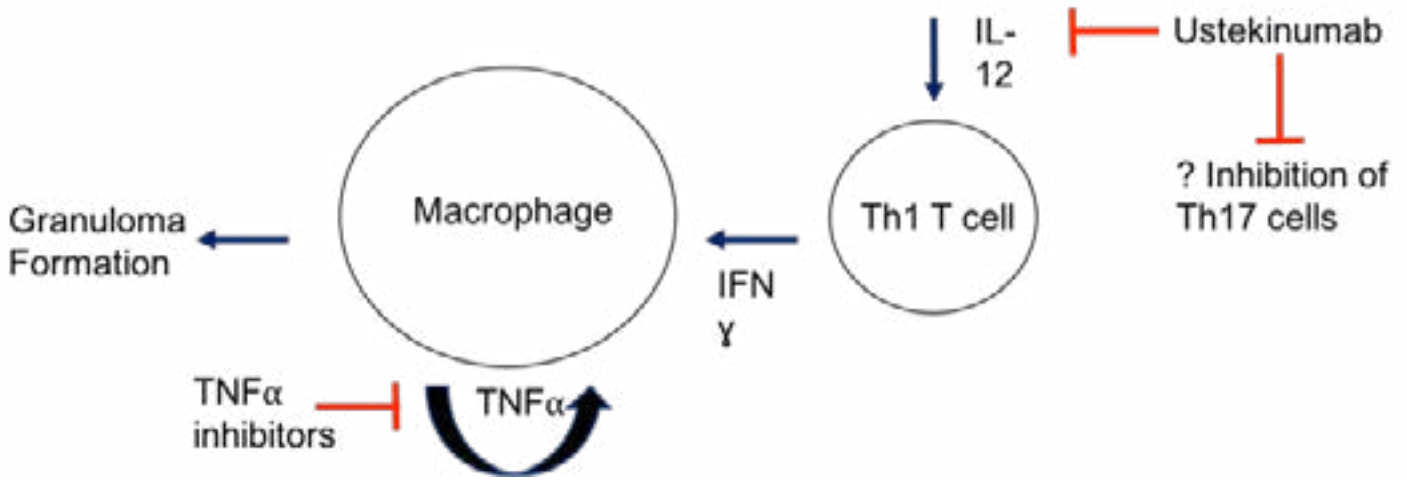

Figure 2. *Proposed mechanism for efficacy of ustekinumab in necrobiosis lipoidica: targeting granuloma formation. NL is a granulomatous disease process, and it is known that granuloma formation requires both macrophages and macrophage activation by the cytokine IFNg. This induces TNF production, which further stimulates macrophage activation in an autocrine manner. We propose that ustekinumab was effective in targeting granuloma formation in our patient, leading to clinical improvement. TNF inhibitors also target this pathway.*

boot application. A trial of infliximab (with concurrent methotrexate to prevent autoantibody formation) was finally effective in resolving her ulcerations, but was halted owing to the development of an anaphylactoid reaction. Lastly, treatment with ustekinumab 45mg every 9 weeks was initiated. On ustekinumab, the patient noted significant reduction of pain and pruritus. To date, she has been maintained on this medication for six months in the absence of recurrent ulcerations (**Figure 1**).

Case Discussion

The persistent and disfiguring nature of ulcerative NL can have a significant impact on quality of life. Thus, a more aggressive approach to ulcerative NL is usually employed with multimodality therapy that often includes high potency topical corticosteroids to affected skin around the ulcer along with systemic agents such as antibiotics and immunomodulators. Recent reports have demonstrated a role for TNF inhibitors, specifically infliximab [5].

Ustekinumab is FDA-approved for use in psoriasis and psoriatic arthritis. Its ability to bind to and inhibit the pro-inflammatory cytokines IL-12 and IL-23 may explain its therapeutic role in those disorders, likely through decreased Th17 cell function [7]. Although the pathogenesis of NL is unclear, it is known to be a granulomatous disorder [1] and we therefore attempted to use ustekinumab to target the Th1 pathway to limit granuloma formation (**Figure 2**). IL-12 is necessary for the formation of Th1 cells, which are essential for macrophage activation and subsequent granuloma formation. Th1 cells interact with macrophages in a CD40-CD40L-dependent manner and secrete IFNg, which binds the IFNg receptor on macrophages, leading to macrophage activation. This signal also prompts macrophages to make TNF, which signals in an autocrine fashion to aid in macrophage activation and granuloma formation [6]. We propose that ustekinumab was successful in our patient by targeting this pathway. In addition to inhibition of the IL-12/Th1 pathway, ustekinumab is known to inhibit Th17 cells by targeting IL-23, which is necessary for maintenance of this population [8]. Although the pathogenesis of NL has yet to be fully elucidated, Th17 cells have recently been reported in lesional skin [9, 10], so the clinical improvement may be multifactorial and related to inhibitory effects of ustekinumab on both the Th1 and Th17 pathways.

Conclusion

This case report suggests a novel application of ustekinumab for the treatment of recalcitrant ulcerative NL. In the future, high quality randomized clinical trials may be helpful to in establishing the role of ustekinumab as an alternative treatment for ulcerative necrobiosis lipoidica.

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