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Significant improvement of dermatitis herpetiformis with tofacitinib

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Abstract

Dermatitis herpetiformis (DH) is a rare autoimmune blistering disorder in which patients with celiac disease, a gluten-sensitive enteropathy, present with a severely pruritic papulovesicular eruption over extensor surfaces such as the knees, elbows, lower back, buttocks, and neck. Patients are instructed to adhere to a gluten-free diet for purposes of improving their skin disease and gluten-sensitive enteropathy; this is the only treatment that lowers risk of enteropathy-associated T cell lymphoma. Patients who adhere to a strict gluten-free diet often have remission of their skin disease over months to years. Dapsone is a rapid and extremely effective first-line treatment option and often used while transitioning to a gluten-free diet. Aside from gluten-free diet and dapsone, second-line treatment options include sulfapyridine, sulfasalazine, and colchicine. Some patients have difficulty adhering to a gluten-free diet or develop intolerable side effects to systemic therapies. Furthermore, there is limited data on the use of the second-line treatments. Recent studies have shed light on the role of JAK-STAT-dependent pathways in the pathogenesis of dermatitis herpetiformis. We present a patient treated with tofacitinib, 5mg twice daily, an oral JAK1/3 inhibitor, who demonstrated clinical improvement of DH and control of new lesion development.

Keywords: dermatitis herpetiformis, JAK inhibitor, tofacitinib

Introduction

Dermatitis herpetiformis (DH) is a rare but chronic autoimmune blistering condition characterized by

an eruption of grouped papulovesicles with an erythematous base that is often symmetric and favors extensor surfaces [1]. These skin manifestations are severely pruritic and often cause psychological distress and reduced quality of life for patients. Overactivity of the Janus kinases (JAK) and signal transducers and activators of the transcription (STAT) signaling pathway is seen in multiple dermatologic conditions such as psoriasis, atopic dermatitis, vitiligo, and alopecia areata. There is recent evidence that the JAK-STAT pathway is also overactive in autoimmune blistering conditions. When compared to normal perilesional skin and control samples, biopsies taken from skin lesions of patients with bullous pemphigoid (BP) and DH show a higher expression of JAK-STAT proteins on immunohistochemistry [2]. These findings suggest that the JAK-STAT pathway is involved in the pathogenesis. Tofacitinib is an oral JAK 1,3 inhibitor FDA approved for adult patients with moderate-to-severe rheumatoid arthritis, ulcerative colitis, and active psoriatic arthritis [3]. Tofacitinib has also recently been approved to treat children with active polyarticular juvenile idiopathic arthritis. We present a patient with DH treated with tofacitinib, who demonstrated clinical improvement and suppression of new lesion formation.

Case Synopsis

A 76-year-old man with a history of biopsy-proven celiac disease and associated biopsy-proven dermatitis herpetiformis presented for management of his DH, present for 5 years. Past medical history was pertinent only for hypertension and he denied a personal or family history of DH or other

autoimmune conditions. At the time of evaluation, the patient had minimal bowel involvement but was concerned about his persistent pruritic eruption that was widespread and severely affecting his quality of life. He had already tried and failed dapsone and sulfasalazine; a gluten-free diet did not control his cutaneous symptoms and was difficult to adhere to. Physical examination revealed a skin phototype II individual with excoriated pink papules and intact small vesicles with clear-yellow fluid on an erythematous base scattered on the bilateral upper and lower extremities, back, buttocks, posterior thighs, and face (**Figure 1**).

A 3mm punch biopsy of the right forearm was taken and hematoxylin and eosin staining showed

neutrophilic microabscesses at the dermal papilla as well as sparse perivascular lymphocytic inflammatory infiltrate (**Figure 2**). Direct immunofluorescence showed 2+ granular IgA staining of the basilar layer of epidermis and the tips of dermal papillae. Unique to these histologic findings is linear granular IgA, a finding seen in linear IgA dermatoses but also DH patients with gluten-sensitive enteropathy [4]. Laboratory workup revealed elevated tissue transglutaminase IgA levels at 153.0 units with no evidence of IgA deficiency. The patient tried oral dapsone which led to rapid improvement but was discontinued after developing a dapsone-hypersensitivity syndrome. He also failed



Figure 1. A-C) Dermatitis herpetiformis pre-treatment. Excoriated pink papules and intact small vesicles with clear-yellow fluid on an erythematous base scattered on the extensor forearms, lower extremities and buttocks. **D-F) Dermatitis herpetiformis post-treatment.** Clearance in areas of prior skin involvement 7 months after treatment with tofacitinib 5mg twice daily.

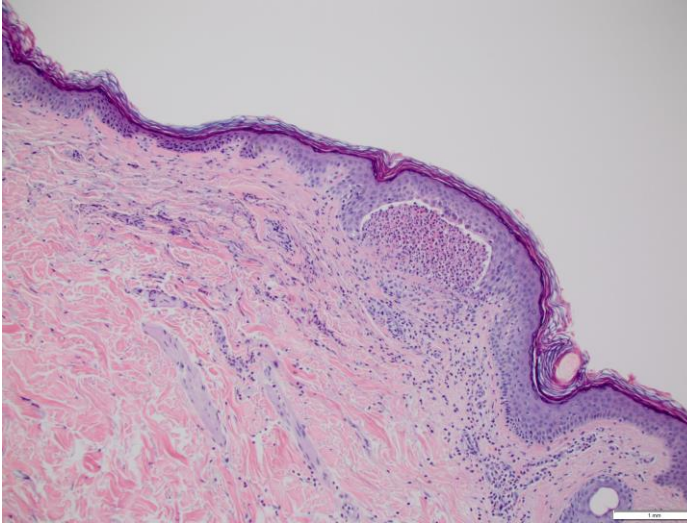


Figure 2. Histopathologic photomicrograph H&E stain. Section shows neutrophils in the papillary dermis with subepidermal clefting at a magnification of 10x.

a gluten-free diet, topical corticosteroids, sulfasalazine, tetracycline and niacin combination, doxycycline and niacin combination, and apremilast. Use of apremilast was considered based on evidence that inhibition of phosphodiesterase type 4B (PDE4B) and PDE4D leads to decreased neutrophil recruitment [5].

The patient was initiated on a trial of tofacitinib 5mg twice daily for his DH. He noticed rapid improvement in pruritus even after one dose. After one month of therapy, he reported notable improvement in both pruritus, existing lesions, and new lesion development. After 7 months of treatment, there was significant improvement with only a few active spots on the upper extremities and clearance of the lower extremities and buttocks (**Figure 1**). The patient did not develop any new lesions and has continued to tolerate this treatment without adverse effects.

Case Discussion

Tofacitinib is an oral JAK 1/3 inhibitor approved by the U.S. Food and Drug Administration for adult patients with moderate-to-severe rheumatoid arthritis (2012), ulcerative colitis (2018), and active psoriatic arthritis (2017), [3]. It is also FDA approved in children with polyarticular juvenile idiopathic

arthritis (2020). Various cytokines including interleukins and interferons utilize the JAK-STAT pathway to transmit signals from the cell membrane to the nucleus. Specifically, intracellular JAK proteins associated with type I/II cytokine receptors become activated and phosphorylate STAT proteins, which dimerize and translocate to the nucleus, the site of gene regulation [6]. A growing number of studies have shown efficacious results for the off-label use of JAK inhibitors in inflammatory dermatoses such as psoriasis, vitiligo, alopecia areata, and atopic dermatitis [7].

Furthermore, the JAK-STAT pathway may play an important role in the pathogenesis of immunobullous diseases such as DH. Although the use of JAK inhibitors in patients with DH has not been tested or reported on clinically, case reports have shown positive outcomes in patients with refractory pemphigus and mucous membrane pemphigoid [8,9].

Conclusion

This case demonstrates that tofacitinib may be an effective treatment option for dermatitis herpetiformis in a subset of patients that fail or have contraindications to a gluten-free diet and dapsone. Although instituting a gluten free diet often improves symptoms in patients with DH, other treatment options must be considered when patients do not respond to or do not wish to adhere to this diet, which is time-consuming and difficult. Our patient unfortunately had persistent skin lesions even after eliminating gluten from his diet. Side effects of JAK inhibitors include potential malignancy, infection, anemia, venous thromboembolism, neutropenia, hyperlipidemia, liver toxicity, gastrointestinal upset, infections, headaches, and acne. It is unclear how JAK inhibitors will affect the known increased risk of lymphoma in celiac disease patients and a gluten-free diet should still be emphasized along with close follow-up with a gastroenterology consultant. Further studies are needed to examine the efficacy and safety of tofacitinib in the treatment of dermatitis herpetiformis.

Potential conflicts of interest

Dr. Rosmarin has received honoraria as a consultant for AbbVie, Boehringer-Ingelheim, Bristol Meyers Squibb, Celgene, Concert, Dermavant, Dermira, Incyte, Janssen, Kyowa Kirin, Lilly, Novartis, Pfizer, Regeneron, Sanofi, Sun Pharmaceuticals, UCB, VielaBio; has received research support from AbbVie,

Amgen, Bristol Meyers Squibb, Celgene, Dermira, Galderma, Incyte, Janssen, Lilly, Merck, Novartis, Pfizer, and Regeneron Pharmaceuticals Inc; and has served as a paid speaker for AbbVie, Amgen, Celgene, Janssen, Lilly, Novartis, Pfizer, Regeneron Pharmaceuticals Inc., and Sanofi. The other authors have no conflicts of interest to declare

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