SKIN

BRIEF ARTICLE

Oral Jak Inhibitor, Upadacitinib Use in Treatment of Pemphigus Foliaceus

Sophie Guénin MSc[1], Syed Shah, MBBS, MRCP, FRCP[2], Mark G. Lebwohl MD[1]

[1] The Kimberly and Eric J. Waldman Department of Dermatology, Icahn School of Medicine at Mount Sinai Hospital, New York, NY
[2] University Hospitals of Morecambe Bay, NHS Foundation Trust, UK.

ABSTRACT

Pemphigus foliaceus (PF) is a rare, blistering autoimmune condition that occurs when desmoglein-1 autoantibodies target and lead to loss of intercellular connections, resulting in blister formation on the skin. Current standard of care consists of highly immunosuppressive therapies such as prednisone, rituximab, and mycophenolate mofetil. A 43-year-old male with new-onset PF was treated with upadacitinib, a JAK inhibitor. He saw resolution of his blisters within 12 weeks of treatment and remains in remission from his PF. Our case demonstrates that JAK inhibition may prove to be an effective strategy in preventing dsg-1-triggered blisters. JAK1 inhibitors also may prove to be a safer, less immunosuppressive alternative to the highly immunosuppressive agents available today. Larger studies will be required to study the drug's efficacy in others with PF.

INTRODUCTION

Pemphigus foliaceus (PF) is a variant of pemphigus, a rare, blistering autoimmune condition.[1] Drugs and compounds known to contain thiol and phenol structures have also been reported to provoke PF. PF occurs when immunoglobulin G (IgG) autoantibodies target intercellular adhesion glycoprotein desmoglein-1 (dsg-1) triggering the loss of intercellular connections between keratinocytes and subsequent subcorneal blister formation.[1] Patients most often present with flaccid, superficial vesicles and bullae of the skin on the scalp, chest, and back with mucosal sparing.[1] Biopsy of PF shows acantholysis at the granular layer of the epidermis and formation of vacuoles and/or subcorneal blisters within the intercellular spaces of the epidermis.[1]

There are few randomized controlled trials for PF. Treatments are largely based in expert opinion, consensus and anecdotal evidence.[2] To date, the mainstay treatment is systemic corticosteroids and rituximab (CD-20 inhibitor).[2] Other commonly used treatments include mycophenolate mofetil (MMF), azathioprine, high dose intravenous immunoglobulins, and cyclophosphamide.[2]

More recently, Janus kinase (JAK) inhibitors have become increasingly used in a variety of autoimmune conditions.[3] Upadacitinib is a JAK1-specific inhibitor which has been approved for psoriatic arthritis, rheumatoid arthritis, ulcerative colitis, atopic dermatitis,

and ankylosing spondylitis.[4] Upadacitinib has also shown efficacy in treatment of psoriasis and eczema overlap condition, PsEma.[5]

Herein, we detail a case of 43-year-old male with severe pemphigus foliaceus which responded to an oral JAK inhibitor, upadacitinib.

CASE REPORT

A 43-year-old male with no significant past medical history presented with a four-month history of a scaly, erythematous pruritic rash consisting of plaques and papules that originated on his head and spread to his chest and scalp. The patient denied any recent changes in medication or medical condition prior to rash presentation. He lived in the Middle East and his work involved frequent exposure to fragrances.

At this time, the differential diagnosis included PF. A biopsy of the patient's chest was performed and sent for hematoxylin & eosin staining (H&E) and direct immunofluorescence (IF). However, the biopsy revealed only spongiotic dermatitis consistent with a contact dermatitis or other eczematous reaction and direct IF failed to show staining for IgM, IgG, IgA, C3 or fibrinogen. Given the patient's spongiotic dermatitis biopsy and psoriasiform lesions, he was started on a course of topical corticosteroids and topical roflumilast for suspected PsEma.

Despite treatment, over the next month, the patient's condition continued to progress. He continued to develop eczematous, pruritic papules and patches until finally presenting with widespread, erythematous scaly, exfoliative lesions with desquamation and bullae (**Figure 1a, Figure 2a**). The patient was started on 60 mg of prednisone; however, he failed to respond within the first week. Thus, he was switched to upadacitinib 15mg daily, to treat suspected, severe, PsEma, a condition which we have successfully treated with JAK inhibitors[5].

Given the unusual progression of disease, the patient underwent serum testing for dsg-1 and dsg-3, which returned positive for dsg1 (>200 RU/mL). Shortly thereafter, a second biopsy revealed subcorneal blisters with neutrophils and positive direct intercellular IF for IgG and C3, which were consistent with pemphigus foliaceus (**Fig 3**). Antinuclear antibodies were negative.

Within one week, the patient saw rapid improvement in his itch and blisters on 15mg of upadacitnib; thus, the patient deferred the start of rituximab treatment for biopsy-confirmed PF. The following week, he was increased to 30mg daily for continued control of a few, newly developed blisters. Within two weeks of daily 30mg upadacitinib, the patient saw great improvement in his blisters and ceased forming new bullae. By week 12 of 30mg daily upadacitinib treatment, he was left with only residual hyperpigmentation at sites of his lesions (**Figure 1b, Figure 2b**).

DISCUSSION

Our patient's rapid response to upadacitinib, a selective JAK1 inhibitor, suggests a novel, steroid-sparing agent for PF treatment. While PF may occur spontaneously in genetically predisposed individuals, our patient's PF could have been triggered by his repeat exposures to phenol-containing fragrances, such as vanillin. Phenol-containing compounds disrupt the cellular adhesion mechanisms by stimulating release of proinflammatory cytokines from keratinocytes that lead to complement and

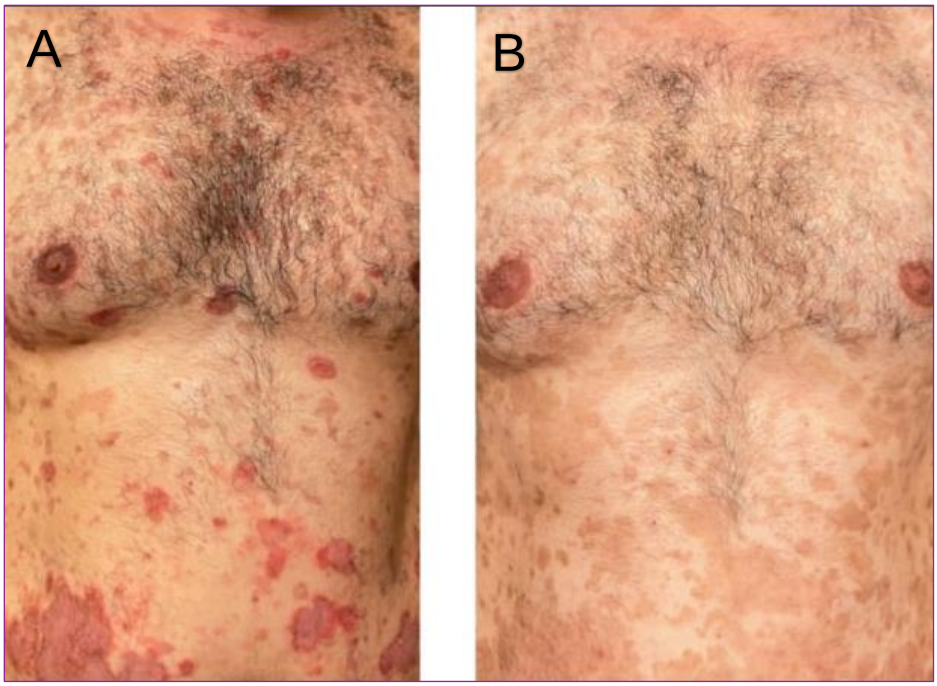

Figure 1. (A) Torso of 43-year-old male with pemphigus foliaceous prior to upadacitinib treatment. **(B)** of 43-year-old male with pemphigus foliaceus after 12 weeks of upadacitinib 30mg QD treatment.

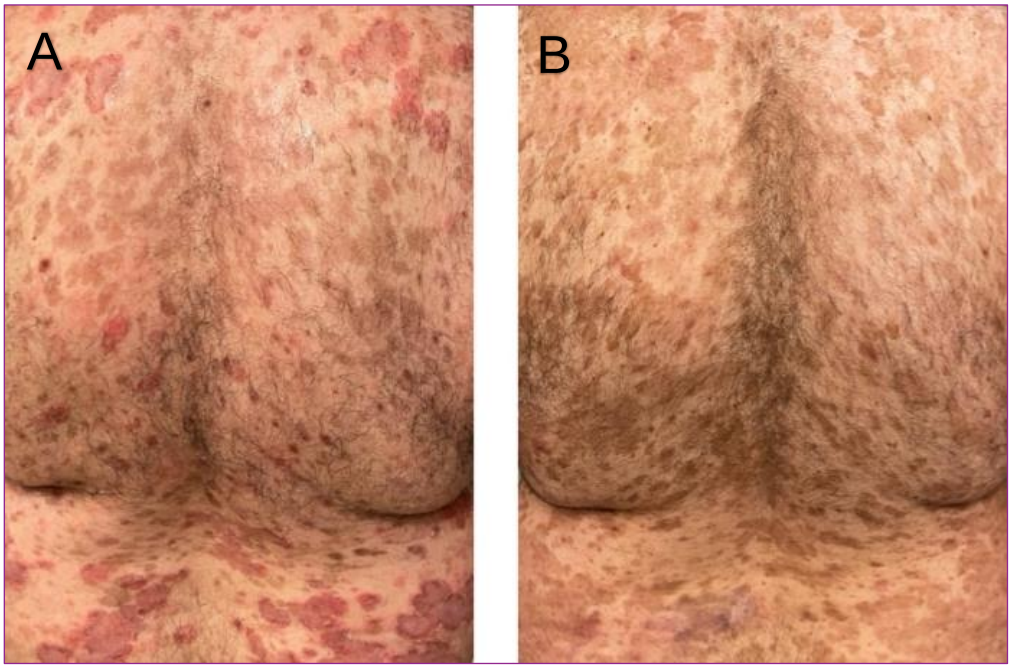

Figure 2. (A) Back of 43-year-old male with pemphigus foliaceus prior to upadacitinib treatment. **(B)** Back of 43-year-old male with pemphigus foliaceus after 12 weeks of upadacitinib 30g QD treatment.

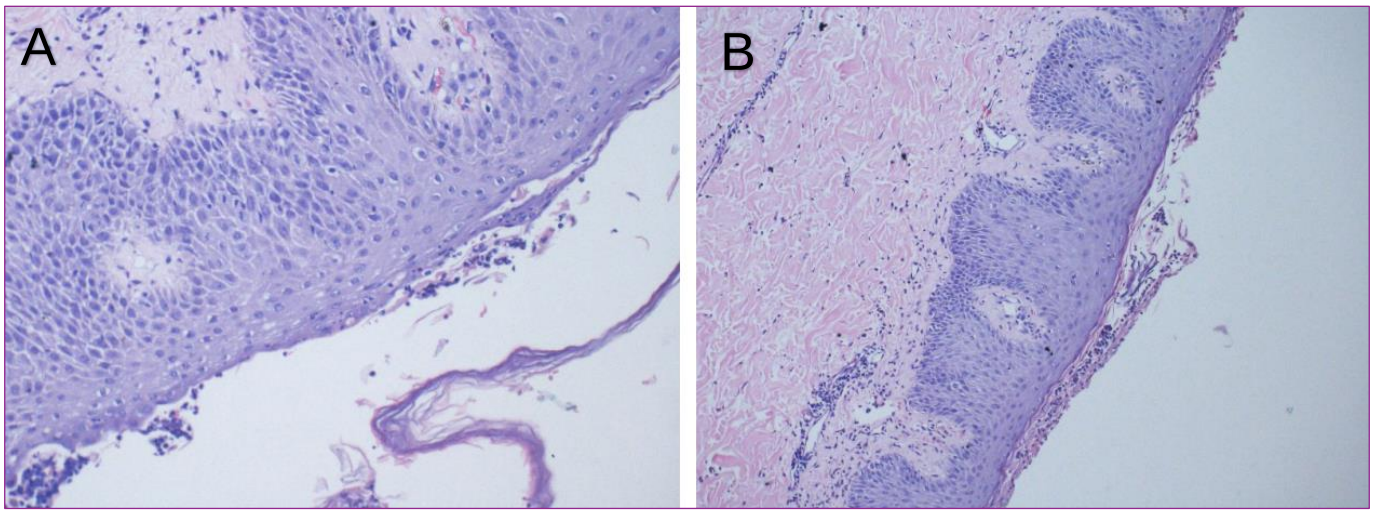

Figure 3. (A) Subcorneal blisters with acantholysis. **(B)** Within the dermis there is a dense chronic inflammatory infiltrate with occasional eosinophils.

protease activation and subsequent acantholysis.[6]

Drug or compound-induced PF blisters likely result from both biochemical and immunologic phenomena. While phenol exposures may have triggered our patient's PF, he had also developed dsg1 antibodies, which play an important role in disease progression. Dsg1 antibodies result in autoantibody-triggered signaling events that further promote keratinocyte dissociation.[7]

Pemphigus has been largely considered a T helper (Th) 2-dominant disease with predominance of Th2 cytokines such as IL-4 in PF patients. IL-4 activates JAK1 and results in increased Th2 differentiation, activation of anti-dsg1-producing B cells, and downstream cytokine signaling that result in blister formation.[8,9] Thus, blocking JAK1 activation may prove to be an effective strategy in blocking the signaling cascade that leads to PF.

CONCLUSION

Our patient's rapid PF remission suggests that upadacitinib may be a novel therapeutic option for pemphigus patients. The oral JAK1 inhibitor would offer a safer, more practical alternative to current treatments which consist of long-term corticosteroid use and intravenous rituximab treatments. Further studies will be required to evaluate the efficacy of the treatment in a larger population.

Patient Consent: Consent for publication of all patient photographs and medical information was obtained by patient prior to article submission. The patient in this case report gave consent for their photographs and medication information to be published in print and online and with the understanding this information may be publicly available.

Conflict of Interest Disclosures: None

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Corresponding Author:
Sophie H. Guénin, MSc
Department of Dermatology, Icahn School of Medicine at Mount Sinai Hospital, 5 East 98th Street, 5th Floor, New York, NY 10029.
Email: Sophiehelene.guenin@gmail.com

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