Bridging to a selective Janus kinase 1 inhibitor in severe atopic dermatitis: An instructive case with upadacitinib

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INTRODUCTION

The management of moderate-to-severe atopic dermatitis (AD) can be challenging in patients refractory to first-line systemic therapies, and inadequate bridging when transitioning between systemic therapies can trigger disease flares. Simultaneously, the ongoing COVID-19 pandemic raises a concern for iatrogenic immunosuppression, particularly with conventional agents, including corticosteroids, cyclosporine, methotrexate, and mycophenolate mofetil. Newer agents may offer less immunosuppression. Dupilumab, a targeted interleukin (IL) 4Rα monoclonal antibody, is Food and Drug Administration-approved for moderate-to-severe AD and has revolutionized AD treatment. However, only 40% of patients achieve clear or almost clear skin after 12 weeks of monotherapy,[1] highlighting the need for additional treatment options.

The Janus kinase (JAK)-signal transducers and activators of transcription pathway is involved in downstream signaling of many proinflammatory cytokines, including those within the Th2 axis (e.g., IL-4, IL-5, and IL-13), and oral JAK inhibitors have emerged as a promising therapeutic class for AD.[2] Several recent clinical trials have investigated selective JAK1 inhibitors as monotherapy for moderate-to-severe AD,[3-5] including recent promising results from a phase III study of abrocitinib[5] and a phase II study of upadacitinib.[3] However, in clinical practice, many patients with severe AD are first managed with systemic immunosuppression prior to starting targeted therapies. Practical approaches for transitioning patients from traditional immunosuppression to JAK inhibition have not been delineated in terms of timing and dosing. We describe a real-world example of a patient with severe AD refractory to dupilumab who was rapidly bridged from cyclosporine to upadacitinib over a 3-week period.

Abbreviations used:

AD: atopic dermatitis
JAK: Janus kinase
IL: interleukin

CASE REPORT

A 39-year-old woman with a history of seasonal allergies and asthma presented for the management of nearly lifelong severe AD primarily involving the trunk and extremities, with prominence over flexural surfaces (body surface area 50%). She was unable to work due to disabling skin itch and pain. After inadequate response to topical therapies (corticosteroids, calcineurin inhibitors, emollients), phototherapy, and conventional systemic immunosuppression (prednisone and cyclosporine), she was started

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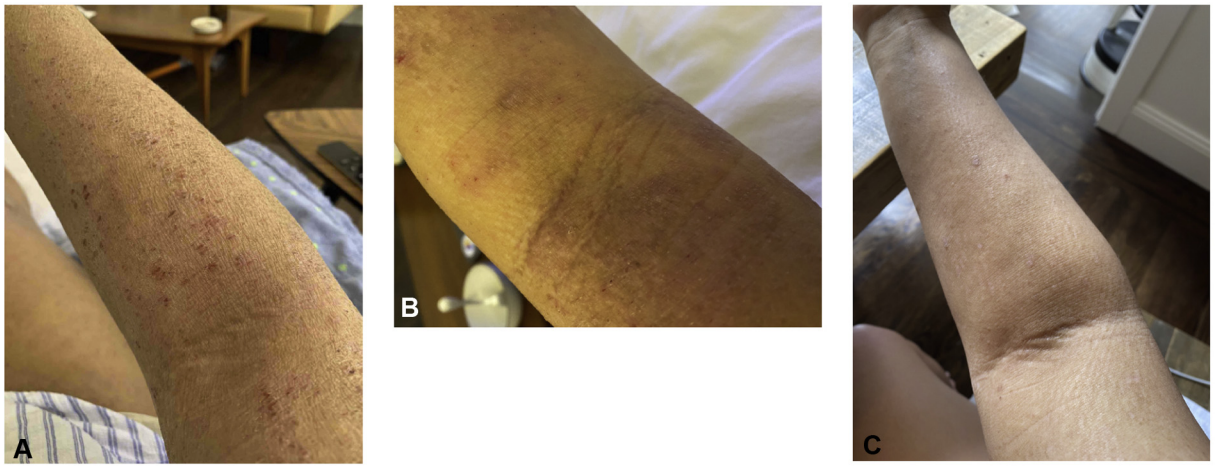

Fig 1. Clinical photographs of the patient's AD disease course. **A**, Persistent erythematous scaly papules and plaques on the antecubital fossa during high-dose cyclosporine treatment (4 mg/kg/day) prior to initiating dupilumab. **B**, AD flared 2 months after stopping dupilumab. **C**, Clinical improvement 1.5 weeks after starting 15 mg of upadacitinib daily and tapering cyclosporine. *AD*, Atopic dermatitis.

on dupilumab with a plan to reduce her ongoing cyclosporine regimen (4 mg/kg/day) (Fig 1, *A*).

Skin biopsy of the thigh prior to initiating dupilumab revealed chronic spongiotic dermatitis with eosinophils. After 6 weeks of dupilumab treatment, she noted improvement of the trunk and extremities, with a body surface area of 10%. However, pruritic erythematous plaques developed on her face and neck, which were suspected to be dupilumab-associated regional dermatosis. A 1-month trial of oral itraconazole offered no benefit for the head and neck dermatitis. After 4 months of dupilumab treatment, cyclosporine was tapered off, with sustained improvement of the AD of the trunk and extremities, but she ultimately opted to discontinue dupilumab due to persistent face and neck involvement.

Two months after dupilumab was discontinued, the face and neck dermatitis partially improved, but the AD of the trunk and extremities flared, and she was restarted on cyclosporine 4 mg/kg/day, with only partial improvement (Fig 1, *B*). Due to insufficient control on high-dose cyclosporine after 6 weeks, she initiated off-label 15 mg of upadacitinib daily with a plan for concurrent rapid downtitration of cyclosporine to reduce global immunosuppression given the concerns for the ongoing COVID-19 pandemic (Fig 2).

During week 2, her itch slightly increased, with a stable rash. Following week 3, she tapered off cyclosporine entirely and was nearly itch-free, with significant improvement in the dermatitis of the face, neck, trunk, and extremities (Fig 1, *C*). Upadacitinib was well tolerated, without clinically notable side effects during this time, and there were no significant abnormalities in complete blood count, comprehensive metabolic panel, creatine kinase, or lipids at 3 weeks. Given her history of herpes labialis, she was advised to start acyclovir for herpes simplex virus prophylaxis. At a 3-month follow-up, the patient's itch and AD were well controlled (body surface area $< 5\%$), without the concomitant use of topical therapies as per patient's preference.

DISCUSSION

In summary, we describe an instructive example of successful rapid bridging from a traditional immunosuppressant to a selective JAK1 inhibitor for severe AD refractory to dupilumab. This real-world experience is consistent with recent phase II trial data suggesting that the maximal efficacy in the eczema area and severity index can be observed by week 4 of upadacitinib treatment.[3] We also delineate a practical approach to quickly tapering cyclosporine, which is similarly known for its rapid kinetics.

This patient's recalcitrant regional dermatosis upon dupilumab treatment, which led to cessation of the treatment, is a well-described clinical phenomenon.[6] The pathogenesis is currently unknown, but hypotheses include a hypersensitivity reaction to dupilumab, site-specific failure, or a shift from Th2- to Th1-mediated inflammation resulting in a Malassezia-related seborrheic dermatitis-like eruption, Demodex folliculitis, rosacea, or allergic contact dermatitis.[6-8] In our patient, the face and neck dermatitis did not respond to the oral itraconazole. We could not exclude allergic contact dermatitis as

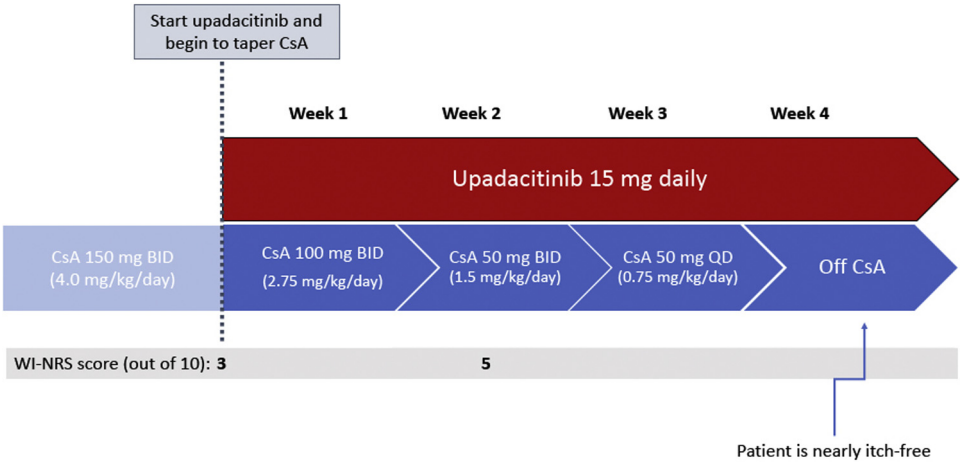

Fig 2. CsA taper strategy upon initiating upadacitinib associated with 11-point WI-NRS from the PROMIS itch questionnaire. Upon starting upadacitinib, CsA was tapered from 4 mg/kg/day to 2.75 mg/kg/day for 1 week and then decreased to 1.5 mg/kg/day, at which time the patient noted an increased itch (WI-NRS 5/10). This dose was maintained for 1 week, tapered more slowly to 0.75 mg/kg/day for 1 week, then discontinued. A few days after CsA was discontinued, the patient was nearly itch-free. *CsA*, Cyclosporin; *PROMIS*, patient-reported outcomes measure information system; *WI-NRS*, worst-itch numeric rating scale.

the patient denied patch testing. Nonetheless, the face and neck dermatitis improved with the cessation of dupilumab and continued to improve with upadacitinib, suggesting that selective JAK1 inhibition may be useful for patients unable to tolerate this uncommon side effect of dupilumab.

Notable adverse effects from earlier-stage studies of upadacitinib include increased risk of infection, acne, mild elevations in liver function tests, dose-dependent decreases in hemoglobin, increases in lipid parameters (low- and high-density lipoproteins), and asymptomatic elevations in creatine kinase. This case highlights the rapid onset of JAK1 inhibitors, which may be beneficial when there is a clinical need to expeditiously taper off traditional immunosuppressants. It further demonstrates that this may be a feasible option in patients in whom dupilumab treatment has failed.

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