JAK-inhibitors as rescue therapy in dupilumab-refractory severe atopic dermatitis: A case series of 6 patients

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INTRODUCTION

Atopic dermatitis (AD) is a chronic, relapsing, inflammatory skin disorder with a heterogeneous clinical presentation and the cardinal symptom of itch, that results in significant patient burden and a significant decrease in patient's quality of life.[1] The pathogenesis of AD is multifactorial and results from an immune response skewed toward the Th2 axis, displaying upregulation of key cytokines, including interleukin 4 (IL-4), IL-5, IL-13, and IL-31.[2,3] Dupilumab, a biologic, which inhibits IL-4 and IL-13 signaling via the inhibition of the IL-4 receptor alpha subunit, was the first targeted treatment approved for AD.[4] More recently, the inhibition of the JAK-STAT pathway with drugs, such as tofacitinib, baricitinib, upadacitinib, and abrocitinib, has shown effectiveness in AD, with the latter 2 gaining U.S. Food and Drug Administration approval in 2022.[5,6]

Although dupilumab is highly effective and used as monotherapy, it might insufficiently treat the signs and symptoms of AD for some patients, necessitating the use of adjunctive therapy. In fact, a single case report has shown a positive response to tofacitinib rescue therapy in a patient who was inadequately controlled with dupilumab monotherapy.[7] Here, we report 6 patients with severe AD who positively responded to an adjunctive JAK-inhibitor (JAK-I) in the setting of inadequate dupilumab treatment without relapse of their disease on subsequent discontinuation of the JAK-I.

Table I summarizes demographic data for this patient cohort. All patients had baseline bloodwork, including screening tests for tuberculosis, hepatitis B, and hepatitis C as well as a complete blood cell count, liver function tests, and a fasting lipid panel before initiating the JAK-I. The complete blood cell count, liver function tests, and lipid panel were rechecked during the treatment period. No patient experienced any laboratory abnormalities while taking dupilumab and a JAK-I concomitantly.

Abbreviations used:

AD:	atopic dermatitis
BSA:	body surface area
IGA:	investigator's global assessment
IL:	interleukin
JAK-I:	JAK-inhibitor

All patients in our cohort either had biopsy and/or clinical confirmation of AD diagnosis and had baseline body surface area (BSA) involvement ranging from 10% to 40% and investigator's global assessment (IGA) from 3 to 4 before dupilumab initiation (Table I). Patients received the dupilumab initial dose of 600 mg followed by a maintenance dosing of 300 mg every other week ranging from 6 to 18 months with subsequent improvement in their disease achieving IGA 0-1. However, all 6 patients experienced a flare of disease at variable time points during dupilumab treatment, resulting in BSA involvement of 3% to 20% and IGA 2-4. After initiating rescue therapy with either tofacitinib or upadacitinib, all 6 patients achieved significant improvement, with resultant BSA ranging from 0% to 4% and IGA 0-1. The JAK-I was successfully discontinued after 2 to 6 months of treatment, and all 6 patients maintained

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Table I. Patient with atopic dermatitis characteristics and clinical response to combination treatment with dupilumab and a JAK-I

Pt	Age, sex, ethnicity	Comorbidities	Baseline BSA involvement (%)	Baseline IGA	Duration of treatment on dupilumab (300 mg QOW) until flare	IGA preflare	BSA during flare (%)	IGA during flare	Post-JAK-I BSA (%), after 4 wks	Post-JAK-I IGA, after 4 wks	Duration of JAK-I treatment until discontinuation	JAK-I used
1	62, Male, White	HTN CVD with stent placement, no history of clotting	30%	4	6 mo	1	10%	3	2	1	6 mo	Tofacitinib 5 mg daily
2	19, Male, Indian	None	10%	3	8 mo	0	3%	2	0	0	4 mo	Upadacitinib 15 mg daily
3	22, Male, White	None	40%	4	6 mo	1	15%	4	4	1	3 mo	Tofacitinib 5 mg twice daily
4	48, Female, White	CVA	20%	3	7 mo	1	6%	3	1	1	2 mo	Upadacitinib 15 mg daily
5	83, Female, White	HTN, CKD, HLD	40%	4	1.5 y	1	20%	4	1	1	2 mo	Upadacitinib 15 mg daily
6	56, Female, White	None	15%	3	6 mo	0	10%	3	0	0	6 mo	Upadacitinib 15 mg daily

BSA, Body surface area; *CKD*, chronic kidney disease; *CVA*, cerebrovascular accident; *CVD*, cardiovascular disease; *HLD*, hyperlipidemia; *HTN*, hypertension; *IGA*, investigator's global assessment; *Pt*, patient.

durable disease control after 3 to 4 months on continued dupilumab monotherapy. There were neither adverse events nor intolerable side effects during the treatment period when both the JAK-I and dupilumab were used concomitantly.

Although dupilumab has greatly improved the treatment options for AD, there still remain some patients who despite dupilumab therapy continue to struggle with long-term control of their disease and require rescue therapy.[7-9] Historically, significant atopic flares have been treated with adjunctive oral steroids or immunosuppressants, such as cyclosporine. However, because of their potential adverse event profile, and the potential for rebound flares on discontinuation, these add-on immunosuppressants are not ideal.[10] JAK-I, however, because of their more targeted inhibition of cytokines directly involved in the pathogenesis of AD, offer a better alternative regarding short-course rescue therapy.[6] In 2021, the U.S. Food and Drug Administration issued a class-wide label update because of concerns that JAK-inhibitors used to treat chronic inflammatory conditions may have similar risks as seen in a tofacitinib safety trial carried out in patients with rheumatoid arthritis with elevated baseline cardiac risk. This study demonstrated a heightened risk for myocardial infarction, stroke, cancer, blood clots, and death in tofacitinib-treated patients with rheumatoid arthritis relative to those receiving a tumor necrosis factor inhibitor (U.S. Food and Drug Administration citation). Because of these potential safety concerns, and the more comforting safety profile of dupilumab as a long-term therapy, short-term JAK-I rescue therapy was preferred over long-term JAK-I maintenance.

In this case series, all 6 patients achieved improved disease control with the addition of a JAK-I. Interestingly, cessation of the JAK-I did not result in disease rebound. Therefore, in addition to using a JAK-I as monotherapy for AD, patients can benefit from the short-term addition of a JAK-I for flares with durable maintenance of disease control both during concomitant therapy with dupilumab and after the discontinuation of the JAK-I.

Although dupilumab is considered generally safe and immunomodulatory as opposed to immunosuppressive, the package labeling for the JAK-I's advises against the use of these drugs concomitantly with a biologic immunomodulator. In this analysis, safety signals were not observed in the setting of this short-term combination treatment. However, future studies looking at the safety and efficacy of combination treatment in larger cohorts of patients are warranted.

Conflicts of interest

None disclosed.

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