Remission of severe atopic dermatitis with dupilumab and rescue tofacitinib therapy

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Key words: dupilumab; jak inhibitor; janus kinase inhibitor; refractory atopic dermatitis; rescue therapy; severe atopic dermatitis.

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by itching that affects 10% of adults in the United States.[1] Advances in the pathogenesis of AD have elucidated a predominant Th2-associated immunopathogenesis pathway with interleukin (IL)-4 and IL-13 acting as key players. This is underscored by the success of dupilumab, which is a monoclonal antibody that blocks the IL-4 receptor α subunit, inhibiting the action of both IL-4 and IL-13 for the treatment of AD.[2,3]

The use of Janus kinase (JAK) inhibitors in AD is based on the IL-4 and IL-13 cytokine signaling pathways, which utilize the JAK-signal transducer and activator of transcription (STAT) pathway as intracellular messengers. Both oral and topical formulations of JAK inhibitors have been demonstrated to be successful for AD.[4,5] However, the use of JAK inhibitors in conjunction with dupilumab for recalcitrant AD has not been previously shown. Here we present a case report of severe AD that was refractory to dupilumab monotherapy and responded to concomitant rescue tofacitinib therapy.

CASE DESCRIPTION

A 35-year-old male presented to our office with severe erythrodermic AD. He had severe AD since the age of 2 and was previously treated with topical corticosteroids with little benefit. He was unable to sleep due to itching and scratching. As with many patients with AD, his disease had a negative psychosocial impact, as he was too embarrassed to wear shorts due to excoriated plaques on his lower legs. Given his severe AD with nearly 75% of the body surface area (BSA) involved, he was started on dupilumab 300 mg every 2 weeks after loading dose in addition to halobetasol ointment 0.05% twice daily. After 9 months of treatment with dupilumab, his symptoms had improved significantly, allowing him to wear shorts in summer and sleep through the night without itching and scratching. The majority of his skin cleared with 10% BSA involvement on dupilumab. Nevertheless, recalcitrant plaques on his face, neck, and nipples remained bothersome and symptomatic. On examination, he had pink-violaceous lichenified plaques with scale on his bilateral areolae and violaceous plaques with lichenification on his upper chest, upper back, and neck (Fig 1, *A*, *B*).

Due to refractory regional AD not responsive to dupilumab, we initiated oral tofacitinib 5 mg twice daily as rescue therapy in addition to continuing dupilumab. Our rationale for starting tofacitnib as opposed to systemic immunosuppressants, such as methotrexate, cyclosporine, or mycophenolate mofetil, is that JAK1/3 inhibition more directly targets the pathogenic cytokines IL-4 and IL-13. Screening laboratory test results for HIV, hepatitis B and C, and tuberculosis were negative before the initiation of treatment. He did not experience any worsening of the head and neck dermatitis, which may occur during dupilumab treatment, as the recalcitrant plaques in these areas failed to respond to dupilumab monotherapy.

Abbreviations used:

AD: atopic dermatitis
BSA: body surface area
JAK: janus kinase

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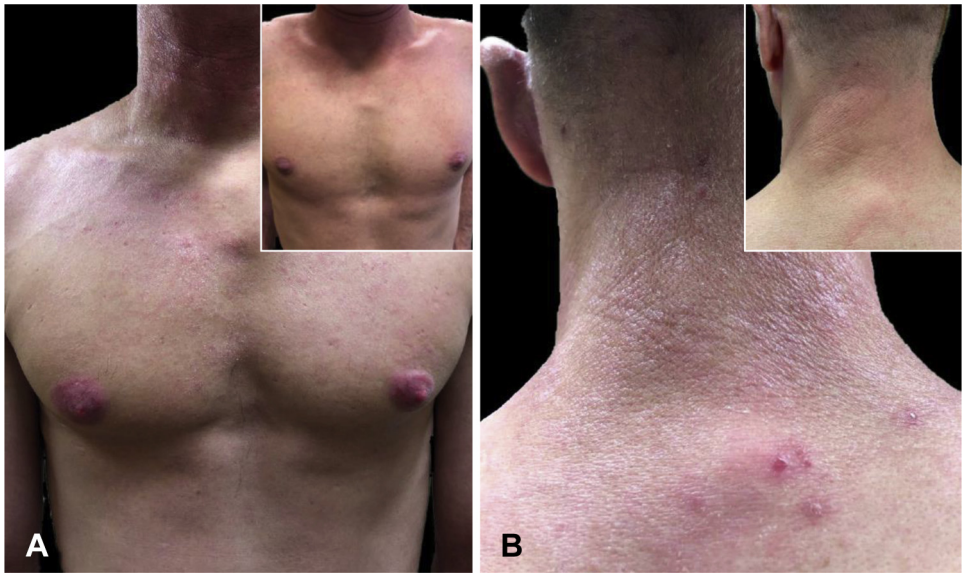

Fig 1. Recalcitrant lichenified, eczematous plaques on the upper chest, including the areola (**A**) and the posterior aspect of the neck (**B**) during dupilumab monotherapy. Two months after the addition of tofacitinib 5 mg twice daily, marked improvement of the plaques on the chest (**A**, inset) and posterior aspect of the neck (**B**, inset) was observed.

Prior authorization for tofacitinib was obtained via our outpatient clinical specialty pharmacy, and the patient's insurance approved coverage. After 2 months of treatment with tofacitinib, he reported improvement of the eczematous plaques on his face, neck, and nipples (Fig 1; *A*, inset and *B*, inset). He had one refractory lesion on his right lower leg to which he applied halobetasol ointment 0.05% twice a day for 2 months. He was treated for a total of 4 months with tofacitinib 5 mg twice daily with no laboratory abnormalities on complete blood count, comprehensive metabolic panel, and lipid panel. He experienced no side effects from the therapy. Tofacitinib was discontinued because of the clearance of his disease, the potential increased risk of serious infections with long-term use, lack of safety studies with this combination, and uncertainty for long-term insurance coverage. Six months since discontinuing tofacitinib, his AD remains well-controlled on dupilumab monotherapy.

DISCUSSION

AD is a chronic inflammatory skin disease, which negatively impacts quality of life, often due to disfiguring skin lesions combined with symptoms of itching and discomfort.[6] The emotional burden of AD is associated with increased depression and suicidality[6] and more significantly impacts patients with severe disease.[7]

While dupilumab has transformed therapy options for AD, not all patients treated with dupilumab monotherapy achieve remission of their disease, and some require additional therapy.[8,9] Oral steroids and other immunosuppressants such as cyclosporin are commonly used to treat refractory AD, but routine use is discouraged due to their poor side effect profile and risk of rebound flares after discontinuation.[10] Instead, for those who do not achieve remission of AD with dupilumab alone, JAK inhibitors are an attractive alternative option for rescue therapy. Tofacitinib is a JAK inhibitor that predominately blocks JAK1 and JAK3. The critical Th2-associated cytokines IL-4 and IL-13 utilize JAK1 (IL-13) and JAK3 (IL-4) for signaling. Second generation selective JAK1 inhibitors (upadacitnib and abrocitinib) have shown efficacy in AD as monotherapy, presumably through the blockade of IL-13 signaling. These newer JAK inhibitors are able to achieve greater selectivity for a particular JAK protein due to the binding of the regulatory portion of the protein. Tofacitinib blocks IL-13 through JAK1 and JAK3 inhibition and IL-4, as well as other common gamma chain cytokines such as IL-2, IL-7, IL-9, and IL-15, through JAK3 inhibition, resulting in a combined and complementary effect when used with dupilumab (Fig 2).

Unlike dupilumab, tofacitinib is not FDA-approved for the treatment of AD. While we were able to obtain insurance approval of tofacitinib for this patient, it has been our experience that tofacitinib may be denied after a number of years, despite remission of a patient's disease, likely due to cost and

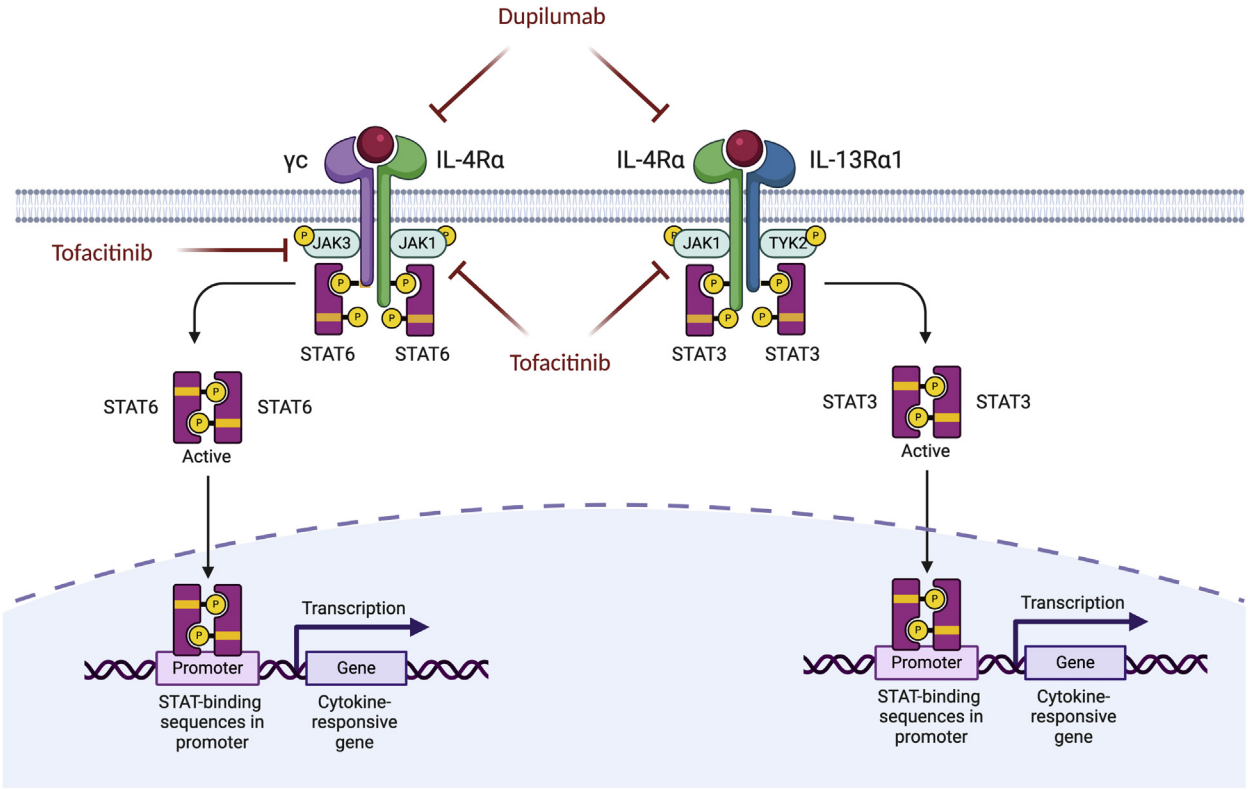

Fig 2. Inhibition of the IL-4 receptor α subunit by dupilumab and inhibition of JAK1 and JAK3 by tofacitinib. JAK3 inhibition by tofacitinib also blocks other γ c cytokines, including IL-2, IL-7, IL-9, IL-15, and IL-21.

Table 1. Reported side effects of dupilumab and tofacitinib

	Mild	Moderate	Severe
Dupilumab	Dry eye Eye pruritis Eosinophilia Injection site reactions	Blepharitis Conjunctivitis Eczema herpeticum Herpes simplex Herpes zoster Keratitis Oral herpes	Hypersensitivity Immunogenicity
Tofacitinib*	Acne Diarrhea Headache Hypertension Nasopharyngitis Nausea Rash Weight gain	Laboratory abnormalities (lymphopenia, neutropenia, anemia, liver enzyme elevation, lipid elevation, increased creatine phosphokinase)	DVT/PE Gastrointestinal perforation Infection (tuberculosis, herpes zoster) Lymphoproliferative disorders Malignancy

DVT, Deep vein thrombosis; *PE*, pulmonary embolism.
*Note that abrocitinib and upadacitinib have similar side effect profiles

off-label usage. Given the uncertainty of future coverage for tofacitinib and the partial success of dupilumab, the decision was made to continue on dupilumab monotherapy, once his disease was remitted.

Both of these medications are not without side effects, but our patient did not experience any. The side effects of dupilumab and JAK inhibitors used as monotherapy in patients are listed in Table 1. The major and only known risk of combining dupilumab

and tofacitinib is an increased risk of serious infection. Considering this risk, long-term use of this combination should be approached with caution and with proper screening tests for infection. Future combination studies are needed to carefully categorize efficacy and risk.

With new JAK1 inhibitors emerging to treat AD, little is known about potential combination therapy of JAK inhibitors and dupilumab for severe, recalcitrant AD. Here we presented a patient with severe, recalcitrant AD responding to rescue JAK inhibitor therapy with concomitant dupilumab therapy. Further investigation evaluating JAK inhibitors as rescue therapy in a larger cohort of patients is warranted.

Conflicts of interest

Dr. Vesely's spouse is an employee of Regeneron Pharmaceuticals, the maker of dupilumab. Dr. Peterson has no conflicts of interest to declare.

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