Eczematous reactions to psoriasis biologics treated with dupilumab: A case series

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INTRODUCTION

Psoriasis is characterized by a T helper (Th)1 and Th17 immune response and a unique cytokine profile, including elevated interleukin (IL)-17 and IL-23.[1] Biologic therapy for psoriasis targets the imbalance of cytokines characteristic of the disease and has revolutionized disease management. However, recent reports have described eczematous eruptions that occur as adverse reactions to biologic therapy for psoriasis and often require discontinuation of the biologic.[2] Here, we report of 3 patients, who developed eczematous reactions while on a biologic targeting Th1 or Th17 cytokines. We successfully treated the reactions with the addition of dupilumab to the existing biologic regimen with no adverse events.

Abbreviations used:

AD:	atopic dermatitis
EASI:	eczema area and severity index
IL:	interleukin
PASI:	psoriasis area and severity index
Th:	T helper

CASE SERIES

Case 1

A 42-year-old man with a 10-year history of psoriasis and no history of atopic dermatitis (AD) presented to dermatology clinic for psoriasis follow-up. Examination revealed erythematous scaly patches on the arms and legs covering >10% body surface area [psoriasis area and severity index (PASI) 8.4]. The patient was on secukinumab and had previously failed triamcinolone, calcipotriene, adalimumab, etanercept, and ustekinumab, of which adalimumab, etanercept, and secukinumab were not tolerable due to recurrent methicillin-resistant *Staphylococcus aureus* skin infections while on these therapies (Table I). The patient was started on 100 mg tildrakizumab (anti-IL-23 agent) every 12 weeks. Significant psoriasis improvement was noted at 4-month follow-up, with only a few plaques on the upper extremities (PASI 1.2). One year after tildrakizumab initiation, the patient presented with a new pruritic rash on both hands. Physical examination revealed erythematous eczematous patches on the dorsal aspects of the hands and palms with superficial excoriations and fissures, consistent with AD. No psoriasis lesions were present, signifying long-term improvement on tildrakizumab. Treatment with crisaborole and triamcinolone followed by clobetasol and tacrolimus (Table I) resulted in no improvement, and new patches and excoriations appeared on the legs one month later [eczema area and severity index (EASI) 9.2]. Biopsy and patch testing were not performed, as the appointment was conducted over telehealth during the COVID-19 pandemic. Risks and benefits of other AD therapies were discussed, including narrowband UVB, Excimer, dupilumab, and discontinuation of tildrakizumab with a trial of a new psoriasis biologic. The patient deferred narrowband UVB and Excimer due to concerns about going to a medical facility during the pandemic and requested to remain on tildrakizumab, given psoriasis clearance after years of trialing other therapeutics that failed to control disease or caused side effects. The patient was started on dupilumab 300 mg every 2 weeks after a 600-mg loading dose, and significant improvement was noted 4 weeks later (EASI 0). At the time of manuscript preparation, the patient had completed 7 months of dual biologic therapy with dupilumab and tildrakizumab with no adverse reactions.

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Table I. Clinical characteristics and treatments

Case	1	2	3
History of atopy or AD	No	No	No
Biologic in use when AD reaction occurred	Tildrakizumab	Ustekinumab	Ixekizumab
Previous failed therapies for psoriasis or Crohn's disease	Triamcinolone 0.1% cream Calcipotriene 0.005% cream Adalimumab Etanercept Ustekinumab Secukinumab	Adalimumab Infliximab	Calcipotriene 0.005 % ointment Phototherapy Halobetasol propionate/tazarotene 0.01%/0.045% lotion Triamcinolone 0.5% cream Adalimumab Secukinumab Ustekinumab
PASI before current biologic	8.4	Not applicable (patient on ustekinumab for Crohn's disease)	9
PASI at follow-up*	1.2	Not applicable (patient on ustekinumab for Crohn's disease)	0.6
Time between initiation of biologic and appearance of eczematous reaction (months)	12	12	2
Localization of eczematous reaction	Hands, legs	Eyelids, back, abdomen	Hands
EASI at baseline	9.2	9.4	3.6
Peak pruritus NRS	7	9	6
AD therapies trialed before dupilumab†	Crisaborole 2% ointment Triamcinolone 0.1% ointment Clobetasol 0.05% ointment Tacrolimus 0.1% ointment	Flurandrenolide tape 4 mcg/cm^2 tape daily as needed Hydrocortisone 2.5% cream Monthly Kenalog injections (total of 6 months) Crisaborole 2% ointment Triamcinolone 0.1% ointment Tacrolimus 0.1% ointment	Crisaborole 2% ointment Halobetasol propionate 0.01% lotion Triamcinolone 0.1% ointment Tacrolimus 0.1% ointment
EASI at follow-up‡	0	0	0
Duration of dual biologic therapy at time of manuscript preparation (months)	7	12	9

AD, Atopic dermatitis; *EASI*, eczema area and severity index; *NRS*, numerical rating scale; *PASI*, psoriasis area and severity index.
*Mean follow-up time of 3 months.
†Duration and frequency of topical use was 2-4 weeks, applied twice a day, unless specified otherwise.
‡Mean follow-up time of 4.6 months.

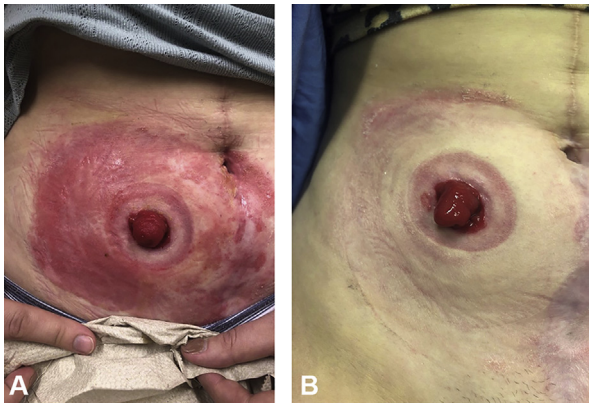

Fig 1. Eczematous reaction to ustekinumab. **A**, Before initiation of dupilumab. **B**, One month after initiation of dupilumab.

Case 2

A 24-year-old female with Crohn's disease and no history of AD presented for follow-up of recurrent pruritic and painful rash present for 1 year. The patient had been taking 45 mg ustekinumab (anti-IL-12/IL-23) every 12 weeks for 2 years for Crohn's. Physical exam revealed pruritic erythematous eczematous patches on the eyelids, back, and abdomen surrounding an ileostomy site (Fig 1, *A*). Over the previous year, the rash had not improved with crisaborole, hydrocortisone, flurandrenolide tape, Kenalog injections, or triple paste ointment (Table I). A patch test targeting more than 70 allergens including the patient's ostomy bag and wipes was negative. A biopsy of the peristomal area revealed spongiotic dermatitis consistent with contact dermatitis or other eczematous reaction. Discontinuation of ustekinumab was not considered, because the patient was in clinical remission with ustekinumab and had failed to control her Crohn's disease in the past with adalimumab and infliximab. Due to increasing severity of pain and pruritus (EASI 9.4) and minimal relief with various topicals, the patient was started on dupilumab 300 mg every 2 weeks after a 600-mg loading dose. Improvement was noted after 1 month (Fig 1, *B*), and complete clearance occurred after 7 months (EASI 0). At the time of manuscript preparation, the patient had completed 1 year of dual biologic therapy with dupilumab and ustekinumab, with no adverse reactions.

Case 3

A 54-year-old female with a 5-year history of psoriasis and psoriatic arthritis and no history of AD presented for psoriasis follow-up. Exam revealed erythematous scaly plaques on the elbows, knees, and scalp (PASI 9). The patient had previously failed phototherapy, triamcinolone, calcipotriene, halobetasol, adalimumab, ustekinumab, and secukinumab (Table I). Ixekizumab (anti-IL-17 agent) was initiated to treat psoriasis and concurrent psoriatic arthritis, with a 160-mg loading dose, followed by 80 mg every 2 weeks until week 12, followed by 80 mg every 4 weeks. Two months after ixekizumab initiation, psoriasis was improved with only mild residual scaling at the scalp (PASI 0.6), and psoriatic arthritis was improved; however, new-onset pruritic patches appeared on both hands. Physical examination revealed erythematous eczematous patches with superficial excoriations on the dorsal and palmar aspects of the hands extending to the wrists bilaterally, consistent with AD (EASI 3.6) (Fig 2, *A*). No improvement was seen with triamcinolone, halobetasol, crisaborole, and tacrolimus (Table I). The patient wished to remain on ixekizumab for psoriasis and psoriatic arthritis given significant improvement after years of trialing other therapies. Dupilumab 300 mg every 2 weeks after a 600-mg loading dose was initiated for AD, and ixekizumab for psoriasis was continued. Six months later, the AD resolved (EASI 0) (Fig 2, *B*). At the time of manuscript preparation, the patient had completed 9 months of dual biologic therapy with no adverse reactions.

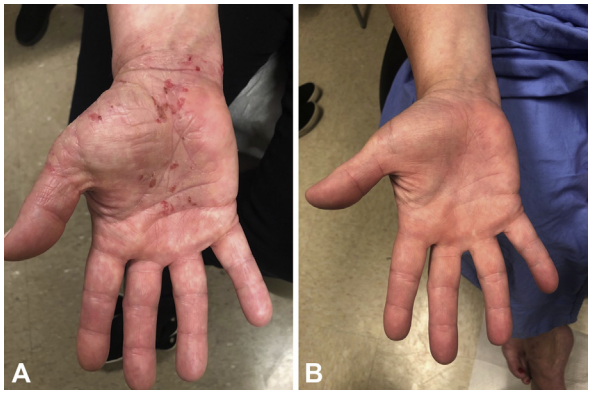

Fig 2. Eczematous reaction to ixekizumab. **A**, Before initiation of dupilumab. **B**, Six months after initiation of dupilumab.

DISCUSSION

Psoriasis and AD are characterized by distinct T-cell-driven immune responses and cytokine profiles. Psoriasis arises from a Th1 and Th17 response, whereas AD is characterized by a Th2 response. Biologic treatment for both psoriasis and AD is aimed at targeting various cytokines that are characteristic of the condition. For example, the monoclonal antibody dupilumab targets the IL-4 receptor alpha subunit, preventing the IL-4 and IL-13 signaling, which is characteristic of the Th2 response in AD.[1] Psoriasis biologics target various interleukins including IL-17, IL-12, and IL-23 that are involved

in the Th1/Th17 immune phenotype characteristic of psoriasis.[3]

In treating the imbalance of the Th1/Th17 to Th2 response in psoriasis or AD with biologics, the resulting shift in cytokine levels may paradoxically favor the opposing cutaneous disease.[4] For example, Napolitano et al. described an eczematous reaction to an anti-IL-17 (ixekizumab) treatment for psoriasis, as well as a psoriasiform eruption to an anti-IL4/IL-13 (dupilumab) therapy for AD.[1,2,5] In the first case, the anti-IL-17 therapy likely dampened the Th1/Th17 phenotype of psoriasis, shifting the balance toward a Th2 phenotype characteristic of AD, causing the appearance of AD in the patient. In the second case, the opposite shift likely occurred. Dupilumab shifted the cytokine balance away from a Th2 response, favoring the Th1/Th17 pathway characteristic of psoriasis.[1]

Our study describes eczematous reactions consistent with AD emerging in 3 patients treated with biologic therapy targeting the Th1 and Th17 pathways, suggesting a shift in balance away from Th1/Th17 and toward Th2. Two patients were treated for psoriasis, and one was treated for Crohn's disease, which is also Th1 mediated.[3] No patient had a history of atopy or AD prior to biologic use.

A handful of case reports have described this phenomenon, including 6 cases of eczematous eruption, which occurred during anti-IL-17 treatment with secukinumab or ixekizumab,[2,4,6] and one occurring during anti-IL-12/IL-23 treatment with ustekinumab.[7] Eczematous eruptions likely occur between 2.2% and 12.2% of patients on anti-IL-17 therapy and typically emerge several months after treatment initiation, a timeline consistent with our reporting.[2,4,8]

A treatment for eczematous reactions to psoriasis biologics is needed. In the majority of the reported cases, discontinuation of the psoriasis biologic was necessary after minimal improvement was observed with topical and systemic steroids.[2] Our 3 patients had minimal responses to various AD therapies but deferred biologic discontinuation, having reached stabilization of disease after years of failure or adverse reactions with other therapeutics. Psoriasis patients often spend years trialing various therapies before finding an effective biologic, and dupilumab may be an important option to allow these patients to remain on biologics that control disease, when treatment-emergent eczematous reactions are unresponsive to topicals.

Little data exists on the safety of dual biologic therapy to treat concomitant psoriasis and AD, likely because AD and psoriasis rarely coexist due to opposing underlying immune phenotypes.[9] To our knowledge, there has been limited reporting on the use of dupilumab for eczematous eruptions to biologics.[1] At the time of manuscript preparation, our patients completed between 7 months and 1 year of dual therapy with no adverse reactions. In all patients, dupilumab was initiated through insurance, and discontinuation was never attempted as the treatment was well-tolerated and provided good disease control. While long-term studies are needed to confirm the safety and efficacy of this practice, our report supports the use of dupilumab to manage eczematous reactions to psoriasis biologics when other treatments have failed.

Conflicts of interest

Saakshi Khattri is an employee of Mount Sinai and a consultant for Abbvie, Eli Lilly, Glenmark, Ichnos Sciences, Janssen, and Novartis. She serves on the Advisory Boards for Eli Lilly, Glenmark, Ichnos Sciences, Janssen, Novartis, and UCB. Merav Koschitzky, Ryan Rivera-Oyola, Kathryn Tan, and Maria Rosa Noliza Encarnacion have no relevant conflicts of interest to declare.

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