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Upadacitinib as a potential option for the management of paradoxical eczema induced by interleukin-23 inhibitors

Anna Paola Lugli,[1,2] Niccolò Gori,[1,2] Elena Ippoliti,[2] Benedetta Ambrosio,[1,2] Ketty Peris[1,2]

[1]Dermatology, Department of Translational Medicine and Surgery, Università Cattolica del Sacro Cuore, Rome; [2]Dermatology Unit, Department of Medical and Surgical Sciences, A. Gemelli University Hospital Foundation - IRCCS, Rome, Italy

Correspondence to: Niccolò Gori, Università Cattolica del Sacro Cuore, Rome, and Fondazione Policlinico Universitario Agostino Gemelli - IRCCS, Largo Agostino Gemelli 8, 00168 Rome, Italy. Tel.: 06-301554227; E-mail: niccolo.gori@policlinicogemelli.it

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Dear Editor,

Paradoxical eczema (PE) is defined as *de novo* onset or flare of eczematous lesions during biologic therapy for psoriasis, regardless of atopic diathesis.[1] PE has been reported with anti-tumor necrosis factor (TNF)-α, anti-interleukin (IL)-17, and more recently with anti-IL-23 agents such as risankizumab, tildrakizumab, and guselkumab, with an estimated incidence of 1-3% among psoriatic patients treated with biologics, likely underestimated.[1-4]

Herein, we report the successful use of upadacitinib, an oral selective Janus kinase (JAK)-1 inhibitor approved for both psoriatic arthritis and atopic dermatitis, in the management of a PE induced by guselkumab.

A 45-year-old obese woman (body mass index: 34.3) with a decennial history of plaque psoriasis was referred to our clinic for a disease flare that occurred after cyclosporine A (CsA) withdrawal. Physical examination revealed multiple psoriatic plaques, mainly located on the extensor surfaces of upper and lower limbs, with a Psoriasis Area and Severity Index (PASI) score of 10 (Figure 1 a,b). The patient was otherwise in good health with normal routine blood tests. Treatment with subcutaneous guselkumab at the approved dosage for psoriasis was initiated, leading to almost complete control of the disease (PASI: 1) after 12 weeks. Nevertheless, after 46 months of therapy, the patient developed itchy bilateral eyelid eczema (Figure 1c).

Her medical history was negative for atopic comorbidities, with normal total IgE levels [31 KU/mL] and negative patch tests. Histological examination of a biopsy from the left upper eyelid showed epidermal spongiosis with mild acanthosis and hyperkeratosis, together with a superficial perivascular lymphocytic and eosinophilic infiltrate, consistent with a diagnosis of eczema.

Considering the temporal relationship between drug exposure and symptom onset, the absence of alternative etiologies, and the clinical findings, the Naranjo score was 6, supporting a probable diagnosis of guselkumab-induced bilateral periocular eczema. Guselkumab was therefore discontinued, and subcutaneous methotrexate (7.5 mg weekly) was initiated, resulting in only partial remission of eczema, while psoriatic plaques recurred on the trunk and limbs (Figure 1d). Consequently, CsA (3 mg/kg/day) was reintroduced, leading to rapid improvement of both eczematous and psoriatic lesions; however, it was discontinued after one month due to the onset of hypertension. To both control psoriasis and eczema, oral upadacitinib (30 mg daily) was prescribed. After 8 weeks of treatment, the patient achieved complete clearance of both eczematous and psoriatic lesions (Figure 1 e,f). At week 48, due to complete remission, the dosage was reduced to 15 mg daily and continued over 72 weeks of follow-up, with no adverse events.

A recent cohort study involving 13,699 patients with psoriasis (24,997 biologic exposures) identified a lower risk of PE with anti-IL-23 agents, particularly guselkumab, compared to anti-TNF-α and anti-IL-17 therapies.[2] PE may develop weeks, months, or even years after treatment initiation, suggesting a mechanism not driven by dose but rather by progressive immune remodeling toward a Th2 phenotype.[1-3] Major risk factors for PE during biologic therapy include female sex and atopic history.[2] Although the pathogenesis is still unclear, one of the best-supported hypotheses is that the development of PE during treatment with IL-23/IL-17 inhibitors may result from the reduction of circulating TNF-α, which normally suppresses interferon (IFN)-α release from plasmacytoid dendritic cells, thereby leading to increased IFN-α production. IFN-α release from plasmacytoid dendritic cells may subsequently induce an overexpression of IL-22 that reduces keratinocyte turnover and lipid synthesis, facilitating antigen penetration and allergic pathway activation.[1,3,5] In this setting, a recent study found overexpression of TNF, IFN-γ, and IFN-α and their signalling pathways in PE, suggesting a predominantly Th1, rather than Th2, driven inflammation.[5]

Treatment should balance eczema control with ongoing psoriasis management.[1] Mild cases can often be managed with topical corticosteroids or calcineurin inhibitors or with systemic therapies (*e.g.*, methotrexate, acitretin) without discontinuing the biologic therapy.[1] In cases of moderate-to-severe eczematous manifestations, treatment discontinuation and switching to a different biologic class are often required; however, paradoxical eczematous reactions have been reported to persist in several psoriatic patients despite these therapeutic adjustments.[1,2]

JAK inhibitors, such as upadacitinib, offer an effective strategy by simultaneously inhibiting multiple cytokine pathways (Th1, Th2, Th22), with proven efficacy in atopic dermatitis and psoriasis.[6-8]

To date, only one other case of a 47-year-old male psoriatic patient with guselkumab-induced PE who was successfully treated with upadacitinib has been reported in the literature. Nevertheless, over the 10-month observation period, the patient was treated with upadacitinib without discontinuing biologic therapy.[9] Instead, in our patient, complete resolution of both eczematous and psoriatic lesions was maintained over a 72-week period after guselkumab withdrawal, with upadacitinib in monotherapy.

In conclusion, this case illustrates that discontinuation of the biologic and switching to a JAK inhibitor can achieve simultaneous control of psoriasis and eczema. Prospective studies are warranted to identify predictive biomarkers and to define optimal switching algorithms.

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Figure 1. Psoriasis: erythematous hyperkeratotic plaques with well-defined margins on elbows (**a**) and dorsum of both hands (**b**). Eczema and psoriasis relapse: erythema, edema, and scales on the eyelids (**c**), small, roundish psoriatic plaques distributed on anterior trunk (**d**). Resolution of both eyelid eczema (**e**) and psoriasis (**f**).