

**Title:** Occurrence of psoriasiform eruption during dupilumab therapy for adult atopic dermatitis: a case series

**Running head:** Dupilumab-induced psoriasiform eruption

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Dear Editor,

Dupilumab is a monoclonal antibody that binds to and inhibits interleukin (IL)-4 and IL-13 receptor subunit  $\alpha$ . It is approved for the treatment of moderate-to-severe adult atopic dermatitis (AD) (*Napolitano, 2018*). Dupilumab has a good safety profile, with conjunctivitis being the main side-effect (*Akinlade, 2019*). Data regarding the frequency and features of other adverse events are scant. Herein, we describe the occurrence of psoriasiform eruption in 3 adult AD patients during treatment with dupilumab.

From July 2018 to March 2019, 90 adult AD patients (52 males, 57.7%; aged 18-66 years, mean age 44.6 years) were treated with dupilumab (600 mg induction dose and then 300 mg every 2 weeks). Among the patients, a history of persistent AD (onset  $\leq 18$  years) was more common than adult-onset AD [61/90 (67.8%) vs 29/90 (32.2%);  $p=0.7$ ]. Seventy-two out of ninety patients (80%) were affected by one or more atopic comorbidities (allergic rhinitis, asthma, and allergic conjunctivitis). The median follow-up time was  $5.7 \pm 3.5$  months. Eczema Area and Severity Index (EASI) 50 and EASI75 were recorded in 75/90 and 55/90 patients, respectively. Conjunctivitis was reported in 15/90 patients (16.6%) and dupilumab was discontinued in 2 cases (2/15; 13.3%). An increased levels of eosinophils ( $>500/\text{mm}^3$ ) were found in 32/90 patients (35.5%).

Three out of ninety patients (3.34%) showed the onset of a psoriasiform eruption during treatment (Table1). These 3 patients suffered from persistent AD, the mean age at symptom onset being  $2.5 \pm 3.8$  years. Cyclosporin represented the most common previously prescribed conventional systemic drug (100% of cases). Mean dupilumab treatment duration at the onset of psoriasiform eruption was 15.2 weeks. Erythematous and hyperkeratotic plaques were

noticed mostly on the scalp and on both the upper and lower limbs, in areas of skin that had not previously been affected by AD or psoriasis (Figure 1a). Diagnosis was made after clinical and histological examination. Histology showed acanthosis with the elongation of rete ridges, parakeratosis, hypogranulosis, and Munro abscesses; the vessels of the superficial derma were dilated; and the dermal inflammatory infiltrate was composed mainly of lymphoplasma cells, T lymphocytes and of Langerhans cells and/or neutrophils (Figure 1b). None of the 3 patients had a personal history of psoriasis. Only one patient reported a family history of psoriasis. Dupilumab treatment discontinuation was required in 1 patient, since topical and systemic corticosteroids were not able to achieve stable and continuous improvement of the eruption. This patient started nb-UVB therapy and is under follow-up.

The temporal relationship between the treatment with dupilumab and the onset of psoriasiform eruption suggests that dupilumab might have contributed to its development in our patients. The eruption had psoriasis-like clinical and histopathologic aspects. However, the histologic features of eczema were scarce, probably because the psoriasiform eruption occurred during the remission phase of AD induced by dupilumab and was located on previously unaffected skin areas. Psoriasis and AD are both T helper (Th) mediated inflammatory diseases. However, AD is considered to be a polar Th2 disease, while psoriasis is considered to be a disease driven by Th1, Th17, and Th22 (*Tracey, 2018*). The relevance of lymphocyte subset balance in inflammatory skin diseases has been demonstrated (*Eyerich, 2018*). The treatment of such diseases by inhibiting subsets of cytokines can induce an imbalance that favors other subsets (*Eyerich, 2018*). For example, cutaneous xerosis and eosinophilia, typical features of Th2-mediated diseases, are side effects of anti-TNF drugs used for psoriasis (*Malisiewicz, 2011*). Furthermore, the treatment of psoriasis with anti-interleukin 17 agents may induce

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eczematous reactions (*Napolitano, 2019*). Similarly, IL-4 and IL-13 blockade by dupilumab could induce a shift toward Th1/Th17 subsets, leading to psoriasis (*Safa, 2019*). It has been highlighted that IL-4 downregulates Th1 and Th17 cells and, can modulate dendritic cells thus suppressing IL-23 production. In addition, it can inhibit the secretion of epidermal IL-1b and IL-6 from psoriatic plaques (*Safa, 2019; Hahan, 2017*). A case of erythrodermic psoriasis (*Tracey, 2018*) and a case of guttate psoriasis (*Gori, 2019*) during treatment with dupilumab have been reported. However, no data regarding the anamnesis of psoriasis were reported (*Tracey, 2018; Gori, 2019*). Safa et al described a 55-year-old man affected by AD without a personal or family history of psoriasis who presented with erythematous and scaly plaques affecting the trunk after 2 months of treatment with dupilumab, which was resolved after a short therapy with a potent topical steroid without the need to discontinue dupilumab (*Safa, 2019*). Only 1 of 3 our patients needed to interrupt the treatment with dupilumab; he had a family history of psoriasis. In contrast, the remaining 2 patients who continued the treatment with dupilumab, had no family or personal history of the disease. It can therefore be hypothesized that a family history of is a risk factor for the appearance of a more serious and more difficult to manage psoriatic eruption. The postmarketing experience with dupilumab is limited and further observations in real life are necessary.

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**Table 1.** Clinical features of atopic patients with psoriasiform eruption. AD= atopic dermatitis; D= dupilumab; NB-UVB= narrow band UVB; CsA= cyclosporine; MTX= methotrexate.

| Pts | Sex | Age | AD onset (years) | Previous therapy | Personal history of psoriasis | Family history of psoriasis | Duration of dupilumab therapy | Psoriasiform eruption details                                                                          | Histological examination                                                                                                        | Dupilumab discontinuation | Psoriasiform eruption treatment                             |
|-----|-----|-----|------------------|------------------|-------------------------------|-----------------------------|-------------------------------|--------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|---------------------------|-------------------------------------------------------------|
| 1   | F   | 74  | 5                | CSA,             | No                            | No                          | 6 months                      | Erythematous and hyperkeratotic plaques on the scalp                                                   | Parakeratosis, hyperkeratosis, Munro microabscess and inflammatory dermal infiltrate composed mainly by lymphoplasmacells       | No                        | Clobetasol lotion                                           |
| 2   | M   | 50  | 3                | MTX, CSA,        | No                            | No                          | 5 months                      | Infiltrated and hyperkeratotic well-defined skin lesions appeared on the scalp, hands and upper limbs. | Hyperkeratosis, parakeratosis, psoriasiform hyperplasia, and dermal infiltrate composed mainly by T lymphocytes and neutrophils | No                        | Calcipotriene/ betamethasone foam                           |
| 3   | M   | 32  | 1                | CSA              | No                            | Yes                         | 1 month                       | Erythematous and scaly plaques on hands, trunk and lower limbs                                         | Parakeratosis, hyperkeratosis, Munro microabscess and dermal infiltrate of lymphocytes, macrophages and neutrophils.            | Yes                       | Clobetasol ointment<br><br>Prednisone tablets<br><br>Nb-UVB |

**Figure 1.**

- a) Clinical features of psoriasis-like eruption during dupilumab therapy in our 3 patients.
- b). Skin biopsy from patient n. 1 showing psoriasiform hyperplasia and dermal lymphoplasmacellular inflammatory infiltrate around the blood vessels and a follicle.

