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Early onset of alopecia areata after dupilumab introduction in a patient with atopic dermatitis

Atopic dermatitis (AD) is a common chronic inflammatory skin disease in which T-helper type 2 (Th-2) inflammatory responses play a central role. Dupilumab is a human monoclonal antibody against interleukin (IL)-4 receptor alpha. It inhibits IL-4 and IL-13 signals that are involved in triggering and maintaining Th-2 inflammation. This is the first targeted biological therapy for moderate-to-severe atopic dermatitis (AD) in adults who do not respond adequately to conventional topical and systemic treatments, or for whom these treatments are not recommended. We report a case of early-onset alopecia areata (AA) after the start of dupilumab therapy in a patient with severe AD.

A 23-year-old white woman had AD since childhood, associated with asthma and allergic conjunctivitis. SCORing Atopic Dermatitis (SCORAD) was 50. She had severe pruritus and many excoriated and lichenified skin lesions. As she had not responded to emollients, topical steroids and tacrolimus, UVB phototherapy, and cyclosporine, dupilumab was started. Topical corticosteroids (betamethasone and clobetasol), an antihistamine (desloratadine), and an anti-asthma drug combination (fluticasone propionate, salmeterol, and salbutamol) were maintained. Her condition and quality of life improved after a few doses of dupilumab. A significant clinical improvement of 76% (SCORAD 12) was observed after eight weeks of treatment (five injections). The skin surface affected was only 1%. Burning

sensations and pruritus had decreased significantly. The patient stopped her anti-asthma treatments because she no longer felt respiratory discomfort. However, she noticed hair loss on her scalp 48 hours after the first injection of dupilumab. After one week of treatment, four alopecia patches were observed. The other hairy areas were unaffected. Hair loss worsened despite daily applications of minoxidil and clobetasol propionate. Therefore, dupilumab was discontinued after eight weeks of treatment. At this stage, there were 12 alopecia patches in the frontal, vertex, and occipital regions (figure 1), and a decrease of capillary density. After dupilumab discontinuation, progressive hair growth was observed, with a return to normal after six months.

We report a chronological relationship between dupilumab introduction and occurrence of AA. In this patient, the time to onset of AA was very short. However, after a single 600-mg subcutaneous dose of dupilumab, the median time to maximum serum concentration is reported to be 3-7 days [1]. Similarly, paradoxical skin reactions have already been described after a few days of anti-TNF-alpha treatment [2]. Three other reported cases of AA after dupilumab administration have been described, but after five, six and 18 weeks of treatment, respectively [3-5]. A total of 116 cases of alopecia after dupilumab therapy have been documented in VigiBase, the WHO database of individual case reports, eight of which were AA. Dupilumab was the only suspected trigger in seven cases. In the two cases in which the time to onset was known, AA occurred within one month of dupilumab administration.

By contrast, two cases of AA remission with dupilumab have been reported [6, 7]. A personal or family history of atopy, especially AD, is the most important risk factor for AA [8]. Since AD is associated with an increased risk of developing AA [9], and cases of AA remission with dupilumab have been reported, a simple association between AD and AA cannot be excluded. The pathophysiology of AA is still poorly known. It involves several inflammatory pathways: T-helper type 1 (Th-1) with increased gamma interferon in the scalp but also Th-2, T-helper type 17 (Th-17)/IL-23, and phosphodiesterase pathways [10]. It is possible that the Th-1 pathway plays a major role in patients who develop AA after administration of dupilumab because of its upregulation by inhibiting the Th-2 inflammatory pathway. Th-2 inflammatory pathways



Figure 1. Development of alopecia areata after seven weeks of treatment with dupilumab.

could be involved in patients with concomitant AA and AD. Based on the cases reported to date, there appears to be a potential risk of developing AA with dupilumab rather than a remission of pre-existing AA.

We report the shortest time to onset of AA after dupilumab introduction. This is an unusual case of AA after a single injection of dupilumab. Clinicians should be aware of the risk of AA in patients treated with dupilumab. Scalp biopsies should be performed to better understand the pathophysiology of AA. ■

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TNF α inhibitor-induced urticaria: a class effect

The introduction of tumour necrosis factor alpha (TNF α) inhibitors and more recent biologics such as ustekinumab or anti-IL17/IL17R blockers have revolutionized the management of moderate-to-severe psoriasis and complete skin clearance can now be attained. However, the use of biologics such as anti-TNF α are associated with several adverse skin events including psoriasiform or lichenoid eruptions and lupus-like syndrome. We report the case of TNF α inhibitor-induced urticaria with adalimumab and infliximab, revealing a class effect reaction.

We describe the case of a 27-year-old woman who suffered from severe psoriasis since childhood with skin lesions affecting her entire body including her scalp and skin folds (*figure 1A*). Many topical and/or systemic therapies including topical steroids, PUVA therapy, methotrexate, and etanercept were unsuccessful in treating her condition (*figure 1C*). Because of the severity of her psoriasis (PASI:16 and DLQI:18), adalimumab treatment was introduced and led to temporary clinical remission. However, 18 months later, the disease flared up, warranting the discontinuation of the adalimumab and a switch to ustekinumab. Due to multiple side effects (weight gain, arthralgia, and depressive state), the patient interrupted the ustekinumab treatment after six months. Three years later, the patient returned to the dermatology clinic and presented with severe psoriasis (PASI:11 and DLQI:23). Because anti-IL-17 blockers were not yet available, adalimumab was proposed with increased injection frequencies (40 mg per week). Again, the psoriasis responded very well to the therapy but eight months later, she developed a urticarial rash with dermographism, associated chronic pruritus and insomnia. The urticarial rash did not start at the sites of injection nor did it coincide with the adalimumab injections. The papules developed on the trunk and limbs, were evanescent during the day, and were partially controlled by antihistamines. Adalimumab was stopped and secukinumab was initiated. The patient immediately noted the disappearance of the urticarial lesions, but anti-IL-17 blocker did not improve the psoriasis lesions. After six months, secukinumab was stopped and it was decided to retarget the TNF α pathway by treating with infliximab (5 mg/kg every six weeks). Despite the efficacy of infliximab as treatment for the psoriasis, a recurrence of the urticarial skin lesions associated with major pruritus was observed (*figure 1B*) two weeks after the second infliximab administration. Antihistamines and methotrexate were added to control the urticarial reaction. The patient presented no systemic symptoms. Blood analyses, eosinophil count (0.22G/L), and tryptase level (2.4 μ g/L) were normal.

Anti-TNF α -induced urticaria can be triggered by different mechanisms [1]. Firstly, an immediate IgE hypersensitivity-mediated reaction may be implicated, as has already been described in previous publications. However, urticaria should then occur within two hours [2, 3]. Delayed hypersensitivity has also been described in anti-TNF α -induced urticaria [4, 5]. However, neither of these two mechanisms were retained because the chronology of urticarial lesions did not coincide with treatment administrations and because the skin tests, performed two months after the beginning