

BRIEF ARTICLES

Hypersensitivity Reactions Secondary to Dupilumab in Two Patients with Moderate to Severe Atopic DermatitisRaina Bembry, MD¹, Navid Malakouti, MD¹, Mary Maiberger, MD¹¹Howard University Hospital**ABSTRACT**

Dupilumab is a human monoclonal IgG4 antibody that is widely used to treat atopic dermatitis. Dupilumab was recently FDA approved to treat moderate to severe atopic dermatitis. Here we describe two cases of patients with moderate to severe atopic dermatitis who developed an acute hypersensitivity reaction within hours of their second dose of dupilumab.

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory disease of the skin with a complex pathogenesis. It has both genetic and environmental factors leading to epidermal barrier defects and immune system derangements.^{1,2} AD occurs in nearly 15-30% of children and 2-10% of adults.^{2,3} Conventional treatment for AD consists of emollients, topical corticosteroids, and topical calcineurin inhibitors. Patients with moderate-to-severe AD not adequately managed by conventional therapies can be treated with cyclosporine, azathioprine, methotrexate, mycophenolate mofetil, and more recently, dupilumab.³ Dupilumab is a human monoclonal IgG4 antibody that inhibits the Th-2 cytokines, interleukin-4 and interleukin-13, by binding to the interleukin-4 receptor alpha subunit.⁴ Dupilumab downregulates the expression of genes encoding inflammatory mediators and epidermal proliferation, and upregulates genes linked

to epidermal barrier, lipid metabolism, and structure.^{4,5} Injection site reactions are the most commonly reported adverse event associated with the use of dupilumab.⁷ Hypersensitivity reactions to dupilumab are rare: less than 1% of trial patients reported having serum sickness, serum sickness-like, or urticarial reactions, which were not reported as adverse effects in phase 3 clinical trials.^{7,8} We present two cases of hypersensitivity reactions on second exposure to dupilumab in two adult-male

CASE PRESENTATION**Case 1**

A 68-year-old Asian man with moderate-to-severe atopic dermatitis presented with worsening pruritus and pain, primarily of the hands, that negatively affected his quality of life. His disease was only partially managed with topical clobetasol ointment and oral methotrexate 12.5 mg, but he still required oral prednisone intermittently for flares. Physical examination findings included

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xerotic, lichenified, excoriated firm plaques on the hands, left foot, buttocks, and inguinal regions. Additionally, hyperpigmentation and lichenification of the buttocks and inguinal region were noted. Methotrexate was discontinued and he was injected with a 600 mg loading dose of dupilumab in clinic which was tolerated well. He reported improving pruritus on a one-week telephone follow-up. Within hours of his second injection, he developed a diffuse eruption and generalized pruritus. Physical examination revealed scaly erythematous patches, plaques and papules involving the thighs, calves, feet, genitals, arms and elbows. The shave-biopsy of the right elbow performed at the time of the reaction showed spongiotic dermatitis with superficial, perivascular chronic inflammation, and rare eosinophils. The biopsy was consistent with a hypersensitivity reaction. Dupilumab was discontinued and he was started on oral prednisone (1mg/kg) tapered over two weeks which improved the rash, but pruritus persisted. He was restarted on his previous dose of methotrexate which lead to moderate improvement in pruritus.

Case 2

A 53-year-old Caucasian male presented with a 10-year history of recalcitrant atopic dermatitis. He had previously attempted and failed many treatments including the following: cyclosporine; mycophenolate mofetil; methotrexate; apremilast; narrowband UVB; high potency topical corticosteroids; topical calcineurin inhibitors; calcipotriene; and crisaborole. Physical examination showed several erythematous papules coalescing into plaques on the upper extremities, lower extremities, and trunk, with eczematous patches on the face and scalp. There were eczematous, slightly erythematous to tan plaques on the bilateral lower legs and a thickened scaly plaque on

the left elbow. He demonstrated clinical dermatographism with associated pruritus. The patient was initiated on dupilumab and tolerated the loading dose well. A scheduled maintenance dose two weeks later resulted in increased pruritus and worsening dermatitis within hours of injection. His physical examination showed eczematous dermatitis with lichenification, excoriations and fissures on his legs, back, and arms. There were erythematous, rough papules on the vertex scalp on a background of erythematous, hyperpigmented skin. Dupilumab was discontinued and he was initiated on azathioprine, which lead to minor resolution of his pruritus and dermatitis.

DISCUSSION

We described two cases of patients with moderate-to-severe atopic dermatitis (AD) who developed an acute hypersensitivity reaction within hours of their second dose of dupilumab.

Given the temporal relationship between the second dose of the dupilumab with the patient's worsening dermatitis, and the skin biopsy consistent with a hypersensitivity reaction, we ascertain these hypersensitivity reactions were possibly a result of exposure to dupilumab.⁹ We also conclude that the discontinuation of dupilumab and aggressive treatment with systemic and topical immunosuppressants returned both patients to baseline levels of their disease. It is unclear why the two patients experienced a hypersensitivity reaction from dupilumab. There is documentation of a non-specific inflammatory response after use of dupilumab, with resolution after cessation of the drug.¹⁰

AD can be classified as either acute or chronic, intrinsic or extrinsic, and can even

be differentiated by ethnicity. Intrinsic AD affects 20% of the adult population, with normal levels of IgE.⁵ In comparison to extrinsic, there is a higher immune system activation with increased levels of Th-22 and Th-17/IL-23 in intrinsic AD.⁵ Extrinsic AD affects 80% of the adult population and is associated with increased levels of IgE and a predominance of Th-2 activation.^{4,5} Dupilumab targets cytokines in the extrinsic pathway, which may lead to a better response in patients with extrinsic AD.

Acute AD is characterized by an over-activation of Th-2 and Th-22 immune profiles, resulting in increased levels of IL-4, IL-13, IL-31, and IL-22.⁵ In chronic AD, there is a switch to a Th-1 mediated pathway and a decrease in IL-4 activity.

The effective use of Th-2 antagonists has resulted in new systemic therapies being investigated for the treatment of AD. The IL-13 antagonists, tralokinumab and lebrikizumab, IL-31 antagonist, Nemolizumab, and other Th-2 antagonists are currently being evaluated.⁶ Antagonists to IgE, Th-22, Th-17/IL-23, PDE-4, Tumor Necrosis Factor, and JAK are also being evaluated for their effectiveness in the systemic treatment of AD.⁶ AD has a complex, multifactorial nature. The multitude of potential targets for pharmacologic intervention, as well as the variable response to common treatments warrants further investigation for the development of future pharmaceutical therapies.

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