

# Something to Sweat About: Two Cases of Dupilumab-Induced Hyperhidrosis and Bromhidrosis

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## Abstract

**Introduction:** Atopic dermatitis (AD, eczema) is familial chronic inflammatory skin disease of complex etiology and increasing prevalence. Dupilumab is an IL-4 receptor subunit alpha (IL-4R $\alpha$ ) antagonist that is the first Food and Drug Administration-approved biological therapy for moderate-to-severe adult AD inadequately controlled with topical therapies. Adverse effects reported in the literature include injection site reactions, conjunctivitis, headache, and nasopharyngitis.

**Objective:** We report the first cases of hyperhidrosis and bromhidrosis as side effects from dupilumab (Dupixent<sup>®</sup>) for the treatment of AD.

**Case Reports:** Case 1 is a 20-year-old woman with controlled allergic rhinitis and severe AD reported axillary hyperhidrosis with bromhidrosis, comparable to sweat from high-intensity exercise, with no relief from several different over-the-counter antiperspirants. Case 2 is a 61-year-old woman with history of chronic asthma, allergic contact dermatitis, allergic rhinitis, and AD noticed markedly increased sweating with bromhidrosis that was reminiscent of her menopausal symptomatology, about 3 months after initiating dupilumab.

**Discussion:** Traditional immunosuppressive agents and corticosteroids have limited efficacy, numerous side effects, and increased risk of infection. The safety profile and efficacy of the newly approved IL-4R $\alpha$  antagonist dupilumab may be favorable to oral immunosuppressants, but its use remains limited to severe recalcitrant cases, due to financial implications and lack of long-term safety data and comparative head-to-head trials.

**Conclusion:** We report improved outcomes with dupilumab, in addition to unpublished cases of bromhidrosis and hyperhidrosis in 2 patients with AD. This report of additional complications may inspire further clinical research and assist clinicians in considering the option of dupilumab for uncontrolled AD, despite aggressive traditional treatment.

## Keywords

dupilumab (Dupixent<sup>®</sup>), atopic dermatitis, eczema, hyperhidrosis, bromhidrosis

## Introduction

Atopic dermatitis (AD, eczema) is familial chronic inflammatory skin disease of complex etiology and increasing prevalence.<sup>1</sup> AD management requires a systematic, multipronged approach to AD that involves skin hydration, topical anti-inflammatory medications, antipruritic therapy, antibacterial measures, and/or elimination of exacerbating factors.<sup>2</sup> Dupilumab is a fully human monoclonal antibody that has been recently approved as a more targeted therapy for moderate to severe AD by the Food and Drug Administration

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(FDA).<sup>3,4</sup> Sustained improvement skin inflammation, pruritus, and quality of life has been demonstrated in clinical trials with common adverse events including nasopharyngitis, conjunctivitis, and injection-site reactions.<sup>4,5</sup> We report the first cases of hyperhidrosis and bromhidrosis as side effects from dupilumab (Dupixent<sup>®</sup>) for treatment of AD.

## Case Reports

### Case 1

A 20-year-old woman with controlled allergic rhinitis and severe AD reported axillary hyperhidrosis with bromhidrosis, comparable to sweat from high-intensity exercise, with no relief from several different over-the-counter antiperspirants. She had begun dupilumab injections (300 mg/2 mL, q2 weeks, subcutaneous solution) 49 weeks (25 subcutaneous) prior with substantial improvement, after multiple topical corticosteroid (TCS) trials with minimal relief. The patient continued on dupilumab as recommended and applied desonide 0.05% external ointment (twice a day) and tacrolimus (Protopic<sup>®</sup>) 0.1% external ointment (twice a day) as needed for acute AD flares. Aluminum chloride (Drysol<sup>®</sup>) 20% external solution (1–2× per week) was prescribed to ameliorate the hyperhidrosis. Referral to dermatology was recommended for botulinum toxin injections, in the case that these symptoms did not improve. The patient also reported substantial improvement of ocular pruritus, since about a year prior, well-managed with olopatadine hydrochloride ophthalmic solution (Pazeo<sup>®</sup>) as needed.

### Case 2

A 61-year-old woman with history of chronic asthma, allergic contact dermatitis, allergic rhinitis, and AD noticed markedly increased sweating with bromhidrosis reminiscent of her menopausal symptomology, about 3 months after initiating dupilumab (300 mg/2 mL, q2 weeks, subcutaneous). She reported using hydroxyzine sparingly to alleviate pruritus, which had significantly improved since starting dupilumab. She also continued her regimen of alclometasone dipropionate (Alclovate<sup>®</sup>) 0.05% external ointment (twice a day as needed) to manage injection site reactions and reported improvement in acute bilateral atopic conjunctivitis.

## Discussion

AD is often the first manifestation of atopy with major diagnostic features of pruritus, dermatitis affecting flexural surfaces in adults or the face and extensor surfaces

in infants, chronic or relapsing dermatitis, and personal or family history of cutaneous or respiratory allergy.<sup>6</sup> Severe AD may be characterized by extensive dermatologic involvement, frequent requirement of high-potency topical glucocorticoids, increased serum IgE, history of hospitalizations for skin infections, ocular or infectious complications, significant impact of quality of life.<sup>2</sup> The key clinical manifestations of xeroderma and, often, anhidrosis is attributable to autonomic imbalance and increased allergic inflammation that significantly reduce expression of claudin-3 and, subsequently, perspiration.<sup>7</sup> Population-based studies suggest that 6.6 million of 16.5 million adults with AD in the United States meet this level of severity.<sup>1</sup>

The first-line treatment approaches include patient education and skin hydration with warm soaking baths, following by the application of moisturizers to improve skin barrier function with ceramide-rich lipids.<sup>2</sup> If moisturizers are insufficient for control of AD, low-dose TCS are recommended for maintenance therapy, and intermediate and high-dose TCS are reserved for management of clinical exacerbations over short periods of time.<sup>2</sup> Inadequate management by or intolerance of TCS indicates need for alternative therapies: wet dressings with TCS, phototherapy with ultraviolet light, systemic immunosuppressants, including hospitalization for isolation from environmental allergens, and allergen immunotherapy when aeroallergens contribute to exacerbations.<sup>2,8</sup> However, the systemic immunosuppressants, including cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil, have not acquired FDA approval and are often associated with serious toxicities that limit its duration of use.<sup>4,8</sup> Dupilumab has been recommended by the National Institute for Health and Care Excellence as an option for treating moderate-to-severe AD in adults, if the patient is unresponsive or cannot tolerate at least 1 other systemic therapy, such as a systemic immunosuppressant, or if its use is contraindicated.<sup>8</sup>

Since the 2012 update on practice parameters for AD,<sup>2</sup> investigative treatments for this T-helper type 2-dominated disease have emerged with our advancing understanding of the complicated interactions between immunoglobulin E (IgE)-bearing Langerhans cells, atopic keratinocytes, monocytes/macrophages, eosinophils, and mast cells with interleukin (IL)-4-, IL-5-, and IL-13-producing T<sub>H</sub>2, regulatory T, and T<sub>H</sub>22 lymphocytes, as well as their products, susceptibility genes, and host environment, that induce its clinical characterizations.<sup>2,8</sup> Recent and ongoing trials are clinical evaluating monoclonal antibodies against IgE, IL-4 receptor subunit alpha (IL-4R $\alpha$ ), IL-5, IL-13, IL-31 receptor A (IL31RA), IL-33, and thymic stromal lymphopoietin

(TSLP).<sup>8</sup> Dupilumab is an IL-4R $\alpha$  antagonist that is the first FDA-approved biologic for moderate-to-severe adult AD inadequately controlled with topical therapies.<sup>6</sup> Randomized, placebo-controlled, phase 3 trials demonstrated a 75% Eczema Area and Severity Index improvement from baseline, compared to the placebo ( $P < .001$ ), as well as improved quality of life and Hospital Anxiety and Depression Scale scores.<sup>4,5</sup>

Ou et al. conducted the first meta-analysis of 8 placebo-controlled, randomized control trials to assess the influence of dupilumab on adverse events in adult patients with moderate-to-severe AD.<sup>9</sup> Low heterogeneity among the comparisons strengthened dupilumab's association with few side effects and decreased risk of skin infection and AD exacerbations.<sup>9</sup> Outcomes identified injection site reactions, skin infections, headaches, and conjunctivitis.<sup>9</sup> The incidence of other infections, such as herpes viral infections, upper respiratory tract infections, nasopharyngitis, and urinary tract infections, was similar between the dupilumab-treated and placebo-controlled groups, suggesting the dupilumab may not directly disrupt normal immunological protection against microorganism invasion.<sup>9</sup> However, funding by the pharmaceutical industry, steroid-combining methods in 2 of the trials, and finding of increased incidence of headache in the dupilumab-treated group warrant further research beyond this initial metanalysis.<sup>9</sup> A more recently published case presentation of a 28-year-old woman with facial and neck rashes that resolved within several days also cited previously reported side effects of alopecia areata and cicatricial extropion.<sup>10</sup>

## Conclusion

AD is a common, chronic pruritic dermatosis, complex, systemic inflammatory disorder of significant psychological and economic burden.<sup>4,6</sup> Traditional immunosuppressive agents and corticosteroids have limited efficacy, numerous side effects, and increased risk of infection.<sup>4,8</sup> Dupilumab has been recently added to the market as a targeted biologic aimed at IL-4R $\alpha$  that inhibits signaling from the type 2 cytokines IL-4 and IL-13 involved in AD pathophysiology.<sup>8</sup> Few studies report adverse effects, such as more common injection site reactions, conjunctivitis, headache, and nasopharyngitis, as well as the rare presentation of alopecia areata and cicatricial extropion.<sup>8,9</sup> We report improved outcomes with dupilumab, in addition to unpublished cases of bromhidrosis and hyperhidrosis in 2 patients with AD. The safety profile and efficacy of dupilumab may be favorable to oral immunosuppressants, but its use remains limited to severe recalcitrant cases, due to

financial implications and lack of long-term safety data and comparative head-to-head trials.<sup>3</sup> This report of additional complications may inspire further clinical research and assist clinicians in considering the option of dupilumab for uncontrolled AD, despite aggressive traditional treatment.

## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Ethical Approval

This study was approved by our institutional review board.

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## Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects.

## Statement of Informed Consent

Verbal informed consent was obtained from the patients for their anonymized information to be published in this article.

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