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Title: Rosacea Associated with Dupilumab Therapy

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Abstract

Background: Dupilumab is used for treatment of atopic dermatitis through blockade of IL-4 and IL-13 signaling of the Th2 pathway. Recent case reports have described alopecia, psoriasis, persistent facial dermatitis, and recall dermatitis at patch test sites after the initiation of dupilumab therapy.

Case report: We describe the case of a 67-year-old female with atopic dermatitis who developed recurrent episodic flares of rosacea temporally associated with dupilumab injections that resolved after dupilumab discontinuation.

Conclusion: The cause of rosacea-like reaction associated with dupilumab treatment is unknown. Th2 pathway inhibition by dupilumab may promote *Demodex* proliferation and increased IL-17-mediated inflammation implicated in the pathophysiology of rosacea.

Key words: dupilumab; atopic dermatitis; rosacea

Abbreviations: atopic dermatitis (AD), interleukin (IL), persistent facial dermatitis (PFD), T-helper cell type 1 (Th1), T-helper cell type 2 (Th2), T-helper cell type 17 (Th17), tumor necrosis factor- α (TNF- α)

Introduction

Dupilumab is a novel, fully humanized monoclonal antibody that selectively binds the interleukin (IL)-4 receptor α -subunit to inhibit both IL-4 and IL-13 signaling of the Th2 pathway (1-3). Approved for asthma and moderate-to-severe atopic dermatitis (AD), dupilumab is generally well-tolerated, with few reported adverse events including injection-site reactions, conjunctivitis, keratitis, blepharitis, headaches, nasopharyngitis, and bacterial and herpetic skin infections (2-4).

While dupilumab has considerable efficacy in the treatment of AD, there is limited data on dupilumab's effect on pre-existing or novel cutaneous conditions. Recent case reports have described new-onset alopecia (5), psoriasis (6, 7), persistent facial dermatitis (1, 8), and recall dermatitis at prior patch test sites after the initiation of dupilumab (9). We present a case of recurrent episodic, flaring papulopustular rosacea exacerbated by dupilumab injection during treatment for AD.

Case Report

A 67-year-old Caucasian female presented to our clinic with severe AD without comorbid asthma or allergic rhinitis/conjunctivitis affecting the face, neck, trunk, and upper and lower extremities recalcitrant to both topical and systemic corticosteroids (Fig. 1). She was initiated on dupilumab with a 600 mg loading dose followed by 300 mg biweekly maintenance doses, with complete clearance of her AD within 2 months. However, beginning 3 months after dupilumab initiation, she began to experience new-onset facial erythema, edema, and pink follicular-based papules on the nose and bilateral cheeks associated with mild burning, consistent with

papulopustular rosacea (Fig 2). She did not experience conjunctivitis or signs and symptoms of ocular rosacea. This reaction resolved at day 12-13 following dupilumab injection but recurred with each dupilumab administration. Metronidazole cream was initiated without improvement. Due to recurring and episodic rosacea flares with dupilumab therapy, oral doxycycline was offered to control her symptoms, but she declined. The patient elected to discontinue dupilumab therapy due to episodic rosacea flares as well as high financial burden due to inadequate insurance coverage for dupilumab. After discontinuation, her rosacea symptoms resolved and have not since recurred.

Discussion

Dupilumab is thought to improve AD via blockade of IL-4 and IL-13 signaling with a subsequent decrease in the Th2 phenotype. Consequently, this dupilumab-mediated IL-4 antagonism and Th2 inhibition shifts the helper T-cell profile to a Th1/Th17 predominant phenotype, as IL-4 is a negative regulator of both the Th1 and Th17 pathways (1-3). This transition in helper T-cell phenotype may then drive the development of Th1-mediated dermatoses. There have been several case reports of new-onset or worsening psoriasis (a classically Th1-mediated disease) during dupilumab therapy (6, 7). Additionally, there are multiple published cases of new-onset alopecia areata after initiating dupilumab for AD (5). Interestingly, dupilumab has conversely been associated with hair regrowth in long-standing alopecia totalis (10), and there is currently an ongoing clinical trial to evaluate the efficacy of dupilumab for the treatment of alopecia areata (11). While the pathogenesis of alopecia areata is poorly understood, prior studies have demonstrated both Th1 and Th2 expression in lesional skin (5), which may explain the conflicting clinical responses to dupilumab therapy.

Rosacea, characterized by persistent facial erythema, flushing, telangiectasias, and centropapular pustules (12, 13), has a complex and multifactorial etiology, including a putative role of microbial organisms, pilosebaceous unit abnormalities, dermal matrix degeneration, neurovascular dysregulation, and immune and environmental factors (12-14). Patients with rosacea, specifically the papulopustular subtype, have demonstrated increased density of follicular *Demodex* (*D. folliculorum* and *D. brevis*), a commensal mite thought to act as a cofactor in the inflammatory etiology of rosacea (12-16). *Demodex* antigens have been shown to induce neutrophil accumulation and proinflammatory cytokine production, including IL-1 β , IL-8 and tumor necrosis factor (TNF)- α , along with upregulated matrix metalloproteinase-9 and cathelicidin secretion (17). Additionally, molecular studies in rosacea have demonstrated elevated Th1/Th17 pathway activation, with upregulation of Th1-signature cytokines, interferon- γ and TNF- α , as well as increased IL-17 expression, particularly in papulopustular rosacea (18).

Our patient represents a heretofore unreported case of new-onset rosacea as an adverse cutaneous effect of dupilumab therapy. Dupilumab-mediated Th2 blockade, with subsequent Th1/Th17 polarization may allow for rapid proliferation of *Demodex* mites in follicular epithelium, as demonstrated in Th2-impaired mouse models (15). The Th1-polarized response, along with overgrowth of *Demodex*, may provide a favorable inflammatory milieu for the development of rosacea. Increased concentrations of IL-17 in tears is strongly associated with *Demodex* blepharitis (19). Similarly, dupilumab-associated conjunctivitis has been suggested as a variant of ocular rosacea (15). Our patient's cyclical flaring of rosacea with each dupilumab administration supports the role of Th1/Th17 predominance in dupilumab-mediated dermatoses.

Other facial dermatoses, such as persistent facial dermatitis (PFD), characterized by fine scaling and edematous pink-to-red plaques involving the face, neck, and forearms has previously been reported with dupilumab therapy (1, 8). Additionally, Suresh and Murase unmasked an underlying allergic contact dermatitis via patch testing in cases of PFD following dupilumab initiation for severe AD that responded well to subsequent allergen avoidance (8). PFD may also represent an adverse effect of dupilumab therapy or a form of head-and-neck dermatitis (1, 20). Head-and-neck dermatitis may be triggered by airborne contact allergy, Type-I hypersensitivity reaction to *Malassezia globosa* proteins, or contact allergy to food, sweat, and saliva (20, 21). In the atopic population, facial dermatitis should also raise concern for steroid-induced rosacea or periorificial dermatitis, particularly in patients who are concomitantly using topical steroids on the face (20). While these differential diagnoses are important to consider, our patient denied topical steroid use since initiating dupilumab, and her follicular-based erythematous facial papules and erythema favor rosacea as the most likely diagnosis.

Although the definitive pathogenesis of inflammatory skin disease during dupilumab treatment remains elusive, the alteration of Th1/Th2 balance via Th2 blockade may predispose these patients to a variety of Th1-mediated dermatoses. Patients receiving dupilumab for AD should be counseled on potential risks of developing additional cutaneous eruptions, including rosacea. Furthermore, in the event of a concurrent dermatosis, a trial of conservative therapy may be warranted prior to discontinuation of dupilumab. Future investigation will aid in better understanding the link between Th2 blockade and Th1/Th17-mediated dermatoses.

Figure Legends

Fig 1. Clinical presentation prior to dupilumab injection showing minimal erythema of the central face and bilateral cheeks.

Fig 2. Clinical presentation 2 days after dupilumab injection. Significant increase in erythema with follicular-based papules involving the bilateral cheeks and nose.

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