

Cicatricial Ectropion in the Setting of IL-13 Inhibition

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ABSTRACT

Introduction: Interleukin (IL)-13 is a key mediator of type 2 inflammation and an important therapeutic target in atopic dermatitis (AD). Although IL-4/IL-13 and IL-13 inhibitors demonstrate favorable safety profiles, ocular adverse events are recognized complications. Conjunctivitis is most commonly reported, and cicatricial ectropion has been described with IL-4/IL-13 inhibition. We report what is, to our knowledge, the first reported case of cicatricial ectropion associated with inhibition of soluble IL-13.

Case Presentation: An 81-year-old man with longstanding AD involving 60% body surface area was treated with dupilumab with marked improvement. Seven months later, he developed ocular pruritus and tearing and was diagnosed with atopic keratoconjunctivitis. One month later, ophthalmologic examination revealed inferior cicatricial ectropion of the left lower eyelid. Discontinuation of dupilumab and treatment with oral prednisone and topical tacrolimus led to resolution. Subsequent treatment with tralokinumab resulted in recurrence of cicatricial ectropion within one month, prompting discontinuation and treatment with topical polymyxin B-trimethoprim and oral prednisone. Upadacitinib was initiated with sustained clearance of AD and no recurrence of ocular symptoms.

Discussion: Cicatricial ectropion has been rarely reported with dupilumab but has not previously been described with soluble IL-13 inhibition. In this case, ectropion developed with dupilumab, resolved after discontinuation, and recurred with tralokinumab, suggesting a direct effect of IL-13 inhibition. This case highlights the need for awareness of rare ocular complications associated with targeted therapies for AD and underscores the importance of multidisciplinary management.

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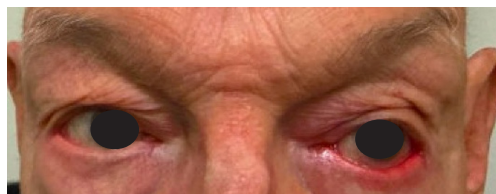
INTRODUCTION

Inhibition of interleukin (IL)-13, a key mediator of type 2 inflammation, is a highly effective and targeted therapeutic strategy for atopic dermatitis (AD).¹ Despite an excellent safety profile, ocular adverse effects are a relatively common cause of treatment discontinuation.¹ Here we describe what is, to our knowledge, the first reported case of cicatricial ectropion associated with soluble IL-13 inhibition.

Case Report

An 81-year-old man presented for evaluation of a widespread rash present intermittently since childhood. His history was notable for seasonal allergies and ocular history of cataracts, dry eyes, and epiphora. At the time of evaluation, he was not receiving treatment, although he had previously used multiple topical corticosteroids. Examination revealed eczematous patches and plaques involving 60% body surface area (BSA) and Investigator Global Assessment (IGA) 3, prompting initiation of dupilumab at standard dosing (600 mg loading dose followed by 300 mg every two weeks). Seven months after initiation, he developed pruritus and tearing of both eyes without pain or visual changes. Examination revealed few eczematous papules and plaques involving the scalp, trunk and extremities, BSA 3% and IGA 1, overall, much improved from prior examinations. Ophthalmologic exam showed bilateral upper and lower lid

FIGURE 1. Cicatricial ectropion of the left lower eyelid.



edema and erythema with injection of the left conjunctiva. Ophthalmology diagnosed atopic keratoconjunctivitis and advised the patient to use lubricating and antihistamine eye drops.

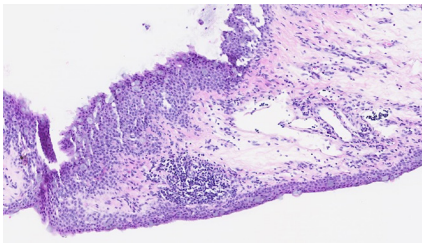
Repeat ophthalmologic evaluation one month later revealed cicatricial ectropion of the left lower eyelid (Figure 1). Treatment was initiated with tacrolimus ointment and oral prednisone (20 mg with a three week taper). Dupilumab was discontinued, and at re-evaluation three weeks later, the ectropion had resolved.

Nemolizumab (60 mg loading followed by 30 mg every 4 weeks) was initiated for AD but was discontinued one month later due to worsening AD without recurrence of ectropion. The patient was transitioned to tralokinumab at standard dosing (600 mg

FIGURE 2. Improvement of cicatricial ectropion after discontinuation of biologic and treatment with prednisone.



FIGURE 3. Hematoxylin and eosin (H&E)-stained section from biopsy of the left conjunctiva with high power view demonstrating focal fibrosis and chronic inflammatory infiltrate.



loading followed by 300 mg every 2 weeks). Within one month, his AD had improved, but cicatricial ectropion recurred and tralokinumab was discontinued. He was treated with topical polymyxin B-trimethoprim twice daily and a 3-week course of oral prednisone 20 mg daily.

Serologic testing and eyelid margin biopsy were performed to exclude mucous membrane pemphigoid or cicatricial pemphigoid. BP 180 and BP230 IgG, desmoglein 1 and 3 IgG, and anti-laminin 332 IgG were negative. Biopsy was notable for sub-epithelial fibrosis compatible with scarring and mild chronic conjunctivitis of the left conjunctiva (Figure 3). Direct immunofluorescence was negative. Age-appropriate malignancy screening was up to date. Upadacitinib 15 mg daily was initiated. At a follow-up visit one month later, improvement in ectropion was noted (Figure 2), along with significant improvement in his AD. At seven months follow up, the patient's AD was clear without recurrence of ocular symptoms.

DISCUSSION

Dupilumab, a human monoclonal IgG4 antibody targeting the IL-4 receptor alpha, inhibits IL-4 and IL-13, and is FDA-approved for the treatment of moderate-to-severe AD. Although generally well tolerated, treatment is associated with ocular adverse events, most commonly conjunctivitis and rarely cicatricial ectropion.^{1,2-4} AD patients also have higher baseline rates of atopic conjunctivitis.⁵

Across dupilumab clinical trials for AD, there was a greater incidence of atopic keratoconjunctivitis compared to placebo, a pattern not observed in the trials for asthma, eosinophilic esophagitis, or nasal polyposis.^{5,6,7} Although ectropion was not reported in early trials, it has since been described in case reports and in a multicenter retrospective study of 210 dupilumab-treated patients, in which cicatricial ectropion occurred in 1% of patients.^{2-4,8} Conjunctivitis has also been reported with tralokinumab and lebrikizumab, monoclonal antibodies targeting soluble IL-13, though at lower rates than seen with dupilumab treatment.^{1,9,10} Cicatricial ectropion has not been reported with these agents.^{1,9,10}

To our knowledge, this is the first reported case of ectropion with soluble IL-13 inhibition.¹¹ Ectropion developed after exposure to dupilumab, resolved after discontinuation, and recurred with tralokinumab, before again resolving after drug discontinuation. This temporal pattern strongly supports a direct effect of IL-13 inhibition.

IL-13 contributes to ocular surface homeostasis by promoting goblet cell differentiation and proliferation and by upregulating genes involved in epithelial barrier integrity.¹² However, the mechanisms underlying ocular complications associated with therapies targeting IL-13 remain incompletely understood. Notably, higher baseline AD severity has been associated with increased conjunctivitis incidence, suggesting that longstanding, severe inflammation can contribute to disease pathogenesis.⁵

Cicatricial ectropion is characterized by outward eversion of the eyelid margin due to shortening of the anterior lamella secondary to scarring or contracture of the skin and subcutaneous tissue.¹³ Previously reported cases of dupilumab-associated cicatricial ectropion occurred within 2-6 months of first exposure.^{2,3,4} Treatment included discontinuing dupilumab, topical and oral corticosteroids, and topical calcineurin inhibitors.^{2,3,4} In cases of drug induced ectropion, early drug discontinuation is critical.¹⁴ In our patient, both episodes of cicatricial ectropion resolved following cessation of the implicated biologic and initiation of systemic corticosteroids, with active inflammation presumably controlled before clinically significant fibrosis developed.

This case expands our understanding of ocular adverse effects associated with IL-13 inhibition, independent of IL-4 receptor alpha blockade. It also underscores the importance of prompt recognition of targeted therapy-related adverse effects and the role of multidisciplinary care in optimizing patient outcomes. Further research is needed to clarify the ocular effects of IL-13 blockade.

DISCLOSURES

AC has received payments for conducting clinical trials (paid to her institution) from Eli Lilly, Incyte, Johnson & Johnson, Moonlake, Novartis, Merck and AbbVie; speaker fees from

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