

Atopic keratoconjunctivitis alleviated with dupilumab



Dupilumab (Dupixent) is a first-in-class biological that was initially approved for the treatment of atopic dermatitis (AD), but has since had its approval expanded for the treatment of other atopic disorders, including asthma and uncontrolled chronic rhinosinusitis with nasal polyps. Dupilumab is a fully human monoclonal antibody that inhibits both interleukin-4 (IL-4) and IL-13, consequently intercepting the Th2 mediated inflammatory pathway that directs major atopic etiologies. Dupilumab has demonstrated statistically and clinically substantial results in mitigating symptoms of AD as demonstrated in SCORing AD (SCORAD), Peak Pruritus Numerical Rating Scale, and Quality of Life Index for AD (QoLIAD) indices.¹

Despite the treatment potential of dupilumab, there have been several documented reports of adverse ocular events. Patients who present with severe AD are more likely to experience ophthalmic complications because the incidence of these symptoms increases with baseline AD severity. Histories of conjunctivitis and ocular surface diseases are also independent risk factors. The most reported ocular manifestations, with incidence rates of 9% to 22%, are ocular surface diseases, including conjunctivitis, keratitis, and blepharitis.² Atopic keratoconjunctivitis (AKC), periocular dermatitis, punctal stenosis, cicatricial conjunctivitis, intraocular inflammation, reactivation of latent infections, and limbal stem cell deficiency have also been noted. Although there are several hypotheses regarding the mechanism of dupilumab-induced ocular events, the most widely accepted hypothesis involves the inhibition of IL-13 and mucin-secreting goblet cells on the conjunctiva. Although research is limited, adverse ocular surface effects have also been observed in other immunobiologics, such as tralokinumab and lebrikizumab.³

Contrary to the evidence that dupilumab is contraindicated in ocular surface disease, there is a subset of these patients who may respond positively to the biologic. We present one of the first

reported cases of dupilumab remediating the severe ocular symptoms of AKC, in addition to improving AD and asthma.

A 16-year-old Asian girl with a history of lifetime AD and asthma was referred for blurred vision and pain when she opened her eyes. Several ocular complications were observed in both eyes, including persistent periocular dermatitis, associated pruritus and tearing, allergic conjunctivitis, superficial punctate keratitis, corneal abrasions, and peri-orbital skin and cheek involvement consistent with AKC.

The patient had previously been placed on mycophenolate, cyclosporine, clobetasol, triamcinolone topical, oral prednisone, and desonide ointment, but discontinued them all owing to adverse effects and a lack of efficacy. She had also been using fluorometholone ophthalmic suspension for relief of her ocular symptoms. The patient reported an initial Ocular Surface Disease Index of 27 and a Total Ocular Symptom Score of 31.25, indicating moderate dry eye and allergic conjunctival symptoms, respectively.

Subcutaneous (SC) treatment of 30 mg benralizumab every 4 weeks was initiated. Within 1 week, her SCORAD decreased by 33% from 53.7 to 36.2, marking an improvement in AD severity from severe to moderate symptoms. However, she remained with recurrent eczematous lesions without improvement in her ocular surface symptoms.

Benralizumab was discontinued after 6 doses, and 2 dosages of 300 mg SC dupilumab were administered to the patient. Two weeks after her initial dose, the patient reported improvement in symptoms. She denied conjunctival injections, itching, or watery eyes. Ocular edema was markedly reduced. The patient then initiated 1 dosage of 300 mg SC dupilumab every 2 weeks, and she remains on this regimen till the present day. After nearly 2 years, the patient's AD, asthma, and ocular symptoms continue to be well-controlled with dupilumab, with a reported Ocular Surface Disease Index of 6.8, Total Ocular Symptom Score of 12.5, and SCORAD of 23.25 (Figure 1).

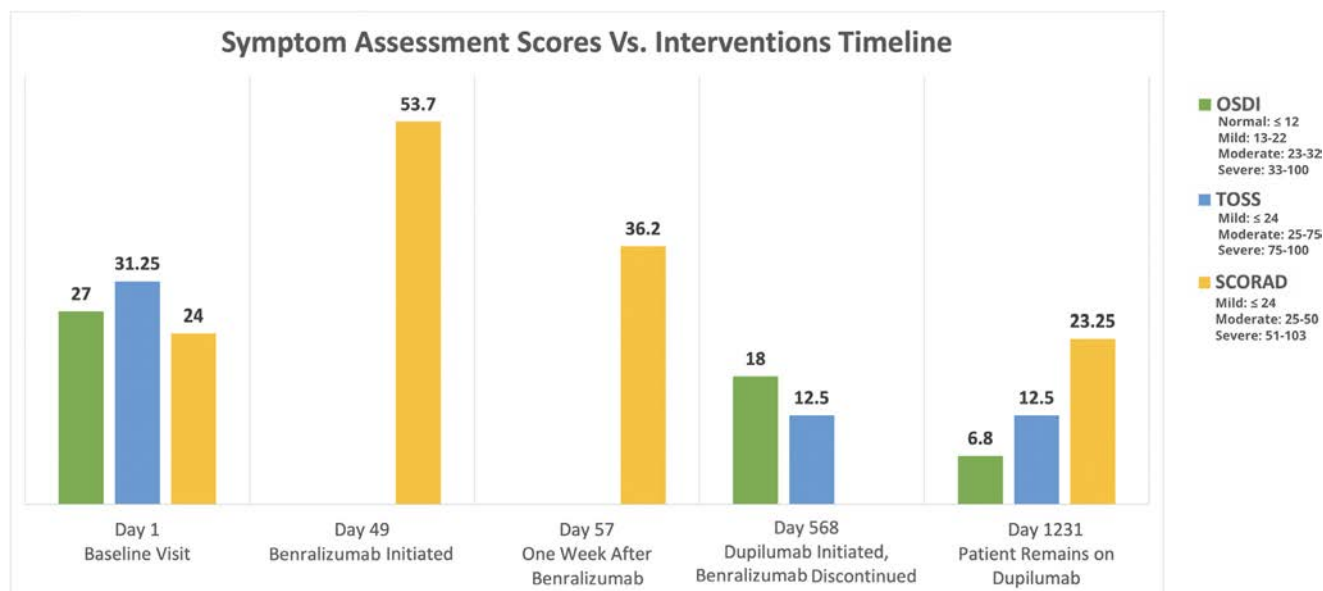


Figure 1. The patient's OSDI, TOSS, and SCORAD values demonstrated at numerous timepoints and interventions. The patient's scores at baseline visit, initiation of 30 mg subcutaneous benralizumab, 1 week after benralizumab initiation, initiation of 300 mg subcutaneous dupilumab and discontinuation of benralizumab, and at nearly 2 years follow-up are captured here. Note that there are no OSDI and TOSS data available for days 49 and 57, and no SCORAD data available for day 568. OSDI, Ocular Surface Disease Index; SCORAD, SCORing Atopic Dermatitis; TOSS, Total Ocular Symptom Score.

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The patient has given written informed consent for the publication of her case details.

The skin and ocular surface share a close relationship, with similarities in immunohistology, steroidogenic properties, and allergic mechanisms.⁴ Their similarities in composition elucidate the numerous ocular surface comorbidities associated with AD. Atopic keratoconjunctivitis remains a complicated chronic ocular surface disease involving the cornea, which is always associated with atopic conditions and is estimated to be present in 25% to 42% of patients with AD. Numerous parallels have been drawn between AD and AKC, particularly in their immunopathogenesis and compromised innate immune response. Similarities in dysregulation of toll-like receptors, antimicrobial peptides, and immunoglobulin (Ig)A secretions found in these atopic disorders lead to the impairment of their respective surface barriers.⁵

Furthermore, AD is a heterogeneous disease that can be classified into multiple phenotypes, with further endotypes and genotypes. Most widely recognized is the existence of extrinsic (elevated IgE) and intrinsic subtypes (normal IgE), although demarcations have also been explored between adults and children, different ethnicities (European American, Asian, and African American), and cytokine profiles.⁶ Because the ocular surface can be considered a derivative of the skin epithelium, multiple phenotypes of AKC may also exist. This could explain the unexpected resolution of the patient's ocular symptoms because she may have presented with an AKC phenotype that could be resolved through the initiation of dupilumab.

It is speculated that the patient has the Asian subtype of AD, which is characterized by Th2/Th17 blended cytokine axes. The AD lesions of Asian patients were found to have significantly higher levels of IL-19, which is induced by IL-4/IL-13 and interleukin-17 (IL-17).⁷ If her AD phenotype could be extrapolated to the epithelium of her ocular surface, the inhibition of IL-4 and IL-13 with dupilumab could elucidate the resolution of her AKC. Tear IL-4 levels were found to be substantially elevated in patients with AKC, along with goblet cell hyperplasia induced by IL-13.^{8,9} Inhibition of these 2 interleukins would remedy these key biomarkers found in AKC. The Th17 cytokine axis in AD is thought to be unique in Asian patients and may act as a protective factor for this subset of patients. Given IL-17 remains uninhibited, it can continue to induce IL-19. This in turn, amplifies IL-17A effects on keratinocytes, including the induction of β -defensins.¹⁰

Despite the adverse ocular surface effects of dupilumab, there exists a subset of patients who may experience relief. Evaluating the close connection between skin and ocular surface and its associated

atopic phenotypes may shed light in the identification of these groups.

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Phenotyping older adults with asthma by means of cluster analysis



Whereas a number of publications have identified asthma phenotypes in adults,¹ few have focused only on older adults.^{2,3} As a component of a randomized controlled trial of older adults (≥ 50 years old) with persistent asthma, Baptist et al,³ identified 4 phenotypic clusters. The purpose of this study was to compare findings from the Baptist et al³ study with cluster analysis findings from a cohort of older adults with asthma participating in a longitudinal observational study.

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Specifics concerning measures and data collection of our study are published elsewhere.⁴ Briefly, participants were 60 years old and older, had exhibited bronchodilator response with a 12% or greater increase in forced expiratory volume in 1 second (FEV1) or forced vital capacity (FVC) and a 200-mL increase of lung volume in either measure after bronchodilator administration or had a methacholine challenge test finding of provocation concentration causing a 20% fall in FEV1 less than or equal to 16 mg/mL. We excluded current smokers, those with a 20-pack year or greater history of smoking, diagnosis of other chronic pulmonary disease, and those living in a skilled nursing facility. Data were collected between 2015 and 2019. The study was approved by the University of Louisville Institutional Review Board.

Self-reported demographic data are noted in Table 1. Participants completed the Asthma Control Test (ACT) and the Mini Asthma