

Blepharoconjunctivitis Secondary to Dupilumab Successfully Treated with Itraconazole

To the Editor:

High rates of conjunctivitis and blepharitis have been seen in those treated with the interleukin (IL)-4 and IL-13 inhibitor dupilumab, the exact pathogenesis of which is unknown. We report a case of dupilumab-induced blepharoconjunctivitis treated successfully with itraconazole.

A 26-year-old female patient was commenced on dupilumab 300 mg every 2 weeks for severe atopic dermatitis. She had proven refractory to treatment with potent topical steroids, phototherapy, ciclosporin, oral tacrolimus, methotrexate, azathioprine, and ustekinumab in the past. She had no history of blepharitis or conjunctivitis. She developed new-onset troublesome blepharoconjunctivitis 6 weeks after commencing treatment, which failed to respond to chloramphenicol, 0.2% sodium hyaluronate drops, and topical tacrolimus 0.1%. We suspected *Malassezia furfur* colonization, and thus, she was commenced on a trial of itraconazole 200 mg twice daily for a week after dupilumab injection. A dramatic improvement in her blepharoconjunctivitis was seen. We reduced her dose to 200 mg once daily for 5 days after dupilumab injection, which resulted in a minor flare that settled quickly. She has since remained clear on 200 mg once daily for 5 days after dupilumab injection.

Dupilumab-induced conjunctivitis and blepharitis are commonly reported in the trial data in atopic dermatitis.^{1–3} This is, for most, of short duration and responsive to standard treatment, with few discontinuing dupilumab as a result.^{1–3} Those with severe atopic dermatitis and preexisting conjunctivitis are more at risk.¹ Some have hypothesized that the blockage of IL-4 and IL-13 may increase the activity of the specific ligands involved in atopic keratoconjunctivitis such as the OX40 ligand in the eye.⁴ Of note, in the trials, there is an inverse relationship between serum concentrations of dupilumab and conjunctivitis, which suggests that local undertreatment, possibly due to higher target burden or lower tissue distribution, may play a role.¹ In the asthma and nasal polyposis trials, conjunctivitis has not been noted, suggesting an atopic dermatitis-specific mechanism; however, the pathogenesis remains poorly understood.¹ Treatment of dupilumab-induced blepharoconjunctivitis includes hyaluronic acid, antihistamine, and steroid eyedrops, with the off-label use of calcineurin inhibitors also proving effective.³ Steroid eyedrops increase the risk of glaucoma and cataract, and thus, topical calcineurin inhibitors such as tacrolimus should be favored in the long term. Our patient failed standard

treatments.³ The etiology of blepharitis is poorly understood, but it is strongly suspected that excessive microbial colonization is a contributory factor, including bacteria, fungi, and demodex.⁵ Itraconazole was trialed in our case because a seborrheic component was suspected, caused by colonization by *M. furfur* (also known as *Pityrosporum ovale*). *Malassezia* species is the most common fungus on healthy skin but contributes to skin inflammation and flares during the course of atopic dermatitis.⁶ It is also a known cause of blepharitis.⁷ Itraconazole, a lipophilic triazole, is fungicidal against filamentous fungi and fungistatic against many yeasts, including *Malassezia* species. It also has antiangiogenic and anti-inflammatory effects, which may well contribute to its effectiveness in this case.⁸ Topical ketoconazole 2% may be an alternative treatment option, avoiding the risk of hepatotoxicity with oral itraconazole.⁹ The rapid resolution of the eye symptoms in this case suggests that *Malassezia*, or other mycotic flora, colonization may be a contributing factor in some cases of dupilumab-induced blepharoconjunctivitis; however, further study is required.

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The authors have no funding or conflicts of interest to declare.

DOI: 10.1097/DER.0000000000000461

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