

Lifitegrast add-on treatment for dupilumab-induced ocular surface disease (DIOSD): A novel case report



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A 37-year-old man with a life-long history of severe atopic dermatitis developed new-onset, severe conjunctivitis approximately 3 months after initiating therapy with dupilumab at the standard, US Food and Drug Administration (FDA)-approved dose regimen and was immediately referred to ophthalmology. He had a history of dry eyes but had not required treatment. There was dramatic thickening of the upper and lower lids along with swelling, redness, and injection of the sclera and conjunctiva. Alternative causes such as allergy, foreign body, and infection were ruled out based on ocular findings and history. The diagnoses of conjunctivitis, blepharitis, and dry eyes were made. Visual acuity was normal. At this time, initiated therapy included oral omega 3 supplements, warm compresses, artificial tears, and topical loteprednol drops 4 times a day in both eyes, tapering over several weeks. Six weeks later, the patient reported that his redness and irritation had improved but not completely resolved with this regimen and recurred after stopping the steroids. The patient underwent 2 more courses of treatment with steroid drops, either with loteprednol or fluorometholone, depending on cost. Each time, his symptoms improved but did not resolve and recurred once he stopped the steroids. At his 3-month visit, cyclosporine 0.5% drops were started twice a day in each eye along with another course of steroids. Although his symptoms were only partially improved with this regimen, his tear film osmolarity decreased from 345 mosm/L (severe) at

Abbreviations used:

DIOSD: dupilumab-induced ocular surface disease
FDA: US Food and Drug Administration

his initial presentation to 293 mosm/L (normal), indicating improvement in his dry eye component. Because of lack of adequate response, he was then started on lifitegrast drops twice a day and was seen for a corneal consultation 2 weeks later. At this appointment, conjunctival cultures were obtained. These eventually grew rare coagulase-negative *Staphylococcus*, which was felt to be part of the normal flora. The patient was instructed to continue to use lifitegrast twice a day in each eye, along with the remainder of his previous regimen. When he returned 6 weeks later, his conjunctivitis signs and symptoms had completely resolved, and he was able to taper his loteprednol drops to once daily, a dose that was not able to control his symptoms previously. He continues to use cyclosporine twice a day, lifitegrast twice a day, and loteprednol once a day in each eye and remains symptom free to date. Visual acuity was not affected at any point in his course.

DISCUSSION

Ocular surface inflammation is the primary known side effect in dupilumab-treated patients, affecting 10% of treated patients in the pivotal

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Refocus, Zeiss, Bausch & Lomb, Mallinckrodt, iCare, and Bruder. Dr Wulff has no conflicts to disclose.

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16-week trials (as opposed to 2% of placebo-treated patients) and 16% of treated patients in the pivotal 52-week trial (as opposed to 9% of placebo treated patients).¹ This finding suggests that the rate of dupilumab-induced ocular surface disease (DIOSD) is 7% to 8% of treated patients. The etiology is unknown, although common triggers of conjunctivitis, such as allergy and infection, have been ruled out.²

We propose the term *dupilumab-induced ocular surface disease* (DIOSD) to describe the constellation of findings seen in these patients, because while the full spectrum of ocular findings in these patients remains to be elucidated, it appears that in many patients it is more than conjunctivitis. Our patient, for example, displayed conjunctivitis, blepharitis, and dry eye. There is little published information regarding treatment or prognosis of DIOSD, although a small case series found partial responsiveness to low-potency steroid eye drops, and another case report showed resolution when dupilumab was discontinued.^{2,3} It is currently unknown if there are potential long-term sequelae from DIOSD, although as in our case, there have been no reports of impaired visual acuity or other serious or permanent damage to the eye from DIOSD.

One of the authors has observed several (>5) patients with DIOSD. All were referred to ophthalmology and treated with cyclosporine eyedrops, low-to-medium potency steroid eyedrops, or both. In all patients, there was partial improvement with steroids with return to baseline severity when steroids were discontinued and cyclosporine drops were continued, as initially happened in this patient. In contrast, there was rapid, dramatic, sustained improvement of the conjunctivitis in this patient after the addition of the lifitegrast drops.

Hyperosmolarity of the tear film is a recognized and validated marker of dry eye.^{4,5} Hyperosmolarity of the tear film occurs through decreased flow of the bulk aqueous component of the tear film from the lacrimal gland or through increased evaporation and instability of the tear film. Increased osmolarity of the tear film stimulates the release of inflammatory cytokines, enhances the rate of cell apoptosis, and results in a decrease in the number of goblet cells.⁴⁻⁶ In this patient, the osmolarity was elevated at baseline and improved with treatment with steroid and cyclosporine drops, but this improvement in osmolarity did not correlate with clinical symptoms, showing that the inflammatory reaction in this patient was not purely a result of dry eye.

Lifitegrast is FDA approved for the treatment of chronic dry eye. It binds to lymphocyte function–associated antigen-1 on white blood cells, blocking

the interaction of lymphocyte function–associated antigen-1 with intercellular adhesion molecule-1 on vascular endothelial cells and thereby preventing white blood cells from trafficking out of the vascular space and into tissue.⁷ Unlike steroid drops, it is considered safe for long-term use, largely based on the results of a 1-year long-term extension trial.⁸

Cyclosporine eye drops are also approved for chronic dry eye, but have a different mechanism of action. There are no published comparative trials between cyclosporine and lifitegrast for dry eye, nor are there published reports of the use of cyclosporine drops or lifitegrast drops for the treatment of DIOSD, although in one of the author's experience cyclosporine eye drops have not been effective. Cyclosporine and lifitegrast may be used together for the treatment of dry eye disease.⁵ These 2 agents, lifitegrast drops and cyclosporine drops, are considered relatively safe for long-term use with proper monitoring. Steroid drops have numerous potential side effects, but as with topical steroids on the skin, although long-term use is avoided if possible, they can be used safely long term in many patients with close ophthalmologic monitoring.

DIOSD is relatively common in dupilumab-treated patients and can be severe enough to lead to discontinuation of the drug.³ Because there are no other FDA-approved treatments for moderate-to-severe atopic dermatitis, and existing off-label therapies (such as phototherapy, systemic cyclosporine, methotrexate, mycophenolate, and azathioprine) are often ineffective or contraindicated, discontinuing dupilumab because of DIOSD can create a situation in which there are no other reasonable treatment options for a patient with moderate-to-severe atopic dermatitis. We present lifitegrast as an alternative treatment option for DIOSD that had striking efficacy in our patient. Management of ocular surface disease in general, and dry eye disease in particular, is quite complex. Although one medication may partially treat the condition, additional therapies may be required. In this particular case, cyclosporine and steroids did show partial efficacy based on improved but not resolved symptoms and a decreased tear film osmolarity. Only after lifitegrast was added was the patient able to obtain complete resolution of signs and symptoms. It is unknown whether lifitegrast alone would have led to complete resolution or if it required all 3 therapies. Over time, attempts to discontinue the steroids and eventually the cyclosporine may allow us to determine if lifitegrast alone could control this condition. Further research is necessary to determine if lifitegrast is reliably effective in DIOSD.

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