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INTENSE PULSED LIGHT (IPL) TREATMENT FOR DUPILUMAB INDUCED OCULAR SURFACE DISEASE (DIOSD): A NOVEL CASE REPORT

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ABSTRACT

Purpose
To report a case of dupilumab induced ocular surface disease (DIOSD) managed with intense pulsed light (IPL) as an effective adjunct therapy to topical steroids and topical immunomodulator lifitegrast.

Methods
Discussion of a patient's case with accompanying anterior segment and meibography photos with diagnosed DIOSD for which adjunct therapy with IPL was an effective treatment after limited relief from and difficulty with adherence to traditional treatment with topical steroids and lifitegrast ophthalmic solutions.

Conclusion
This case demonstrates the complexity of management required to treat patients with DIOSD and its chronic nature. IPL as a nonpharmaceutical adjunct therapy to topical steroids and immunomodulators in the treatment of DIOSD showed improved signs and symptoms of DIOSD.

Keywords: atopic dermatitis; dupilumab induced ocular surface disease; intense pulsed light

INTRODUCTION

Dupilumab (Dupixent) is the first biologic indicated to treat recalcitrant forms of moderate-to-severe atopic dermatitis, asthma, eosinophilic esophagitis, and chronic rhinosinusitis with nasal polyposis (CRSwNP).[1] It is an injected formulation of a human monoclonal antibody recognizing Interleukin (IL) 4 receptor α (IL-4Rα) and blocking IL-4 and IL-13 signals.[2] IL-4 and IL-13 are signature type 2 cytokines that play pivotal roles in the pathogenesis of allergic diseases, thus targeting them is an effective strategy for the treatment of allergic diseases. Dupilumab was approved by the FDA in 2017 and has quickly gained recognition for safely and significantly improving the signs and symptoms of atopic dermatitis including pruritus and the symptoms of anxiety, depression, and quality of life.

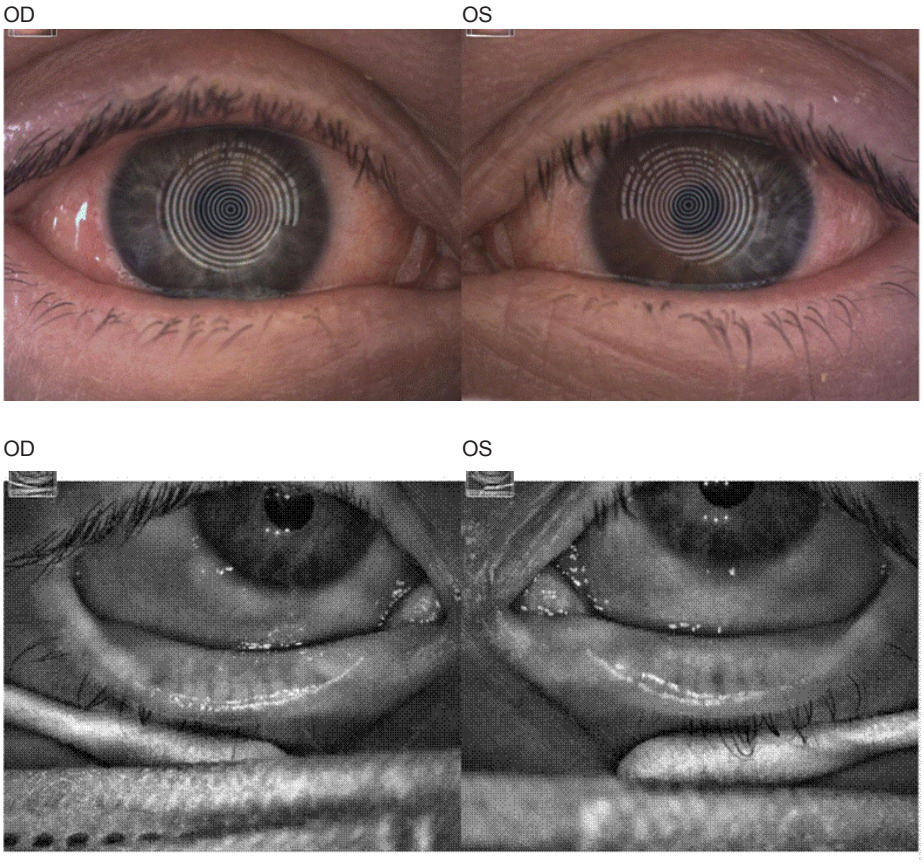
While dupilumab has been shown to be a very effective treatment for atopic dermatitis (AD),

approximately 32% (with some reports as high as 70%)[3] of patients treated with dupilumab experience ocular side effects including severe epiphora, blepharitis, conjunctivitis, keratitis, and meibomian gland dysfunction. This constellation of symptoms now is termed dupilumab induced ocular surface disease (DIOSD).[4] Typical DIOSD treatments involve topical steroids and off-label use of topical immunomodulators such as calcineurin inhibitors tacrolimus and cyclosporine and LFA-1 antagonist liftigrast.[5,6] Given the well-known, long-term topical steroid side effects of potential intraocular pressure increase, the risk for glaucoma, cataract development, and patient challenges with adherence to topical, alternative, and complementary treatment options are desirable. In this case, we report intense pulsed light (IPL) as a novel nonpharmaceutical treatment option in conjunction with steroids and lifitegrast for DIOSD.

CASE REPORT

In October 2020, a 39-year-old female presented with severe photophobia, eyelid swelling, epiphora, conjunctivitis, keratitis, and angular blepharitis for the past four weeks. Medical history was significant for topical therapy-resistant AD for 10+ years and the recent addition of dupilumab biweekly injections for the past 3 months. The patient was satisfied with the near 100% clearance of her skin lesions. The referring dermatologist noted that her severe ocular symptoms had not responded to oral antibiotics and topical steroids. She had experienced several similar ocular flare-ups within the last few months with variable success with treatment with oral and topical antibiotics and topical steroids. Examination on the initial visit showed reduced VA cc 20/30 OU, severe eyelid edema with associated closed canaliculi, elevated tear meniscus height, macerated and

FIG. 1 Initial presentation in October 2020.



inflamed angular blepharitis, 3+ conjunctival injection, 2+ conjunctival edema, 3+ corneal fluorescein staining, and severe inflammation on meibography (Figure 1). InflammaDry testing revealed a very high positive MMP-9. Pharmaceutical management was initiated with omega fatty acid supplementation, lifitegrast 5% ophthalmic solution 1 gtt BID OU, and a combination of antibiotic/steroid tobramycin 0.3%/dexamethasone 0.1% ophthalmic ointment to the eyelids, lateral canthus, and conjunctival sac TID OU.

At 3 weeks of follow-up, the patient reported only ~50% improvement in symptoms and noted the difficulty in adhering to the topical therapy regimen. Given the significant disruption of her ocular symptoms on her work and home life, she was offered IPL treatment as a nonpharmaceutical approach for addressing her severe eyelid inflammation, eyelid edema, angular blepharitis, and ocular surface inflammation associated with DIOSD. Treatment with Lumenis M22 IPL using Fitzpatrick III, rosacea telangiectasia, Toyos, vascular, and hair removal settings with 159 pulses was also performed using the four-step Periman protocol (Tables 1 and 2).

The patient returned for two more sequential IPL treatments: the second IPL was performed 30 days later in November 2020 using Fitzpatrick III, acne, rosacea telangiectasia, and Toyos's settings with noted immediate improvement in lid erythema and edema. The final IPL treatment was performed 18 days later in December 2020 using age, rosacea telangiectasia, Toyos, vascular, and hair removal settings with 143 pulses. These three sequential IPL treatments were performed using the four-step Periman protocol, and the maintenance therapy used lifitegrast 5% ophthalmic solution BID. The omega fatty acid supplementation showed dramatic improvement in her ocular signs and symptoms and aided in the return to normal ocular appearance and function at work and home.

Given the challenges with adherence to at-home therapy, the patient returned in March 2021 with a similar clinical presentation of conjunctival hyperemia, epiphora, ocular pruritus, and decreased vision. She reported using lifitegrast 5% ophthalmic solution QID OU, omega-3 supplementation, hypochlorous acid 0.01% spray BID, and artificial tears >5X a day. Combination antibiotic/steroid tobramycin 0.3%/dexamethasone 0.1% ophthalmic ointment

TABLE 1 Periman Protocol.

Preprocedure preparation	• Have patient remove face and eye makeup with Trader Joe's or simple micellar makeup remover wipes and eyelid cleaning with commercial lid wipes as needed. • Instill 1 gtt proparacaine OU. • Instill 1 gtt NPAT OU. • Insert sterilized laser-grade corneal shields OU. • Apply a thin-medium layer of clear ultrasound gel (take great care to avoid getting gel into eyes) using the long edge of a tongue depressor.
Step 1	• Full face rosacea pass (choose either telangiectasia or erythema settings based on clinical findings).
Step 2	• Toyos settings tragus to tragus. • Double pass.
Step 3	• Switch to small light guide. • Treat lids (avoid eyelashes by 2 mm). • Double pass.
Step 4	• Aesthetic clean-up: angioma (VL presents), facial telangiectasia (VL presents), chalazia, etc. For chalazia stack three extra Toyos pulses.
Postprocedure	• Remove gel with the long edge of the tongue depressor and use a gauze to remove any residual gel. Take care as to no gel entering into the eyes. • Wipe the face with warm water. • Pat one drop of AlphaganP mixed with EltaMD, Skin Medica, or Kinesys unscented sunscreen into the skin. • Instill 1 gtt 1:16 dilution AlphaganP in refresh mega AT OU.

was last used approximately 3 weeks ago. IPL with Fitzpatrick III, age, rosacea erythema, Toyos, vascular, and hair removal settings with 160 pulses was performed, and treatment with Durezol 0.05% ophthalmic emulsion steroid QID OU for 7 days with a taper to BID OU for 7 days, then QD OU 7 days was initiated. Two additional IPL sessions: one 14 days later with age, rosacea erythema, Toyos, vascular, and hair removal settings with 160 pulses and the final IPL an additional 35 days later with age, rosacea erythema, Toyos, vascular, and hair removal settings with 160 pulses achieved complete remission of her severe DIOSD despite poor adherence to home therapy (Figures 2– 4).

TABLE 2 IPL settings by Fitzpatrick Skin Score.

Skin type	Fluence (J/cm^2)	Filter (nm)*	Pulse structure	Pulse duration (msec)	Delay (msec)
I	15	590	Triple	6	50
II	14	590	Triple	6	50
III	12	590	Triple	6	50
IV	11	590	Triple	6	50

FIG. 2 Before and after images. (A) OD left image Oct 2020, right image April 2021 and (B) OS left image Oct 2020, right image April 2021.

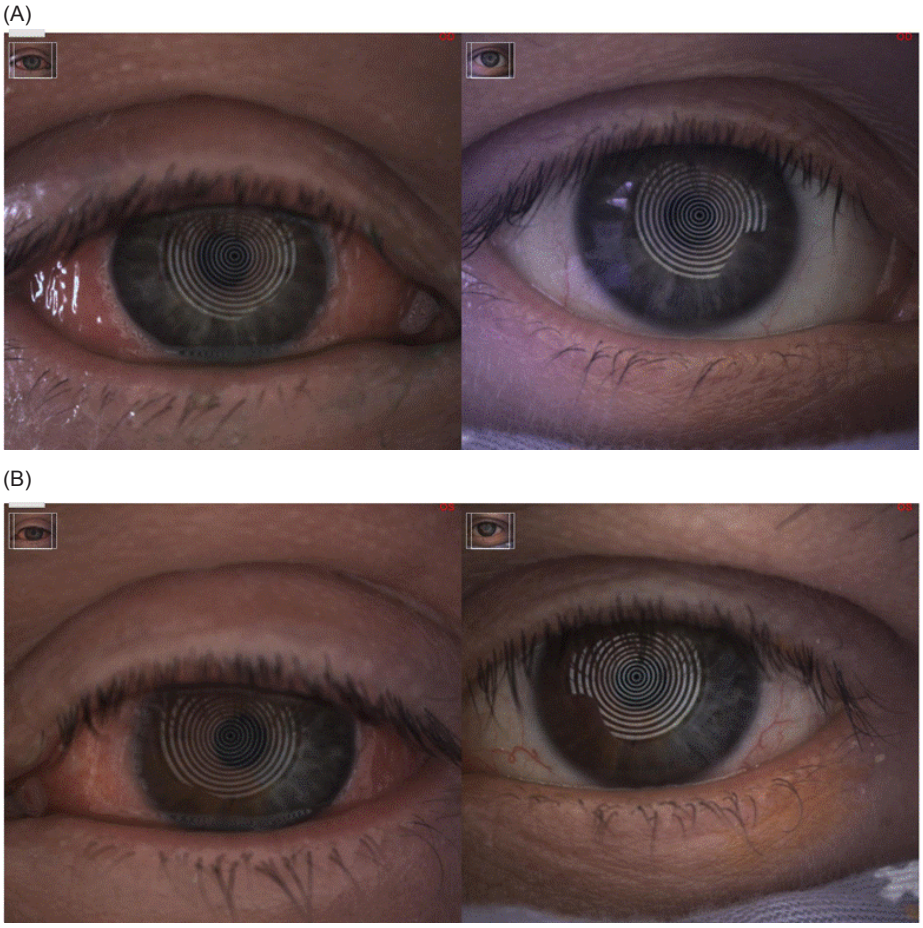
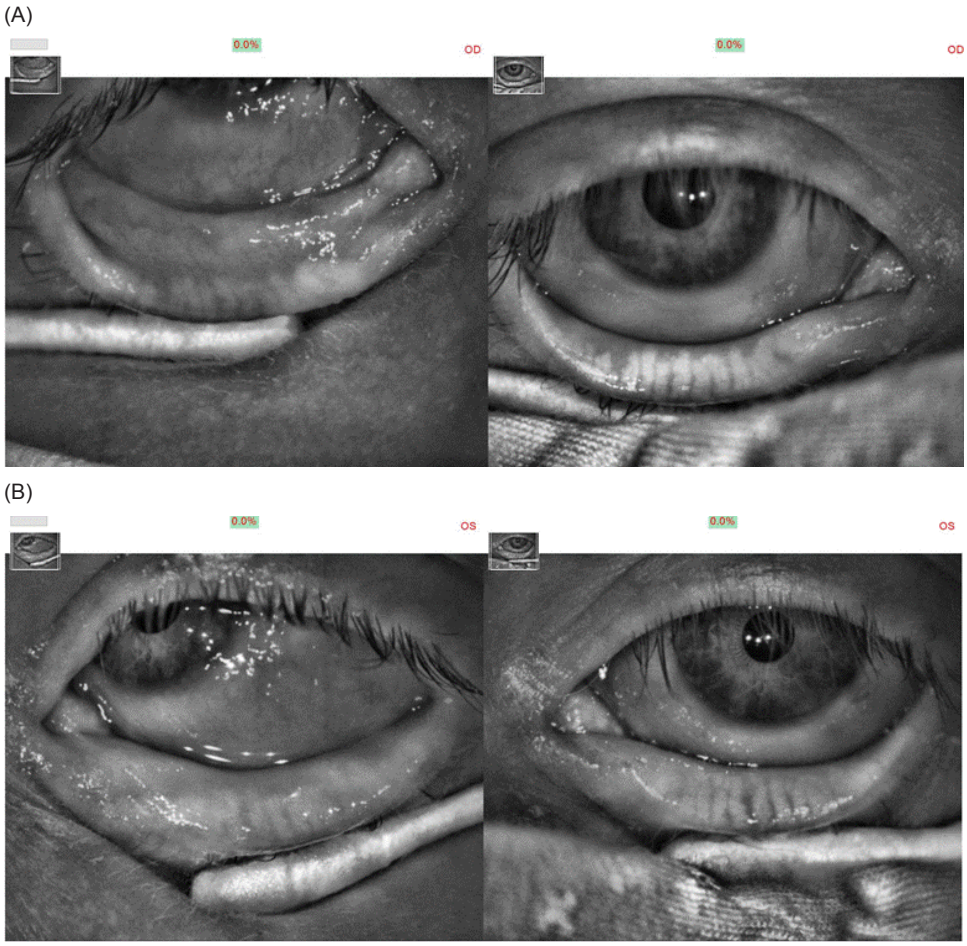


FIG. 3 Meibography images before (A) and after (B). (A) OD meibography: left image Oct 2020, right image Apr 2021 and (B) OS meibography: left image Oct 2020, right image Apr 2021.



DISCUSSION

Dupilumab is a very effective treatment for AD via the anti-IL-4a antagonist activity. However, it also has an anti-IL-13 activity which is critical for maintaining goblet cell density in the conjunctiva.[7] The anti-IL-13 activity of dupilumab may help in explaining DIOSD pathophysiologic features including loss of goblet cell density, immunoregulation of Th1 and Th17 cells, and the severe, fulminant clinical presentations. The exact pathogenesis of DIOSD is not yet known. However, rates of conjunctivitis are higher in patients using dupilumab for AD versus other type-2 inflammation diseases, indicating it has a particular mechanism specifically related to AD and is not an inherent side effect of dupilumab itself.[8] Patients reporting DIOSD also have shown to have had more severe AD before treatment.[9] Other potential hypotheses for driving the development of conjunctivitis and DIOSD in these patients include eosinophilia, increased OX40 ligand interaction, and alterations in cytokine activity leading to increased Demodex counts.[10]

Since dupilumab is the most effective FDA-approved treatment for AD and provides a marked relief, it is critical to continue the medication while clinicians aggressively manage the DIOSD with topical steroid drops, ointments, and topical

FIG. 4 DIOSD 30 minutes after IPL.

dermal and eye drop formulated immunomodulators. In cases of severe disease or challenges with adherence to therapy, IPL can be used as an FDA-approved method for addressing benign inflammatory skin lesions and dry eye associated with meibomian gland dysfunction (MGD). Several studies reported IPL as an effective treatment for dry eye disease and MGD.[11] Primarily IPL was used in dermatology for treating rosacea, acne, and skin lesions like telangiectasia. It uses noncoherent polychromatic light with wavelengths between 500 nm and 1200 nm. This light directed at the skin is absorbed by chromophores like melanin and hemoglobin, leading to blood vessel ablation.[12] Toyos et al.[13] first found improved dry eye symptoms in patients undergoing IPL treatment for rosacea, and it has since been found to be a very effective treatment for patients with dry eye disease and MGD. The exact mechanism of IPL is still unknown. Several potential mechanisms include abnormal blood vessel ablation, which eliminates a major source of inflammation to the eyelid and meibomian glands, photomodulation, Demodex eradication, suppression of matrix metalloproteinases, and modulation of pro and anti-inflammatory molecules secretion.[14] Given the chronic nature of AD, it is likely that dupilumab will be used by patients long-term. Thus, it is imperative to find safe long term treatment options for DIOSD such as IPL.

Even though IPL is an excellent adjunct therapy for this patient, it has limitations. In particular, it cannot be performed on patients with a Fitzpatrick skin score higher than four. More research to determine the number of sessions is needed and at what intervals. Retreatments for long-term DIOSD flare-ups will likely be required.

CONCLUSION

To our knowledge, this is the first reported case of IPL clinically being employed as an effective adjunct therapy to steroids and lifitegrast in addressing severe blepharitis, eyelid edema, and painful angular blepharitis in a patient with severe DIOSD. In the context of this patient with challenges with adherence to at-home topical therapy, IPL appears to have been of excellent clinical benefit. More research is needed to confirm the contributing benefits of this in-office approach to addressing severe DIOSD.

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