

# Chronic tearing induced by apremilast



The therapeutic potential of phosphodiesterase 4 (PDE-4) inhibitors has been studied for various hyperproliferative skin disorders, such as psoriasis and atopic dermatitis. Inhibition of PDE-4 activity leads to elevated levels of intracellular cyclic adenosine monophosphate (this results in anti-inflammatory effects in almost all inflammatory cells).<sup>1</sup> Apremilast is an oral PDE-4 inhibitor that is FDA approved for the treatment of psoriatic arthritis in adults as well as patients with moderate to severe plaque psoriasis. The most common adverse reactions to apremilast ( $\geq 5\%$ ) are diarrhea, nausea, headache, and upper respiratory tract infection.<sup>2</sup> We report a case that shows a novel adverse reaction, persistent epiphora secondary to apremilast diagnosed through history and drug challenge.

A 53-year-old woman was referred to the allergy service for evaluation of “conjunctivitis” associated with chronic bilateral eye tearing. Over the course of a year and a half, the patient experienced daily tearing without itching, with the worst symptoms occurring between 10:00 AM and 3:00 PM. She had previously developed cutaneous reactions to dust mite and various mold extracts during aeroallergen skin prick testing. Oral antihistamines, punctal plugs, and loteprednol 0.02% failed to provide any relief. The use of loteprednol 0.05% twice daily during this time offered mild relief. The patient noticed tear reduction the day after forgetting to take apremilast. Symptoms fully resolved within 2 days of intentionally stopping her medication. She reported having taken apremilast daily for psoriasis over the past 18 months without missing a dose out of fear of having a flare. She also recollected that her chronic tearing began a few months after beginning apremilast. She was instructed to discontinue the medication and return after a month. She remained asymptomatic during this time. Five days after restarting her medication, she began developing symptoms that progressively worsened in a stepwise pattern each day over the ensuing week. She reported daily tearing between the hours of 10:00 AM and 3:00 PM and lasted between 2 and 3 hours similar to complaints that occurred before the challenge procedure. At her 2-week follow-up, we observed periorbital swelling and tearing, suggesting that her chronic tearing was secondary to apremilast. She was again instructed to stop the apremilast. Her tearing stopped 2 days later, and she was instructed to see her dermatologist to discuss alternative medications for her psoriasis. The patient has not experienced symptoms since discontinuing apremilast.

Dry eye disease involves breakdown of the pre-ocular tear film that results in dehydration and irritation of the eye. Tear film consists of three layers: an inner mucous layer, a middle aqueous layer, and an outer lipid layer. The Meibomian glands are responsible for production of meibum that makes up the outer lipid layer. The lacrimal glands are the main contributor to the aqueous layer of the tear film. Activation of cyclic adenosine monophosphate/protein kinase A can induce the translocation of aquaporin 5 from cytosol to the apical membrane, which was recently proposed as being associated with water secretion into the tear.<sup>3</sup> The PDE-4 inhibitors are currently being used to treat hyperproliferative skin disorders. In addition to psoriasis, the PDE-4 inhibitor crisaborole (Eucrista, Pfizer, New York, New York) was approved by the US Food and Drug Administration in December of 2016 for the treatment of mild to moderate atopic dermatitis.

Apremilast in the treatment of a patient with plaque psoriasis has been reported to assist in the concomitant resolution of cicatricial ectropion secondary to severe lamellar ichthyosis.<sup>4</sup> The PDE-4 inhibitors have been investigated in the past as potential therapeutic agents for dry eye disease. In 2002, a patent was filed by Alcon Inc. for “an intervention directed to the use of PDE-4 inhibitors in the treating of dry eyes and other disorders requiring the wetting of the eye in

mammals.”<sup>5</sup> In 2008, the topical PDE-4 inhibitor Cilomilast (Alcon, Fort Worth, Texas) was licensed to Alcon for the treatment of eye disorders. A letter to the editor was published in 2010 describing the formulation of a novel PDE-4 inhibitor the authors named “Coumarin 18,” which was shown to be effective in both a rabbit model of dry eye disease and tear secretion tests in rats.<sup>6</sup> In 2012, Sadrai et al<sup>7</sup> showed that Cilomilast had comparable or superior therapeutic efficacy to that of dexamethasone and cyclosporine for dry eyes syndrome induced in mice.<sup>7</sup> No further developments have been reported regarding the use of PDE-4 inhibitors for dry eye disease or tear secretion, nor could any cases be found in which excessive tear production was linked to oral PDE-4 inhibitors.

Apremilast would not be the first drug indicated for a dermatologic pathologic condition that had unintended effects on the eye. Dupilumab is an interleukin-4 receptor antagonist that is indicated for the treatment of patients with moderate-to-severe atopic dermatitis that has been associated with conjunctivitis, blepharitis, ocular pruritus, and dry eye disease.<sup>8</sup> Furthermore, long-term corticosteroid use may be complicated by cataract formation and open angle glaucoma. Although differences exist, both corneal epithelial cells and thin skin are made up of nonkeratinized, stratified squamous epithelium that is derived from the ectoderm germ layer. Histological similarities between these tissues may help explain why pharmacologic interventions intended for the skin have an effect on the ocular surface.

The patient's tearing began around the time apremilast was started, persisted for over a year while receiving treatments for chronic epiphora, resolved completely within 36 hours of discontinuing the drug, remained in complete remission for a month during a trial of discontinuation, reappeared 5 days after restarting the medication, persisted for a week while continuing to take the drug, and after stopping it for a second time went back into complete remission. These observations support the conclusion that the patient's epiphora was secondary to her taking phosphodiesterase 4 inhibitors. Although the reaction was not life-threatening, it caused significant morbidity and extensive utilization of the health care system. For these reasons, physicians should be aware of this possible effect.

Matthew R. Norris, MD\*

Leonard Bielory, MD†

\* Department of Medicine  
Overlook Medical Center  
Summit, New Jersey

† Rutgers University Center for Environmental Prediction  
New Brunswick, New Jersey  
bielory@rutgers.edu

## References

- [1] Wittmann M, Helliwell PS. Phosphodiesterase 4 inhibition in the treatment of psoriasis, psoriatic arthritis and other chronic inflammatory diseases. *Dermatol Ther (Heidelb)*. 2013;3(1):1–15.
- [2] Available at [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2015/205437s005lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205437s005lbl.pdf). Accessed May 8, 2018.
- [3] Nakamachi T, Ohtaki H, Seki T, et al. PACAP suppresses dry eye signs by stimulating tear secretion. *Nat Commun*. 2016;7:12034.
- [4] Abboud JJ, Whittington A, Ahmed M, et al. Apremilast use in a case of cicatricial ectropion secondary to severe lamellar ichthyosis. *Ophthalmic Plast Reconstr Surg*. 2018;34(3):e76–e77.
- [5] Gamache DA, Yanni JM. U.S. Pat. No. 6,872,382. 2005.
- [6] Govek SP, Oshiro G, Anzola JV, et al. Water-soluble PDE4 inhibitors for the treatment of dry eye. *Bioorg Med Chem Lett*. 2010;20(9):2928–2932.
- [7] Sadrai Z, Stevenson W, Okanobo A, et al. PDE4 inhibition suppresses IL-17-associated immunity in dry eye disease. *Invest Ophthalmol Vis Sci*. 2012;53(7):3584–3591.
- [8] Available at [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/761055lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761055lbl.pdf). Accessed May 8 2018.