

Prostaglandin-Associated Periorbitopathy

A postmarketing surveillance observation.

BY LOUIS R. PASQUALE, MD

As the reports of prostaglandin-associated periorbitopathy (PAP) accumulate, clinicians and their patients face some new questions regarding the management of glaucoma.

EARLY CASES

In 2008, my colleagues and I described a series of five patients with significant periorbital changes ipsilateral to the eye treated with bimatoprost. On inspection of the adnexal tissues, there was an absence of dermatochalasis, a deep crease in the upper eyelid suggestive of levator dehiscence, ptosis of the upper lid, decreased prominence of the inferior orbital fat pads, and approximately 2 mm of enophthalmos relative to the fellow untreated eye. The power of these cases is that the unilateral nature of the glaucoma allowed each patient to serve as a control for age-related changes to the eyelids. Furthermore, in two cases, no other glaucoma medicines were used, and there was clear documentation that these adnexal changes were not preexisting. Discontinuing bimatoprost in these two cases resulted in a significant reversal of the aforementioned findings, ruling out the unlikely possibility that a diagnosis of glaucoma contributed to the adnexal changes. Finally, in one case, the adnexal findings confounded the workup of concomitant neuro-ophthalmic disease, prompting the performance of magnetic resonance imaging. In this case, neuroimaging ruled out primary orbital pathology as the source of the periorbitopathy.

Collectively, this case set unequivocally proved that bimatoprost caused the adnexal changes described. Interestingly, only two of the five patients were cognizant of the changes. After several unsuccessful attempts to publish these findings, they were ultimately accepted by *Ophthalmic Plastic and Reconstructive Surgery*.¹

PREVALENCE AND MEDICATION

As of this writing, 15 cases of PAP have been reported with bimatoprost, and three cases have been reported with travoprost.²⁻⁷ Exactly how pervasive is this side



Figure 1. External photograph of a patient with advanced normal-tension glaucoma taking three glaucoma medicines, including bimatoprost, in both eyes for several years. Note the deepening of the upper lid sulcus and ptosis of the upper lid bilaterally.



Figure 2. External photograph of a patient with severe, unilateral, chronic angle-closure glaucoma in his right eye. The patient uses three glaucoma medicines in this eye, including latanoprost. Note the loss of the crease in his right upper eyelid, ptosis of the right upper lid, right inferior scleral show, and blunting of the right inferior orbital fat pad relative to the fellow eye.

effect? If one accepts that the patient on bilateral bimatoprost treatment shown in Figure 1 also has PAP and not merely age-related periorbital changes, then I suspect this side effect is relatively common.

Do patients taking latanoprost experience this side effect? Yes, Figure 2 shows a patient with unilateral glaucoma in his right eye who clearly has signs of PAP. He presented with acute primary angle-closure glaucoma in his right eye and an occludable angle in his left eye. After

bilateral laser iridotomies, the patient required multiple medicines to control the IOP in his right eye, including latanoprost, and his insurance carrier has covered the drug throughout his illness (6 years). He required no glaucoma medications for his left eye after the laser iridotomy. Researchers from Korea also claim that PAP occurs with latanoprost but did not provide supporting photodocumentation.⁸

CLINICAL CONSEQUENCES

Aside from the obvious cosmetic alterations, are there other serious clinical consequences of PAP? I have encountered several patients on long-term therapy with prostaglandin analogues (PGAs) whom I would describe as *Goldmann applanation tonometry (GAT) challenges*. The patient depicted in Figure 1 is cooperative with GAT, yet due to her ptosis and tight upper eyelid tissue, my most experienced technician had difficulty measuring her IOP. I used a cotton swab to lift the lashes, elevating the upper lid in the process (Figure 3). This maneuver facilitates corneal applanation.

I suspect there are other important deleterious clinical effects of PAP, and I urge all readers of this article to report such consequences to the FDA at www.eyedrugregistry.com as well as to Stanley Berke, MD, and myself.

MECHANISM

It is interesting to speculate on the mechanism of PAP. Dr. Berke and I suspect that the periorbital absorption of PGAs produces some combination of smooth muscle contraction in the eyelid retractors and periorbital fat cell atrophy. With respect to the former, Romano and Lograno showed that bimatoprost induced smooth muscle contraction.⁹ Some patients with PAP have inferior scleral show (Figure 2), which could be related to contraction of the inferior eyelid's smooth muscle retractors.

In terms of atrophy, the number of a person's fat cells increases from birth until young adulthood and then remains relatively constant thereafter.¹⁰ Thus, it is the volume of lipid fat per cell that dictates one's physical appearance from middle age onward. Investigators in Korea analyzed preaponeurotic fat biopsies from patients with PAP induced by all of the PGAs versus con-



Figure 3. To perform GAT on the patient shown in Figure 1, Dr. Pasquale uses a cotton swab to gently elevate the upper lid, exposing the cornea for applanation.

trol subjects not using any glaucoma medicines.⁸ The researchers found the highest density of adipocyte cells in patients with PAP using bimatoprost relative to controls, which was statistically significant. This indicates that the volume of lipid per cell was reduced in patients using bimatoprost. Interestingly, the groups using travoprost and latanoprost also had higher adipocyte cell densities versus controls, but only the results for travoprost were statistically significant, probably because of the small sample size. There was no evidence of inflammation in any of the fat biopsies. There was no mention of whether the measurements of cell density were performed in a masked fashion. Prostaglandin F receptor (FP) activation is linked to the inhibition of preadipocyte differentiation in many cell lines.¹¹ FP receptor agonists also down-regulate fatty acid-binding protein expression, a key element in the uptake of free fatty acids and triglyceride synthesis in adipocytes.¹²

IMPLICATIONS

PGAs have become first-line therapy for glaucoma due to their once-daily dosing and high efficacy as well as the paucity of systemic side effects noted to date. (Postmarketing observations, however, may reveal novel systemic side effects not previously appreciated.) Now that PAP is becoming accepted as a side effect, how will glaucoma management change? This is new territory. I will share my ideas, but more deliberation by other thought leaders is needed.

I strongly believe that all newly diagnosed patients should be informed about PAP before initiating treatment with a PGA. Some of them may not be bothered by this possibility, whereas others will find the development of PAP an unacceptable possibility.

It is more complex to address the issue of how physicians should communicate with patients already using PGAs. Ideally, these individuals should also be informed about PAP, but I believe clinicians need to prioritize how to handle the matter without causing mass hysteria in their practices. First, I recommend a careful adnexal

(Continued on page 28)

A PREVIOUSLY UNDERRECOGNIZED BUT IMPORTANT SIDE EFFECT

By Stanley J. Berke, MD

I remember when Simmons Lessell, MD, stated the following during my glaucoma fellowship year (1985-1986) at the Massachusetts Eye and Ear Infirmary in Boston: "He who ignores the German literature discovers many new things." His words rang in my head recently when a patient asked me, "Why is my left eyelid drooping?" My patient had a history of pseudoexfoliation glaucoma in his left eye only, and he had been using a prostaglandin analogue (PGA) drop in that eye only for more than 5 years (travoprost for 3.5 years, then bimatoprost for 1.5 years).

At first glance, the patient appeared to have marked ptosis of his left upper lid (Figure 1). On closer examination, however, he had only mild ptosis of the left upper lid but also exhibited marked deepening of the superior lid sulcus, relative enophthalmos (measuring 2 mm), inferior scleral show, periorbital fat atrophy, and involution of dermatochalasia. I subsequently observed these symptoms in the next few patients I saw who were using a PGA unilaterally (Figures 2 and 3). These changes were also present in most patients using PGAs bilaterally (Figure 4) but without the asymmetry.

I thought I had discovered a new side effect of PGAs, but a Google search led me to the page in Wikipedia about the fat-reducing properties of bimatoprost. Three articles listed in the reference section described my findings exactly,¹⁻³ but they also revealed why I had not been aware of this complication. The first was written in German¹; Dr. Lessell had been right. The second had appeared in an ophthalmic plastic surgery journal, and the third had appeared in an optometric journal.

Further research led me to four more articles involving all three available PGAs by researchers in Korea, China, and England.⁴⁻⁷ I then found a good photographic example in a textbook coauthored by Wiley Chambers, MD, of the FDA. The figure was described as "allergic reaction to topical bimatoprost left eye." It shows periorbital fat atrophy, deepening of the superior lid sulcus, ptosis, enophthalmos, and involution of dermatochalasia.⁸

IMPLICATIONS

Aside from the obvious cosmetic effects, prostaglandin-associated periorbitopathy (PAP) makes it difficult, if not impossible, to examine the eye or to perform applanation tonometry, surgery in the superior location, laser suture lysis, bleb needling, or argon/selective laser trabeculoplasty. In addition, some affected patients have undergone unnecessary



Figure 1. A 62-year-old white man with pseudoexfoliation glaucoma in his left eye only had been treated with travoprost for 3.5 years and then bimatoprost for 1.5 years. In addition to the well-known side effect of longer eyelashes, he exhibited structural periorbital and lid changes consisting of mild ptosis, deepening of the superior lid sulcus, periorbital fat atrophy, inferior scleral show, relative enophthalmos, and involution of dermatochalasia.



Figure 2. A 60-year-old white woman had a well-functioning bleb in her right eye. She had been treated with latanoprost in her left eye only for 8 years.

medical and imaging workups to evaluate the visible asymmetry of their orbits and eyelids.

Topical PGA drops may play a role in the newly described tight orbit syndrome, which the article's authors asserted is a cause of open-angle glaucoma.⁹ All six of the young patients were using one of the three currently available PGAs.

I myself have found that PAP is more apparent in young patients, probably because they have less dermatochalasia and orbital fat prolapse than elderly individuals. I therefore exercise and recommend caution in the prescription of PGAs for young patients and individuals with preexisting, anatomically deep-set eyes and tight lids.

The good news is that PAP seems to be reversible; I have seen its effects subside 1 to 3 months after patients discontinued using PGAs. It is also possible that PGA drops could benefit some patients with thyroid ophthalmopathy (medical decompression) or blepharochalasia (Figure 5).

A PREVIOUSLY UNDERRECOGNIZED BUT IMPORTANT SIDE EFFECT (CONTINUED)



Figure 3. A 67-year-old Hispanic woman had a well-functioning bleb in her left eye. She had been treated with latanoprost for 6 years and then bimatoprost for 9 years in her right eye only (A). Side view of her left, untreated eye (B). Side view of her right, treated eye (C).

REPORTS NEEDED

Since I posted my findings along with clinical photographs on the Web site of the American Glaucoma Society (AGS) on April 3, 2011, I have seen many more patients with PAP, either unilaterally or bilaterally. Many other members of the AGS have since made similar reports to the group. In early April, Dr. Chambers stated in an e-mail on the AGS.net that he was making a recommendation to all of the PGA manufacturers that they add the side effects of periorbital fat loss, deepening of the superior lid sulcus, etc., to their product labels.

It is important that clinicians report cases of PAP as an adverse event to all of the PGA manufacturers, the FDA (www.eyedrugregistry.com), and their medical societies. I would also encourage practitioners to share their cases with Louis Pasquale, MD, and me. Our goal is to increase awareness of PAP among physicians and patients.

Further research is needed to determine the frequency of PAP, how long it takes to occur, how long it takes to resolve after the discontinuation of topical PGAs, and any differences in PAP based on the patient's age, his or her race/ethnicity, and/or the type of PGA used.

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Figure 4. A 74-year-old white woman was treated with bimatoprost in both eyes for 5 years. Note the extremely deep superior lid sulcus and lid erythema bilaterally.



Figure 5. An 88-year-old white man with a well-functioning bleb in his right eye. He used bimatoprost in his left eye only for 6 years. Note the periorbital fat atrophy of the left lower lid, which actually improved cosmesis.

sciences at the Albert Einstein School of Medicine in Bronx, New York, and he is the chief of the Glaucoma Service at Nassau University Medical Center in East Meadow, New York. He is on the speakers' bureaus of and has received research grants from Alcon Laboratories, Inc.; Allergan, Inc.; Merck & Co., Inc.; and Pfizer, Inc. Dr. Berke may be reached at (516) 593-7709, ext. 207; sberke@ocli.net.

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(Continued from page 25)

examination to document the patient's current external appearance. I am doing this now in my practice. Many patients show no signs of PAP and, in fact, may have significant dermatochalasis. It may be sensible simply to observe them for evolution to early PAP. For these patients, it is reasonable to defer a discussion of PAP to a later date. Patients with overt PAP may not have other viable options to lower their IOP, and unless they have eyelid tightening that compromises their vision, it may be fair to defer a discussion of PAP to another date.

Patients with PAP who are GAT challenges represent a high priority for a discussion of the side effect. These individuals deserve to understand why it is difficult to measure their IOP. This whole conversation would be informed by a better understanding of the attack rate and risk factors for PAP, as Dr. Berke points out in his sidebar discussion.

CONCLUSION

We already knew that PGAs had myriad side effects not previously encountered in the medical care of glaucoma. It remains to be determined whether PAP will alter the medical management of this disease. ■

Louis R. Pasquale, MD, is the director of the Glaucoma Service and associate director telemedicine at the Massachusetts Eye and Ear Infirmary in Boston. He is also an associate professor of ophthalmology at Harvard Medical School in Boston.



Dr. Pasquale is an inventor on a patent regarding medicinal uses of prostaglandin analogues to reduce body fat. He retains no ownership rights to and has never received any royalties from this patent. Dr. Pasquale may be reached at (617) 573-3674; louis_pasquale@meei.harvard.edu.

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