Supplement to

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The Evolving Role of NSAIDs in Cataract Surgery

Strategies for ocular surface management with the newly approved q.d. formulation of bromfenac 0.09%.

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The Evolving Role of NSAIDs in Cataract Surgery

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STATEMENT OF NEED

The goal of this CME supplement is to educate ophthalmologists on the current issues surrounding the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in conjunction with cataract and refractive surgery. In the anterior segment surgical setting, clinicians must pay careful attention to the importance of managing inflammation. A growing body of evidence supports the routine practice of using NSAIDs in cataract and refractive surgeries to avert complications such as cystoid macular edema and pain and to provide the best outcomes postsurgery. While advances in therapy and technology have significantly increased the opportunity for optimal outcomes in anterior segment eye surgery, evidence indicates that many ophthalmologists do not fully use these advances for the benefit of their patients.[1,2]

Translation of research into clinically focused advice is needed because of continuing developments in this area. The expert faculty includes investigators who participated in clinical trials of the new q.d.-dosed NSAID, bromfenac. The as-yet-unpublished data significantly expand on the current therapeutic strategies available and enhance patient care. Previous studies show an optimal NSAID regimen should start treatment 3 days before surgery and last for a minimum of 4 weeks post surgery, with some studies continuing treatment for 8 weeks postoperatively.[3]

1. Pepose JS, Qazi MA, Davies J, et al. Visual performance of patients with bilateral vs combination Crystalens, ReZoom, and ReSTOR intraocular lens implants. *Am J Ophthalmol*. 2007;144(3):347-357.

2. Schallhorn SC, Farjo AA, Huang D, et al; American Academy of Ophthalmology. Wavefront-guided LASIK for the correction of primary myopia and astigmatism; a report by the American Academy of Ophthalmology. *Ophthalmology*. 2008;115(7):1249-1261.

3. Asano S, Miyake K, Ota I, et al. Reducing angiographic cystoid macular edema and blood-aqueous barrier disruption after small-incision phacoemulsification and foldable intraocular lens implantation: multicenter prospective randomized comparison of topical diclofenac 0.1% and betamethasone 0.1%. *J Cataract Refract Surg*. 2008;34(1):57-63.

TARGET AUDIENCE

This certified CME activity is designed for general ophthalmologists and cataract and refractive surgery specialists.

LEARNING OBJECTIVES

Upon completion of this activity, the participant should be able to:

- Improve pre- and postoperative inflammation therapy in cataract and refractive patients
- Gain a greater understanding of the benefits of nonsteroidal anti-inflammatory treatments
- Understand the role of NSAIDs in ocular surface management
- Demonstrate greater knowledge regarding the prevention of cystoid macular edema
- Understand the new treatment options available with q.d. bromfenac ophthalmic solution

METHOD OF INSTRUCTION

Participants should read the continuing medical education (CME) activity in its entirety. After reviewing the material, please complete the self-assessment test, which consists of a series of multiple-choice questions. To answer these questions online and receive real-time results, please visit http://www.dulaneyfoundation.org and click "Online Courses."

Upon completing the activity and achieving a passing score of over 70% on the self-assessment test, you may print out a CME credit letter awarding 1 *AMA PRA Category 1 Credit.*™ The estimated time to complete this activity is 1 hour.

ACCREDITATION AND DESIGNATION

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Dulaney Foundation and *Cataract & Refractive Surgery Today*. The

Dulaney Foundation is accredited by the ACCME to provide continuing education for physicians. The Dulaney Foundation designates this educational activity for a maximum of 1 *AMA PRA Category 1 Credit.*™ Physicians should claim credit only commensurate with the extent of their participation in the activity.

DISCLOSURE

In accordance with the disclosure policies of the Dulaney Foundation and to conform with ACCME and US Food and Drug Administration guidelines, anyone in a position to affect the content of a CME activity is required to disclose to the activity participants: (1) the existence of any financial interest or other relationships with the manufacturers of any commercial products/devices or providers of commercial services; and (2) identification of a commercial product/device that is unlabeled for use or an investigational use of a product/device not yet approved.

FACULTY CREDENTIALS

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FACULTY/STAFF DISCLOSURE DECLARATIONS

Dr. Gayton is on the speakers' bureau for Alcon Laboratories, Inc., Inspire Pharmaceuticals, Inc., and ISTA Pharmaceuticals, Inc., and he is a consultant for ISTA Pharmaceuticals, Inc.

Dr. Bacharach is on the speakers' bureau for Allergan Laboratories, Inc., and Lumenis Inc. He has obtained research funding from Alcon Laboratories, Inc., Allergan, Inc., Lumenis, Inc., Merck & Co., and ISTA Pharmaceuticals, Inc. He is a clinical investigator for ISTA Pharmaceuticals, Inc.

Dr. Katsev is on the board of the Caribbean Eye Meeting as well as the editorial board of Cataract & Refractive Surgery Today. *He is a consultant for Abbott Medical Optics Inc. and ISTA Pharmaceuticals, Inc., and he is a speaker for Alcon Laboratories, Inc., Allergan, Inc., Bausch + Lomb, and TruVision.*

Dr. Rowen is on the speakers' bureau for Allergan, Inc., Bausch + Lomb, ISTA Pharmaceuticals, Inc., and Inspire Pharmaceuticals, Inc.

Dr. Tyson is a clinical investigator for ISTA Pharmaceuticals, Inc.

All others involved in the planning, editing, and peer review of this educational activity have indicated they have no financial relationships to disclose.

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The Evolving Role of NSAIDs in Cataract Surgery

Strategies for ocular surface management with the newly approved q.d. formulation of bromfenac 0.09%.

Dr. Gayton: During the past 20 years, nonsteroidal anti-inflammatory drugs (NSAIDs) have become an integral part of pre- and postoperative cataract care. The purpose of this roundtable is to discuss the evolving nature of topical NSAID treatments in cataract and refractive surgeries in general and to specifically discuss the recent approval of and our clinical experience with the once-a-day dosing of bromfenac ophthalmic solution 0.09% (Bromday; ISTA Pharmaceuticals, Inc., Irvine, CA).

I'd like to begin by asking each participant how you currently use NSAIDs in your practice.

Dr. Katsev: I began using NSAIDs after an episode in which my patients' incidence of cystoid macular edema (CME) increased dramatically. Ever since then, I have been a strong proponent of these drugs. The first NSAID I used was flurbiprofen (Ocufen 0.03%; Allergan, Inc., Irvine, CA). Since then, I have gravitated toward NSAIDs that require less-frequent dosing because my patients seem to prefer them. I also appreciate how NSAIDs have helped minimize CME in my presbyopia-correcting IOL population and allowed me to direct more energy to the refractive care of these patients.

Dr. Bacharach: I agree with Dr. Katsev that ophthalmic NSAIDs are an excellent surgical adjunct. I find these agents especially useful for performing cataract surgery in challenging eyes, such

as those with small pupils and irises that might be bound down from synechiae or the extended use of pilocarpine, which can induce significantly more inflammation.[1] I use NSAIDs in every case—premium, complex, and routine.

Dr. Gayton: There was a time when ophthalmologists had to stop using NSAIDs due to a safety issue.[2] What is the panel's opinion about the safety of our current NSAIDs?

Dr. Rowen: I was using ocular NSAIDs at the time that other practitioners experienced complications with generic diclofenac. I was using branded diclofenac sodium ophthalmic solution 0.1% (Voltaren; Novartis Pharmaceuticals Corporation, East Hanover, NJ) and never experienced any corneal melts or other problems. In fact, a retrospective analysis I conducted of my patients in the early 1990s showed that my use of that NSAID had reduced the incidence of CME in my practice.

Today's ophthalmic NSAIDs are very good. I prescribe them to patients 2 days prior to their scheduled surgery. I have recently begun using the once-daily version of bromfenac ophthalmic solution 0.09% after hearing it was supposed to be effective yet comfortable for patients. I saw no problems with my patients' corneas, and none of them have reported stinging or burning sensations. I feel today's NSAIDs are quite safe.

Dr. Gayton: My staff and I discovered the corneal melting problems associated with generic diclofenac.

TABLE 1. APPROVED OPHTHALMIC NSAIDs*

NSAID	Approved Indications	Dosing	Date of Approval
Bromfenac 0.09% q.d. (Phenylacetic acid) ISTA	Treatment of postoperative inflammation and reduction in ocular pain after cataract surgery	1 d 1 x daily, starting 24 h before surgery, continue on day of surgery, and through 2 wks postop	10/16/10
Diclofenac sodium 0.1% (Phenylacetic acid) Novartis/generics	Treatment of postoperative inflammation in patients after cataract extraction. Temporary relief of pain and photophobia in patients undergoing corneal refractive surgery.	1 d 4 x daily, starting 24 h after surgery and through 2 wks postop	3/28/91
Flurbiprofen sodium 0.03% (Phenylalkanoic acid) Allergan/Generics	Inhibition of intraoperative miosis	4 d on day of surgery, 1 every half-hr, starting 2 h before surgery	12/31/86
Ketorolac tromethamine 0.5% (Pyrrolo-pyrrole group) Allergan	Temporary relief of ocular itching due to seasonal allergic conjunctivitis. Treatment of postoperative inflammation after cataract extraction.	1 d 4 x daily, starting 24 h after surgery and through 2 wks postop	12/9/92
Ketorolac tromethamine 0.45%, preservative free Allergan	Treatment of pain and inflammation following cataract surgery	1 d 2 x daily starting 24 h before surgery and through 2 wks postop	7/23/09
Nepafenac 0.1% (Arylacetic acid) Alcon	Treatment of pain and inflammation associated with cataract surgery	1 d 3 x daily, starting 1 day prior to surgery, continue on day of surgery, through 2 wks postop	8/19/05

* Source: Pharmacy Benefits Management Services, United States Department of Veterans Affairs. Available at http://www.pbm.va.gov/Clinical%20Guidance/Drug%20Class%20Reviews/Ophthalmic%20Nonsteroidal%20Anti-Inflammatory%20Drugs%20(NSAIDs)%20Review.pdf. Accessed March 24, 2011.

We subsequently suspended our use of NSAIDs, because most of our prescriptions were being substituted with generic diclofenac. When we reviewed our cataract outcomes some time after this hiatus, we found a significant spike in the development of CME. Fortunately, we were able to resume using topical NSAIDs after the generic diclofenac was voluntarily removed from the marketplace. What has been the panel's experience with bromfenac ophthalmic solution 0.09% from a safety standpoint (Table 1)?

Dr. Tyson: I have not experienced any safety concerns with this drop. The b.i.d. formulation of bromfenac (Xibrom; ISTA Pharmaceuticals, Inc.) has been used in more than 20 million eyes internationally with no reported safety issues. I like that the twice-per-day formulation delivers much less benzalkonium chloride (BAK) to the cornea compared with other available NSAIDs that are dosed q.i.d.

Dr. Gayton: I decided to tabulate the amount of NSAID that a patient using ketorolac over a 6-week period receives from both the generic and branded formulations. A patient using ketorolac tromethamine ophthalmic solution 0.5% (Acular; Allergan, Inc.) would receive 42 mg of active drug over a 6-week period. Patients using ketorolac tromethamine ophthalmic solution 0.4% (Acular LS) receive approximately 36 mg of ketorolac. With ketorolac tromethamine ophthalmic solution 0.45% (Acuvail; Allergan, Inc.), patients receive about 19 mg of active drug in 6 weeks. These are significant amounts of NSAIDs. A 6-week course of diclofenac 0.1% delivers 8.4 mg, and nepafenac 0.1% delivers 6.3 mg of active drug. A person who uses bromfenac 0.09% once per day will receive approximately 1.6 mg of NSAID, and b.i.d. dosing will deliver about 3.3 mg of active drug over a 6-week period (Figure 1). I believe this lower dosage is one of the reasons that bromfenac is kinder to the ocular surface than other NSAID drops.

As Dr. Rowen mentioned, I also noticed a lack of burning and stinging in my patients who used bromfenac. Furthermore, because the bromfenac drop is not sticky, people do not blink or rub their eyes as much to clear their vision after instillation, which reduces reflex tearing. It is a comfortable drop that does not cause blurring and thus has much less impact on the normal tear film.

Dr. Bacharach: I wanted to add to Dr. Tyson's comments about BAK. Although we want to minimize the amount of BAK that reaches the eye, there are two benefits of having this preservative in the bottle. First, BAK may allow more of the NSAID molecule to penetrate the eye, loosening some tight junctions between corneal epithelial cells. Second, BAK provides some security against the growth of fungi and bacteria in the bottle.[3]

Dr. Gayton: Although I agree that there is some benefit to having BAK in the bottle, I think most surgeons would acknowledge that increasing the dosage of topical drops containing BAK raises the risk of BAK toxicity to the cornea.

I feel that bromfenac solution has an excellent, long-lasting analgesic effect. I have my patients instill a drop of the NSAID at the beginning of their day, so that they receive the benefit of the analgesia as their day starts. Although all ocular NSAIDs ultimately control inflammation effectively, as anterior segment surgeons, we want to reduce the inflammatory byproducts diffusing through the back of the eye to help prevent CME.[4] In phase 3 studies, twice-a-day bromfenac achieved statistical significance in controlling inflammation in 2 to 3 days.[3] In separate clinical trials, once-daily bromfenac significantly reduced inflammation and pain on the first postoperative day (Figure 2).[5-7]

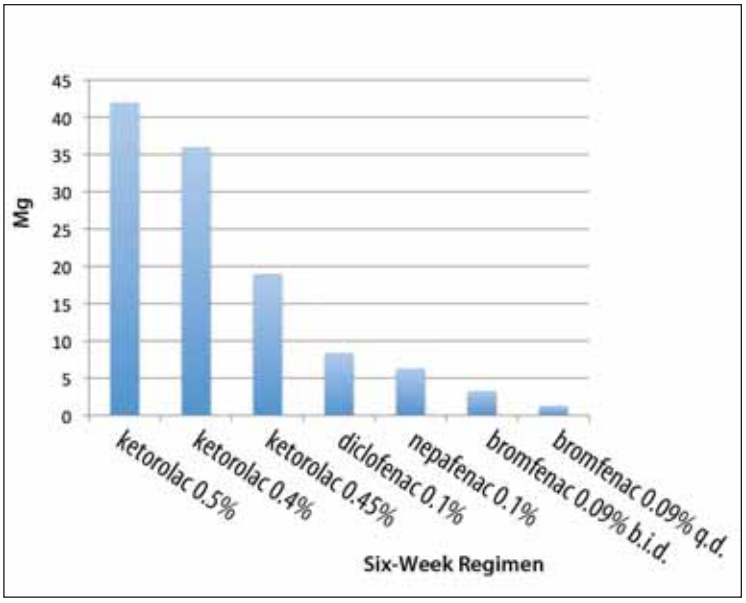

Figure 1. Milligrams of NSAIDs instilled in eyes after a 6-week dosing regimen. Chart constructed from Dr. Gayton's data.

Dr. Rowen: Interestingly, in the trials performed for b.i.d. bromfenac, the subjects' summed ocular inflammation score (SOIS) was already at a 3, meaning they were highly inflamed eyes. Bromfenac still produced a remarkable decrease in inflammation in these eyes—as early as study day 3—and the median time to pain resolution was 2 days. These results demonstrate bromfenac's potency.

Dr. Gayton: We know from organic chemistry that halogenation makes a molecule more potent by enabling it to more effectively bind to the enzyme it is meant to block. Therefore, one of the reasons difluprednate is so potent is that it is halogenated with two fluorines attached to the molecule. The bromfenac molecule has been halogenated with bromine, which makes it bind with the cyclo-oxygenase (COX 1 and 2) enzymes very tightly.[8] This halogenation is what distinguishes bromfenac from the other NSAIDs, and it is the major reason why the drop works so effectively in such low dosages. While all other ocular NSAIDs are effective in reducing pain and inflammation, they all require more medication to achieve the desired result. Two basic science studies and the phase 3 studies for bromfenac q.d. illustrated this point.[7] Therapeutic levels were found in the ocular tissue of rabbits 24 hours after instillation of one drop of 0.09% bromfenac.[9] The Bromday phase 3 study demonstrated there was no clinical difference when the concentration of bromfenac was doubled to 0.18%.

Although Maxwell's study of nepafenac[10] demonstrated that the drug reduces inflammation when dosed less frequently, the effect was diminished with the decreased dosing (Figure 3). This finding was very different from the bromfenac data, which showed that higher concentrations or greater frequency did not result in any difference in inflammatory control. This indicates that bromfenac q.d. saturates the COX enzyme, whereas nepafenac does not achieve saturation until it reaches t.i.d. dosing.

DOSING AND COMPLIANCE

Dr. Katsev: For patients to be able to use the bromfenac NSAID once per day is unquestionably a boon for compliance.

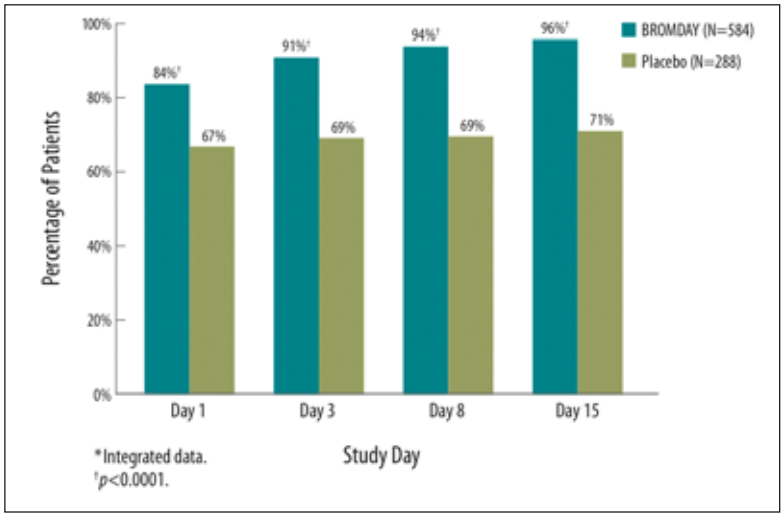

Figure 2. The percentage of subjects with an ocular pain score of 0 at each study visit (bromfenac vs placebo). (Adapted from: Chandler SP, Henderson BA, Gayton JL, et al. Integrated phase 3 clinical trials of bromfenac sodium ophthalmic solution dosed once daily for ocular surgery. Poster 281 presented at: The AAO/MEACO Annual Meeting; October 17-18, 2010; San Francisco, CA.)

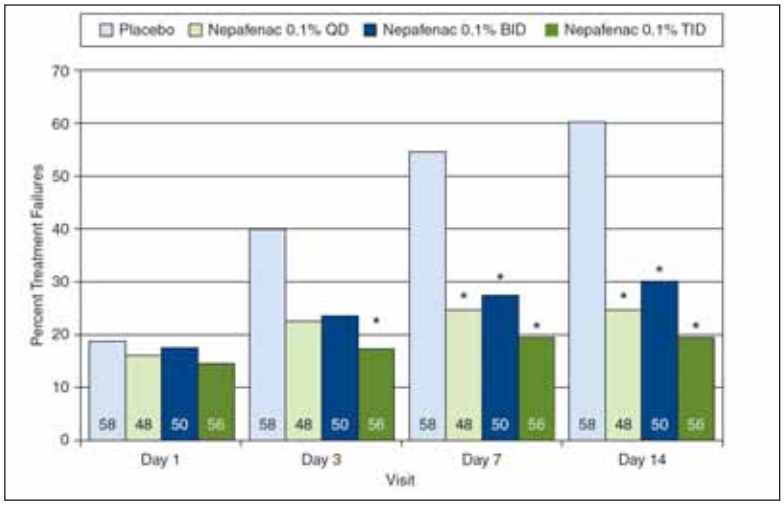

Figure 3. This graph shows the cumulative percentage of treatment failures by visit. Note: The numbers at the bottom of each bar represent the number of subjects in each treatment category. (Reprinted with permission from: Maxwell WA, Reiser HJ, Stewart RH, et al. Nepafenac dosing frequency for ocular pain and inflammation associated with cataract surgery. *J Ocul Pharmacol Ther.* 2008;24(6):593-599. The publisher of this copyrighted material is Mary Ann Liebert, Inc. publishers.)

Dr. Rowen: I agree. When we do not have to worry about patients' postoperative compliance, we know that they will receive the benefit of the drug and be happier for it.

Dr. Tyson: Dosing once versus four times per day makes a big difference to patients, especially the elderly, who have a hard time keeping track of which medications they must take at what time of the day.

Dr. Katsev: I often counsel individuals who want cataract surgery but are afraid of being able to take all of the requisite drops. A b.i.d. dosing schedule is something that almost any family can manage, and of course, a once-daily regimen is even better.

Dr. Bacharach: Most people, especially older individuals, are much more likely to remember to take their medication when they can do it first thing in the morning. The second easiest time to take medication is in the evening before bed; remembering to take it at lunch or dinner is more difficult. This is particularly true with patients who are given their drops by a family member or other caregiver for whom the reduced frequency certainly makes this task easier. Being able to prescribe an ophthalmic NSAID that patients can use once in the morning for all-day relief of signs and symptoms of inflammation is a significant advancement.

Dr. Tyson: With patients' out-of-pocket expenses for drugs constantly rising, I have changed my postoperative prescriptions. Whereas I used to prescribe an antibiotic, an NSAID, and a steroid four times per day, I now prescribe an antibiotic and an NSAID twice per day. This regimen has worked quite effectively in uncomplicated surgeries on healthy eyes (I have heard no complaints from these patients), and it has increased my patients' compliance and savings.

CLINICAL SUPPORT FOR Q.D. DOSING

Dr. Gayton: Dr. Bacharach, the change from a b.i.d. to a q.d. NSAID represents a paradigm shift in perioperative care. The basic science studies caused me to switch to q.d. dosing with bromfenac more than 2 years ago. What clinical studies made you comfortable with a q.d. NSAID regimen?

Dr. Bacharach: I recently participated in the clinical trial for once-daily bromfenac (unpublished data; on file with ISTA Pharmaceuticals, Inc.). The outcomes demonstrated that q.d. dosing was at least equally efficacious (if not more so) than a b.i.d. regimen. In many eyes, the q.d. dosing of bromfenac controlled pain and cell and flare more effectively. Based on these data, I am confident about prescribing this NSAID as a once-a-day treatment. I instruct my patients to use the drop in the morning for all-day relief from pain. Anecdotally, the patients that have been using the q.d. dosing pattern have been happy with its ease and have had extremely quiet eyes postoperatively.

In addition to my drug protocol, I still patch my patients' eyes for the first postoperative night. I think this practice is beneficial for reducing the risk of developing a leaky wound and to reduce scratchiness on the first night. I feel that I receive fewer calls from patients when I patch them, and one application gives them coverage for 24 hours.

Dr. Gayton: Dr. Tyson, please share with us some of the cell and flare data from the bromfenac q.d. clinical study.

Dr. Tyson: In the bromfenac q.d. study, the investigators

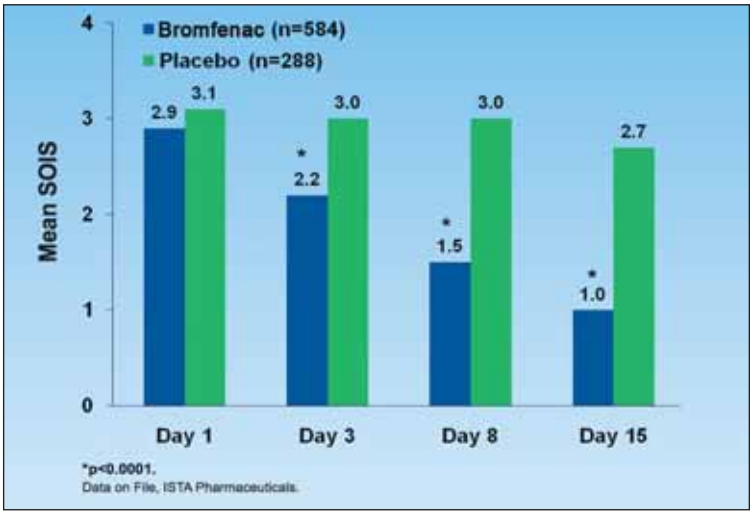

Figure 4. Patients treated with bromfenac showed a clinically significant reduction of inflammation as early as 8 days postoperatively (after 10 drops). At day 15, 51% of the bromfenac subjects achieved complete clearance of inflammation (SOIS of 0), compared to 27% of those treated with placebo. Adapted from: Chandler SP, Henderson BA, Gayton JL, et al. Integrated phase 3 clinical trials of bromfenac sodium ophthalmic solution dosed once daily for ocular surgery. Poster 281 presented at: The AAO/MEACO Annual Meeting; October 17-18, 2010; San Francisco, CA.

initially predosed the patients one day prior to surgery. According to the SOIS scoring, 51% of the patients showed zero cell or flare at day 15, compared with only 27% in the placebo group (Figure 4). Thus, it is a very fast-acting medication. At days 8 and 15, the cell and flare data in the bromfenac group were statistically significantly different from the placebo group.

DURATION OF TREATMENT

Dr. Gayton: One topic receiving a lot of attention recently, due in part to cost-consciousness, is how long postoperatively we should treat patients with NSAIDs. How long do each of you treat your routine cataract patients?

Dr. Tyson: My staff and I pretreat our routine cataract patients with an NSAID and an antibiotic 3 days prior to surgery. Postoperatively, we have patients continue this regimen for 1 month.

Dr. Rowen: I prescribe my routine patients an antibiotic and NSAID for 2 days before surgery and for 5 weeks postoperatively.

Dr. Katsev: I pretreat routine patients with topical azithromycin for 2 weeks preoperatively and with an NSAID and an antibiotic 2 days preoperatively. I have my patients continue this regimen for 4 weeks postoperatively.

Dr. Bacharach: I have my routine patients use bromfenac for 1 day preoperatively and then continue using it after surgery until the bottle is empty. For most people, the bottle lasts several weeks after surgery. For patients who are at risk for CME, such as diabetics, I believe in using a longer course of treatment, such as 4 weeks or more. Particularly if the patient's first eye displayed CME, then I will treat the second eye for a longer time frame.

Dr. Gayton: My staff and I accidently performed a duration-of-therapy study that confirmed in my mind the need for multiple weeks of NSAID therapy. Last year, our representative left us a lot of patient samples of bromfenac NSAID. My staff gave these samples to all our patients. As you can imagine, these patients did not get their prescriptions filled and ran out of the samples after 1 to 2 weeks. Subsequently, I began to notice an increased number of patients presenting with postoperative CME, which I had not seen since we suspended our use of NSAIDs following the generic diclofenac problem. This experience convinced me that we needed to follow a longer course of NSAID therapy. The literature has confirmed that the peak incidence of CME is 4 to 6 weeks postoperatively.[11,12] With modern surgical techniques and with dosing NSAIDs preoperatively, we may not have to prescribe a 6-week regimen in routine patients. Of course, I agree with Dr. Bacharach that high-risk patients warrant a longer course of therapy in order to give them their best possibility of a good visual outcome.

OFF-LABEL APPLICATIONS

The following discussion regards off-label usage of ophthalmic NSAIDs.

Dr. Gayton: Ophthalmic NSAIDs have come of age in their applications beyond perioperative care. What are some off-label uses of NSAIDs that you panelists have found effective? Dr. Bacharach, I understand you are using NSAID drops in conjunction with selective laser trabeculoplasty (SLT)?

SLT

Dr. Bacharach: Yes. For many years, I prescribed patients steroids after SLT, but those drugs inhibit the up-regulation of the cytokine cascade. Then I tried using bromfenac b.i.d. for 4 days after SLT. This therapy significantly reduced the volume of postoperative complaints and unscheduled patient visits I received regarding pain. Thus, I feel that NSAID therapy has been a beneficial adjunct to the SLT procedure.

Dr. Gayton: After hearing you describe this use of NSAIDs about 1 year ago, I also switched to using bromfenac on all my SLT patients. Unquestionably, I hear fewer postoperative complaints, and subjectively, I feel that the therapy may actually enhance these patients' outcomes. Of course, all NSAIDs should work similarly for SLT patients.

PTERYGIUM SURGERY

Dr. Katsev: When I operate on pterygia (which I see frequently in southern California), I still perform a graft. The change in corneal elevation as the graft swells can cause the patient a lot of discomfort. It is important to make sure these individuals lubricate their eyes, and I have found that bromfenac dosed once per day markedly decreases their pain. Any drug that minimizes the pain for these patients is a practice builder. I also use q.d. bromfenac to manage pain in PRK patients. Although I have never seen a corneal melt with brom-

fenac, I feel it should always be considered in these patients if the medication is used chronically.

Dr. Gayton: I have noticed that some pterygium patients develop a corneal dellen postoperatively. Of course, we worry about the possibility of a corneal perforation in these patients. Does that potential concern you when you are using bromfenac q.d.?

Dr. Katsev: I am not concerned about using bromfenac q.d. in eyes that may develop a corneal perforation; I have used it in many of these eyes and have never seen a corneal melt. Again, the most important thing is to lubricate these eyes well. Also, we do not want to completely cover up the pain, because it may help me diagnose a dellen. The bromfenac helps mitigate discomfort, but it does not knock out all of the pain. I tell patients to increase their use of artificial tears when they feel more pain.

PRK

Dr. Rowen: I do not hesitate to use bromfenac in surface ablation procedures. I've been using twice-daily bromfenac with epi-LASIK and PRK, and none of these patients experience postoperative pain. Their eyes remain comfortable until the bandage lens comes off.

Dr. Gayton: Some patients experience severe pain after undergoing PRK. Since I began administering bromfenac postoperatively, my patients have also enjoyed a much more comfortable healing process.

DRY EYE

Dr. Gayton: Dr. Rowen, you and I have been using bromfenac successfully to manage dry eye, although all FDA labeling for NSAIDs says these drugs are contraindicated for dry eye. What has been your experience?

Dr. Rowen: I first tried using NSAIDs in conjunction with topical cyclosporine A (Restasis; Allergan, Inc.), after reading reports in the literature that NSAIDs provided a more immediate inflammatory suppression[13] while the cyclosporine began to work (cyclosporine begins to be effective after approximately 3 months). I first tried loteprednol etabonate ophthalmic suspension 0.5% (Lotemax; Bausch + Lomb, Rochester, NY), but my patients experienced IOP spikes. Then, I tried the b.i.d. formulation of bromfenac, and my patients reported that their eyes felt much more comfortable. Corneal staining with lissamine green and fluorescein confirmed an improvement in the tear film of these eyes. Thus, I began using bromfenac as a drop before the cyclosporine so that the latter would not cause a burning sensation. Many of my patients even said that they liked the bromfenac drop better than the cyclosporine drop. These patients all maintained ocular comfort and their tear film improved.

My colleagues and I were able to conduct a phase 2 study using a lower dose of bromfenac to treat dry eye syndrome. The overall results were very promising.[14] There was a remarkable improvement in the subjects' OSDI scores. They experienced an improvement in both their symptoms and corneal staining with lissamine green. It actually looked like there could be a true treatment benefit beyond just the known analgesic effect.

Dr. Gayton: I was one of the early adopters of using topical azithromycin 1% (Azasite; Inspire Pharmaceuticals, Inc., Durham, NC) to treat blepharitis. Because some patients complained of significant pain upon instillation of the azithromycin, especially early in the treatment, I started giving them a drop of bromfenac 15 minutes prior to the azithromycin. Interestingly, the blepharitis improved more quickly in the patients who received both treatments. I think this benefit was due to less tearing as well as a significant anti-inflammatory effect and improvement of the dry eye from the NSAID.

Over the past year, I developed dry eye myself. I have found that when I feel discomfort, such as mild corneal erosions upon waking, I use a drop of bromfenac early in the morning and feel a significant improvement. I follow the NSAID drop with an artificial tear, and I often will not need further drops for the entire day. The convenience of such infrequent dosing is really nice.

Dr. Gayton: Dr. Tyson, I understand that you also use bromfenac to treat ocular infections in your practice.

Dr. Tyson: My staff and I see a lot of viral conjunctivitis in our area. These patients' eyes are irritated and inflamed, and they are looking for something to control the pain and irritation. Because steroids are contraindicated in such eyes, we started using the q.d. formulation of bromfenac. Soon after, follow-up calls from our conjunctivitis patients ceased. Bromfenac seems to work well at controlling these symptoms while the virus runs its course. We have no hesitation about using bromfenac this way because of its good safety protocol (Table 2).

Dr. Gayton: I am living proof of the problems that can develop after using steroids for viral conjunctivitis. I

TABLE 2. SAFETY OF BROMFENAC OPHTHALMIC SOLUTION

	BROMFENAC SODIUM OPHTHALMIC SOLUTION	
	Pooled Active	**Pooled Placebo**
Safety population (n)	559	278
Subjects with any adverse event, n (%)	196 (35.1)	153 (55.0)
Conjunctival hyperaemia	28 (5.0)	12 (4.3)
Corneal oedema	16 (2.9)	10 (3.6)
Headache	19 (3.4)	3 (1.1)
Lacrimation increased	9 (1.6)	19 (6.8)
Eye pain	27 (4.8)	46 (16.5)
Ocular discomfort	5 (0.9)	7 (2.5)
Eye inflammation	37 (6.6)	45 (16.2)
Eye pruritis	15 (2.7)	6 (2.2)
Ocular hyperaemia	7 (1.3)	23 (8.3)
Foreign body sensation in eyes	28 (5.0)	28 (10.1)
Photophobia	22 (3.9)	45 (16.2)
Intraocular pressure increased	13 (2.3)	5 (1.8)
Vision blurred	19 (3.4)	13 (4.7)

Bromfenac dosed q.d. had a lower overal incidence of adverse ocular events compared with placebo (greater than or equal to 2% incidence). (Adapted from: Chandler SP, Henderson BA, Gayton JL, et al. Integrated phase 3 clinical trials of bromfenac sodium ophthalmic solution dosed once daily for ocular surgery. Poster 281 presented at: The AAO/MEACO Annual Meeting; October 17-18, 2010; San Francisco, CA.

developed epidemic keratoconjunctivitis at age 40 and was steroid-dependent for 2 years. My IOP rose in excess of 60 mm Hg, and I developed bilateral posterior subcapsular cataracts.[15] Thus, I agree with limiting our use of steroids whenever possible. I also use bromfenac drops in patients with epidemic keratoconjunctivitis as well as in those who have corneal foreign bodies. It has been years since I have pressure-patched someone who had a significant abrasion after the removal of a foreign body. Now, I just fit these patients with a bandage contact lens and treat them with bromfenac, an antibiotic, and artificial tears. Frequently, they can return to work the same day. This regimen is certainly a much better treatment than using a pressure patch and an ophthalmic ointment that sometimes gets underneath the epithelial cells.

Dr. Rowen: I use bromfenac for episcleritis and even as an adjunct therapy for allergic conjunctivitis, because many patients have dry eye syndrome as well as allergies. When I prescribe the q.d. formulation of bromfenac for dry eye, patients tell me their eyes do not itch as much from their allergies. When the ocular surface has been affected by chronic inflammation, the effect of the anti-inflammatory agent will be to improve the surface. This allows us a wealth of treatment parameters to use in this new NSAID paradigm.

Dr. Bacharach: There has also been evidence in the literature that using NSAIDs prior to trabeculectomy will reduce the failure rate and encapsulation rate of that procedure.[16] My staff and I have used bromfenac in a few patients who have been on multiple medications

prior to glaucoma surgery, and anecdotally, we have found a decreased rate of encapsulation.

Dr. Katsev: Some cataract patients continue to complain about mild discomfort up to 6 weeks after surgery. If I cannot find a source of the pain, I will put these patients on the once-a-day formulation of bromfenac for 4 weeks and see if the pain subsides. The relief from pain gives these individuals time to heal.[3]

Dr. Gayton: I agree that it is worth trying a course of bromfenac drops to treat nondescript ocular pain. I have had excellent success with that therapy as well. It is interesting to note that we have all chosen to use bromfenac as our NSAID of choice for off-label treatments of ocular surface conditions. Although all NSAIDs might work in these conditions, bromfenac's unique chemistry gives it a variety of advantages in treating ocular surface conditions.

Dr. Tyson, are you using NSAIDs in other applications of glaucoma surgery?

Dr. Tyson: I perform a lot of endoscopic cyclophotocoagulation (ECP). Usually, this procedure does not induce much inflammation, but some patients experience a severe response, where it almost looks like it is snowing inside of the eye. I have changed my treatment course for these patients from a steroid and an NSAID dosed q.d. to b.i.d. treatment with bromfenac and difluprednate 0.05%. This combination has significantly reduced these patients' breakthrough inflammation.

Also, I have seen bromfenac have a surprising effect on toxic anterior segment syndrome (TASS), which can be a sight-threatening pathology if not caught and treated quickly. Therefore, we want to treat TASS with a potent drug that penetrates the eye quickly. I find that the combination of bromfenac and difluprednate shuts down the inflammatory cascade quickly and allows the patient to recover faster.

REFRACTIVE IOLs

Dr. Gayton: One of the most important changes ophthalmology has undergone in the past few years is the adoption of premium refractive IOLs. These lenses have positively affected our patients' lives and enabled us physicians to receive fair compensation for our time and expertise. How does the use of NSAIDs coincide with these implants?

Dr. Rowen: Through personal experience, I have found that any corneal surface abnormality significantly compromises the performance of presbyopia-correcting lenses. Therefore, it is important to test these eyes preoperatively for dry eye and any irregularities in staining patterns on the cornea. We may need to delay implanting these lenses to treat the corneal surface first. NSAIDs can be used as part of this therapy, as we have already described.

Dr. Katsev: I was involved in the Wittpenn study[17] that examined the implantation of multifocal IOLs in healthy eyes. All my multifocal lens patients received an optical coherence tomography (OCT) scan, because I did not want to implant the lens if they had an epiretinal membrane or CME. In Wittpenn's study on ketorolac, a significant number of subjects developed some type of OCT thickening that was presumed to be early CME, and it affected their results. The patients may have seen 20/20 postoperatively, but they were not 20/happy. Implanting a multifocal lens in an eye with CME is a disaster, and elective IOL recipients are more critical of their results because they are paying out of pocket. It is important that we provide these patients with NSAIDs.

Dr. Gayton: How long do you treat your premium IOL recipients?

Dr. Katsev: The same as my routine cataract patients: I treat them for 3 days preoperatively and for 4 weeks postoperatively.

OTHER NSAIDs

Dr. Gayton: I have used and lectured on all of the ophthalmic NSAIDs since Novartis developed diclofenac 0.1%. In my experience, all of the NSAIDs work. I personally prefer bromfenac because of its safety, efficacy, and the convenience of its dosing. What is the panel's opinion?

Dr. Katsev: The first clinical study I participated in was examining papillary dilation with flurbiprofen 0.03%. The study concluded that the NSAID did not increase pupillary dilation but that it lessened their constriction during surgery. I continued to use flurbiprofen for a few years until other NSAIDs were developed. If a patient reports allergies to a preservative, I use ketorolac tromethamine 0.45%, the only preservative-free NSAID. Although I have never witnessed a corneal melt with bromfenac, this problem has occurred with other NSAIDs and should always be considered a possibility.

Dr. Rowen: I was also involved in the studies of the brand-name diclofenac in the 1990s. As I mentioned previously, my colleagues and I performed a retrospective analysis in a large practice that found that the incidence of CME was remarkably reduced with pretreatment of the drug. Based on these findings, I was committed to the use of NSAIDs early on, and I pretreated my patients for 2 days preoperatively. I have seen the clinical evidence that topical NSAIDs control surgical inflammation and make patients much more comfortable during their postoperative recovery. They are also easy for patients to use and rarely, if ever, induce side effects. I also prefer bromfenac for my patients, as it is the most potent, efficacious, and comfortable NSAID I have ever used. The ease of the once-daily formulation will be an added bonus to improve patient compliance.

Dr. Bacharach: Most ophthalmologists have had to use generic "equivalents" of NSAIDs at some time, unfortunately, due to managed-care formularies. My patients have complained of stinging and burning when they have had to use a generic NSAID. As a clinician, I am concerned that there can be up to 10% of discrepancy in the active molecule between generics and branded drugs, and I also distrust potential buffers and other parts of the vehicle that are allowed in generic formulations. Obviously, I prefer to use brand-name drugs whenever possible so that I am assured of their quality.

Dr. Gayton: I agree completely. I have participated in studies on all of the branded NSAIDs and found that they all work. The primary reason I prefer bromfenac is because it provides rapid control of inflammation, and there is less medication in the drop. Consequently, I have found this NSAID to be kinder to the corneal surface, which I believe is due to the reduced amount of both the medication and the total amount of BAK. It also had a significant analgesic effect, and it induces less reflex tearing because it does not sting the cornea.

Thank you all for your time. ■

1. Vasavada A, Singh R. Phacoemulsification in eyes with a small pupil. *J Cataract Refract Surg*. 2000;26(8):1210-1218.
2. True extent of NSAID problems now becoming clearer. *Ocular Surgery News*. February 1, 2000. http://www.osnsupersite.com/view.aspx?rid=13937. Accessed March 9, 2011.
3. Donnenfeld ED, Holland EJ, et al. Global experience with Xibrom (bromfenac sodium ophthalmic solution) 0.09% Study Group. Bromfenac ophthalmic solution 0.09% (Xibrom) for postoperative ocular pain and inflammation. *Ophthalmology*. 2007;114(9):1653-1662.
4. Loewenstein A, Zur D. Postsurgical cystoid macular edema. *Dev Ophthalmol*. 2010;47:148-159.
5. Jones J, Francis P. Ophthalmic utility of topical bromfenac, a twice-daily nonsteroidal anti-inflammatory agent. *Expert Opin Pharmacother*. 2009;10(14):2379-2385.
6. Bromday prescribing information, ISTA Pharmaceuticals, Inc. http://www.istavision.com/pdf/BromdayPI1016.pdf
7. Chandler SP, Henderson BA, Gayton JL, et al. Integrated phase 3 clinical trials of bromfenac sodium ophthalmic solution dosed once daily for ocular surgery. Poster 281 presented at: The AAO/MEACO Annual Meeting; October 17-18, 2010; San Francisco, CA.
8. Waterbury LD, Silliman D, Jolas T. Comparison of cyclo-oxygenase inhibitory activity and ocular anti-inflammatory effects of ketorolac tromethamine and bromfenac sodium. *Curr Med Res Opin*. 2006;22(6):1133-140.
9. Baklayan GA, Patterson HM, Song CK, et al. 24-hour evaluation of the ocular distribution of (14)C-labeled bromfenac following topical instillation into the eyes of New Zealand White rabbits. *J Ocul Pharmacol Ther*. 2008;24(4):392-398.
10. Maxwell WA, Reiser HJ, Stewart RH, et al. Nepafenac dosing frequency for ocular pain and inflammation associated with cataract surgery. *J Ocul Pharmacol Ther*. 2008;24(6):593-599.
11. Jaffe NS, Luscombe SM, Clayman HM, et al. A fluorescein angiographic study of cystoid macular edema. *Am J Ophthalmol*. 1981:92:775.
12. Berrocal JA. Incidence of cystoid macular edema after different cataract operations. *Mod Probl Ophthalmol*. 1977;18:518-520.
13. Cakanac, CJ. What's new with NSAIDs and steroids. *Review of Optometry*. 2007. http://www.revoptom.com/content/d/news_review/c/15457/. Accessed March 9, 2011.
14. Chandler SP, Rowen SL, Sher NA, et al. Bromfenac ophthalmic solution for treating the signs and symptoms of dry eye disease. Poster presented at: The Tear Film and Ocular Surface Society Meeting; September 22-25, 2010; Florence, Italy.
15. Bernstein HN, Mills DW, Becker B. Steroid-induced elevation of intraocular pressure. *Arch Ophthalmol*.1963;70:15-18.
16. Khaw PT, Occleston NL, Schultz G, et al. Activation and suppression of fibroblast function. *Eye* (Lond).1994;8(Pt 2):188-195.
17. Wittpenn JR, Silverstein S, Heier J, et al; Acular LS for Cystoid Macular Edema (ACME) Study Group. A randomized, masked comparison of topical ketorolac 0.4% plus steroid vs steroid alone in low-risk cataract surgery patients. *Am J Ophthalmol*. 2008;146(4):554-560.

The Evolving Role of NSAIDs in Cataract Surgery

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1. The once-daily formulation of bromfenac is stronger than the twice-daily formulation.

a. True

b. False

2. Generic formulations of NSAIDS are the same as the branded formulations.

a. True

b. False

3. Which two are potential benefits of using a once-daily NSAID drop versus a drop with b.i.d. or t.i.d. dosing?

a. Improved compliance, less expensive

b. Improved compliance, decreased toxicity

c. Improved compliance, improved analgesic effect

d. Improved analgesic effect, less expensive

4. Studies have shown that a variety of off-label surgical procedures could benefit from an NSAID drug regimen. Which of the following is not a potential off-label use for a topical NSAID?

a. PRK

b. Dry eye

c. Pterygium

d. Herpes simplex virus

5. NSAIDs are primarily indicated for pain and inflammation following cataract surgery. However, which of the following has been shown in the literature to be one of the most important off-label uses?

a. To decrease dry eye

b. To prevent corneal melting

c. To decrease the risk of a retinal detachment

d. To decrease the risk of cystoid macular edema

6. Why is halogenation of a molecule beneficial?

a. It makes it last longer before breaking down

b. It makes a molecule more potent by enabling it to more effectively bind to the enzyme it is to block

c. It causes a halogen particle to be removed from a molecule, accelerating reactions

d. It allows the molecule to introduce functional groups onto the benzene ring

7. The prophylactic use of NSAIDs is based on the rationale that these drugs inhibit the production of cyclo-oxygenase and thereby protect ocular blood vessels that are susceptible to inflammation.

a. True

b. False

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