Prevention of Pseudophakic Cystoid Macular Edema

KEITH A. WALTER, MD  Thanks to today’s microsurgical techniques, sophisticated intraocular lenses (IOLs), and antiinflammatory drugs, cataract surgery patients often go into surgery expecting marvelous results. Many hope to achieve freedom from glasses altogether. And while these results are certainly possible—and frequently achieved—postoperative vision may still be compromised by a variety of conditions, one of which is pseudophakic cystoid macular edema (CME). Now more than ever, preventing CME is a priority for cataract surgeons.

Pseudophakic CME, which affects thousands of Americans each year, is the leading cause of unexpected vision deterioration following cataract surgery. Estimates of its incidence vary, influenced by a range of factors including characteristics of the population studied, prophylactic antiinflammatory regimen, criteria used to define CME, and timing of the examination following surgery. Overall, somewhere between 0.1% and 4% of patients who undergo routine small incision phacoemulsification surgery with IOL implantation develop clinical CME.1-5

A higher proportion of patients develop detectable macular edema without associated symptoms. Studies that have examined pre- and post-surgical macular appearance (regardless of patients’ symptoms) have found rates of subclinical CME of 4% to 11% by optical coherence tomography (OCT) and 9% to 19% by fluorescein angiography.2,4

The apparent discrepancy between the numbers in the clinical and subclinical categories can be better understood by examining the composition of the latter group. First, some patients with OCT evidence of CME are truly subclinical, with no symptoms, no visual aberrations, and near normal visual acuity. Such patients may have swelling due to minor vessel leakage.3 Other patients may notice a small amount of visual loss but don’t feel the need to report it or it simply goes unnoticed because it pales in comparison to the dramatic overall improvement from the surgery.

Conceivably, a third category of “subclinical” patient might be more accurately characterized as simply “undiagnosed.” Patients expect their surgery to be uneventful; and since most cases of subclinical CME resolve spontaneously over weeks to months, surgeons may be tempted to reassure patients...
TOPICS IN OCULAR ANTIINFLAMMATORIES, ISSUE 1

STATEMENT OF NEED

The indications for topical ophthalmic antiinflammatory drugs (both steroidal and nonsteroidal) are evolving rapidly, as new agents and new applications emerge. Many of these are novel—e.g., the perioperative use of nonsteroidal antiinflammatory drugs (NSAIDs) to prevent cystoid macular edema—and/or fly in the face of older thinking—e.g., the use of steroids to calm inflammation and reduce the risk of melting or scarring from infection. Neither of these important applications is on-label.

In addition, new steroidal and nonsteroidal agents continue to come to market, expanding the utility of both classes. Antiinflammatory drop regimens are now used for: the treatment of ocular surface disease and allergic conjunctivitis; prevention of perioperative pain and inflammation in ocular surgery; infection management; cystoid macular edema prophylaxis following cataract surgery; haze prevention in PK; and much more. What has regrettably not followed this expansion of indications, formulations, and new mechanisms are protocols for drug selection and use. These are vital because significant differences in safety, tolerability, and efficacy exist between and within both antiinflammatory drug classes. C-20 ester steroids, for example, have demonstrated a lower risk of intraocular pressure (IOP) elevation than ketone steroids. Since a range of steroid formulations exists for a variety of indications, clinicians need up-to-date information about the indications and optimum uses for each.

Although topical NSAID formulations have been associated with a reduction in anterior chamber (keratopathy ranging from superficial punctate keratits to corneal melt), recent work shows these to be uncommon and less severe with newer steroids. Indications for novel NSAIDs make use of lower concentrations and less frequent dosing, potentially impacting safety profiles and reducing risk from long-term use.

Although both are “antiinflammatory” steroids and NSAIDs act at different points in the inflammatory cascade, and thus offer opportunities for physicians to fine-tune their drug selection. And although they are frequently used together, whether or not the two drug classes can act synergistically is controversial. In the context of recent clinical data, a clear mechanistic understanding of each drug class generally—and of newer formulations specifically—will equip clinicians to make effective, evidence-based prescribing decisions across the many situations that call for ocular inflammation control.

REFERENCES


OFF-LABEL USE STATEMENT

This work discusses off-label uses of antiinflammatory medications.

GENERAL INFORMATION

This CME activity is sponsored by the University of Florida College of Medicine and is supported by an unrestricted educational grant from Bausch + Lomb, Inc. and Abbott Medical Optics.

Directions: Select one answer to each question in the exam (questions 1–10) and in the evaluation (questions 11–16). The University of Florida College of Medicine designates this activity for a maximum of 1.0 AMA PRA Category 1 Credit™. There is no fee to participate in this activity. In order to receive CME credit, participants should read the report and take the posttest. A score of 80% is required to qualify for CME credit. Estimated time to complete the activity is 60 minutes. On completion, tear out or photocopy the answer sheet and send it to:

university of Florida CME Office
PO Box 102033, Gainesville, FL 32610-0233
PHONE: 352-733-0064 FAX: 352-733-0007

You can also take the test online at http://cme.ufl.edu/toai.

Or you can take the test online at http://cme.ufl.edu/toai.

System requirements for this activity are: For PC users: Windows® 2000, XP, 2003 Server, or Vista; Internet Explorer® 6.0 or newer, or Mozilla® Firefox® 2.0 or newer (JavaScript™ and Java™ enabled). For Mac users: Mac OS® X 10.4 (Tiger®) or newer; Safari® 3.0 or newer, Mozilla® Firefox® 2.0 or newer; Java® 1.4 or newer. Internet connection required: Cable modem, DSL, or better.

DATE OF ORIGINAL RELEASE

August 2013. Approved for a period of 12 months.

ACCREDITATION STATEMENT

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCE) through the joint sponsorship of the University of Florida College of Medicine and Candeo Clinical/Science Communications, LLC. The University of Florida College of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

The University of Florida College of Medicine designates this educational activity for a maximum of 1.0 AMA PRA Category 1 Credit™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

FACULTY AND DISCLOSURE STATEMENTS

Lisa A. Abisher, MD

Lisa A. Abisher, MD, is a consultant to Eyecare Products, Inc., Alcon Laboratories, Inc., Bausch & Lomb, Inc., and Abbott Medical Optics. She states that in the past 12 months, she has participated in a stand-alone B+L advisory board meeting.

Penny A. Asbell, MD, FACS, MBA (Faculty Advisor), is a professor of ophthalmology and director of the cornea and refractive services at Icahn School of Medicine at Mount Sinai. She states that in the past 12 months, she has been as consultant for R-Tech, Senju, and B+L, has given CME lectures for Merck, and has received a research grant from Alcon.

William E. Smiddy, MD (Faculty Advisor), is a professor of Ophthalmology at the Bascom Palmer Eye Institute, University of Miami Miller School of Medicine. He states that in the past 12 months, he has attended a steering committee meeting of Alimera Scientific.

Pruvin U. Dugel, MD, is managing partner of Retinal Consultants of Arizona. Pruvin is a clinical associate professor of ophthalmology, Ophthomy Eye Institute, Keck School of Medicine at the University of Southern California, Los Angeles. He states that in the past 12 months, he has served as a consultant to Allergan, Alcon, AMO, Eisai, Genentech, and Heidelberger Diagnostics.

Terrence P. O’Brien, MD, is a professor of ophthalmology, Charlotte Breyer Rodgers Distinguished Chair and director of corneal microbiology at the Bascom Palmer Eye Institute of the University of Miami School of Medicine in Palm Beach, FL. Dr. O’Brien has served as a non-salaried ad hoc consultant to Alcon, Allergan, Bausch + Lomb, Nicois, Omeros, Rapid Pathogen Screening, Inc, and Santen.

Keith A. Walter, MD, is an associate professor of ophthalmology at Wake Forest University. He states that in the past 12 months, he has served as a consultant for Bausch + Lomb and Abbott Medical Optics and as a member of the Bausch + Lomb speakers bureau.

DISCLAIMER

Participants have an implied responsibility to use the newly acquired information to enhance their patient outcomes and professional development. The information presented in this activity is not meant to serve as a guideline for patient care. Procedures, medications, and other courses of diagnosis and treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patients’ conditions and the risks and benefits of the procedures or devices in use, applicable manufacturer’s product information, and comparison with recommendations of other authorities.

COMMERCIAL SUPPORTERS

This activity is supported by an unrestricted educational grant from Bausch + Lomb, Inc.
fluorescein angiography or OCT, which is less invasive and currently the more popular option. OCT typically reveals mild to moderate thickening or even a cystic space in the macula, evidence of CME.3,5 (Technically, cysts should be present to meet the definition of CME.)

MECHANISM AND RISK

CME is thought to result from multiple processes that culminate in the development of a fluid-filled cyst within the macula; inflammation plays a primary role.1 Surgery (of any type) causes damage to cell membranes, which releases phospholipids and leads to activation of phospholipase. This is the start of a series of chemical events that leads eventually to the production and release of prostaglandins. The resulting prostaglandins (and other mediators) can migrate from the front to the back of the eye, where they may cause increased vascular permeability, compromise the integrity of the blood–ocular barrier, and allow pooling of fluid in the outer layers of the retina.3,4

The risk of developing CME following ocular surgery is increased in patients with certain ocular comorbidities or intraoperative factors.5 Ocular conditions that disrupt retinal homeostatic mechanisms—including diabetic retinopathy, age-related changes, hypertension, epiretinal membrane, and retinal vein occlusion—increase the risk of further disruptions induced by surgical inflammation.1,3,5

Other patients at increased risk of CME include diabetics (with or without retinal pathology) and patients with acute uveitis, a history of CME in the fellow eye, or preoperative exposure to prostaglandin analogs (typically used for IOP control in glaucoma).3,5

Complicated surgery with additional tissue manipulation is also associated with increased inflammation and CME risk. Problematic events include iris trauma, broken posterior capsule, vitreous prolapse, retained lens fragments, and prolonged surgical time.1,3

ANTINFLAMMATORY PROPHYLAXIS

Pre- and postoperative treatment with antiinflammatory drops is now standard in many centers to reduce surgically induced inflammation and CME risk. Corticosteroids are the most commonly used; they work by penetrating into the nucleus and binding DNA receptors to shut down the formation of arachidonic acid. They prevent the formation of prostaglandins by blocking arachidonic acid formation in the very first stages of the inflammatory cascade. Steroids present considerable downsides, however. Steroids are lipophobic, which limits their ability to reach their target. A second problem is that most steroid formulations are suspensions that require patients to shake the bottle numerous times for the active agent to distribute properly within the supernatant. This can be difficult for some elderly patients to do. A third factor relates to compliance. Steroids may require dosing 4 (or more) times per day, and many patients do not remember to use them that frequently. Because of these limitations, many surgeons have turned to NSAIDs to control inflammation and prevent CME.

NSAIDs work in the cytoplasm where they directly inhibit COX-1 and COX-2 enzymes, blocking prostaglandin synthesis. NSAIDs are lipophilic and pass readily through the cell membrane to their target. Halogenated NSAIDs are even more lipophilic; the bromine atom at the C-4 position of bromfenac, for example, enhances its lipophilicity and cell penetration, as well as its ability to block COX-2.6 Even though formulated at low concentration (0.07%), it is still approved for once-a-day dosing, with the same clinical activity as higher concentration (0.09%).7 The recent reformulation of nepafenac—in this case raising its concentration—also allows once-a-day dosing.

NSAID-ONLY PROPHYLAXIS

Many surgeons regard NSAIDs and steroids as synergistic and use both for inflammation control after cataract surgery. This practice stems from studies showing that adding an NSAID to a steroid-based regimen reduced inflammation more effectively than a steroid alone.8-10 But these studies lacked an NSAID-only arm, so we were not able to learn what an NSAID might be capable of on its own.

As newer research continues to demonstrate advantages to NSAID monotherapy for antiinflammatory prophylaxis, a paradigm shift could be underway.11-14 Seeing that generic steroids were often substituted for name brands, possibly affecting the efficacy of combination prophylaxis, I began using an NSAID-only approach (with bromfenac) in 2010. Our study suggests that bromfenac alone is at least equivalent to steroids in the control of postsurgical inflammation and prevention of CME. Initiating NSAID therapy 2 days before surgery inhibits intraocular COX-1 and COX-2 production well before any tissue insult occurs. My current practice is to use only the NSAID in all patients regardless of CME risk. It is given once a day starting 2 days before surgery and continued for approximately 30 days afterwards. In my experience, patients’ eyes appear as quiet the day after surgery as they were when I used steroids; and I have seen only one case of CME in the last 1,300 eyes.
STUDY RESULTS

Our research also supports the use of NSAID alone to control inflammation. My colleagues and I studied two groups of patients who underwent cataract surgery at our institution before and after our switch to NSAID-only prophylaxis: group A included 200 surgeries between January and August 2010 in which patients received postsurgical prednisolone acetate 1% (four times daily for 2 weeks followed by a 3 week taper); group B included 200 eyes operated on between September 2010 and May 2011 who received only bromfenac 0.09% either once or twice daily beginning 2 days prior to surgery through 4 weeks after. Approximately 20% of eyes in group A received adjunctive NSAID due to risk factors such as diabetes.15

CME rates were low in both groups; there were two cases of CME (1%) in group A and one case (0.5%) in group B. Best corrected visual acuity and measures of inflammation (anterior chamber cell and flare) were equivalent between the groups. After correcting for two cases of retained lens fragment, a higher proportion of steroid-exposed patients developed elevated IOP compared to those exposed to NSAID only: 8% vs 2.5%, respectively (P = 0.02).15

Small studies of other NSAIDs, including diclofenac and nepafenac, have demonstrated efficacy comparable to steroids for preventing CME.12,13 There are presently three ophthalmic NSAIDs available on the US market that are approved for once daily dosing: bromfenac 0.09% and 0.07% and nepafenac 0.3%, the latter being a tripled concentration formulation of its NSAIDs available on the US market that are approved for just 1% of patients.

Even those surgeons who routinely use NSAID-only prophylaxis may sometimes find an adjunctive steroid helpful for patients with pain or evidence of inflammation on follow-up examination. Since switching to NSAID-only prophylaxis, my group has prescribed adjunctive steroid in 1% of patients.

CONVENIENCE, COMPLIANCE, AND COST

Simpler dosing regimens have eased the burden of remembering to take drops for patients and their families. Patients no longer have to create elaborate charts, and children or grandchildren providing care for an older family member are less burdened by repeated dosing. Compliance is enhanced because patients feel as if they can handle what is being asked of them; the family is happier; and the results are the same as with more complicated regimens.

Concerns about cost are almost universal among patients. Simplifying the prophylactic regimen helps reduce the number of patient co-pays, easing their financial burden. Since I prescribe a branded drug, I preempt callbacks by preparing patients for the cost of their medication. This brief conversation goes a long way in managing expectations.

CONCLUSION

For many cataract surgery patients, an NSAID alone may provide adequate and effective antiinflammatory prophylaxis. The advantages of NSAID monotherapy include increased safety and convenience compared to steroids.

REFERENCES

7. Prolensa® (bromfenac ophthalmic solution) 0.07% product information. Tampa, FL: Bausch and Lomb; 2013.
16. Ilevro (nepafenac ophthalmic suspension) 0.3% product information. Fort Worth, TX: Alcon; 2012.
17. Nevanac (nepafenac ophthalmic suspension) 0.1% product information. Fort Worth, TX: Alcon; 2011.
18. Bromday® (bromfenac ophthalmic solution) 0.09% product information. Tampa, FL: Bausch and Lomb; 2012.
New Perspectives on Ocular Antiinflammatory Drugs

TERRENCE P. O’BRIEN, MD, AND PRAVIN U. DUGEL, MD

Although inflammation is a normal physiologic response to injury, in a delicate tissue like the eye an overly robust or misplaced inflammatory reaction can lead to tissue destruction, ocular disease and loss of vision. A variety of pharmacotherapeutic agents from several classes are available to tame ocular inflammation, and new corticosteroids and NSAIDs—with fresh capabilities and formulations—have recently received approval for ophthalmic use. More exciting, innovative immunomodulators, entirely new classes of agents for the control of ocular inflammation, like selective glucocorticoid receptor agonists (SEGRAs), as well as novel biologic response modifiers are in the pipeline.

While we like to think of the eye as a series of compartments—the ocular surface, the anterior segment, and the posterior segment—these “compartments” are far from watertight, and inflammatory mediators formed in one compartment can easily affect adjacent tissues. We see this in uveitis when an inflamed uveal tract extends its effects to multiple ocular tissues or, more commonly, when mediators from focal inflammation in response to cataract surgery diffuse to the back of the eye where they can interfere with the integrity of the blood-ocular barrier, leading to postoperative cystoid macular edema (CME) or chronic uveitis.

Anatomical compartmentalization remains useful as a basis for thinking about the eye and for understanding and managing the wide range of inflammatory conditions ophthalmologists endeavor to prevent and/or treat. We shall make use of it in the following brief review of the sources of ocular inflammation and current and coming ocular antiinflammatory agents for management thereof.

SOURCES OF INFLAMMATION

The systematic evaluation of the ocular inflammation involves three steps: 1) identifying the tissue that is inflamed, 2) determining the cause of the inflammation (in particular, whether that cause is infectious), and 3) determining whether the ocular inflammation is primary or the result of an underlying systemic condition.

Inflammation of the ocular surface can have several causes: allergy, infection, toxins and trauma, including injury related to ocular surgery. The complex group of conditions that can produce dry eye disease are a common cause of ocular surface inflammation. In addition, chronic ocular surface irregularities, such as pinguecula and pterygia, can sometimes become inflamed.

Within the eye, conditions associated with significant inflammation include episcleritis, anterior scleritis, and anterior uveitis (iritis, iridocyclitis or pars planitis), which may originate from toxin exposure, infection, injury or autoimmune disease. Iritis, for example, may be an isolated occurrence or related to a systemic autoimmune process such as rheumatoid arthritis. Similarly, intermediate uveitis may occur in isolation, as may happen in younger people, or secondary to a systemic process such as multiple sclerosis.

Inflammation of the retina may be due to a broad range of conditions. When it occurs, the first task is to discern whether the inflammation is primary or secondary. For example, retinitis related to acute retinal necrosis is a primary condition originating in the retina. On the other hand, uveitis involving multiple compartments including the retina, eg, choriorétinitis, or the vitreous, vitritis, could represent secondary involvement.

Although perhaps not primarily inflammatory in etiology, several common diseases of the retina, including diabetic retinopathy and age-related macular degeneration, are thought to have inflammatory components.
**APPROACHING ANTIINFLAMMATORY TREATMENT**

Medical treatment of inflammation begins with an attempt to target the underlying cause. When an active infection is the cause, antimicrobial agents can decrease inflammation by eliminating the inciting infection. (Even after the infectious organisms have been eliminated, however, endotoxins left behind can continue to incite inflammation.) For non-infectious ocular surface inflammatory conditions like dry eye, lubricating drops can make eyes more comfortable by restoring physiologic osmolarity, reducing friction between the ocular surface and the lid, limiting tissue damage and removing a source of inflammation. Although their action is indirect—lubricating drops reduce friction, which means less tissue damage, which means less incitement to inflammation—these drops can be said to be effectively “antiinflammatory.”

An ideal antiinflammatory agent for treating the ocular surface and anterior chamber would have several characteristics. First, its formulation should make it comfortable to apply, so that patients are not bothered by taking it and will comply with their regimen given excellent tolerability. Drug formulation also determines viscosity and pH, factors that can influence absorption and penetration. Higher viscosity can result in greater retention time on the ocular surface thus allowing increased contact time for enhanced penetrability across the corneal epithelial barrier.

Ideally, a topical antiinflammatory agent would also have analgesic properties, as the surface of the eye is abundantly supplied with sensory nerve endings, making it exquisitely sensitive to pain. The analgesic effect improves comfort while the anti-inflammatory action takes place. Of course, antiinflammatory agents should be nontoxic to ocular cells with excellent biocompatibility. Ideally, they would also contain some of the molecules present in tears and serum that promote healing.

**TOPICAL DROPS AND INTRAOCULAR STRUCTURES**

Topically administered drug can penetrate the cornea to reduce inflammation in the anterior chamber, including the iris, providing one route to the intraocular space. However, rapid reduction of intraocular inflammation is essential to limit damage and preserve or reestablish the blood-ocular barrier. To achieve these ends, two additional drug delivery routes are available, with selection based on the compartment to be reached. Periocular (subconjunctival or sub-Tenon’s) injection creates a depot of drug adjacent to the sclera that can gradually diffuse out to achieve tissue concentrations that cause immunosuppression in nearby compartments and spaces. Intravitreal injection provides a bolus of drug directly into the posterior cavity that can act immediately and sometimes last over the course of 7 to 10 days in the posterior eye. Typically the drug of choice for injection is a longer-acting corticosteroid. Of note, no corticosteroid agent has received FDA approval for intravitreal treatment of uveitis, so the choice of an (off-label) drug must be based on other factors. Triamcinolone acetonide is readily accessible, cost effective, and therefore commonly used for intravitreal antiinflammatory therapy.

Systemic antiinflammatory delivery via oral or intravenous routes may be necessary for severe or recalcitrant cases, although this route risks limitation of effective absorption into ocular tissues and potential creation of systemic side effects. Systemically administered steroids have measured low bioavailability in the eye.

**FIGURE 1** The root from insult to inflammation via prostaglandin and thromboxane biosynthesis. (Adapted from Cho, et al 2009, reference 8.)

- **COX** = cyclooxygenase; **Coxibs** = COX-2 inhibitors; **PG** = prostaglandin; **ASA** = aspirin; **NSAIDs** = nonsteroidal antiinflammatory drug; **TXA** = thromboxane A2

**ANTIINFLAMMATORY CLASSES**

Agents with direct antiinflammatory action fall into one of four principle categories, of which corticosteroids and nonsteroidal antiinflammatory drugs (NSAIDs) are the two most clinically relevant groups in ophthalmology. A third antiinflammatory class, selective glucocorticoid receptor agonists (or SEGRAs) is emerging. SEGRAs are neither steroid nor NSAID. The fourth category includes immunomodulators (eg, cyclosporine, tacrolimus) that act on immune cells rather than specific enzymes or receptors.

**STERoids**

Corticosteroids have been used in medicine for over 50 years to reduce inflammation and treat conditions of excess immunological activity. Corticosteroids block multiple steps in the inflammatory cascade, including the conversion of membrane-bound phospholipids into arachidonic acid that is catalyzed by phospholipase A (Figure 1). Topical corticosteroids—including prednisolone acetate, prednisolone phosphate, loteprednol etabonate, dexamethasone, fluorometholone, rimexolone, difluprednate, and others—are mainstays for controlling inflammation related to surgically induced trauma.

Newer ophthalmic steroids have been structurally modified to improve upon certain properties of their parent molecules. Dual fluorination of C-6 and C-9 atoms increases the binding specificity of difluprednate ophthalmic emulsion.
Relative to steroids, NSAIDs work further downstream in the inflammatory cascade where they inhibit the enzymes cyclooxygenase (COX) 1 and 2. Acting at that point in the cascade, they block the conversion of arachidonic acid to prostaglandins (Figure 1). COX is primarily expressed in the anterior segment including the iris and ciliary body. COX-1 is constitutive, meaning it is always present and active whereas COX-2 is inducible, becoming upregulated during trauma. Topical ophthalmic NSAIDs include diclofenac, ketorolac, nepafenac, and bromfenac.

Ocular NSAIDs (and steroids as well) are most frequently prescribed to control and prevent inflammation caused by ocular surgery. In ocular surgery cell membranes are damaged causing arachidonic acid to be released. In intraocular surgeries, such as cataract surgery, arachidonic acid in the anterior chamber stimulates the formation and release of prostaglandins, followed by a predictable sequence of events: leukocyte migration, increased vascular permeability, and protein accumulation in the aqueous humor, all of which leads to ocular erythema, chemosis, and pain.

Some patients are at greater risk for inflammation than others: those whose surgeries take longer and/or involve more manipulation of the iris; younger patients (who tend to have a more robust inflammatory response than older patients); patients with prior history of eye surgery or of ocular inflammatory disorders, such as uveitis; non-Caucasian race; diabetic patients; and patients with brown irides.

NSAIDs, which may be given prior to surgery, provide a means to interrupt this cycle before it begins, limiting prostaglandin formation and keeping the proverbial “horse from leaving the barn.” In addition to reducing inflammation and potentially preventing CME, perioperative NSAIDs perform two additional functions: they provide analgesia that supplements anesthetic agents, and they sustain intraoperative pupillary mydriasis, further reducing the risk of surgical complications. NSAIDs are also often co-administered with corticosteroids following surgery to control pain and inflammation and to treat CME should it develop. In contrast to steroids, NSAIDs do not increase risk for infection, development of cataract or raised IOP.

(EDITOR’S NOTE: Many ophthalmologists today start steroids preoperatively and claim that the eyes are quieter on day one. Of note, steroids also fortify tight junctions between endothelial cells, theoretically reducing the likelihood of edema [although this is not strictly an antiinflammatory effect, and NSAIDs have no such action].)

**SEGRAS**

Selective glucocorticoid receptor agonists (SEGRAs) comprise a class of experimental compounds in development for the treatment of chronic ocular inflammation and other inflammatory disorders. The aim in developing them is to improve on the therapeutic index of steroids. These molecules are structurally similar to steroids and bind the same glucocorticoid receptor (GR) that is ubiquitous in cells. SEGRAs are not steroids, however, in that, once bound to the GR, they modulate genes differently, ie, more selectively. By virtue of their design, SEGRAs maintain the transrepressive actions of steroids, which underlie their antiinflammatory efficacy, but are “dissociated” from transactivation, which is thought to underlie side effects such as increased IOP and cataract formation.

In vitro studies have shown that the experimental SEGRA mapracorat is associated with reduced expression of mammalian myocilin, a trabecular meshwork protein the production of which is boosted by steroids. This may represent the mechanism of steroid-induced glaucoma. Studies in rabbits have shown a reduced propensity to increase IOP with mapracorat compared with dexamethasone. Mapracorat is in development for the treatment of dry eye (phase 2) and post-cataract surgery inflammation (phase 3).

**IMMUNOMODULATORS**

Immunomodulatory agents do not bind receptors; rather they work directly or indirectly on lymphocytes, neutrophils, macrophages, and other effector cells of the immune system. Topical cyclosporine is a T-cell modulator that reduces inflammation on the ocular surface associated with dry eye. Cyclosporine has been shown to increase aqueous tear production as well as improve tear film stability in patients with meibomian gland dysfunction.

Tacrolimus is another T-cell modulator but with greater potency and different pharmacokinetics compared to cyclosporine. Although not FDA approved, tacrolimus has been useful in the treatment of severe inflammatory ocular surface diseases, including atopic keratoconjunctivitis, cicatrizating conjunctivitis, necrotizing scleritis, and Mooren’s ulcer.

**BIOLOGICS**

Biologic response modifiers (often referred to as biologics) are proteins produced by recombinant DNA or monoclonal
antibody technology designed to block specific mediators of the cell-mediated immune response. These biologic agents have been used with considerable success in managing challenging uveitic conditions, thereby reducing the need for chronic corticosteroids.8,16-17

Systemic biologics, including TNF-alpha inhibitors, are potent immunosuppressives, and are not recommended for the treatment of infectious uveitis. Class effects of such biologics include risk of serious infection, most significantly reactivation of tuberculosis and fungal infections, as well as increased risk of malignancy.

Biologics are potent new medications that may benefit some patients with refractory noninfectious posterior uveitis. Side effects of biologics are common and can be potentially serious. Cost is also significantly greater than steroids and can be a limiting issue. Biologics are typically reserved for patients for whom the potential benefits outweigh the risks and justify the costs of these potent agents.

LOOKING AHEAD

Human amniotic membrane, as a transplant or bandage contact lens, has been used as a means of treating ocular surface burns, severe dry eye, severe bacterial keratitis, and other diseases of the cornea that have a significant inflammatory component.17,20 The success of human amnion, at least in part, derives from the wealth of natural immunosuppressive factors it contains and its low immunogenicity. In the future, the ability to identify, extract, and formulate critical bioactive components of amniotic membrane tissue could pave the way for new classes of very potent natural antiinflammatory agents to manage ocular surface disorders.

Terrence P. O’Brien, MD, is a professor of ophthalmology, Charlotte Breyer Rodgers Distinguished Chair and co-director of ocular microbiology at the Bascom Palmer Eye Institute of the University of Miami School of Medicine in Palm Beach, FL. Dr. O’Brien has served as a non-salaried ad hoc consultant to Alcon, Allergan, Bausch + Lomb, Nicox, Omeros, Rapid Pathogen Screening, Inc., Santen and Senju. Pravin U. Dugel, MD, is managing partner of Retinal Consultants of Arizona in Phoenix; clinical associate professor of ophthalmology, Doheny Eye Institute, Keck School of Medicine at the University of Southern California, Los Angeles; and founding member of the Spectra Eye Institute in Sun City, AZ. Dr. Dugel states that he is a consultant for Alcon, AMO, ArcticDx, Ora, Regeneron, and ThromboGenics. He can be reached via email at pdugel@gmail.com. Medical writer Noelle Lake, MD assisted in the preparation of this article.

REFERENCES

12. Budzynski ESA, López FJ, Ward KW. BOL-303242-X, a selective glucocorticoid receptor agonist (SEGRA), offers a better in vivo side effect profile than dexamethasone in intraocular pressure elevation in normotensive rabbits. ARVO Annual Meeting; 2009 May 3-7; Fort Lauderdale (FL).
This CME program is sponsored by the University of Florida College of Medicine and supported by an unrestricted educational grant from Bausch + Lomb, Inc.

**Directions:** Select the one best answer to each question in the exam (Questions 1–10) and in the evaluation (Questions 11–16) below by circling one letter for each answer. Participants must score at least 80% on the questions and complete the entire Evaluation section on the form below. The University of Florida College of Medicine designates this activity for a maximum of 1.0 AMA PRA Category 1 Credit™. There is no fee to participate in this activity. You can take the test online at http://cme.ufl.edu/toai.

### Examination Questions

1. Compared to a steroid-only or steroid-NSAID regimen, NSAID-only CME prophylaxis:
   - A. Is more difficult for patients to manage
   - B. May provide equivalent prophylactic efficacy
   - C. Is significantly more expensive
   - D. All of the above are true

2. Which of the following is NOT a consideration in the evaluation of ocular inflammation?
   - A. Underlying cause of the condition
   - B. Which tissues are involved
   - C. Relationship to systemic illness
   - D. Ratio of axial length to anterior chamber depth

3. Which of the following patient situations warrants further evaluation for pseudophakic CME?
   - A. Increasing blurriness at 5 weeks after uneventful cataract/IOL surgery
   - B. Glare and halos while driving at night 2 weeks after multifocal lens implant
   - C. Normal acuity but reduced contrast sensitivity 6 weeks after complicated surgery
   - D. Both A and C are correct

4. At what point after surgery is pseudophakic CME most like to present?
   - A. Within the first 24 hours
   - B. At 1 week
   - C. At 4 to 6 weeks
   - D. At 15 to 20 weeks

5. Which of the following classes do NOT bind receptors?
   - A. NSAIDs
   - B. Corticosteroids
   - C. Immuneomodulators
   - D. SEGRAs

6. Which of the following is NOT true of ophthalmic NSAIDs?
   - A. They can be analgesic
   - B. They block phospholipase A
   - C. They sustain pupillary mydriasis
   - D. They block cyclooxygenase

7. Which of the following statements about ophthalmic NSAIDs is true?
   - A. NSAIDs may be given in advance of surgery to reduce inflammation
   - B. Halogenation does not affect NSAID potency
   - C. NSAIDs are contraindicated in patients with glaucoma
   - D. Both A and C are true

8. Which of the following is NOT a risk factor for pseudophakic CME?
   - A. Caucasian race
   - B. Diabetes without retinopathy
   - C. Prolonged duration of surgery
   - D. Retained lens fragment

9. Which of the following mechanisms may allow inflammation in the anterior segment to affect the posterior segment?
   - A. Diffusion of inflammatory mediators between adjacent tissues
   - B. Enzyme transactivation
   - C. Genetic transrepression
   - D. A and B above are correct

10. Which of the following statements about ophthalmic steroid medications is accurate?
    - A. Dual fluorination of difluprednate allows for increased receptor binding
    - B. Loteprednol is associated with increased risk of IOP elevation
    - C. Esterases prolong the activity of loteprednol in the eye
    - D. Difluprednate was designed for increased safety

### Examination Answer Sheet

This CME activity is jointly sponsored by the University of Florida and Candoo Clinical/Science Communications, LLC, and supported by an unrestricted educational grant from Bausch + Lomb, Inc. Mail to: University of Florida CME Office, PO Box 100233, Gainesville, FL 32610-0233.

**DIRECTIONS:** Select the one best answer for each question in the exam (Questions 1–10) and in the evaluation (Questions 11–16) below by circling one letter for each answer. Participants must score at least 80% on the questions and complete the entire Evaluation section on the form below. Participants must score at least 80% on the questions and complete the entire Evaluation section on the form below. The University of Florida College of Medicine designates this activity for a maximum of 1.0 AMA PRA Category 1 Credit™. There is no fee to participate in this activity. You can take the test online at http://cme.ufl.edu/toai.

If you wish to receive credit for this activity, please fill in the following information. Retain a copy for your records.

**PLEASE PRINT CLEARLY**

**FIRST NAME** ___________________________ **LAST NAME** ___________________________ **DEGREE** ___________________________

**ORGANIZATION/INSTITUTE**

**ADDRESS LINE 1**

**ADDRESS LINE 2**

**CITY** ___________________________ **STATE** ___________________________ **ZIP** ___________________________

**PHONE** ___________________________ **FAX** ___________________________

**E-MAIL ADDRESS** ___________________________