Topics in OCULAR ANTIINFLAMMATORIES

A CONTINUING MEDICAL EDUCATION PUBLICATION

ISSUE 6

How Do Ocular Corticosteroids and NSAIDs Work?

DANIEL R. SABAN, PHD **Corticosteroids and NSAIDs are, by far, the most important drugs used to manage ocular inflammation. Although drugs from both classes can provide effective inflammation control, they act by very different molecular and cellular mechanisms.**

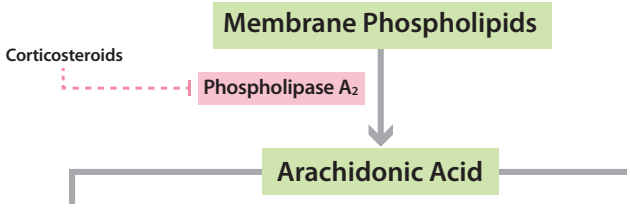

FIGURE 1 See the full biosynthesis on page 3.

Corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) are essential weapons in the fight against ocular inflammation, which, if left unchecked, can cause significant morbidity and loss of vision. Because of their potency and broad range of effects, corticosteroids have been the treatment mainstay for all types of ocular inflammation since the 1940s, while topical NSAIDs represent a more recent therapeutic advance in ophthalmology.

While they both tame inflammation, corticosteroids and NSAIDs each have their own molecular mechanisms of action and pharmacologic effects. These distinctions result in differences in efficacy, adverse effect profiles, and clinical application. This article will briefly review their mechanisms of action and basic pharmacokinetics, including recent developments.

CORTICOSTEROIDS: BROAD MECHANISMS

Coopman and his colleagues have classified corticosteroids into 4 groups: hydrocortisones (eg, prednisone or hydrocortisone), acetonides (eg, triamcinolone acetonide), betamethasones (eg, dexamethasone), and ester betamethasones (eg, methyl prednisolone).[1] All corticosteroids have a four-ring core structure with 21 carbon atoms; modifications to this basic structure produce different biological properties including antiinflammatory activity.

Corticosteroids act through the cytosolic glucocorticoid receptor alpha, which is expressed in almost all cells and mediates effects across multiple signaling pathways.[2] Because corticosteroids are lipophilic, they can easily cross cell membranes and gain access to the cytoplasm. After the corticosteroid enters the cytoplasm and binds to and activates the glucocorticoid receptor alpha, the corticosteroid-receptor complex translocates to the nucleus, where it modulates the expression of thousands of genes directly (by binding to glucocorticoid-responsive elements) or indirectly (by modulating the activity of other transcription factors such as AP1 and NFkB).[2,3] In addition to the classic genomic mechanism, corticosteroids also act through rapid, nongenomic mechanisms, including nitric oxide-dependent vasorelaxation and inhibition of the release of proinflammatory prostaglandin PGE2.[3,4]

These effects control inflammation by upregulating the expression of antiinflammatory genes and suppressing the expression of proinflammatory genes. One antiinflamma-

See INSIDE for:
Despite Risks, Intravitreal Corticosteroid Implants Remain Useful *by Peter K. Kaiser, MD*

TARGET AUDIENCE This educational activity is intended for ophthalmologists and ophthalmologists in residency or fellowship training.

LEARNING OBJECTIVES Upon completion of this activity, participants will be able to:

1. Evaluate the mechanisms of action and pharmacokinetic properties of ophthalmic corticosteroids and NSAIDs in order to provide the most appropriate antiinflammatory therapy for their patients.
2. Identify uveitis patients for whom the risks of intravitreal corticosteroid implant may outweigh benefits.

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tory protein induced by corticosteroid is annexin I (lipocortin-1), which can interact with and inhibit phospholipase A2, thereby blocking the release of arachidonic acid and its subsequent conversion to eicosanoids (prostaglandins, thromboxanes, leukotrienes, and other hydrolytic products of cell membrane phospholipids).[5,6]

Beyond inhibition of prostaglandin and leukotrienes formation, other antiinflammatory effects of corticosteroids include vasodilation suppression, macrophage and neutrophil migration inhibition, reduction of inflammatory T cells and B cells, and stabilization of intracellular and extracellular membranes.[3,7]

NSAIDS: COX INHIBITORS

NSAIDs specifically inhibit the activity of cyclooxygenase (COX) enzymes. These enzymes are active in the inflammatory process that catalyzes the biosynthesis of eicosanoids from arachidonic acid to produce prostaglandins, which can act on iris smooth muscle, with effects that include miosis, pain, vasodilation, breakdown of the blood-ocular barrier, and leukocyte migration.[8,9] Unlike corticosteroid, which suppresses phospholipase A2 and thus both arms of the inflammatory cascade, NSAID does not block lipoxygenase and formation of leukotrienes (Figure 1).

COX enzymes have two main isoforms: COX1 and COX2.[10] COX1 exists in most tissues as a constitutive enzyme and plays a role in normal physiologic functions; COX-2, the inducible isoform, is expressed during inflammatory responses.[11] The antiinflammatory effects of NSAIDs are thought to result largely from the inhibition of COX2.[9] Currently available ophthalmic NSAIDs nonselectively inhibit both isoforms of COX but differ markedly in their relative COX1:COX2 inhibitory potential.

All NSAIDs fall into one of six major classes based on chemical structure: salicylates, indole acetic acid derivatives, aryl acetic acid derivates, aryl propionic acid derivatives, enolic acid derivatives, and fenamates. The topical NSAIDs used in eyecare belong to the relatively water soluble classes: indole acetic, aryl acetic, and aryl propionic acids.[12]

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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—eg, the perioperative use of nonsteroidal antiinflammatory drugs (NSAIDs) to prevent cystoid macular edema—and/or fly in the face of older thinking—eg, 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 drugs 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 PRK; and much more.

What has regrettably not followed this expansion of indications, formulations, and new molecular entities are protocols for drug selection and use.[1] 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 a demonstrated lower risk of intraocular pressure (IOP) elevation than ketone steroids.[2,3] Since a range of steroid formulations and concentrations is available, clinicians need up-to-date information about the indications and optimum uses for each.[3]

Although topical NSAID formulations have been associated with significant adverse events (keratopathy ranging from superficial punctate keratitis to corneal melt), recent work shows these to be uncommon and less severe with newer formulations.[4] Indeed, novel NSAIDs make use of lower concentrations and less frequent dosing, potentially impacting safety profiles and reducing risk from long-term use.[5]

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.

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CLINICAL IMPLICATIONS

Because of their strong antiinflammatory and immunosuppressive activity, corticosteroids are commonly used as a first-line therapy in all types of ocular inflammatory disease. They are particularly suited to the treatment of cases in which there is an acute or strong inflammatory reaction, such as in anterior or posterior uveitis or corneal graft rejection.

However, corticosteroid effects are not limited to the signaling systems involved in inflammation; they also affect signaling mechanisms involved in normal physiologic functions. As a result, the antiinflammatory efficacy of systemic corticosteroids may be accompanied by multiple adverse effects: immunosuppression, hypertension, osteoporosis, inhibition of wound repair. In the eye, adverse effects can also include cataract formation and intraocular pressure (IOP) elevation. The wide range of potentially serious side effects greatly limits clinicians' ability to use corticosteroid agents in high doses or for prolonged periods; this is equally true in both topical and systemic applications.

NSAIDs, on the other hand, block only the COX pathway, but their antiinflammatory activity may be insufficient to control severe, vision-threatening inflammatory disease. NSAIDs are notable, however, for infrequency of severe adverse effects,

CORE CONCEPTS

- Corticosteroids are stronger antiinflammatory agents than NSAIDs and are used more extensively in the management of ocular inflammation.
- Corticosteroids act primarily on the glucocorticoid receptor alpha and mediate their broad therapeutic effects through both genomic and nongenomic mechanisms. They block the inflammatory cascade at the upstream level of phospholipase A2.
- The broad effects of corticosteroids account not only for their therapeutic strength but also for the significant risk of side effects associated with prolonged or high dose corticosteroid therapy.
- All NSAIDs inhibit both COX1 and COX2 with varying degrees of specificity.
- By inhibiting the COX2 enzyme, NSAIDs reduce the production of prostaglandins. They do not affect the other arm of the inflammatory cascade, which is catalyzed by lipoxygenase to produce leukotrienes.
- Corticosteroids with an acetate base penetrate the cornea better than other corticosteroids.

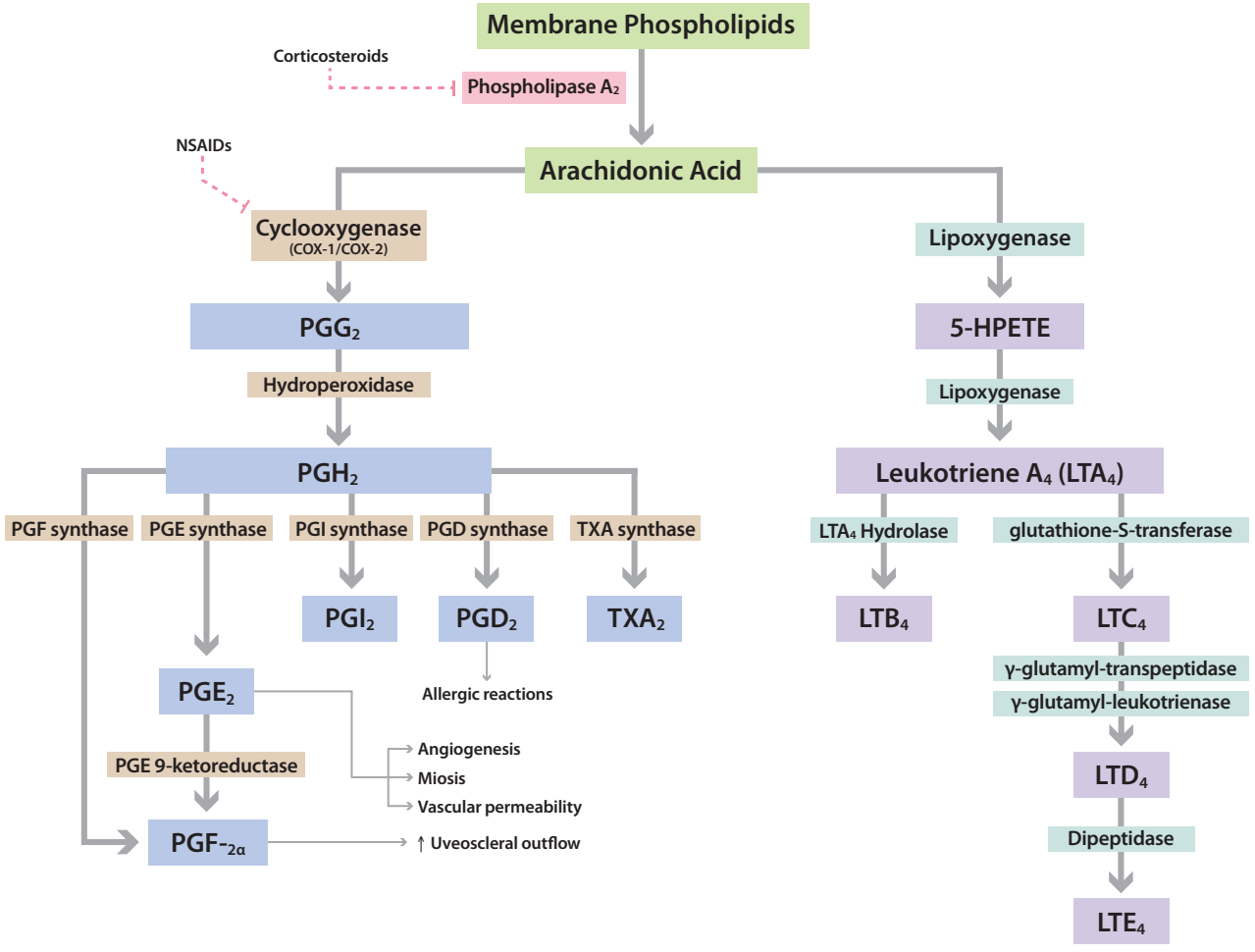

FIGURE 1 Biosynthesis of eicosanoids from membrane bound arachidonic acid. *(Adapted from reference 6.)*

and their topical formulations have proved effective in preventing miosis during cataract surgery, minimizing postoperative inflammation, preventing and treating cystoid macular edema following cataract surgery, and relieving ocular discomfort and inflammation after cataract and refractive surgery.

PHARMACOKINETICS

Pharmacokinetic properties are important to consider in drug design. Corneal absorption is critical in pharmaceuticals formulated for topical ophthalmic application. The better a drug penetrates the cornea, the more likely it is to be effective. The greatest barrier to corneal penetration is the lipid-rich corneal epithelium, which is much more effective at blocking polar, hydrophilic molecules than their lipophilic derivatives.[13]

For topical corticosteroids, corneal penetration largely depends on the form of corticosteroid used. The lipophilic acetate forms penetrate better than their alcohol and hydrophilic phosphate derivatives.[13] The problem with acetate corticosteroids is that their low aqueous solubility requires that they be formulated as suspensions rather than solutions, and the patient must shake the suspension before administering it. Forgetting this step can affect the dose delivered.

Topically applied NSAIDs differ in corneal permeability. Nepafenac, a nonpolar prodrug, may penetrate the cornea better than all other NSAIDs including flurbiprofen, diclofenac, ketorolac, and bromfenac, which have more polar and water-soluble acidic structures.[6] A prodrug, nepafenac has little effect on COX enzymes, but it is rapidly converted by intraocular hydrolases into the more potent amfenac. In vivo study in humans has shown that nepafenac has a faster time to C_{max} and higher aqueous concentration than bromfenac or ketorolac.[14] However, bromfenac, which is structurally identical to amfenac except for a bromine atom at the C4 position, also penetrates well, appears to stay longer in the anterior chamber, and acts more selectively on COX-2.[9]

NEW DEVELOPMENTS

Corticosteroid and NSAID compounds and formulations have continued to evolve over the past decade. The original ketorolac 0.5% was reformulated with a lower drug concentration (0.4%), less preservative (0.006% benzalkonium chloride), and a more physiologic pH value. Nepafenac became the first prodrug approved in the NSAID class for the treatment of postoperative pain and inflammation after cataract surgery. Newer formulations with longer ocular surface residence time have also reduced the NSAID concentration required for efficacy.

As for corticosteroid therapy, intravitreal implants that steadily release medication for months or years are the new trend in the management of intermediate or posterior ocular inflammatory disease. Most recently, a topical gel formulation of 0.5% loteprednol etabonate was developed for better drug delivery and approved for the treatment of postoperative inflammation and pain.[15] These developments result in varying pharmacokinetics, but with the introduction of newer drugs, newer formulations, and newer delivery systems, antiinflammatory therapy is becoming increasingly effective and safe.

FUTURE DIRECTIONS

While the clinical benefits and limitations of corticosteroid and NSAID therapy seem clearly defined, there are still gaps in our understanding of the agents' molecular mechanisms. For example, only recently have we begun to recognize the presence of the glucocorticoid receptor beta and its role in the generation of resistance to corticosteroid by inhibiting the glucocorticoid receptor alpha.[2]

We also need to learn more about the biology of inflammatory conditions. In uveitis, for example, we have very little idea of what triggers the condition; and when the patient improves, the clinician has no way of knowing whether that reflects the efficacy of antiinflammatory treatment or some other endogenous or environmental influence. A better understanding of the disease as well as the molecular mechanisms of the antiinflammatory therapies may allow us to formulate and deliver medication more effectively and provide patients with better care.

Daniel R. Saban, PhD, is assistant professor of ophthalmology and immunology at Duke University School of Medicine in Durham, NC. He states that in the past 12 months, he has not had a financial relationship with any commercial organization that produces, markets, re-sells, or distributes healthcare goods or services consumed by or used on patients. Ying Guo, MBBS, PhD, assisted in the preparation of this article.

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Despite Risks, Intravitreal Corticosteroid Implants Remain Useful

PETER K. KAISER, MD

Intravitreal implants that release dexamethasone or fluocinolone acetonide allow targeted drug application, significantly extend the duration of treatment, and reduce the need for intravitreal injections. Used prudently, they offer a viable treatment option for several serious posterior segment diseases, including uveitis, diabetic macular edema, and retinal vein occlusion.

CORE CONCEPTS

- Intravitreal corticosteroids allow target-specific delivery of medication and are associated with minimal systemic side effects.
- Intravitreal corticosteroids are frequently used in the treatment of posterior uveitis and retinal conditions that cause macular edema, eg, diabetes and retinal vein occlusion.
- There are three intravitreal corticosteroids in current clinical use: triamcinolone, dexamethasone, and fluocinolone acetonide. Injected tramcinolone suspension typically remains effective for about 3 months in the vitreous cavity.
- The nonbiodegradable, extended-release fluocinolone implant lasts for close to 3 years but must be sutured to the sclera. It is approved for the treatment of noninfectious posterior uveitis.
- The biodegradable, extended-release dexamethasone implant is approved for the treatment of noninfectious posterior uveitis and macular edema due to retinal vein occlusion.
- Intravitreal corticosteroids are associated with serious ocular side effects, and both corticosteroid implants are associated with high rates of cataract and IOP elevation.

A number of posterior segment eye diseases have sight-threatening sequelae caused by inflammation, macular edema, and angiogenesis. Corticosteroids can be useful in treating these conditions due to their antiinflammatory and antiangiogenic effects, and their ability to restore the blood-retinal barrier.

Although multiple routes are available for delivering corticosteroid agents to the back of the eye, each is associated with some disadvantage: topical ophthalmic drops may not penetrate well enough to achieve adequate concentrations at the retina; orally administered corticosteroids are associated with multiple systemic side effects, especially when used long-term; and sub-Tenons injections, though able to achieve adequate posterior segment corticosteroid concentration, can allow significant levels of drug to enter systemic circulation.

The one remaining route is direct intravitreal corticosteroid placement. This has two distinct advantages: assured delivery of drug to the target tissue, and minimal systemic absorption. In the past decade intravitreal corticosteroid implants have joined intravitreal injections as a treatment option for uveitis and macular edema due to diabetes and retinal vein occlusion. Implantable sustained-release devices designed for prolonged, continuous delivery of a small dose of drug offer a potentially useful treatment option for those chronic or recurrent retinal diseases that require long-term corticosteroid therapy.

IMPLANTS VS INJECTIONS

Intravitreal corticosteroid administration began in the 1970s, when intravitreal dexamethasone was reported to have been used adjunctively in patients with postoperative bacterial endophthalmitis.[1] While dexamethasone has great potency, it has a very short half-life and so requires frequent injections to maintain therapeutic levels within the eye.[2,3] Triamcinolone, which superseded dexamethasone as the intravitreal corticosteroid of choice, is less potent; but it is delivered as a crystalline suspension, the crystals of which act as miniature sustained-release devices.

Intravitreal triamcinolone suspension has an average elimination half-life of just 18.6 days, although it remains detectable in nonvitrectomized eyes for about 12 weeks.[4] In vitrectomized eyes, triamcinolone clears even more rapidly, with a half-life as short as 3.2 days. Because it is cleared so readily, intravitreal triamcinolone injection is poorly suited to the treatment of chronic conditions. By contrast, corticosteroid implants can extend the eye's intraocular exposure to corticosteroid for as long as several years.

APPROVED DEVICES

There are two FDA-approved intravitreal implants. The first is a nonbiodegradable device that contains 0.59 mg fluocinolone acetonide and releases about 0.5 µg of drug per day, over a period of about 3 years. It is the first sustained-release device approved for the treatment of noninfectious posterior uveitis.

A second device, a completely biodegradable dexamethasone implant, is approved for the treatment of noninfectious posterior uveitis and macular edema secondary to retinal vein occlusion, and provides intravitreal dexamethasone for up to 6 months.[5] Unlike the fluocinolone implant, which has a shell that lasts essentially forever unless it is removed and

replaced, the dexamethasone device is an erodible polymer that slowly dissolves into water and carbon dioxide and leaves no residue or implant behind.

In addition, the fluocinolone implant must be sutured to the sclera in the operating room, while the biodegradable device can be injected in an outpatient setting, via a 22-gauge applicator through the pars plana.

It is important to note that the length of time an intravitreal implant lasts can vary considerably from patient to patient because differences in the intraocular environment affect the degradation rate of the polymer. The fluocinolone implant lasts about 2.5 years in many patients but longer in others; the dexamethasone device usually lasts from 3 to 6 months.

A third intravitreal implant has been approved outside the US for the treatment of recalcitrant diabetic macular edema (DME). It is also a nonbiodegradable fluocinolone device that lasts for about 3 years, but it is much smaller in size than the US-approved device and can be injected in the clinic using a 25-gauge needle.

CLINICAL EFFICACY

Clinical studies have demonstrated the efficacy of intravitreal corticosteroid implants. The US-approved fluocinolone implant significantly reduced uveitis recurrence and improved visual acuity in uveitis patients.[6,7] The dexamethasone device improved vision and reduced central macular thickness in patients with macular edema secondary to retinal vein occlusion and recalcitrant to intravitreal bevacizumab.[8,9]

The implants have also shown efficacy against DME, improving both visual and anatomical (vascular leakage and central retinal thickness) outcomes.[10-12] However, intravitreal corticosteroids are not approved in the US for treatment of DME.

Some large clinical studies have found the effects of intravitreal corticosteroids on DME and retinal vein occlusion somewhat underwhelming.[13-15] In particular, studies of DME have found that, in terms of visual outcome, laser and anti-VEGF therapies are superior to corticosteroids.[13,14] While the conclusion is valid, these studies failed to take cataract formation into account; if a patient undergoing treatment develops a cataract, the end result could well be no change in visual acuity even if the macular edema is improving. Indeed, the visual results of pseudophakic patients in the same studies are considerably better and similar to those with anti-VEGF treatment—but with far fewer injections.[13,14]

DME and retinal vein occlusion have been found to respond well to anti-VEGF therapy, which has become the gold standard for both diseases because of its efficacy and relative lack of side effects. But these diseases, especially DME, involve many other pathophysiologic mechanisms beyond VEGF-driven vascular effects; and corticosteroids still have an important role to play in their management.

SIDE EFFECTS

Intravitreal corticosteroids have the same ocular side effects—primarily cataract formation and intraocular pressure (IOP) elevation—as corticosteroids administered via other routes. The implantable devices, which prolong drug exposure, are associated with particularly high rates of side-effects.[6,7,9-15]

Among intravitreal corticosteroids, the fluocinolone implant is associated with the highest rate of IOP elevation and cataract formation simply because it creates the greatest duration of exposure. At 6 months following implantation, the side effect profile of the permanent fluocinolone device is very similar to that of the biogradeable dexamethasone implant; at 3 months, the side effect profiles of both implants are similar and essentially the same as injected triamcinolone. Duration of exposure is what drives the differences in safety.[16]

Topical anti-glaucoma eye drops work reasonably well for most patients that have developed elevated IOP due to an intravitreal corticosteroid implant.[7-9] Some eyes also need to be treated with laser trabeculoplasty or trabeculotomy surgery to maintain IOP control.

As with any intraocular procedure, intravitreal implantation is associated with a small chance of intraocular infection. Clinicians should talk to patients about the risk and employ topical antibiotic prophylaxis at the end of the procedure.

PATIENT SELECTION

Although intravitreal implants last a relatively long time, they are not a "one-and-done" type of treatment. Patients with uveitis who require corticosteroid therapy usually need to be treated for very long periods, so long that even the fluocinolone implant needs to be replaced. By contrast, in DME or retinal vein occlusion, often all the patient needs is a single course of corticosteroid, especially when it is an adjunct to other treatments.

The clinician must weigh the benefits of intravitreal corticosteroid therapy against its potential complications before placing a long-term implant. In an older patient who already has cataract, it may be perfectly acceptable to hasten the cataract's rate of progression. But for a younger diabetic patient with no apparent cataract, the benefits of a long-term corticosteroid implant may not justify the high risk of cataract.

Patients with glaucoma—or risk factors for glaucoma, such as family history—are poor candidates for intravitreal corticosteroids. In the normal population, about one-third of individuals will have significant IOP elevation in response to corticosteroids.[17,18] Unless the patient is already known to be a corticosteroid responder, the only way to tell is to challenge them with corticosteroid eye drops. If the patient's IOP does not rise after an adequate trial period, then the risk from a sustained-release device may be acceptably low.

In the case of the fluocinolone implant, because it lasts about 3 years and has to be removed if the patient develops an IOP elevation, we often try an intravitreally injected corticosteroid first. If the patient has an IOP response to the trial treatment, it can almost always be managed with topical antihypertensive drops until the corticosteroid is cleared from within the eye.

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EXAMINATION QUESTIONS TOPICS IN OCULAR ANTIINFLAMMATORIES | ISSUE 6

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 enduring material 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**.

1. Which of the following statements about NSAIDs is NOT correct?
   A. They inhibit the formation of prostaglandins
   B. They selectively inhibit either COX1 or COX2
   C. They lack multiple side effects associated with corticosteroid therapy
   D. They are less potent than corticosteroids

2. Which of the following is true about measures to reduce IOP risk in patients with intraocular corticosteroid implants?
   A. Glaucoma drops are ineffective in these eyes
   B. Laser trabeculoplasty cannot be used
   C. Risk can be reduced by not implanting known corticosteroid responders
   D. None of the above is true

3. By what mechanism(s) do corticosteroids control inflammation?
   A. Inhibition of phospholipase A2 and the subsequent formation of eicosanoids
   B. Vasodilation suppression
   C. Downregulating the number of T cells responsible for inflammation
   D. All of the above are true

4. Which of the following ophthalmic NSAIDs is a prodrug that is metabolized to amfenac within the eye?
   A. Ketorolac
   B. Bromfenac
   C. Nepafenac
   D. Diclofenac

5. Which of the following most accurately describes the corticosteroid backbone?
   A. A polypeptide
   B. 21 carbon atoms arranged in four rings
   C. An aptamer structure that binds the membrane glucocorticoid receptor
   D. All of the above are true

6. Use of intravitreal corticosteroids is FDA-approved for which of the following condition(s)?
   A. Retinal vein occlusion
   B. Diabetic macular edema
   C. Noninfectious posterior uveitis
   D. Both A and C

7. Which cytoplasmic receptor mediates the therapeutic effects of corticosteroids?
   A. The glucocorticoid receptor alpha
   B. The glucocorticoid receptor beta
   C. The glucocorticoid receptor kappa
   D. None of the above

8. Which statement about intravitreal corticosteroids is NOT correct?
   A. They are associated with high rates of cataract and IOP elevation
   B. The longer the corticosteroid remains in the eye, the more likely it is to induce side effects
   C. Placement of corticosteroid implants carries a small risk of infection
   D. With implants, the duration of effect does not vary from patient to patient

9. Which injected corticosteroid has extended effect because it is a crystalline suspension that dissolves slowly in the vitreous?
   A. Triamcinolone
   B. Dexamethasone
   C. Fluocinolone
   D. Prednisolone

10. Which intravitreal corticosteroid implant must be placed in the operating room?
    A. The non-US-approved fluocinolone implant
    B. The biodegradable dexamethasone implant
    C. The US-approved fluocinolone implant
    D. None of the above

EXAMINATION ANSWER SHEET TOPICS IN OCULAR ANTIINFLAMMATORIES | ISSUE 6

This CME activity is jointly sponsored by the University of Florida and Candeo 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 above (Questions 1–10). Participants must score at least 80% on the questions and complete the entire Evaluation (Questions 11–16) to receive CME credit. CME exam expires December 31, 2014.

ANSWERS:

1.	A	B	C	D	**6.**	A	B	C	D
2.	A	B	C	D	**7.**	A	B	C	D
3.	A	B	C	D	**8.**	A	B	C	D
4.	A	B	C	D	**9.**	A	B	C	D
5.	A	B	C	D	**10.**	A	B	C	D

EVALUATION:

1=Poor 2=Fair 3=Satisfactory 4=Good 5=Outstanding

11. Extent to which the activity met the identified
    Objective 1: 1 2 3 4 5
    Objective 2: 1 2 3 4 5
12. Rate the overall effectiveness of how the activity:
    Related to my practice: 1 2 3 4 5
    Will influence how I practice: 1 2 3 4 5
    Will help me improve patient care: 1 2 3 4 5
    Stimulated my intellectual curiosity: 1 2 3 4 5
    Overall quality of material: 1 2 3 4 5
    Overall met my expectations: 1 2 3 4 5
    Avoided commercial bias/influence: 1 2 3 4 5
13. Will the information presented cause you to make any changes in your practice? Yes No
14. If yes, please describe: _____
15. How committed are you to making these changes? 1 2 3 4 5
16. Are future activities on this topic important to you? Yes No

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

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