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Inflammation and success in refractive cataract surgery

New anti-inflammatory therapeutics

"There are factors that we know have helped improve outcomes in patients who are receiving advanced technology IOLs," said **Terry Kim, MD**, professor of ophthalmology, Duke University School of Medicine, Durham, N.C. Among the more familiar factors are patient selection, improved biometry and keratometry, OCT imaging, and femtosecond laser technology.

One variable tends to be overlooked in terms of how important it is to the outcomes of refractive cataract procedures: inflammation. The goal with these procedures, said Dr. Kim, should be to eliminate post-cataract inflammation.

Dr. Kim joined a faculty of experts to look at "Knocking Down Inflammatory Barriers to Success in Refractive Cataract Surgery" at an EyeWorld CME Education symposium held at the 2013 ASCRS•ASOA Symposium & Congress. Their objectives were to recognize the impact of ocular inflammation on outcomes in refractive cataract surgery, understand the role of anti-inflammatory therapies in mediating and preventing anterior and posterior segment ocular tissue response throughout the inflammatory cascade, and identify strategies to prevent edema and relieve pain by maximizing the formulation of anti-inflammatory agents to enhance their penetration into target tissues.

"A lot of us are not aware of some of the recent advances in therapeutic agents," said Dr. Kim. "We've had some new and exciting developments in terms of our choices for anti-inflammatory therapy with regard to both topical corticosteroids and nonsteroidal agents," he said.

In terms of nonsteroidal anti-inflammatory drugs (NSAIDs), there have been some notable reformulations of familiar agents. Prolensa (bromfenac 0.07%), which received FDA approval in April, provides a lower concentration of the active ingredient than Bromday (bromfenac 0.09%). The new drug is approved for once-a-day daily dosing 1 day preop, the day of surgery, and 14 days postoperatively.

Financial Interest Disclosures

The faculty have disclosed the following financial interest relationships within the last 12 months:

David F. Chang, MD, has received a retainer, ad hoc fees, or other consulting income from: Abbott Medical Optics, Clarity Medical Systems, LensAR, and Transcend. He is a member of the speakers bureaus of:Allergan and Zeiss Certified. He has received research funding from Glaukos. Dr. Chang has investment interests in Calhourn Vision, ICON Bioscience, PowerVision, and Revital Vision. He receives a royalty or other financial gain from Eyemaginations and SLACK Inc.

Uday Devgan, MD, has received a retainer, ad hoc fees, or other consulting income from: Aaren Scientific, Bausch & Lomb, Gerson Lehman Group, Hoya Vision Care, and ISTA. He is a member of the speakers bureau for Alcon. Dr. Devgan has an investment interest in Specialty Surgical and receives a royalty or other financial gain from Accutome.

Terry Kim, MD, has received a retainer, ad hoc fees, or other consulting income from: Alcon, Bausch & Lomb, ISTA, Ocular Systems, Ocular Therapeutix, PowerVision, and SARCode Bioscience.

Francis S. Mah, MD, has received a retainer, ad hoc fees, or other consulting income from: Alcon, ForSight Labs, and ISTA. He is a member of the speakers bureau of Allergan and Bausch & Lomb.

Keith A. Warren, MD, has received a retainer, ad hoc fees, or other consulting income and is a member of the speakers bureau of: Alcon, Dutch Ophthalmic USA, and Genentech.

Staff member **Laura Johnson** has no financial interests to disclose.

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Educational Objectives

Ophthalmologists who participate in this course will:

- Identify the impact of ocular inflammation on outcomes in refractive cataract surgery;
- Understand the role of anti-inflammatory therapies in mediating or preventing ocular tissue response throughout the inflammatory cascade; and
- Identify strategies to prevent edema and relieve pain by maximizing the penetration vehicle of anti-inflammatory agents into target tissues.

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"The optimized pH represents an advanced formulation designed to facilitate penetration into the eye," said Dr. Kim, adding that it will be available as 1.6 mL and 3 mL in a 7.5-mL bottle.

Nepafenac, on the other hand, is now available in a *higher* concentration of 0.3%, Ilevro. Originally available at a concentration of 0.1% (Nevanac), the new formulation is also approved for once-a-day dosing 1 day preop, on the day of surgery, and 2 weeks postoperatively, and will be available as 1.7 mL in a 4-mL bottle.

In terms of corticosteroids, Durezol (difluprednate emulsion 0.05%) is not new, having been launched in 2008. However, said Dr. Kim, "The launch of difluprednate represented a new class of corticosteroid medication that we had not seen in quite a few years. It is indicated for the treatment of inflammation and pain associated with ocular surgery and anterior uveitis with QID dosing."

More recently approved for the same indications is Lotemax gel (loteprednol ophthalmic gel 0.5%), which uses a unique and innovative mucoadhesive technology to ensure adherence to the ocular surface and enhance penetration into the eye.

Impact of inflammation on the posterior segment and the role of anti-inflammatory therapy

"As a retinal surgeon dealing with patients who have posterior segment disease, many times I'm the person that's bringing a gun to a knife fight," said **Keith A. Warren, MD**, professor of ophthalmology, University of Kansas, and founder, Warren Retina Associates, Overland Park, Kan. "For these patients, you really don't want any inflammation so it becomes very important to try to stem that."

Dr. Warren offered a retina specialist's perspective on the effects of inflammation during refractive cataract surgery, highlighting its impact on the posterior segment and the role of anti-inflammatory therapy.

Dr. Warren believes that patients undergoing refractive cataract surgery "have little or no tolerance" for any intraocular inflammation. Advanced technology IOLs, such as multifocal IOLs in particular, don't work if inflammation is present.

"Basically, [patients] want to get their money's worth," he said. "Inflammatory control in refractive cataract surgery patients is tantamount to any successful outcome."

Common pathophysiology

Many retinal diseases share a common inflammatory pathophysiology. In particular, surgeons performing refractive cataract surgery should remember that pseudophakic cystoid macular edema (CME) occurs by similar mechanisms.

During surgery, inflammation is caused by the release of cytokines and other signals meant to induce protection against insults to the body. In the uveal tract, inflammation thus occurs by a number of mechanisms, but is ultimately characterized by a breakdown in the blood–retina barrier. This in turn leads to leakage of proteinaceous fluid, leading to swelling in the retina and in the ocular media.

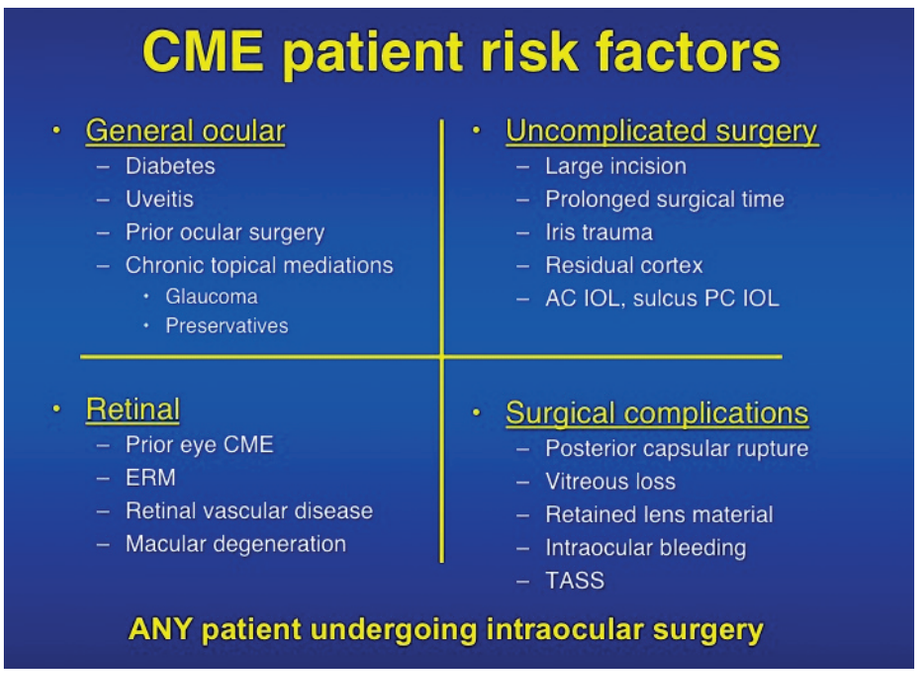

Figure 1. Risk factors for CME

This inflammation, with its resulting prostaglandin-mediated breach of the blood–retina barrier, puts any patient undergoing refractive cataract surgery at high risk for CME.

CME is a late onset complication, usually occurring 4-6 weeks after surgery. Studies have shown that increased retinal thickening occurs in a staggering 12% of cases following uncomplicated cataract surgery,[1] appearing 4-6 weeks after surgery.[2]

A full evaluation of each patient should be conducted prior to surgery. This includes identifying risk factors in the clinical history by examining factors such as duration of systemic disease, length of surgery, complications that may have occurred during surgery, and co-morbidities such as diabetes, as well as conducting a thorough preop exam to look for any signs of pre-existing retinopathy (Figure 1).

Dr. Warren also recommended performing optical coherence tomography (OCT) during preop evaluation. The precise measurement of the retinal thickness provided by OCT allows surgeons to evaluate risk, helps them educate patients regarding their pre- and postop outcomes, and provides an objective way to monitor response to therapy.

Steroids, NSAIDs, anti-VEGF

When approaching the patient at risk, corticosteroids are the drug of choice for treating inflammatory diseases including CME and should be used at maximum strength pre- and postop to control inflammation. They are the best agents because their mechanism of action is very broad and non-specific: They regulate VEGF production and expression as well as inhibit the release of cytokines and other inflammatory mediators; in short, they influence multiple pathways in the inflammatory cascade.

Prednisolone acetate 1% has been the "standard of care" in the U.S.,[3] having been used as a comparator in clinical trials for more than 20 years, but newer formulations such as difluprednate and loteprednol gel are certainly worth considering.

For instance, being a prodrug allows difluprednate to rapidly penetrate the corneal epithelium and maintain a consistent concentration of a high level of drug in the target tissue. The drug is formulated as an emulsion to further improve dose uniformity—without requiring shaking—compared with prednisolone suspension.

Meanwhile, the mucoadhesive technology used in loteprednol gel facilitates better adherence to the ocular surface, thus also allowing for better penetration of the drug and higher concentrations in the target tissue.

In addition to corticosteroids, NSAIDs can be used as indicated for postoperative pain and inflammation. It should be noted that while none are indicated for CME, studies have shown that newer NSAIDs have some efficacy in both prophylaxis and treatment of the condition.[4,5]

NSAIDs have a narrower, more specific mechanism of action. They are believed to work by cyclooxygenase (COX) enzyme inhibition, thereby reducing prostaglandin production. Of the two COX isoforms, COX-2 is induced by trauma—i.e., surgery—and so is the primary target for inhibition with NSAIDs. Newer NSAIDs may address more COX-2-mediated prostaglandin synthesis.

The use of NSAIDs has other benefits, including the induction of a larger pupil for a longer duration of time, as well as reductions in both postoperative pain and photophobia.[5,6]

A third modality for treating inflammation comes from the retinal surgeon's arena. Anti-VEGF therapy uses molecules designed to competitively inhibit the VEGF molecule—which is known to induce endothelial cell vasodilation and promote vascular permeability, leading to vascular leakage and the formation of secondary CME. Indicated for exudative macular degeneration and used off-label to treat a variety of ocular conditions, anti-VEGF therapy is particularly useful in eyes that have had longstanding CME that is unresponsive to other treatment modalities.

In cases where first-line treatment with a single agent fails, combination therapy is useful. By combining different modalities—corticosteroids with NSAIDs and/or anti-VEGF therapy—pharmacological intervention occurs at multiple, separate sites of action, allowing for a synergistic effect.

Treatment stratification

Dr. Warren stratifies his approach to CME treatment according to the duration of the disease. For acute CME occurring 4-6 weeks postop, he uses a combination of a topical steroid and NSAID. For persistent or resistant CME (around 8 weeks postop), he uses a topical steroid or sub-Tenon's injection and an NSAID. For chronic/resistant CME (around 12 weeks postop), he uses an intraocular steroid injection combined with an NSAID. For recalcitrant CME (4-6 months or greater), he would combine an intraocular steroid, an anti-VEGF agent and an NSAID, and may consider vitrectomy and/or a steroid implant.

Surgeons should keep in mind that up to 20% of patients treated for CME may rebound after discontinuation of treatment. For such cases, Dr. Warren uses a steroid and an NSAID, with the steroid tapered over 6-8 weeks.

But what's really important to keep in mind, said Dr. Warren, is that once CME occurs, the patient will have persistent reduction in contrast sensitivity and color desaturation. "The goal here is to prevent this with prophylaxis," he said.

- **Acute CME: 4-6 weeks post-op – Treat with topical steroid and NSAID**
- **Persistent or resistant CME (8 weeks or greater) – Treat with topical steroid or sub-Tenon's injection + NSAID**
- **Chronic/resistant CME (12 weeks or greater) – Treat with intraocular steroid injection + NSAID**
- **Recalcitrant CME (4-6 months or greater) – Treat with intraocular steroid + anti-VEGF + NSAID, vitrectomy or perhaps steroid implant**
- **Rebound CME, recurring after discontinuation of topical therapy – Treat with steroid + NSAID, with the steroid tapered over 6-8 weeks**

Figure 2. CME treatment, stratified by duration of disease

Impact of inflammation on the anterior segment and the role of anti-inflammatory therapy

"Inflammation affects the entire eye, front to back," said **Uday Devgan, MD**, chief of ophthalmology, Olive View UCLA Medical Center, and associate clinical professor, UCLA School of Medicine, Los Angeles. It affects the cornea, the anterior chamber and angle, the iris and ciliary body, the lens capsule, as well as the posterior segment and retina.

In the anterior segment, inflammation manifests clinically as hyperemia, miosis, impaired vision, and pain; in the posterior segment, diminished visual acuity may be seen secondary to CME. Postop inflammation typically consists of mild iritis, with clinical signs of ocular inflammation, including cells and flare in the anterior chamber; more severe cases may also include significant reduction in vision, as well as pain, redness, and periocular swelling.

Postop inflammation, said Dr. Devgan, is "certainly something that we need to treat, especially with premium lenses that require a really quiet eye, good tear film, and no inflammation for the best visual results."

"Inflammation slows visual recovery," he added. Fighting inflammation with NSAIDs and steroids together can therefore not only reduce postop inflammation and pain, but also improve visual recovery.

Inflammation cascade

Several factors influence inflammation after refractive cataract surgery—inherent patient factors such as cataract density, iris color, and the patient's age, as well as surgical factors such as the volume of balanced salt solution run through the eye during surgery and total surgical time. The surgery itself is associated with physical trauma that induces the inflammatory response.

Inflammation is the endpoint of the arachidonic acid cascade, which, physiologically, follows the conversion of arachidonic acids into prostaglandins. The cascade thus provides targets for pharmaceutical therapy: Anti-inflammatory medication can block different portions of the pathway, with steroids interfering with the activity of phospholipase A2, thus inhibiting the release of arachidonic acid and arachidonic acid metabolites early in the cascade, and NSAIDs interfering with the activity of COX-1 and COX-2 receptors to inhibit prostaglandin synthesis.

Together, steroids and NSAIDs can be used to resolve the anterior chamber cells and flare of inflammation and increase patient comfort. NSAIDs are also used routinely in prophylaxis, administered to prevent inflammation, and while steroids are not used routinely, they can be, said Dr. Devgan. In fact, in his routine preop dosing regimen, Dr. Devgan starts both steroids and NSAIDs together.

"If you're going to start with NSAIDs, you may as well start with steroids too," said Dr. Devgan.

A logical approach

Since inflammation starts immediately, it is logical to get both steroids and NSAIDs into the eye before the first incision. Starting the drugs before the surgery allows the drug to

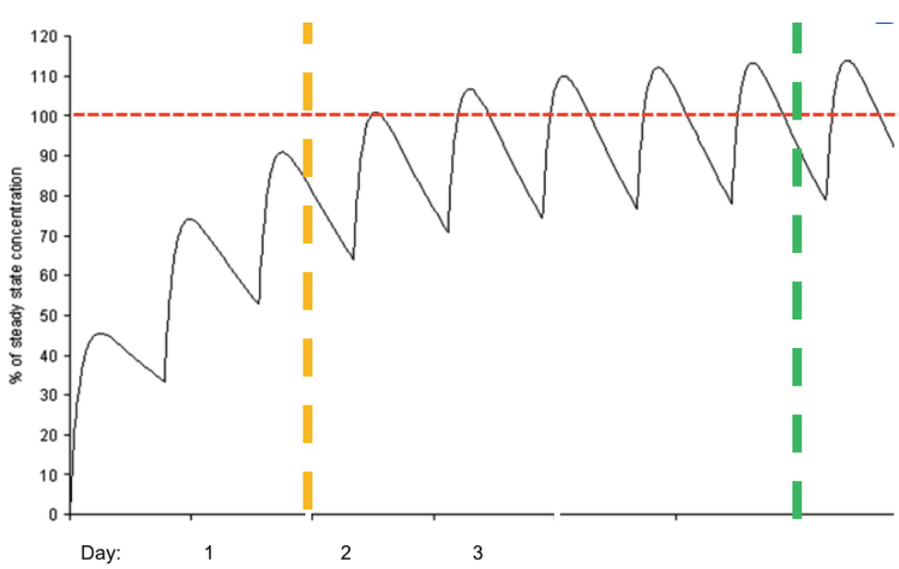

Figure 3. Achieving therapeutic steady state: 1 day vs. 3 days preop

achieve tissue levels before surgery, since it takes about three to five doses on average to achieve steady state (Figure 3). Preop dosing also attenuates the inflammatory response and gets patients in the habit of using drops.

After surgery, both steroids and NSAIDs are indicated for use out to 14 days postop. Steroids in particular should be used to "hammer the inflammation"—hit inflammation hard with more frequent dosing initially, taking advantage of the immediate postop period when compliance is at its best. When the steroids are no longer needed, they should be tapered off, unlike NSAIDs, which are simply discontinued.

Dr. Devgan's routine is to begin topical NSAIDs, steroids, and an antibiotic 3 days before surgery, continuing the NSAID out to 6 weeks, the steroid BID for 1 week followed by once a day for another week, and the antibiotic TID for 1 week after surgery.

The bottom line, said Dr. Devgan, is "use your clinical judgment. Determine when the inflammation is resolved, and tailor the treatment to the patient."

Postop recovery, he added, is as important as surgical technique.

Risk factors for steroid response among cataract patients

In his own private practice, **David F. Chang, MD**, clinical professor of ophthalmology, University of California, Los Altos, Calif., had noticed how an occasional patient would present with an alarming increase in IOP shortly after cataract surgery.

"The IOP would be up to 50 or 60 mm Hg, and the patients had called because their vision was blacking out when they would bend over," he said. "They always seemed to be young, really high myopes, and they might present less than one week following uncomplicated surgery."

Dr. Chang diagnosed these patients as steroid responders because these were pressure spikes following normal postop day 1 tonometry, and the pressure would normalize after stopping the topical steroid.

Dr. Chang described the results of a retrospective study he conducted to identify the risk factors in these cases, presenting data recently published in the *Journal of Cataract & Refractive Surgery*.[7] "If you review the literature, the only published risk factor for a steroid response is open-angle glaucoma," he said.

In a chart review covering a 2-year period, Dr. Chang and his colleagues gathered data on 1,642 consecutive patients. All the patients underwent phacoemulsification with IOL implantation and had received a uniform treatment regimen of 1% prednisolone acetate three times a day for 2 weeks, then twice a day for 2-3 weeks. Each patient also received a topical NSAID and an antibiotic.

Dr. Chang analyzed age and axial length measurements using the IOLMaster, always taking the first eye in a bilateral cataract surgical patient. IOP measurements were recorded preop, at postop day 1, and at least one additional time between 2 and 4 weeks after surgery.

He defined steroid responders as patients who underwent uncomplicated surgery but had an IOP measurement of at least 28 mm Hg beyond the first 72 hours after surgery, to exclude surgical factors such as retained OVD or corneal edema. Exclusion criteria included any hyphema, endophthalmitis, or TASS. "We decided to use 28 mm Hg as our threshold because many of us would alter or initiate treatment at this IOP level," Dr. Chang explained.

To be sure that it was drug induced, an IOP elevation of ≥25% on steroid and an IOP drop of ≥25% off steroid was required for the patient to be classified as a steroid responder.

After excluding patients who were not prescribed steroids (e.g., known responders, herpetic eye disease), a total number of 1,613 consecutive patients had uncomplicated surgeries and were taking topical steroids postoperatively. Of these patients, 39 (2.4%) had IOPs of ≥28 mm Hg, 15 (0.9%) had IOPs of ≥35 mm Hg, and 7 (0.4%) had IOPs in the range of 40-68 mm Hg. Of the 7 patients with alarmingly high IOPs, 6 were <65 years old, 4 were high myopes, and 6 were diagnosed early—between 5 and 14 days after surgery. Of the 39 patients exceeding the threshold 28 mm Hg IOP for steroid response, only 6 had a known risk factor—open-angle glaucoma.

This left 85% without any known risk factors. By analyzing the 39 steroid respon-

Cumulative % steroid responders by age and AL groups

AGE	< 25.0 mm	≥25.0 mm	≥27.0 mm	≥29.0 mm	All events <.0001
40-54	2/53 **3.8%**	9/63 **14.3%**	6/35 **17.1%**	5/14 **35.7%**	11/116 **9.5%**
55-64	3/150 **2.0%**	10/128 **7.8%**	3/49 **6.1%**	1/11 **9.1%**	13/278 **4.7%**
≥65 yrs	7/955 **0.7%**	8/264 **3.0%**	4/39 **10.3%**	1/7 **14.3%**	15/1219 **1.2%**
All events <.0001	12/1158 **1.0%**	27/455 **5.9%**	13/123 **10.6%**	7/32 **21.9%**	39/1613 **2.4%**

Figure 4. Cumulative % steroid responders by age and axial length

Steroid responder risk Odds ratios

	< 25.0 mm	25.0-27.0 mm	27.0-29.0 mm	≥ 29.0 mm
40-54 yrs	3.8% ***4.1 x***	10.0% ***7.9 x***	5.3% ***15.8 x***	35.7% ***46.1 x***
55-64 yrs	2.0% ***2.5 x***	8.9% ***5.2 x***	5.3% ***9.7 x***	9.1% ***31.8 x***
≥65 yrs	0.7% ***1***	1.8% ***2.4 x***	9.4% ***5.4 x***	14.3% ***14.4 x***

Figure 5. Steroid responder odds ratios, with treatment stratification by risk

ders, Dr. Chang and his colleagues were able to identify two factors significantly associated with IOP response.

First was age. The mean age of the steroid responders was significantly lower than the mean age of the non-responders, 61.3±11.8 years vs. 71.8±11.7 years, respectively ($p<0.01$).

Second was axial length. The responders had significantly longer eyes than the non-responders, 25.59±3.0 mm vs. 24.33±1.75 mm, respectively ($p<0.01$).

The significance of these risk factors becomes even clearer when the data is stratified (Figures 4 and 5). In terms of age, patients 40-54 years old are four times more likely to be steroid responders than patients ≥65 years old. In terms of myopia, the risk of steroid response rose with increasing axial length. Compared to eyes <25.0 mm long, eyes longer than 27 mm had a more than 5-fold increase in risk and those longer than 29.0 mm had more than a 14-fold increase in risk (Figures 4 and 5).

Taken together, the youngest patients (40-54 years old) with the longest eyes (≥29.0 mm) have a markedly greater 46-fold increase in steroid response risk compared to older patients (≥65 years old) with normal axial length (<25.0 mm)—35.7% vs. 0.7%, respectively.

Interestingly, these ratios were the same across the spectrum of steroid responders regardless of the severity of IOP increase—meaning these risk factors do not appear to influence the severity of the response.

This risk stratification has given Dr. Chang the opportunity to customize his approach to postoperative steroid use following cataract surgery, particularly in light of published studies that suggest steroid responders may be more tolerant of loteprednol etabonate 0.5% than of other corticosteroids.[8,9] Where patients have a significantly higher odds ratio of a steroid response —i.e., patients less than 65 years old with an axial length of 25.0-29.0 mm (red box in Figure 5)—he uses loteprednol, avoids difluprednate, and monitors the IOP more closely. For patients at highest risk—i.e., patients of all ages with axial lengths >29.0 mm (green box in Figure 5)—he uses topical NSAIDs only, opting to add loteprednol only if necessitated by factors such as greater inflammation, with the addition of prophylactic topical glaucoma medication to prevent an IOP spike.

This study is the first to correlate steroid response to high myopia and the first to tie steroid response to younger age in terms of topical as opposed to intravitreal medication.

The two risk factors combined result in a very high percentage of steroid responders. For these eyes, loteprednol etabonate 0.5% offers a possibly safer alternative, and Dr. Chang's subsequent clinical experience bears this out.

Medication vehicles: Strategies to prevent edema and relieve pain

"Medications, as we all know, are a little bit more than just the active ingredients," said **Francis S. Mah, MD**, director, cornea and external disease, and co-director, refractive surgery, Scripps Clinic, La Jolla, Calif. Every bottle of medication includes other components, such as preservatives, drug delivery systems, viscosity increasing agents, buffers, stabilizers, and carrier vehicles.

"It's a very special scenario that we have with the eye because we put these eye drops directly onto the place of therapy," said Dr. Mah. The medication vehicle thus "plays a huge role in terms not only of efficacy, but of safety and tolerability as well."

In fact, safety is a major part of the design of newer formulations of steroids and NSAIDs, particularly in terms of medication vehicles. "We want to reduce as much as possible the baggage that comes along with medications," he said. "In general, we try to have the lowest concentrations that will provide the efficacy of the drug, and we try to optimize the preservatives so that we reduce any potential for toxicity."

In addition to safety, medication vehicles provide opportunities to enhance efficacy through increased penetration and tissue concentrations. Medication vehicles can, for instance, increase the solubility of drugs. The cornea, said Dr. Mah, provides a strong barrier to the entry of these drugs into the eye due to its biphasic structure, with lipophilic epithelial and endothelial layers combined with a hydrophilic stroma. Medication vehicles provide ways to overcome that barrier, thus helping to optimize dosing, ideally reducing dose frequency, resulting in improved patient compliance.

Improving drug delivery

The basic challenge, said Dr. Mah, is that typically out of an average of 50 microliters of medication dropped onto the eye and through various mechanisms including spillage, lacrimation and blinking, tear film turnover, and conjunctival and scleral absorption, only about 5% of the total dose actually enters the eye to work as intended[10,11,12] (Figure 6).

Attaining an optimal drug concentration at the site of action thus presents a major problem in ocular therapeutics.

Strategies to improve drug delivery focus on overcoming two basic challenges: minimizing precorneal drug loss and maximizing corneal drug absorption. This is achieved by increasing the effective dose, utilizing molecular design, and/or utilizing formulation science (Figure 7).

The first strategy, increasing the effective dose, may mean increasing the concentration of the active drug, such as with the latest formulation of nepafenac (0.3% from 0.1%), and/or decreasing the size of the suspension particles such as the 40% reduction of the new nepafenac formulation. Although increasing the dosing frequency may also increase the effective dose, Dr. Mah said, increasing the dosing frequency is not a very favorable approach since it also decreases patient compliance. Reducing drug concentrations may seem counter to increasing the effective dose, if the efficacy can be optimized using other methods, the advantage is the potential to reduce unwanted side effects. This was the strategy for the new formulation of bromfenac (0.07% from 0.09%).

The second strategy uses molecular design to increase lipophilicity and solubility.

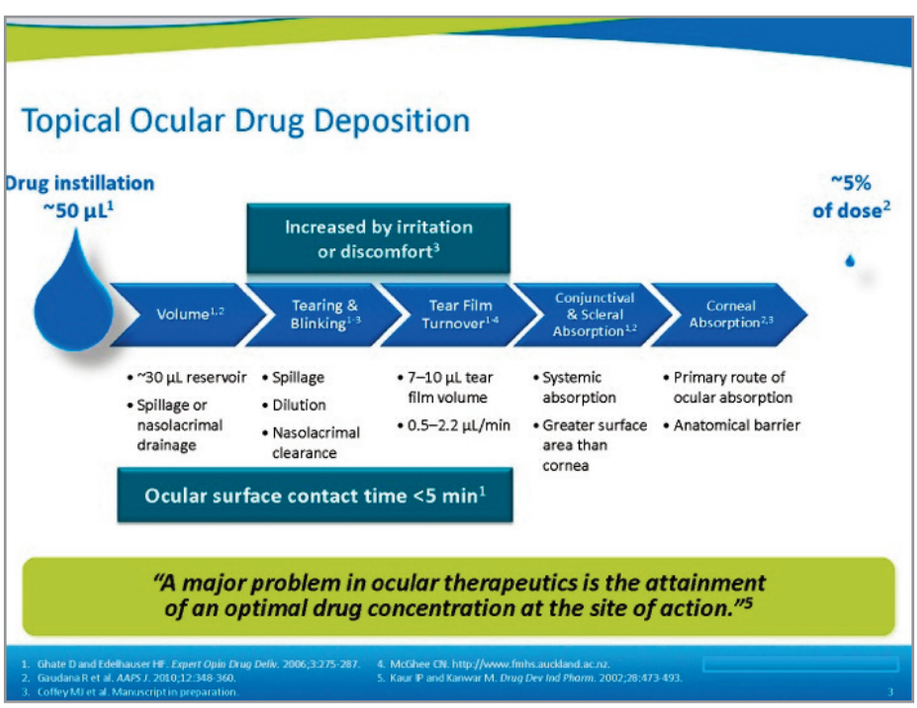

Figure 6. Topical ocular drug deposition

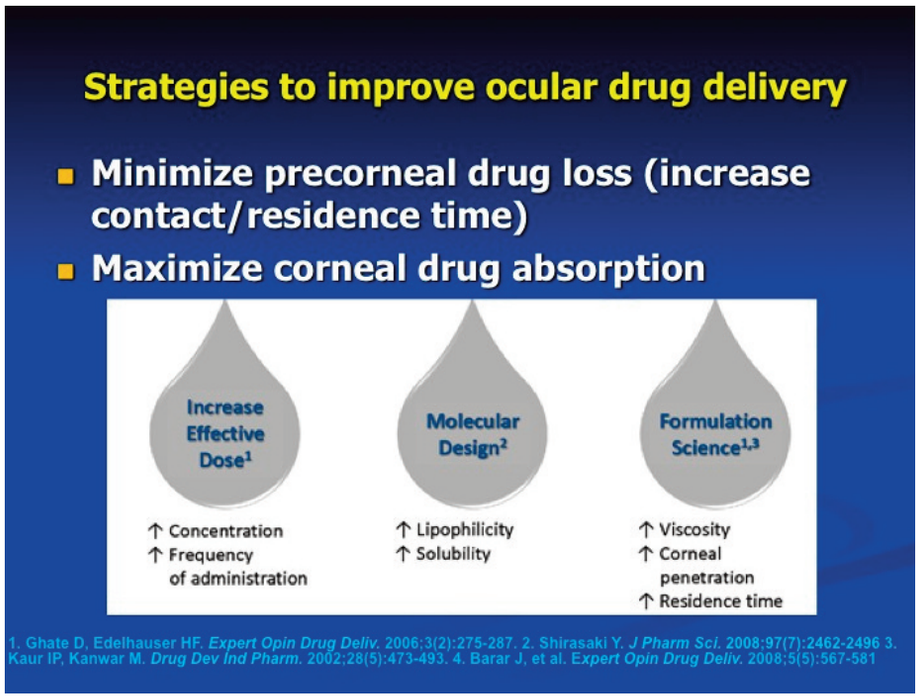

Figure 7. Strategies to improve ocular drug delivery

Lipophilicity can be increased by using unique chemical structures. The chemical nature of bromfenac is hydrophilic, thus formulation pH and vehicle are key to facilitating rapid penetration to produce early and sustained drug levels, which has been accomplished in the new formulation. Meanwhile, nepafenac is a prodrug, a property that allows it to rapidly and safely cross the cornea.

Lowering the pH can decrease the charge, increasing lipophilicity, and facilitate corneal penetration of NSAIDs. The newer bromfenac formulation lowers the pH of the original bromfenac formulation, from 8.3 to 7.8 (closer to the 7.4 pH of tear fluid). This decreases the charge, increases the lipophilicity, and so increases the drug delivery into the eye. This strategy has also been used by the new nepafenac formulation showing the importance of this property for topical NSAIDs.

A third strategy is to use formulation science to increase viscosity. An example of this is to use a mucoadhesive matrix such as polycarbophil USP, which stays in contact with the conjunctiva and delivers the drug to the surface of the eye over a period of hours, thus increasing the bioavailability of the drug. This is the vehicle used in loteprednol gel. Other medications such as the new nepafenac formulation use guar gum, which acts as a stabilizer, emulsifier, thickening, and suspending agent, or lipid emulsion technology such as the difluprednate formulation to increase viscosity, corneal penetration, and residence time, and so bioavailability.

These technologies also mean that the newer drugs do not need shaking—the drug remains suspended evenly. This improves drug delivery so that drop-to-drop variance of drug does not occur. This is especially important considering prednisolone acetate 1%, for example, may vary from 0% drug to 700% depending on shaking or not and bottle inversion.

Preservatives – a necessary evil

Recent years have seen some controversy over another component of modern drugs—preservatives. However, Dr. Mah called them a "necessary evil," used to prevent microbial activity and prolong the shelf life of drugs. Two primary preservatives are used in anti-inflammatory agents: sorbic acid and benzalkonium chloride (BAK).

Sorbic acid has long been used in artificial tears because it causes only minimal irritation or damage to the ocular tissues and is thus recommended for sensitive eyes. Meanwhile, according to Dr. Mah, 72% of ophthalmic medications are preserved with BAK. One of the benefits of using this substance with its mild toxicity is that it enhances drug penetration through the cornea by breaking epithelial bonds. This toxicity is dose dependent, and newer anti-inflammatory formulations contain lower concentrations.

Not all the same

It is important to note that not all medication vehicles are the same. The distinction is particularly important when considering generic drugs. Unlike branded drugs, generics can be approved without clinical studies to show efficacy or safety; rather, they only need to show 80% bioequivalence in the bottle.

"I personally recommend branded medications to all my patients," said Dr. Mah.

An additional issue surrounding generic drugs is the Supreme Court ruling that states that companies that manufacture generic medication are not responsible for the product insert and the label, and are therefore not liable if a patient has a complication with these drugs. This may shift the liability to the prescribing surgeons and their offices, hospitals, and surgical centers. Dr. Mah suggested that it may be necessary to provide written consent or acknowledgement stating that patients prescribed with generic drugs have been informed of and accept the risks of taking medication not backed by efficacy and safety studies.

The issues of liability aside, it is a significant comfort to know that there are excellent quality products available, designed to deliver the optimum therapeutic effect with the fewest unwanted side effects, rigorously studied in clinical trials to show efficacy and safety.

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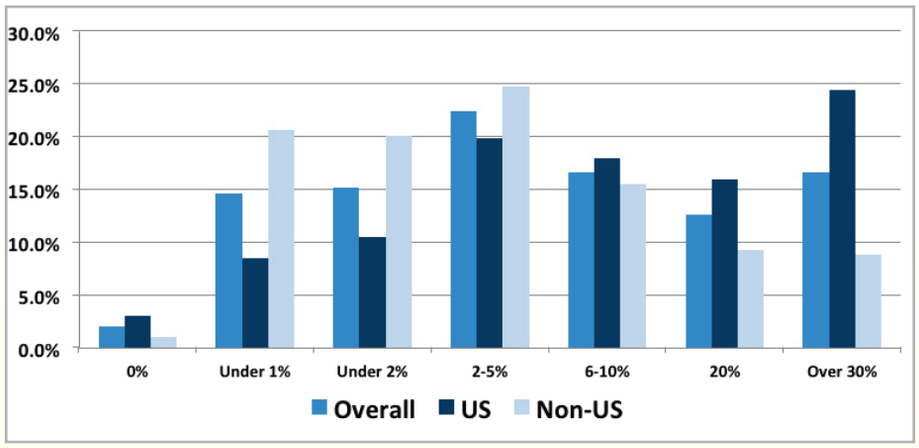
Key inflammation practice patterns and clinical opinions of ASCRS members

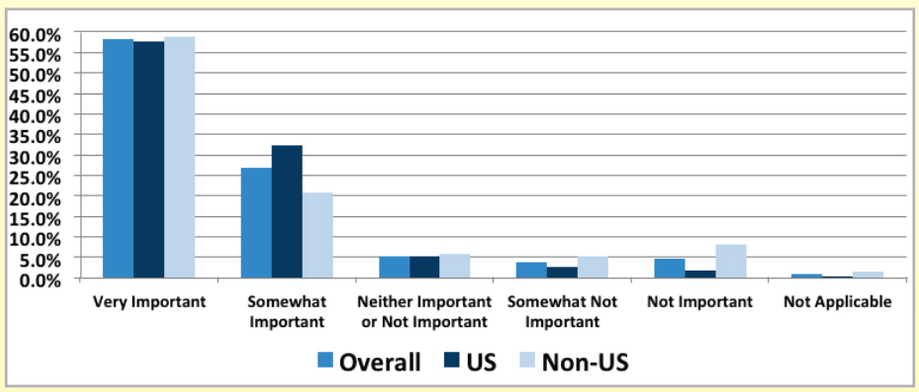
What percentage of your cataract patients has 1+ cells/flare or greater postoperatively?



Percentage of survey respondents using the following pharmaceuticals at the following timeframes before and after cataract surgery:

	Steroids	NSAIDs	Antibiotics
3 days preop	19%	43%	43%
1 day preop	16%	32%	33%
Intraop	27%	16%	40%
1 day postop	67%	42%	51%
Do not use	5%	14%	3%

How important do you believe that it is to use BOTH NSAIDs and corticosteroids to block the inflammatory cascade after cataract surgery, when indicated?



At the 2013 ASCRS•ASOA Symposium & Congress, more than 1,000 physicians responded to an important new clinical trends survey that will continue to be assessed each year. The survey asked ASCRS members more than 85 key questions relating to current issues they face on a regular basis. The goal is to obtain opinion from a significant percentage of the membership and to have the results reviewed and interpreted by the ASCRS Clinical Committees. If the Committees determine there exists a gap between current programming and membership viewpoints, understanding or practice patterns, the information will be used to address future education efforts, both in the main program and through ASCRS' CME educational grants. Data collected from the annual survey will provide a solid basis for tracking ASCRS' progress in resolving these education gaps.

Many topics related to post cataract surgery inflammation were a part of this survey. These included topics on the level of inflammation currently seen by ASCRS members, the impact of low to moderate inflammation on outcomes, current therapeutic trends, and perspectives on generic substitutions.

When asked the normal levels of inflammation they would expect after cataract surgery, most responded that they would consider between trace to 1+ cell and flare at day 1 postop after cataract surgery as normal. Specifically, 56% view this level as normal, while 30% of members expect between zero and trace cell and flare postop on an average basis. Only 15% expect to see 1+ cell and flare in postop "normal" cataract patients.

In another question, survey respondents were asked to move from their expected inflammation levels to the actual percentage of cataract patients they see who have 1+ cell and flare postoperatively. Sixteen percent have under 1% of patients at this 1+ cell/flare level, while 32% have under 2% at this level. On the other hand, 29% of respondents have 20% or more of their patients with 1+ cell/flare. So there seems to be a relatively wide variation in the incidence of moderate inflammation among survey respondents.

The clinical impact of low to moderate ocular inflammation is often debated. When survey respondents were asked about the clinical impact of this level of inflammation, most agreed that it had a significant impact on variability in visual acuity and quality results (71%), visual recovery time (81%), or patient comfort and satisfaction (83%).

CME Questions (Circle the correct answer)

1. According to Dr. Devgan, how many days after cataract surgery are steroids and NSAIDs indicated for?

a. 1 day

b. 7 days

c. 14 days

d. 28 days

2. According to Dr. Chang, which of the following factors were associated with "steroid responders" or patients who presented with an elevated IOP after cataract surgery?

a. High myopia and younger age

b. Low myopia and younger age

c. High myopia and older age

d. Low myopia and older age

3. According to Dr. Mah, of the 50 microliters of medication dropped into the eye, what percentage of the total dose actually enters the eye to work as intended?

a. 50%

b. 25%

c. 10%

d. 5%

4. Which of the following is NOT a strategy identified by Dr. Mah on how to improve drug delivery to the eye?

a. Increase effective dose

b. Increase lipophilicity and solubility with molecular design

c. Increase viscosity with formulation science

d. Combine with other drugs

To claim credit, please fax the test and fully completed form to 703-547-8842 or mail to: EyeWorld, 4000 Legato Road, Suite 700, Fairfax, VA 22033, Attn: July CME Supplement

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