CME MONOGRAPH

EARN CREDITS CME

TEN TIPS
FOR TREATING INFLAMMATION WITH TOPICAL STEROIDS

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LEARNING METHOD AND MEDIUM

This educational activity consists of a supplement and ten (10) study questions. The participant should, in order, read the learning objectives contained at the beginning of this supplement, read the supplement, answer all questions in the post test, and complete the Activity Evaluation/Credit Request form. To receive credit for this activity, please follow the instructions provided on the post test and Activity Evaluation/Credit Request form. This educational activity should take a maximum of 1.5 hours to complete.

ACTIVITY DESCRIPTION

Topical corticosteroids, including dexamethasone, difluprednate, fluorometholone, loteprednol, and prednisolone, are potent anti-inflammatory medications that are prescribed for a wide range of indications in ophthalmology. Their uses include control of inflammation associated with cataract and other ocular surgeries, dry eye disease, eyelid disorders, allergic eye conditions, and anterior uveitis. New topical corticosteroid products have recently been approved, including new formulations of loteprednol etabonate. Additionally, some topical corticosteroid products have recently or will soon become available as generic versions. The desired results of this educational activity are for ophthalmologists to help their patients with a variety of inflammatory conditions achieve better outcomes.

TARGET AUDIENCE

This educational activity is intended for ophthalmologists.

LEARNING OBJECTIVES

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

- Discuss the efficacy of newer topical corticosteroids to control ocular inflammation
- Explain the formulation characteristics and safety of newer topical corticosteroids to control ocular inflammation
- Identify optimal strategies for control of postoperative inflammation for patients undergoing ophthalmic surgery
- Identify optimal strategies for control of inflammation for patients with ocular inflammatory disease such as dry eye
- Use appropriate strategies to discuss the differences between generic and brand name anti-inflammatory agents

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OFF-LABEL DISCUSSION

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TEN TIPS
FOR TREATING INFLAMMATION WITH TOPICAL STEROIDS

Introduction

Topical steroids have an essential role for treating inflammation associated with a range of ophthalmic conditions and surgical procedures. Several different steroids are available for topical ophthalmic use, and options have recently expanded. This educational activity presents information about newer topical steroids, regimens for some of their most common uses, and strategies for optimizing outcomes, including approaches for patient counseling.

Tip #1: Keep Up With What's New

Several novel ophthalmic steroid products have become available in recent years or are currently under investigation **(Table 1)**,[1-7] adding to the broad treatment armamentarium of corticosteroids available to treat ocular inflammation **(Table 2)**.[8-17]

The newest options for topical steroid treatment represent new formulations of loteprednol etabonate:

- Loteprednol etabonate gel, 0.38%, is formulated with submicron particles of the active ingredient that increase loteprednol bioavailability.[4,18] It is indicated for the treatment of postoperative pain and inflammation, with a 3-times-daily dosing schedule.[4]
- Loteprednol etabonate suspension, 1%, uses mucus-penetrating particle (MPP) technology to increase loteprednol bioavailability.[7,19] It is indicated for the treatment of postoperative pain and inflammation, with twice-daily dosing.[3]
- Loteprednol etabonate suspension, 0.25%, also uses MPP technology to increase loteprednol bioavailability.[5] Not yet US Food and Drug Administration approved, this loteprednol product is being developed for the temporary relief of the signs and symptoms of dry eye disease (DED). A phase 3 study investigating this product met its primary and key secondary end points.[5]

Also among the newer ophthalmic steroids are 2 novel products providing sustained release of dexamethasone and aiming to overcome some of the drawbacks associated with conventional topical medications:

- Dexamethasone intraocular suspension, 9%, is indicated for the treatment of postoperative inflammation.[1] It is injected into the posterior chamber behind the iris at the end of surgery and provides control of inflammation for up to 30 days.
- Intracanalicular dexamethasone insert, 0.4 mg, is indicated for the treatment of postoperative inflammation and pain.[2] It is inserted into the inferior punctum and releases dexamethasone for up to 30 days.

Dr Yeu: What are the advantages of these newer steroid formulations?

Dr Donnenfeld: The use of submicron particles and MPP improves loteprednol bioavailability. The smaller submicron particles of loteprednol etabonate gel, 0.38%, dissolve faster than the larger micronized particles found in loteprednol etabonate gel, 0.5%, and result in better penetration into target tissues.[18] The MPP technology uses nanoparticles of drug formulated to enhance loteprednol penetration through the tear film.[7]

Table 1. Novel Ophthalmic Steroids

Product (Brand Name)	Date of FDA Approval	Indication	Administration	Preservative	Delivery System
Dexamethasone intraocular suspension, 9% (Dexycu)[1]	February 2018[6]	Treatment of postoperative inflammation	Behind iris at end of surgery	None	Sustained release, controls inflammation for up to 30 days
Intracanalicular dexamethasone insert, 0.4 mg (Dextenza)[2]	November 2018 (pain)[6] June 2019 (inflammation)[2]	Treatment of postoperative pain and inflammation	Inserted into inferior punctum	None	Sustained release for up to 30 days
Loteprednol etabonate suspension, 1% (Inveltys)[3]	August 2018[6]	Treatment of postoperative pain and inflammation	Topical twice daily	BAK, 0.01%	Mucus-penetrating particle technology[7]
Loteprednol etabonate gel, 0.38% (Lotemax SM)[4]	February 2019[4]	Treatment of postoperative pain and inflammation	Topical 3 times daily	BAK, 0.003%	Submicron particles
Loteprednol etabonate suspension, 0.25% (Eysuvis)[5]	Investigational	Temporary relief of signs and symptoms of DED	Topical 4 times daily	NA	Mucus-penetrating particle technology

Abbreviations: BAK, benzalkonium chloride; DED, dry eye disease; FDA, US Food and Drug Administration; NA, not available.

Table 2. Conventional Topical Ophthalmic Steroids

Product (Brand Name)	Concentration, %	Delivery System	Generic Available
Dexamethasone sodium phosphate[8]	0.1	Solution Suspension	Yes
Difluprednate (Durezol)[9]	0.05	Emulsion	No
Fluorometholone acetate (Flarex)[10]	0.1	Suspension	No
Fluorometholone (FML)[11]	0.1	Suspension Ointment	Yes No
Fluorometholone (FML Forte)[12]	0.25	Suspension	No
Prednisolone acetate (Pred Forte)[13]	1	Suspension	Yes
Prednisolone acetate (Pred Mild)[14]	0.12	Suspension	Yes
Prednisolone sodium phosphate[15]	1	Solution	Yes
Loteprednol etabonate (Alrex)[16]	0.2	Suspension	No
Loteprednol etabonate (Lotemax)[17]	0.5	Suspension Ointment Gel	Yes No No

With their improved bioavailability, the newer topical formulations of loteprednol provide increased efficacy with reduced dosing frequency. A need for less frequent administration can enhance patient compliance.[20] These newer products also allow steroid treatment with the favorable intraocular pressure (IOP) safety profile of loteprednol.[21,22] As such, the newer products are now my treatment of choice when I am using a topical steroid to treat inflammation after cataract surgery.

Other topical corticosteroids, such as fluorometholone and prednisolone acetate, are also a good choice for uncomplicated surgery and are available at decreased cost as a generic alternative.

The intraocular and intracanalicular dexamethasone products have the benefit of being preservative free, unlike the topical products.[1,2] Their main advantage is that they can often eliminate the need for topical steroid treatment.[23,24] Therefore, use of these products can overcome problems with patient compliance or inability to administer topical medications. With the topical products, however, it is easier to withdraw the medication when needed to manage an adverse event.

Dr Yeu: Do you think any of the newer products have taken on added value in our current environment with the COVID-19 (coronavirus disease 2019) pandemic?

Dr Singh: There is increased interest now in decreasing the number of postoperative follow-up visits for patients. Having less frequent follow-up intensifies the need for treatments that will be reliably safe and effective for controlling inflammation. The advantages of the newer steroid products in terms of increased bioavailability and potential for improving patient compliance give me greater confidence about treatment efficacy. Using loteprednol minimizes my concern about an undetected IOP response to the steroid.

Dr Donnenfeld: Thinking about the recommendations for limiting close contact during the pandemic, there are a few reasons to prefer medications that eliminate the need for topical treatments. Many older patients have to depend on someone else to administer their topical medications; this can be an issue considering advice to limit contact with people living outside the household. In addition, regardless of who is administering the medication, the use of topical drops involves touching the face with the fingers.

Tip #2: Know the Relevance of Formulation Differences

The 2 recently approved topical loteprednol products use different technologies to formulate the active ingredient, and both are effective for improving drug delivery that allows for efficacy in treating inflammation after cataract surgery with less than 4-times-daily dosing.[7,18,19,25] The products differ in other formulation aspects that have potential implications for efficacy and safety.

Formulation differences include preservative content and other inactive ingredients. Both medications are preserved with benzalkonium chloride (BAK); the concentration of BAK is 0.01% in loteprednol etabonate suspension, 1%, and 0.003% in loteprednol etabonate gel, 0.38%.[3,4] Both products contain glycerin, which has moisturizing properties that may contribute to drop comfort. Loteprednol etabonate gel, 0.38%, contains a second moisturizer—propylene glycol.[4]

One of the most basic differences between the 2 newer loteprednol products pertains to dosage form, ie, suspension vs gel. A suspension needs to be shaken prior to use to disperse and distribute the particles of active ingredient. The prescribing information for loteprednol etabonate suspension, 1%, states that the bottle should be shaken for 1 to 2 seconds before using.[3] In loteprednol etabonate gel, 0.38%, submicron particles of the active ingredient are homogenously distributed, and the container needs to be shaken once to fill the tip before dispensing the medication.[4]

Dr Yeu: What is the potential clinical relevance of the formulation differences between the 2 newer loteprednol formulations? Are there implications for safety and/or efficacy?

Dr McDonald: The difference in BAK concentration between the 2 products is noteworthy because BAK is known to cause ocular surface toxicity and discomfort, which could result in poor treatment adherence.[26] The additional moisturizing ingredient in loteprednol etabonate gel, 0.38%, might further enhance comfort of that agent.[25]

The need for more shaking with a suspension is potentially problematic, considering research documenting that patients often do not shake the medication container sufficiently before use. In a study in which 100 patients were given bottles of different ophthalmic steroids with clear instructions to shake well before using, approximately two-thirds of the patients did not shake the bottle at all, and most of the remaining patients did not shake the bottle enough to dispense the labeled concentration of active ingredient.[27] If patients are not adequately shaking the steroid suspension bottle when they are starting treatment, they may be administering a subtherapeutic dose.

Dr Singh: Safety also becomes an issue when a steroid suspension is not properly shaken. During the early postoperative period when the steroid is needed the most, if the active drug settles at the bottom of the bottle because of lack of adequate shaking, patients run the risk of poor inflammation control. Conversely, because the concentration of active ingredient in the dispensed drop increases with time by settling in the bottle, exposure to the higher steroid dose could potentially increase the risk for IOP elevation in steroid responders as patients continue to use the medication.

Tip #3: Minimize Intraocular Pressure Concerns With Careful Steroid Selection and Knowing Who Might Be a Steroid Responder

The development of a clinically significant increase in IOP is a potential adverse reaction to topical steroid treatment.[21,22] The risk varies depending on certain demographic and clinical characteristics and among the different steroids that are used topically.

Reported risk factors for IOP elevation with the use of topical steroids include younger age, personal or family history of primary open-angle glaucoma, angle-recession glaucoma, connective tissue disease, high myopia, and type 1 diabetes.[21,28] The development of elevated IOP is much more common with dexamethasone or prednisolone than with fluorometholone or loteprednol etabonate.[21,22] Difluprednate may be associated with a particularly marked IOP elevation. Awareness of patient-related risk factors for a steroid IOP response, judicious selection of a topical steroid, and careful monitoring will help minimize IOP concerns and increase the safety of steroid treatment.

Dr Yeu: Dr Singh, how do you control inflammation after cataract or glaucoma surgery in patients with glaucoma, considering the increased risk for a steroid response in this population and concern about its consequences?

Dr Singh: Because of its favorable safety profile and efficacy data, I do use loteprednol etabonate. I do not feel there is a need to prescribe a tapering regimen. We have not seen significant IOP spikes in our standalone and combination cataract and glaucoma surgery patients.

Dr McDonald: Although we are talking about the effect of loteprednol on IOP, I think it is important to clarify the meaning of the term "soft steroid" that is sometimes used to describe loteprednol. I believe the term "soft steroid" is often misinterpreted as meaning that loteprednol is less potent or less effective than other topical steroids. Rather, a "soft drug" describes an agent that undergoes predictable metabolism to inactive metabolites after exerting its therapeutic effect.[29] Loteprednol is structurally a derivative of the primary metabolite of prednisolone, but it is less likely than prednisolone to cause IOP elevation because it is rapidly inactivated by tissue esterases in vivo.[30]

Tip #4: Recognize the Broad Use of Topical Steroids to Treat Ocular Diseases—Not Just Routine Phacoemulsification

Topical steroids have a wide role for treating ocular diseases. They are used to control inflammation after ocular surface or anterior segment surgery, including keratorefractive procedures, keratoplasty, cataract surgery, glaucoma surgery, pterygium surgery, ocular surface reconstruction, and lamellar keratectomy. Topical steroids are also used to treat inflammation associated with lid and ocular surface disease, such as DED, meibomian gland dysfunction (MGD), blepharitis, and allergic conjunctivitis. In addition, topical steroids are used to manage inflammatory conditions of the anterior segment, including anterior uveitis, episcleritis, and scleritis.

Dr Yeu: I would like to discuss some of the uses for topical steroids in greater depth. Dr McDonald, what is your current steroid regimen for treating inflammation after laser keratorefractive surgery?

Dr McDonald: I prescribe loteprednol etabonate because I think it eliminates inflammation faster than does prednisolone acetate. Therefore, patients need to be on the steroid for a shorter duration. I prescribe loteprednol 4 times daily for just 1 week in most patients, but continue it for 2 weeks in patients treated for higher levels of hyperopia or myopia.

Dr Yeu: With cataract procedures, a steroid is often continued for 4 or 5 weeks. Dr Singh, does your steroid regimen differ if you are doing cataract surgery alone vs in combination with minimally invasive glaucoma surgery?

Dr Singh: I am using loteprednol postoperatively in both settings because of its favorable IOP safety profile.[21,22] For the most part, I use the same dosing regimen I use for my cataract surgery patients, but it can vary depending on the minimally invasive glaucoma surgical procedure. Different procedures can cause various levels of tissue disruption and therefore differ in their potential to cause inflammation.[31]

The amount of inflammation after phacoemulsification with insertion of a trabecular microbypass stent is similar to that following phacoemulsification alone.[32] In these cases, I generally

prescribe loteprednol twice daily for 1 month. Procedures that involve cutting or stripping the trabecular meshwork may result in more significant inflammation. With these procedures, I have patients use loteprednol 3 or 4 times daily for 1 month. I use the same, more intensive steroid regimen in trabeculectomy and ab interno subconjunctival bypass cases because significant postoperative inflammation is a risk factor for bleb fibrosis and failure of those procedures.[33,34]

Dr Yeu: Are there scenarios in which you are using a topical steroid on a chronic basis? I have done this—more often on a chronic, intermittent basis—to limit growth of a pterygium in patients with a lesion that is starting to encroach on the visual axis who are not yet candidates for surgery, particularly if they cannot avoid sun exposure. I also use a topical steroid drop daily as a maintenance dose to prevent graft rejection in patients undergoing corneal transplantation.

Dr Donnenfeld: I think some patients with DED or allergy may need to be on chronic steroid therapy for optimal disease control. I would use a lower concentration of loteprednol—0.2% or 0.38%—and dose it just once or twice daily. This is a particularly reasonable thing to do in patients who are pseudophakic and are not steroid responders, and I think it is widely underused. Published papers have reported on the safety and efficacy of loteprednol for long-term management of DED and ocular allergy.[35,36] One retrospective study comparing loteprednol with fluorometholone for treating severe dry eye associated with Sjögren syndrome found both steroids to be effective, but that loteprednol had a lower risk for increasing IOP.[35] No adverse effects were reported in a series of 159 patients who were treated for allergic conjunctivitis with loteprednol etabonate, 0.2%, for more than 12 months.[36]

Chronic steroid treatment is also used to limit corneal neovascularization in eyes with inflammatory keratitis. This can be seen in a variety of conditions, including rosacea blepharitis, herpes simplex virus, herpes zoster, and allergic keratitis. Neovascularization will increase the odds of graft failure if the patient progresses to need a corneal transplantation.[37] This risk makes the possibility of needing cataract surgery because of chronic steroid treatment an acceptable tradeoff.

Dr McDonald: I have some patients who need to be kept on a low dose of a topical steroid long term after keratoplasty. These patients may need to use just 1 drop a day, 2 days a week. As Dr Donnenfeld said, some patients need to be kept on a steroid to maintain control of symptoms from DED. I am treating 2 such patients; they are using 1 drop of loteprednol etabonate once daily just 1 or 2 days a week.

It is important that patients who are using a steroid long term understand the potential risks, can be trusted not to overuse the medication, and are deemed reliable to return for follow-up visits. The 2 patients I am treating for DED are phakic and understand they may develop a cataract earlier than they might have if they were not using a steroid.

Dr Singh: Some of my patients who have DED associated with the use of topical glaucoma medication cannot tolerate cyclosporine or lifitegrast. I find that their DED-related inflammation can be safely and effectively controlled with loteprednol once or twice daily. I also have patients with DED not related to topical medication who need to be on a long-term steroid. Regardless of its cause, DED is an inflammatory condition. I also use loteprednol as a test to see if a patient would benefit from cyclosporine or lifitegrast. For instance, if a patient has symptoms suggestive of ocular surface disease, but with minimal clinical signs and I am unsure of the cause, I will often conduct a 2-week trial of loteprednol; if there is significant improvement in symptoms, then one of the long-term immunomodulators is indicated.

Tip #5: Carefully Include Steroids in Chronic Dry Eye Disease and Allergy Management

Dry eye and allergy are 2 common conditions that may be treated with a topical steroid. Because steroids can provide fast-acting control of inflammation, they are often prescribed as a short course to treat a flare of DED or allergy that can occur despite existing appropriate maintenance therapy.[38,39]

A topical steroid can also be used as induction therapy when patients are being started on maintenance treatment of DED with cyclosporine or lifitegrast.[40,41] The steroid acts faster than these other, immunomodulatory drugs to reduce inflammation. Therefore, patients feel better faster, and they are more able to tolerate the cyclosporine or lifitegrast, which can particularly cause stinging or burning when applied to an inflamed ocular surface.[40] Because of its fast action, a topical steroid is often used in a short course to rehabilitate the ocular surface prior to cataract, refractive, or glaucoma surgery.[42]

Dr Yeu: What is your regimen for using a steroid to treat DED?

Dr McDonald: I prescribe loteprednol with a tapering dose. The duration depends on the severity of the ocular surface disease. I usually administer it for 2 to 4 weeks, but sometimes 1 week is sufficient. Dr Donnenfeld published a study showing that loteprednol etabonate, 0.5%, used 4 times daily rehabilitated the ocular surface after just 2 weeks.[40] Results of the phase 3 study investigating loteprednol etabonate, 0.25%, as a treatment of DED showed statistically significant improvements in ocular discomfort severity, conjunctival hyperemia, and total corneal staining at day 15.[5] Topical fluorometholone has also been shown to provide rapid improvement of the ocular surface in patients with DED.[43] Because of the rapid symptomatic relief patients get from the steroid, I think they have greater confidence that their entire treatment regimen will be effective, which in turn motivates compliance.

Dr Singh: I use a steroid to calm down DED flares that can occur with the use of topical glaucoma medications. I put the patient on a holiday from the glaucoma drop and see if a short course of the steroid improves the ocular surface and the patient's symptoms. I believe that discomfort from DED is a reason for poor patient compliance with glaucoma medications, therefore explaining uncontrolled IOP. In fact, in an unpublished study, we found that by treating DED in patients on multiple glaucoma medications, approximately 50% of patients were able to reduce the number of glaucoma medications.

I also find that a large proportion of patients already have DED when I first diagnose them with glaucoma, which is not unexpected, considering that the prevalence of both diseases increases with age.[38,44] I start these patients on loteprednol for a couple of weeks and usually start cyclosporine or lifitegrast at the same time. In a study by Leung et al, 60 patients with glaucoma (59%) reported DED symptoms in at least 1 eye. Severe symptoms were reported by 27 patients (27%). Schirmer testing showed 62 patients (61%) with a decrease in tear production in at least 1 eye. Severe tear deficiency was presented in 35 patients (35%). Tear breakup time (TBUT) showed abnormal tear quality in

79 patients (78%), and severe decrease in tear quality was found in at least 1 eye in 66 patients (65%). After adjustment for age and sex, each additional BAK-containing eyedrop was associated with an approximately 2 times higher odds of showing abnormal results on the lissamine green staining test.[45]

Dr Yeu: Are there situations in which you use a steroid periodically by itself to treat dry eye and not as an addition to maintenance therapy?

Dr Donnenfeld: Some patients develop problems with dry eye only under certain circumstances. For example, when I go skiing in Colorado, my eyes become very dry for a week or 2 likely owing to the higher altitude. I think it makes sense to use a steroid by itself in that setting for dry eye flares. Loteprednol etabonate suspension, 0.25%, with nanotechnology is a new corticosteroid concentration that is seeking US Food and Drug Administration approval for short-term use in the setting of dry eye flares.[5]

Tip #6: Hit Inflammation Hard and Fast—Don't Suppress Inflammation, Eliminate It

Inflammation causes pain and can result in complications from tissue damage. Inflammation after cataract surgery can lead to cystoid macular edema and delayed or decreased visual recovery, and it increases the failure rate after trabeculectomy.[33,46] Collectively, the problems caused by inflammation can decrease patient satisfaction with the provider and with the care received. These adverse consequences provide a rationale for using a treatment strategy that aims to eliminate inflammation as quickly as possible.

Dr Singh: Whether it is glaucoma or cataract surgery, our goal is to achieve that "20/happy" patient. We conducted a study in which we asked cataract surgery patients at their 3-month follow-up visit when they had expected to be able to see well and feel healed after surgery. The most common answer was "at 1 week", which reinforces the importance of rapidly eliminating inflammation to achieve patient satisfaction.

Dr Donnenfeld: Patient expectations following cataract surgery have never been higher than they are today, and inflammation plays a major role in failure to meet these expectations. The new normal for cataract surgery should not be to control or suppress inflammation with corticosteroids, but to prevent it from occurring in the first place. For this reason, high levels of potent corticosteroids applied in the immediate postoperative period are key to achieving optimal results following cataract surgery.

Dr McDonald: Patient expectations regarding postoperative comfort and the speed of return of vision after any kind of eye surgery are "through the roof" now. Patients compare their outcomes to those of their friends, family members, and neighbors. Eliminating inflammation quickly certainly builds patient satisfaction and loyalty. If it routinely takes a patient weeks or even months to achieve a good result, that is not a practice builder.

Tip #7: Manage Postoperative Inflammation With Lessons From PREMED

Supported by the European Society of Cataract & Refractive Surgeons, PREMED (Prevention of Macular Edema After Cataract Surgery) was a multicenter, randomized clinical trial comparing the effectiveness of a nonsteroidal anti-inflammatory drug (NSAID), a steroid, or a combination of both for preventing cystoid macular edema after cataract surgery.[46] One arm of PREMED enrolled 914 patients without diabetes who were randomized to receive topical NSAID treatment alone (bromfenac, 0.09%), topical steroid treatment alone (dexamethasone, 0.1%), or a combination of both. The medications were started 2 days preoperatively and tapered for several weeks after surgery. The results showed that the risk for developing clinically significant macular edema was significantly lower in the combination group than in either monotherapy group **(Table 3)**.[46]

Table 3. Incidence of Clinically Significant Macular Edema Within 6 and 12 Weeks[46]

Visit Week	Incidence of Clinically Significant Macular Edema, %		
	Bromfenac (n = 274)	Dexamethasone (n = 273)	Combination (n = 275)
6	3.6	5.1	0.7
12	3.6	5.1	1.5

A second arm of PREMED included 213 patients with diabetes.[47] All patients received topical bromfenac and dexamethasone, and were randomized to receive no additional treatment, subconjunctival triamcinolone acetonide 40 mg, intravitreal bevacizumab 1.25 mg, or both triamcinolone and bevacizumab. Compared with those receiving no additional treatment or bevacizumab alone, patients receiving subconjunctival triamcinolone acetonide had a lower macular thickness and macular volume at 6 and 12 weeks postoperatively. No patient receiving triamcinolone developed cystoid macular edema.

Dr Yeu: What messages does PREMED provide about anti-inflammatory regimens for preventing cystoid macular edema after cataract surgery?

Dr Donnenfeld: Before PREMED, the role of NSAIDs to treat inflammation and prevent cystoid macular edema after cataract surgery was controversial. The PREMED study provided level I evidence that the use of a topical NSAID with a corticosteroid reduces the risk of cystoid macular edema.[46,47] I think that PREMED established that this combination is the optimal treatment of postoperative inflammation and that both corticosteroids and NSAIDs play an important role in improving outcomes following cataract surgery.

Dr McDonald: The importance of these large multicenter randomized prospective clinical trials cannot be overestimated. They fundamentally change the way that medicine is practiced for the better.

Tip #8: Consider Starting Steroids Preoperatively

Surgical trauma incites a pathway leading to the production of inflammatory mediators. Steroids reduce inflammation by inhibiting the enzyme phospholipase A2 early in the inflammatory cascade.[48] According to the prescribing information, topical steroids used to treat postoperative pain and inflammation should be started ***after*** surgery. In theory, however, starting the steroid preoperatively so that it is present in a therapeutic concentration when surgery begins would limit the inflammatory response.

In designing the PREMED study, planners decided to start the anti-inflammatory treatments 2 days before surgery according to evidence from previous research reporting that the incidence of cystoid macular edema was lower when the medications were started preoperatively.[46]

Dr Yeu: I have all patients start the steroid on the day before surgery. Although this is my routine, I think it is particularly helpful

in cases in which I expect the patient to be at risk for more severe postoperative inflammation, such as those in patients with a dense cataract, short eye, posterior synechiae, or history of uveitis. In these and other complicated cases, I also dose the steroid more frequently and may continue the steroid for longer after surgery.

Are you starting the steroid preoperatively?

Dr McDonald: I start loteprednol 4 times daily beginning 3 days preoperatively and continue it on a 1-month taper in routine cases, decreasing the frequency to 3 times a day for the second week, 2 times a day for the third week, and once a day for the fourth week. I continue the treatment for an extra 2 weeks in anyone with diabetes. Considering the safety of loteprednol and the potential benefit for starting treatment preoperatively, I feel there is nothing to lose with this approach and everything to gain. In cases in which there has been significant intraocular manipulation that I expect could incite a lot of inflammation, such as the removal of a black cataract with an extracapsular technique, I also give an intravenous injection of hydrocortisone sodium succinate 100 mg intraoperatively.

Dr Donnenfeld: I agree that preoperative use of anti-inflammatory therapy improves outcomes. In the PREMED trial, the NSAID was given preoperatively.[46] We had established the importance of preoperative NSAIDs and preoperative corticosteroids in reducing inflammation and improving cataract surgical outcomes in 2 earlier trials.[49,50] I routinely start a topical NSAID 3 days prior to cataract surgery and a corticosteroid on the day of surgery.

Dr Singh: I have all patients start an NSAID, an antibiotic, and a steroid 3 days before surgery. I also believe that starting the medications early carries very little risk. By getting patients into the routine of using their medications, I think they may be more compliant with their treatment regimen postoperatively. In addition to the situations Dr McDonald mentioned, I also continue the steroid for longer in patients with an epiretinal membrane, diabetes, or a history of trabeculectomy or other subconjunctival glaucoma surgery.

Dr Yeu: Is anyone combining the intracameral or intracanalicular dexamethasone products with a postoperative topical steroid?

Dr Singh: I have done that for patients who need intensive steroid therapy because they are at risk for increased postoperative inflammation, such as those with a history of uveitis, and for some patients undergoing certain types of glaucoma surgery. Just recently, during the COVID-19 pandemic, I implanted a tube in a patient with neovascular glaucoma. I was worried about the patient's treatment compliance, and I placed intracanalicular dexamethasone inserts into the upper and lower puncta and started loteprednol twice daily. With the intracanalicular inserts, it may be possible to flush out the medication to some extent, if needed, to manage a steroid-related adverse event. I have also used intracameral dexamethasone for patients needing iris manipulation, with risk factors such as epiretinal membranes and uveitis. I like to use intracameral phenylephrine/ketorolac for pupil dilation during surgery and also because ketorolac mitigates the inflammation cascade caused during surgery.

Tip #9: Provide Effective Patient Instructions to Optimize Treatment of Postoperative Inflammation

Patient compliance with prescribed medications remains a limiting factor for minimizing the risk of infection and inflammation-related complications after surgery. Therefore, extra attention is needed to educate patients about the importance of using their medications as directed and to establish their ability to use them properly.

Dr Yeu: How do you counsel patients to optimize use of their postoperative medications?

Dr McDonald: Patients can easily become confused about how to use their medications, so I believe there is no such thing as too much repetition. In addition to our verbal instructions, we give patients an information sheet to take home; the sheet has pictures of all the medications we might use after surgery and instructions for each. We circle the medications that the individual will be using and highlight in yellow the most important instructions. I find this approach works well, and I think it is better than referring patents to an online resource.

Dr Singh: I like to be sure that patients are able to administer their medications properly. I evaluate this by asking them to instill a drop of an artificial tear in front of me. Many patients have difficulty using their drops. I think the reasons for this vary, so there is no one-size-fits-all solution. Therefore, while I am watching to see if patients have difficulty, I also try to identify the cause, so I can suggest how they can most easily be successful.

I no longer give patients a handout with instructions on dosing frequency because I have simplified my regimen. All medications are used twice daily, the antibiotic is stopped after 1 week, and the steroid and NSAID are used for 1 month or whatever longer duration I think is appropriate, depending on the individual's risk for inflammation. I do not taper the steroid or the NSAID.

Tip #10: Increase the Chance Your Patient Gets What You Prescribe at the Pharmacy

Some physicians and patients believe that generic medications are simply lower-priced versions of innovator drugs.[51,52] Depending on the dosage form, however, generic ophthalmic drugs may be approved for marketing without any clinical testing demonstrating their safety and effectiveness.[53] In addition, generic medications can be formulated with different inactive ingredients, which has implications for efficacy, safety, and tolerability, and their packaging may differ, which has ramifications for ease of dispensing the medication.[54,55]

There are no generic versions of the newer loteprednol products. At the pharmacy, however, patients may be told about generic steroids that are less expensive than what was prescribed for them. Educating patients about differences between brand name and generic medications and providing counseling that allows them to appreciate the rationale for prescribing specific products can increase the likelihood that they will get those products at the pharmacy.

Dr Yeu: What conversation do you have with patients when you feel it is important for them to use certain brand name medications?

Dr Singh: I think it is important to educate patients about the differences between brand name and generic products so they understand that cost is not the only difference. We did a study, which is unpublished, that included 20 patients who were given a prescription for a brand name prostaglandin analogue as primary therapy for glaucoma but had it filled with a generic option instead because the pharmacist told them the generic option was cheaper. After the patients were provided with education and

given an information sheet explaining the differences between brand name and generic medications, 13 of the 20 patients converted to the brand name medication when it was time to get a refill. Cost seemed to play a role in influencing a patient's decision to switch: for the group that switched, the average cost difference between the brand name and generic medications was $30, whereas the difference was approximately $100 for those who stayed with the generic medication.

Whenever I prescribe a brand name medication, I give patients a sheet—which is nonbranded—that explains the objective differences between brand name and generic products. The purpose of the information is not to sell them on the brand name product, but to educate them that the difference compared with a generic goes beyond cost and brings value to their treatment. With that understanding, some patients are more willing to get the higher-cost brand name medication. I even have patients who decide to cut back on some of their other spending so they can afford the brand name medication.

I also talk to patients about the medications I am prescribing as part of the preoperative counseling. I have a check box on my consent form that I mark when a patient insists on getting generic medications instead of the brand name medications I recommend. I think this reinforces in the patient's mind the importance I place on using particular medications to achieve the best outcome.

Dr Donnenfeld: I prescribe certain brand name medications because I believe they are better than the generic medications. I always tell patients that I feel it is important they use the brand name medications I am prescribing. Still, I am sensitive to the cost of pharmaceuticals, and I think it can be reasonable to prescribe a generic medication if a patient cannot truly afford the brand name medication. However, sometimes the branded medication may cost less than the generic medication.

Dr McDonald: I tell my surgical patients that they are having a procedure that gives them a once-in-a-lifetime opportunity to improve their vision and that I am prescribing specific medications I want them to use because I believe they are the best in class and will help them get the best outcome. I do not think it is necessary to spend a great deal of time discussing formulary issues.

I agree with Dr Donnenfeld about the difference in cost between brand name and generic products. With the availability of samples, coupons, and rebate offers, we can increase the likelihood that patients can use the prescribed brand name drug without having to incur a substantial out-of-pocket expense.

Case 1: Steroid Treatment of Acute Rehabilitation of the Ocular Surface Prior to Cataract Surgery

From the Files of Eric D. Donnenfeld, MD

A 72-year-old male presented with a visually significant cataract. He had no prior ocular surgery or disease and had no complaints of DED. Responses on his DED screening questionnaire, however, showed he had fluctuating vision, light sensitivity, and watering eyes.

*On examination, refraction was +1.50 -1.25 × 173 and best-corrected visual acuity was 20/50. The axial power map from topography showed irregularity **(Figure 1A)**. The patient wanted surgery as soon as possible to be rid of his eyeglasses for distance vision. On further testing, tear osmolarity was 318 mOsm/L OD and 320 mOsm/L OS, matrix metalloproteinase-9 (MMP-9) result*

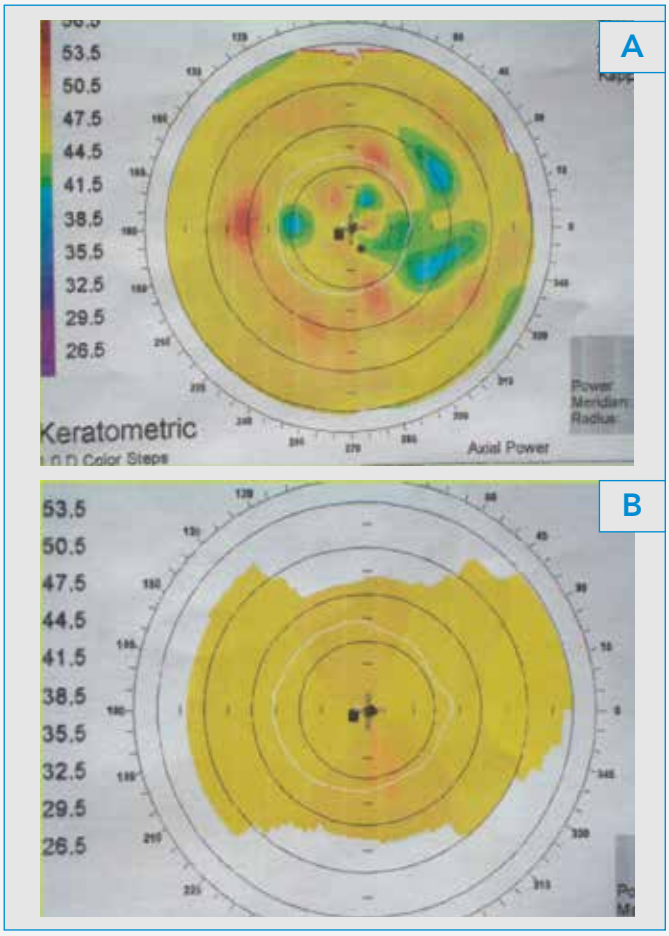

Figure 1. Topography images of the patient in Case 1 on presentation for cataract surgery evaluation (A) and after treatment of dry eye disease (B)

was positive OU, corneal staining was moderate OU, TBUT was 5 seconds OU, and meibomian glands were inspissated on expression OU.

The patient was started on lifitegrast, 5.0%, twice daily; loteprednol, 0.38%, submicron formulation 4 times daily; artificial tears 4 times daily; and an oral omega-3 supplement. He was treated in-office with thermal pulsation and microblepharoexfoliation.

*The patient returned after 2 weeks. On topography, the ocular surface had regularized **(Figure 1B)**. The patient underwent uncomplicated cataract surgery, with an uneventful recovery and good outcome.*

Dr Donnenfeld: Performing cataract surgery in the setting of DED can affect surgical success and patient satisfaction because DED affects measurements used for surgical planning, limits visual function, causes discomfort, and can increase the risk of postoperative infection.[42] Therefore, it is important to identify and treat significant DED before performing cataract surgery.

All cataract surgery candidates complete a screening questionnaire, and our technicians are empowered to conduct further testing for DED according to patients' responses. The finding of irregular astigmatism on the initial topography map in this case was noteworthy. Although there are quite a few ocular surface conditions that are included in the differential diagnosis for irregular astigmatism, I consider it a sign of DED until proven otherwise because DED is so common in the cataract surgery population.[38]

Presence of any corneal staining is an indicator to me that the ocular surface has to be rehabilitated before cataract surgery. From the findings on examination, this patient was diagnosed with mixed aqueous deficient DED and MGD, and was treated for both conditions.

I like using lifitegrast as immunomodulatory treatment of DED because it can improve the signs and symptoms of DED in as little as 2 weeks.[56] Using a topical steroid is really key, however, for improving the ocular surface quickly.

Case 2: Steroid Treatment of a Patient With Mild to Moderate Dry Eye Disease

From the Files of Marguerite B. McDonald, MD, FACS

A 54-year-old female accountant presented with complaints of developing fluctuating vision and burning eyes after working at her computer for 45 to 60 minutes. She reported using preserved artificial tears that she said provided minimal relief but burned on instillation. The patient is on montelukast for mild well-controlled asthma and metoprolol for hypertension.

Findings on examination were refraction -3.00 -0.50 × 180, 20/25 OD, and -3.25 -0.50 × 175, 20/20+2 OS; positive MMP-9 test result OU; tear osmolarity of 320 mOsm/L OD and 329 mOsm/L OS; 1+ meibomian gland inspissation; 1 to 2+ conjunctival erythema; decreased tear lake; and 1 to 2+ central superficial punctate keratitis OU.

The patient was diagnosed with mild to moderate DED, and started on cyclosporine twice daily; loteprednol etabonate 4 times daily for 1 week, then twice daily for 1 week; preservative-free artificial tears 4 times daily and as needed; and an oral omega-3 supplement. At a return visit 1 month later, she reported 85% to 90% improvement in her symptoms. Best-corrected visual acuity was 20/20-2 OU, MMP-9 test result was weakly positive OD and negative OS, tear osmolarity was 305 mOsm/L OD and 299 mOsm/L OS, and corneal staining was absent.

Dr McDonald: Ophthalmologists are becoming more aware of the importance of recognizing DED before cataract or refractive surgery and of being more aggressive about treating it because they want to get the patient into the best condition possible before surgery for all the reasons described previously by Dr Donnenfeld. In situations such as this case, in which there is no deadline to get the patient better, some ophthalmologists may just recommend artificial tears.

On the basis of her appearance at the slit lamp, the patient had mild MGD, but her positive MMP-9 test result indicated she had ocular surface inflammation that made her a candidate for immunomodulatory therapy.[57] The patient's report of burning with artificial tears was a red flag indicating she could have significant discomfort when started on lifitegrast or cyclosporine. Therefore, I prescribed a 2-week course of loteprednol as induction therapy.

Dr Donnenfeld: I agree that ophthalmologists sometimes do not take the symptomatic complaints of patients with DED seriously enough. Then, the only recommended treatment is to switch to another artificial tear product. It is unlikely that repeating what has already failed will provide effective therapy.

Furthermore, DED can be a chronic and progressive disease that is easier to treat early when it is mild rather than at a later stage. Early effective intervention makes patients feel better and can help stop the DED from worsening.

Dr Singh: Just as with the management of glaucoma, the earlier we treat DED, the less aggressive we need to be with our treatment. In addition, earlier treatment is more likely to be effective because if left untreated, DED-related inflammation can cause permanent damage to the goblet cells and meibomian glands that are involved in tear production.

Case 3: Controlling Inflammation After Combined Cataract and Glaucoma Surgery

From the Files of I. Paul Singh, MD

*A 68-year-old male who was on a prostaglandin analogue for open-angle glaucoma presented with complaints of fluctuating vision and decreased vision at night. He had a 3+ nuclear sclerotic, 1+ posterior subcapsular cataract OD **(Figure 2)**, and a 3+ nuclear sclerotic cataract OS.*

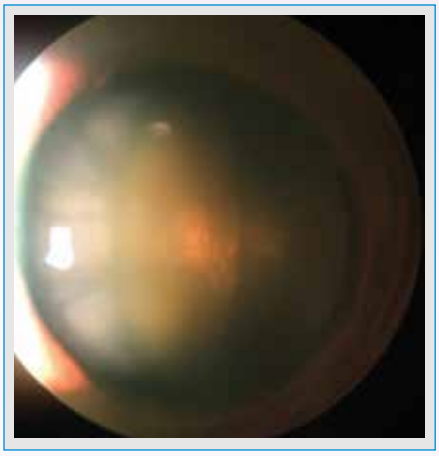

Figure 2. Slit-lamp photograph of the patient in Case 3 shows a 3+ nuclear sclerotic, 1+ posterior subcapsular cataract OD

His maximum IOP was 32 mm Hg OD and 33 mm Hg OS. With topical medications, the IOPs were stable in the middle teens, but lately have been fluctuating in the lower 20s and now demonstrates progressive glaucomatous damage in the visual field OD. He had a history of previous successful treatment with selective laser trabeculoplasty, and had become a candidate for combined cataract/glaucoma surgery. The patient was also interested in reducing dependence on eyeglasses for distance vision.

*Manifest refraction was -6.0 +2.00 × 180 OD. Mires on the topography image were irregular. The patient had 1-2+ fluorescein corneal staining **(Figure 3)**, 1+ MGD OU **(Figure 4)**, TBUT of 6 seconds OD, and tear osmolarity of 320 mOsm/L OD.*

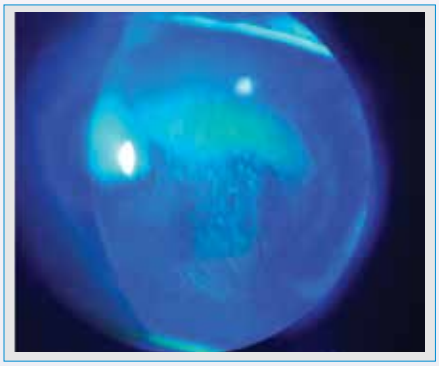

Figure 3. Slit-lamp photograph of the patient in Case 3 shows 1-2+ fluorescein corneal staining OD and poor tear film

He was started on topical lifitegrast, 5.0%, and loteprednol, 0.38%, and treated for 6 to 8 weeks. After confirming good agreement in keratometry readings from different devices,

Figure 4. Meibomian glands of the patient in Case 3 with thickened meibum

the patient underwent surgery OD with phacoemulsification, implantation of a monofocal toric intraocular lens, and viscodilation with stent placement. Postoperative medications were loteprednol twice daily for 4 weeks, bromfenac twice daily for 6 weeks, and besifloxacin, 0.6%, twice daily for 1 week. His glaucoma medication was discontinued.

Uncorrected visual acuity was 20/25 at 1 day after surgery and 20/20- at 1 week and 4 weeks after surgery. Intraocular pressure was 14 to 15 mm Hg at the postoperative visits while off his topical glaucoma medications. No steroid IOP spike was observed. The patient was told to continue lifitegrast and use artificial tears as needed. He was very happy with his outcome.

Dr Singh: Even when patients with glaucoma are undergoing glaucoma surgery, they can still be at risk for an increase in IOP from the steroid used to control inflammation. Using loteprednol minimizes my concern of that risk.

Dr Donnenfeld: The glaucoma procedure in this patient might help address his DED by reducing his need for topical IOP-lowering medication. In a case such as this, I will start appropriate DED therapy preoperatively and stop the glaucoma drops for a few weeks. I would put the patient on an oral medication for IOP control, if needed; I would like to see how the ocular surface improves if the patient is off the topical glaucoma drops because that gives me some idea about what it might be like after glaucoma surgery.

Dr Yeu: Treatment with a prostaglandin analogue can affect the periorbital tissues and can cause MGD.[58,59] Therefore, I am careful to evaluate meibomian gland architecture in patients using a prostaglandin analogue. Patients may be asymptomatic before surgery, but in my experience, they may have significant meibomian gland dropout or truncation that puts them at risk for decompensation and developing symptoms ***after*** surgery. These patients already have a compromised ocular surface from the chronic use of topical glaucoma medications. Thus, using a preservative-free topical loteprednol can aid in both mitigating medication-related adverse effects and suppressing postoperative inflammation.

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1. Which is an advantage associated with both of the 2 newly available topical loteprednol etabonate products?
   a. Twice-daily dosing
   b. Novel preservative-free packaging
   c. Improved bioavailability
   d. Sustained-release delivery

2. The 2 newly available topical loteprednol etabonate products differ in all the following ways, EXCEPT:
   a. Active ingredient concentration
   b. Approved indication
   c. Benzalkonium chloride concentration
   d. Recommendation for amount of shaking before use

3. Which pair of steroids is reported to have reduced potential to cause an IOP response?
   a. Dexamethasone, difluprednate
   b. Prednisolone, loteprednol
   c. Prednisolone, difluprednate
   d. Loteprednol, fluorometholone

4. Which is NOT a patient-related risk factor for IOP elevation with the use of topical steroids?
   a. High hyperopia
   b. Family history of glaucoma
   c. Younger age
   d. Diabetes

5. A patient with mild glaucoma controlled on a single topical medication needs cataract surgery. It is decided to implant a trabecular microbypass stent to eliminate the need for the IOP-lowering medication. Your standard topical steroid after routine phacoemulsification is loteprednol etabonate for 4 weeks. What would you use to control inflammation in this case?
   a. Topical prednisolone acetate
   b. Add subconjunctival triamcinolone
   c. Taper the loteprednol over 6 weeks
   d. Standard regimen of loteprednol for 4 weeks

6. According to results of PREMED, which is the best regimen for controlling inflammation after cataract surgery in patients without diabetes?
   a. Topical NSAID with topical steroid
   b. Adding subconjunctival injection of triamcinolone to topical NSAID and topical steroid
   c. Combining intraocular dexamethasone with topical NSAID
   d. Combining intracanalicular dexamethasone with topical NSAID

7. Which treatment improved outcomes in patients with diabetes in PREMED?
   a. Intraocular dexamethasone
   b. Subconjunctival triamcinolone
   c. Intravenous hydrocortisone
   d. Subconjunctival dexamethasone

8. Which steroid regimen is NOT appropriate for the management of DED?
   a. Short-course induction therapy to improve tolerability of immunomodulatory treatment with cyclosporine
   b. Short-course treatment to control a flare in patients on maintenance immunomodulatory treatment
   c. Chronic low-dose treatment of long-term symptom control
   d. All the above are appropriate

9. A patient with mild glaucoma controlled on topical latanoprost presents complaining of fluctuating and blurred vision. Examination shows a 2+ nuclear sclerotic cataract and MGD-related DED. A decision is made to perform phacoemulsification, with placement of a trabecular microbypass stent. What treatment would you use to rapidly rehabilitate the ocular surface?
   a. Oral omega-3 supplement
   b. Thermal pulsation
   c. Topical cyclosporine
   d. Topical steroid

10. Strategies for optimizing postoperative medication treatment might include all the following, EXCEPT:
    a. Checking the formulary for the patient's insurance to choose the least expensive alternatives
    b. Ensuring patients are able to effectively administer their topical drops
    c. Educating patients about the differences between generic and brand name medications
    d. Providing patients with verbal and written instructions on dosing regimens