Starting a new chapter

Eric D. Donnenfeld, MD

Over the past 6 years, it has been my privilege to work as the Infection Section Editor of THE THERAPEUTIC UPDATES IN OPHTHALMOLOGY. Under the leadership of Peter McDonnell, MD, this newsletter has matured into one of the pre-eminent clinician-oriented periodicals in the field of opthalmology. While other ophthalmic publications emphasize the surgical nature of ophthalmology, THE THERAPEUTIC UPDATES IN OPHTHALMOLOGY has remained true to its mission statement — to provide clinical updates in cornea, external disease and glaucoma.

The majority of ophthalmologists practice in a clinical setting and diagnose and manage a host of these ophthalmic conditions. While many of the conditions encountered are common, they are often difficult to manage, requiring tremendous expertise on the part of the treating physician.

For the past 7 years, THE THERAPEUTIC UPDATES IN OPHTHALMOLOGY has provided clinicians with information regarding advances in ophthalmology, including new antibiotics, anti-inflammatories, allergy medications, steroids and new glaucoma medications. Helping clinicians use new medications in the management of...
Reformulation of ketorolac for ocular pain

John Wittpenn, MD

Typical of all drugs, topical nonsteroidal anti-inflammato
tory drugs (NSAIDs) have been associated with some
adverse events, such as surface toxicity. Patients often report burning or sting-
ing upon instillation of NSAIDs.

Ketorolac tromethamine ophthalmic solution 0.5% (Acular, Aller-
gan) is an NSAID with proven analgesic and anti-inflammatory
activity and safety. The new formulation, ketorolac tromethamine ophthal-
ic solution 0.4% (Acular LS), has a 20% reduction in the concentra-
tion of the active ingredient. The pH has been adjusted from 7.2 to 7.4, and there is a significant reduction in preservatives. The hypothesis is that reformulated ketoro-
lac tromethamine 0.4% ophthalmic solution would reduce the incidence of adverse events and enhance patient comfort while maintaining clinical effi-
cacy. While 5% of patients have cystoid macular edema (CME) after cataract surgery, 100% of patients have some pain during or after the procedure. Pain-free surgery would lead to an increase in patient satisfaction.

Traditionally, NSAIDs have been prescribed because patients using them are more likely to have excellent macu-
lar function than those who are not. To preserve macular function, physicians must minimize intraocular prostaglandins and control intraocular inflammation. The recovery of visual acuity after cataract surgery is directly related to the amount and duration of postoperative inflammation.

In 1991, physicians used NSAIDs to inhibit intraoperative miosis and cyclooxygenase. At that time, NSAIDs were also clinically proven to be as effective as steroids for the control of routine postoperative inflammation. In 2003, physicians have additional rea-
sons for using NSAIDs: for prophylaxis and treatment of CME; to reduce the pain of clear corneal incisions; to main-
tain a widely dilated pupil; and to control postoperative inflammation. A change in the definition of CME has also occurred, so that any decrease in visual function is the result of macular edema.

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Methods

My colleagues and I performed a multicenter, randomized, double-
masked, vehicle-controlled, parallel-group phase 3 study of 157 patients undergoing unilateral photorefractive keratectomy (PRK). After surgery, patients were treated with one drop of ketorolac or its vehicle four times a day for up to 4 days. There were no significant differences between groups. Pain intensity, pain relief and use of escape medication [acetaminophen 300 mg with codeine 30 mg (Tylenol No. 3, McNeil Pharmaceuticals)], were recorded in electronic diaries. Adverse events, severity of ocular symptoms and visual acuity were recorded at office visits. Patients exited the study when reepithelialization occurred and they were pain free. (Note: this was only true if reepithelialization occurred during the 4-day treatment phase. If the patient went into posttreatment, then the only criterion to exit was reep-
ithelialization.) The objective of the study was to evaluate the safety and analgesic efficacy of reformulated ketorolac in PRK patients.

Clinical efficacy

Figure 1 shows the distribution of ketorolac-treated and vehicle-treated patients by pain intensity during the first 12 hours post-PRK. Pain intensity was assessed by the patient and record-
ed on an electronic diary using a 5-point scale, where 0 = no pain and 5 = intoler-
able pain, immediately prior to each dose of masked study treatment. Patients also recorded the pain intensity in their diaries imme-
 diately prior to use of escape medica-
tion. On the day of surgery, pain intensi-
 ty was recorded approximately at hours 3, 7 and 11 postoperatively. The maxi-
ung pain intensity during each 12-
hour period post-PRK was used for analysis.

During the first 12 hours post-PRK, there was a significant difference in the distribution of pain intensity (P<.001). There were fewer ketorolac-treated patients in the “severe pain” and “intol-
erable pain” categories (43.1%) than vehicle-treated patients (87.2%). Ketorolac continued to be superior to the vehicle throughout the first 48 hours post-PRK.

In Figure 2, the arrows indicate median time to first report of “no pain.” There was a significant difference in cumulative incidence rates of time to
first “no pain” in favor of ketorolac-treated patients (P<0.001). The median time to first “no pain” for ketorolac-treated patients was 24 hours compared with 54 hours in the vehicle-treated patients (arrows). During the first 12-hour post-PRK surgery period, 44.3% of ketorolac-treated patients achieved first “no pain,” compared with 7.8% of vehicle-treated patients.

Patients rated and recorded pain relief approximately 2 hours after instillation of masked study treatment (Figure 3). Pain relief was scored on a 5-point scale, where 0 = complete pain relief and 4 = no pain relief. Ketorolac-treated patients reported greater pain relief than did vehicle-treated patients throughout the study. During all 12-hour post-PRK surgery periods, there was a significant difference in the distribution of pain relief (P<0.002). There were fewer ketorolac-treated patients in the “little” and “no pain relief” categories (46.2%) than vehicle-treated patients (86.5%) during the first 12 hours post-PRK.

Patients were dispensed an escape medication to be taken as one tablet, up to every 4 hours as needed for intolerable pain (Figure 4). During the first 12 hours post-PRK, significantly fewer ketorolac-treated patients (46.8%, 37 of 79 patients) required escape medication than vehicle-treated patients (92.3%, 72 of 78 patients; P<0.001). Significantly fewer ketorolac-treated patients took escape medication 12 to 48 hours post-PRK (P<0.006, compared with vehicle).

Patients rated symptoms at each office visit on the days after surgery. Symptoms were scored on a 5-point scale, where 0 = none and 4 = severe (Figure 5). Only 2.5% (2 of 79 patients) of ketorolac-treated patients reported severe burning/stinging on the first day (approximately 24 hours after surgery) compared with 23.1% (18 of 78 patients) of vehicle-treated patients. Significantly more ketorolac-treated patients (70.9%, 56 of 79 patients) than vehicle-treated patients (47.4%, 37 of 78 patients) reported none to mild symptoms of burning/stinging on the first day after surgery. On the first day post-PRK, there was a significant difference in the distribution of severity in symptoms of burning/stinging (P<0.001). On the first day post-PRK, ketorolac continued on page 7.
Topical cyclosporine A spares postkeratoplasty steroid-related complications

Avi A. Wallerstein, MD, FRCSC,
Henry D. Perry, MD,
Eric D. Donnenfeld, MD

Topical corticosteroids are routinely used after keratoplasty to reduce the postoperative inflammation and to decrease the incidence of immune rejection episodes. Unfortunately, their use is associated with several undesirable side effects including aggravating pre-existing glaucoma, inducing glaucoma in steroid responders, inducing cataract formation in phakic patients, increasing the likelihood of infectious complications and delaying wound healing. Topical cyclosporine A, like steroids, is capable of modulating the local ocular immune response. It acts by suppressing antigen-activated T lymphocytes. However, it does not raise intraocular pressure (IOP), cause cataracts or inhibit wound healing.

Case study
A 42-year-old patient diagnosed with keratoconus and high myopia was followed since 1979. Over the years, the keratoconus gradually progressed. By January 1994, the patient had become intolerant of gas permeable contact lenses and complained of marked discomfort. Several unsuccessful attempts were made to refit his lenses. Uncorrected visual acuity at this time was 20/400 in the right eye and counting fingers at 4 feet in the left eye. Visual acuity with the hard lenses was 20/40 in the right eye and 20/50 in the left eye. Refraction was –11 D + 4 D x 140 in the right eye and -13.25 D + 5.25 D x 55 in the left eye. Topography showed characteristic inferotemporal steepening in both eyes, and keratometry readings were 46 D/49 D x 137 in the right eye and 48 D/54 D x 40 in the left eye. External examination was noncontributory, whereas slit lamp examination revealed scattered punctate epithelial erosions in both eyes. Inferiorly decentered oval cones were evident in both eyes, with slightly greater apical scarring in the left eye. Moderate superficial peripheral corneal blood vessel ingrowth was noted bilaterally. The remaining anterior segment was normal, with applanation tonometry 19 mm Hg in both eyes. Dilated fundus examination was normal except for bilateral posterior vitreous detachments. A penetrating keratoplasty was performed in the patient’s left eye in March 1994. Eight interrupted 10-0 nylon sutures were used together with 16-bite running 10-0 nylon stitches.

Postoperative course
The postoperative course was initially uneventful. The graft was clear with a vision of 20/80 uncorrected in the left eye and a pinhole of 20/60 on the first postoperative visit. Appplanation tonometry was 20 mm Hg in both eyes, and the patient was maintained on dexamethasone (Decadron, Wyeth Ayerst), one drop four times daily in the operated eye. Two weeks postoperatively, the patient’s IOP had risen to 24 mm Hg in the left eye, and 6 weeks later, his IOP was 41 mm Hg. Acetazolamide (Diamox, Wyeth Ayerst) 500 mg orally and two drops of timolol maleate (Timoptic, Merck & Co., Inc.) 0.5% were administered. The patient’s IOP was brought down to 24 mm Hg in the left eye. Gonioscopic evaluation revealed an open angle for 360°, with a clear view of the ciliary body band and no peripheral anterior synechiae. Humphrey visual fields demonstrated a mild generalized depression, refraction related, with no focal defects. The patient was felt to be a steroid responder so dexamethasone was discontinued and replaced with fluorometholone (Liquifilm, Allergan Inc.) twice daily. The steroid drops were not discontinued altogether due to the possibility of graft rejection. Over the next 6 weeks, the patient’s pressure was controlled at 20 mm Hg in the left eye with acetazolamide sequences 500 mg twice daily and timolol maleate 0.5% twice daily. The corneal graft was clear with uncorrected vision at 20/60, pinhole to 20/30. There was a central posterior subcapsular cataract noted for the first time at the 3-month visit.

At 5 months postoperatively, the patient presented with an acute episode of graft rejection. The slit lamp examination revealed scattered keratic precipitates with marked inferior stromal edema. Dexamethasone was started and administered hourly for 2 days and tapered to six times daily by the seventh day. Within a week, there was marked improvement in the corneal graft rejection, but even with medical therapy, the patient’s IOP had risen to 25 mm Hg. In addition, the patient developed a large non-healing epithelial defect. Considering the patient’s...
When last seen in January 1997, the patient’s visual acuity was 20/40 -2 with glasses, and the corneal graft was clear and compact. The patient’s IOP remained controlled at 16 mm Hg, and there had been little, if any, progression in the posterior subcapsular cataract. The patient continues to be maintained on topical cyclosporine A 0.5% twice daily and timolol maleate 0.5% once daily.

### Managing postkeratoplasty with cyclosporine A

Cyclosporine A is an immunosuppressive agent that has demonstrated success in prolonging the survival of solid organ transplantation, including the heart, liver and kidney. It also has shown benefit in the treatment of high-risk corneal transplants and immune graft rejections.\(^1\)\(^2\) This case report illustrates how the secondary complications associated with routine, prolonged use of corticosteroids after corneal transplantation can be avoided if topical cyclosporine A is used.

This patient is an example of the difficulty in managing postkeratoplasty glaucoma when topical corticosteroids need to be used to treat inflammation and graft rejection. Only after steroid discontinuation was the patient’s IOP manageable despite maximal medical therapy. Steroid substitution with cyclosporine A may help significantly in both the prevention and management of ocular hypertension.

Since topical cyclosporine A is not cataractogenic, it may be used indefinitely, particularly in young individuals with keratoconus. After 3 years of follow up, the patient tolerated a twice daily dose exceptionaly well and had no subsequent rejection episodes. A longer cyclosporine A treatment duration may result in patients with keratoconus showing a decreased incidence of secondary cataracts and lower immune rejection rates.

With the advent of commercially available cyclosporine A (Restasis; Allergan), we now routinely substitute cyclosporine 0.05% for corticosteroids in patients who are corticosteroid responders. The Restasis vehicle dramatically increases the contact time of the cyclosporine to the ocular surface to provide increased clinical efficacy. In addition, there is less burning and better patient compliance with Restasis. We now routinely taper our corticosteroids after 2 to 3 months in patients with phakic grafts and maintain these patients on Restasis twice daily until suture removal.

Unlike corticosteroids, cyclosporine A has relatively little effect on phagocytosis and does not inhibit wound healing.\(^3\) Discontinuing topical steroids simplified the management of the patient’s non-healing epithelial defect, with eventual resolution. The use of topical cyclosporine A may lead to a decrease in secondary infections and late wound dehisceance following suture removal.

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Eric D. Donnenfeld, MD, is the medical director at the TLC Laser Center in New York, a partner with Ophthalmic Consultants of Long Island and Connecticut and is the chief medical editor of THERAPEUTIC UPDATES IN OPHTHALMOLOGY.

### References


Changing treatment options for dry eye

Douglas Katsev, MD

Traditionally, the best way to improve the clinical symptoms of patients with dry eye has been to close the lacrimal punctum. Punctal plugs result in less foreign body sensation, irritation, photophobia, tearing and visual fluctuation and, in some cases, improved topographical corneal mires. However, the use of permanent punctual plugs represents treatment of symptoms as opposed to the causes of dry eye.

Early in my career (1990), the typical treatment for dry eye disease was artificial tears. Punctal plugs were not often used because the available styles were difficult to place and often fell out. As an alternative, thermal punctal occlusion procedures with cautery or laser were more common. After being in practice for 14 years, I have learned that it is best to avoid making permanent changes when treating dry eye. I no longer perform permanent occlusion and I have decreased my use of silicone plugs. My changes in practice are significantly related to recent advancements in medical treatment.

The evolution of punctual plugs

A better variety of artificial tears is available than in the past and includes varied viscosity tears, gels and ointments such as Refresh Tears (Allergan) and Genteal (Novartis Ophthalmics). Patient response can help the clinician achieve the right mix of tear replacement. However, many patients require more than just tear replacement, due to patients’ lack of compliance. For this group of patients punctal plugs should be considered.

Ten years ago, if treatment with artificial tears failed, I would discuss permanent occlusion (cautery or laser) not long enough for the patient to understand the benefit of punctal occlusion. Second, the cost for this short treatment time is high, and lastly, the collagen plugs did not always fully block the tear drainage because they dissolve quickly.

Two years ago, the 3-month Soft Plug Extended Duration Absorbable (Oasis Medical, Glendora, Calif.) was introduced. The Soft Plug is made of an absorbable copolymer material, is 2 mm in length and is available in diameters of 0.3 mm, 0.4 mm and 0.5 mm. The larger of the plugs is more difficult to insert, but the learning curve is small. The Soft Plug is easy to place without special instrumentation and lasts approximately 2 to 4 months — a long enough period to allow patients to notice a difference in their symptoms and to justify the cost.

Only after the patient realizes the benefit of the 3-month Soft Plug will I consider placing a silicone plug. I no longer perform thermal closure because some of my patients have had chronic epiphora after the procedure. The newer silicone plugs, such as the Soft Plug Silicone (Oasis Medical) and the Tear Saver (CIBA Vision), are easier for the physician to insert and are more tolerable for the patient than older silicone plugs.

New medical treatment for dry eye

The most significant advancement to occur in therapeutics for the treatment of patients with dry eye is the approval of cyclosporine 0.05% (Restasis, Allergan). Cyclosporine 0.05% is the only medication that works to treat dry eye disease by increasing the function of the lacrimal gland while stopping inflammatory disruption of the neuronal feedback loop. Dosing of cyclosporine 0.05% is only twice a day, which enhances patient compliance.

Other uses for temporary plugs

Laser in situ keratomileusis (LASIK) is another procedure when a temporary plug is beneficial. The potential LASIK patient with dry eye is often concerned about whether he or she is a candidate for the procedure. Using temporary plugs to prepare these patients for surgery works well. Additionally, LASIK often spurs short-term keratoconjunctivitis sicca (KCS) in patients with healthy eyes. KCS can be caused by the keratome, which cuts the nerve fibers of the cornea and decreases the neuronal feedback loop that produces tears. Thus, temporary plugs are often a good solution for post-LASIK dry eye treatment.

While I believe that there will always be a use for punctal plugs in dry eye treatment, the type of material and the way they are used will continue to evolve. Permanent punctal occlusion is rarely used and silicone plugs are beginning to take a back seat to the longer lasting absorbable plugs. The approval of cyclosporine 0.05% and the popularity of LASIK have increased this trend. As with all fields of medicine, progress means change, and the physician must re-evaluate the use of punctal plugs as newer treatment and surgery options develop.

Douglas Katsev, MD, specializes in corneal and refractive surgery at the Santa Barbara Medical Foundation Clinic in California.
(KETOROLAC, continued from page 3)

There was a significant difference in the distribution of severity in symptoms (associated with the surgery itself, such as foreign body sensation, photophobia and tearing \( (P<.005) \)).

There were few treatment-related adverse events, although one patient treated with vehicle experienced treatment-related corneal infiltrates. There were no serious adverse events or deaths, and none of the patients reported irritation, burning or stinging upon instillation. Adverse events were tracked by the number of patients who reported adverse events at any time. Whether a patient reported an adverse event once or 50 times, it was recorded as a single event.

There was a significant difference in the time to reepithelialization \( (P=.016) \). However, the median time to reepithelialization occurred after day 2 and by day 3 for both treatment groups.

The changes in visual acuity and biomicroscopy were as expected with the PRK procedure.

Summary

The use of NSAID prophylaxis results in reduction of postoperative inflammation, preservation of macular function and pain suppression.

Ketorolac tromethamine 0.4% (Acular LS) ophthalmic solution is efficacious. It reduces pain intensity, produces pain relief, and reduces the use of escape medication. The solution was also comfortable to instill for patients, and found to be safe and tolerable.

Ketorolac tromethamine 0.4% (Acular LS) maintains the efficacy of the NSAIDs for the post-cataract and post-refractive surgery patient without the adverse events of burning, stinging and surface toxicity.

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**New Infection Section Editor**

Eric D. Donnenfeld, MD

Please welcome Henry D. Perry, MD, as the new Infection Section Editor of THERAPEUTIC UPDATES IN OPHTHALMOLOGY.

Dr. Perry is the chief of Cornea Service at North Shore University Hospital and Nassau County Medical Center. He serves as the director of the Research Pathology Laboratories of the New York Eye and Ear Infirmary and is medical director of the Lions Eye Bank for Long Island at North Shore University Hospital.

Dr. Perry is recognized as one of the leading corneal and refractive surgeons in the United States; he is internationally renowned and lectures throughout the world. He is a nationally recognized expert in diseases and surgery of the cornea and corneal pathology. He has also written more than 120 papers and books on corneal and refractive surgery.

Dr. Perry is a Board Certified Ophthalmologist and winner of the senior honor award and honor award from the American Academy of Ophthalmology. Dr. Perry received his Bachelor’s degree from Hofstra University cum laude and his Medical Degree with honors from the University of Cincinnati College of Medicine.

After completing his residency at the Nassau County Medical Center and the University of Pennsylvania Scheie Eye Institute in Philadelphia, Pa., Dr. Perry completed fellowships in Ophthalmic Pathology at the Armed Forces Institute of Pathology in Washington D.C., in cornea and external disease at the cornea service of the Massachusetts Eye and Ear Infirmary, Harvard University, and cornea research at Eye Research Institute of Retina Foundation.

Dr. Perry has served as attending surgeon and consultant for numerous hospitals including: North Shore University Hospital; New York Eye and Ear Infirmary; Winthrop University Hospital; Nassau County Medical Society; Mercy Hospital; John T. Mather Memorial Hospital; and Long Island Jewish, Hillside Medical Center.

Dr. Perry is a fellow of the American College of Surgeons and the American Association of Ophthalmic Pathologists and is a member of several professional societies including: the American Medical Association; the American Medical Association; the Association for Research in Vision and Ophthalmology; Nassau County Medical Society; New York State Medical Society; and the International Society of Refractive Keratoplasty.
ocular disease has consistently been the goal of Therapeutic Updates in Ophthalmology.

As the Chief Medical Editor, Dr. McDonnell has led Therapeutic Updates in Ophthalmology with efficiency, intelligence and a knack for understanding what clinicians need to know. The Wilmer Eye Institute of Johns Hopkins University, where Dr. McDonnell trained as a resident, has recently brought him back to his origins in Baltimore. I offer congratulations to Dr. McDonnell, the new chairman of the Department of Ophthalmology at Wilmer Eye Institute.

The entire Editorial Board of Therapeutic Updates in Ophthalmology wishes Dr. McDonnell well in his new endeavor. As the next editor of Therapeutic Updates in Ophthalmology, I can only hope to continue the tradition of clinical excellence that he has brought to this newsletter.

As a firm believer in term limits, my conviction is that change and new perspectives are beneficial. So it is my pleasure to inform you that Eric D. Donnenfeld, MD, will assume the role of Chief Medical Editor of this publication. Now is a good time for the editorial board of Therapeutic Updates in Ophthalmology to take stock of its successes and to look for new opportunities to do an even better job of addressing the key, common issues confronting the busy practitioner.

Dr. Donnenfeld is the perfect choice for this role. A graduate of Dartmouth College and a graduate of Peter Laibson’s corneal fellowship at Wills Eye Hospital in Philadelphia, Dr. Donnenfeld is an internationally respected specialist in anterior segment disease whose work has been published extensively in the peer-reviewed literature on topics including dry eye disease, antimicrobial therapy, management of pterygia and cicatrising conjunctival disease and keratorefractive surgery.

A talented surgeon and clinician, Dr. Donnenfeld has also been an active member of our editorial board since the founding of Therapeutic Updates in Ophthalmology. His credentials as clinician-scientist and practitioner make him particularly well-suited to this role. Dr. Donnenfeld will identify the key topics that need to be addressed in these pages over the next several years.

I thank Dr. Donnenfeld for his service as an editorial board member for the last several years and for his willingness to take over as Chief Medical Editor, and look forward to reading future issues of Therapeutic Updates in Ophthalmology as they arrive in my office.