FUNCTIONAL LENS regeneration may be moving a step closer to reality from hypothesis. Kang Zhang, MD, PhD, and colleagues reported results of a clinical trial in which functional lens regeneration was achieved after congenital cataract surgery performed with a novel minimally invasive technique [Lin H, et al. Nature. 2016;531:323-328].

Dr. Zhang is professor of ophthalmology and chief of ophthalmic genetics, University of California-San Diego.

Designed to maintain lens capsule integrity and preserve the lens epithelial stem cells (LECs), the surgical strategy involves removal of the lens contents and/or cortical opacities through a small, 1- to 1.5-mm, peripheral capsulorhexis using a 0.9-mm phacoemulsification probe.

After demonstrating in rabbit and macaque models that the surgical technique resulted in functional lens regeneration, the research advanced into a pilot clinical trial co-led by Yizhi Liu, MD, PhD, professor and director, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou, China.

The randomized study enrolled infants aged 0 to 1 years with bilateral congenital cataract and assigned 12 children to be operated on with the new method and 25 children to undergo conventional cataract surgery. The procedure in the control group involved a 6-mm anterior continuous curvilinear capsulorhexis.

By Cheryl Guttman Krader; Reviewed by Kang Zhang, MD, PhD
INDICATIONS AND USAGE:

DUREZOL® Emulsion is a topical corticosteroid that is indicated for:

• The treatment of inflammation and pain associated with ocular surgery.
• The treatment of endogenous anterior uveitis.

Dosage and Administration:

• For the treatment of inflammation and pain associated with ocular surgery instill one drop into the conjunctival sac of the affected eye 4 times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the postoperative period, followed by 2 times daily for a week and then a taper based on the response.
• For the treatment of endogenous anterior uveitis, instill one drop into the conjunctival sac of the affected eye 4 times daily for 14 days followed by tapering as clinically indicated.

IMPORTANT SAFETY INFORMATION

Contraindications: DUREZOL® Emulsion, as with other ophthalmic corticosteroids, is contraindicated in most active viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.

Warnings and Precautions:

• Intracocular pressure (IOP) increase — Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. If this product is used for 10 days or longer, IOP should be monitored.
• Cataracts — Use of corticosteroids may result in posterior subcapsular cataract formation.
• Delayed healing — The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order beyond 28 days should be made by a physician only after examination of the patient with the aid of magnification such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.
• Bacterial infections — Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.
• Viral infections — Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).
• Fungal infections — Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use.
• Contact lens wear — DUREZOL® Emulsion should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of DUREZOL® Emulsion. The preservative in DUREZOL™ Emulsion may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of DUREZOL™ Emulsion.

Most Common Adverse Reactions:

• Post Operative Ocular Inflammation and Pain — Ocular adverse reactions occurring in 5–15% of subjects included corneal edema, ciliary and conjunctival hyperemia, eye pain, photophobia, posterior capsule opacification, anterior chamber cells, anterior chamber flare, conjunctival edema, and blepharitis.
• In the endogenous anterior uveitis studies, the most common adverse reactions occurring in 5–10% of subjects included blurred vision, eye irritation, eye pain, headache, increased IOP, iritis, limbal and conjunctival hyperemia, punctate keratitis, and uveitis.

For additional information about DUREZOL® Emulsion, please refer to the brief summary of Prescribing Information on adjacent page.

Ocular Surgery

Instill one drop into the conjunctival sac of the affected eye 4 times daily for 14 days followed by tapering as clinically indicated.

Contraindications

The use of DUREZOL® Emulsion, as with other ophthalmic corticosteroids, is contraindicated in the treatment of active ocular infections. DUREZOL® Emulsion should not be administered to a nursing woman.

DUREZOL® Emulsion is not indicated for use in the presence of active herpes simplex infections of the cornea and conjunctiva, or in cases of infection from pathogens including herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.

Warnings and Precautions

IOP Increase

Prolonged use of corticosteroids may result in glaucoma, with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in patients with a history of glaucoma. If this product is used for 10 days or longer, intraocular pressure should be monitored.

Cataracts

Use of corticosteroids may result in posterior subcapsular cataract formation.

Delayed Healing

The use of corticosteroids after ocular surgery may delay healing and increase the incidence of bleb formation in those diseases causing thinning of the cornea or sclera, perforations have been known to occur in patients treated with topical steroids. The initial prescription and renewal of the medication for up to 4 weeks should be made by a physician only after examination of the patient. The use of high levels of steroids for prolonged periods may cause thinning of the skin; all of which were due to the effect of corticosteroids on collagen metabolism.

Bacterial Infections

Prolonged use of corticosteroids may suppress the host’s immune response and increase the hazard of secondary ocular infections. In acute purulent conjunctivitis, steroids may mask infection or enhance existing infection. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.

Viral Infections

Employment of a corticosteroid medication in the treatment of patients with a history of herpetic infections requires great caution. Use of corticosteroids may mask infection and may exacerbate the severity of many viral infections of the eye (including herpes simplex).

Fungal Infections

Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungal invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use.

Topical Ophthalmic Use Only

DUREZOL Emulsion is not indicated for intravenous administration.

Contact Lens Wear

DUREZOL Emulsion should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of DUREZOL® Emulsion. The preservative in DUREZOL® Emulsion may be absorbed by soft contact lenses. Lenses may be reininserted after 15 minutes following administration of DUREZOL® Emulsion.

Adverse Reactions

Adverse reactions associated with ophthalmic corticosteroids include elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects; posterior subcapsular cataract formation; secondary iritis from pathogens including herpes simplex; and perforation of the globe where there is thinning of the cornea or sclera.

Ocular Surgery

Ocular adverse reactions occurring in 5-15% of subjects in clinical studies with DUREZOL® Emulsion included corneal edema, hypea, conjunctival hyperemia, eye pain, photophobia, posterior capsule opacification, anterior chamber cells, anterior chamber flare, conjunctival edema, and blepharitis. Other ocular adverse reactions in cataract surgery in 5-15% of subjects included reduced visual acuity, punctate keratitis, eye inflammation, and itch. Ocular adverse reactions occurring in <1% of subjects included application site discomfort or irritation, corneal pigmentation and striae, episcleritis, eye pruritus, eyelash irritation and crusting, foreign body sensation, increased lacrimation, macular edema, sclera hyperemia, and uveitis. Most of these reactions have been the consequence of the surgical procedure.

Contraindications

A total of 200 subjects participated in the clinical trials for endangered ocular adverse reactions, of which 106 were exposed to DUREZOL® Emulsion. The most common adverse reactions of those exposed to DUREZOL® Emulsion occurring in 5-10% of subjects included blurred vision, eye pain, eye pruritus, headache, increased IOP, iritis, limbal and conjunctival hyperemia, punctate keratitis, and uveitis. Adverse reactions occurring in 1-5% of subjects included anterior chamber flare, corneal edema, dry eyes, indocyanine, photophobia, and reduced visual acuity.

Use in Specific Populations

Pregnancy

Teratogenic Effects

Pregnancy Category C. Difluprednate has been shown to be embryotoxic (died in embryonic body weight and a delay in embryonic ossification) and embryotoxic (soft palate and skeletal anomalies) when administered subcutaneously to rabbits during organogenesis at a dose of 1–10 mcg/kg/day. The no-observed-effect level (NOEL) for these effects was 1 mcg/kg/day and 10 mcg/kg/day was considered to be a teratogenic dose that was concomitantly found in the toxic dose range for fetuses and pregnant females. Treatment of rats with 10 mcg/kg/day subcutaneously during organogenesis did not result in any reproductive toxicity, nor was it maternally toxic. At 100 mcg/kg/day after subcutaneous administration in rats, there was a decrease in fetal weight and delay in ossification, and affects on weight gain in pregnant females. It is difficult to extrapolate these doses of difluprednate to maximum daily human doses of DUREZOL® Emulsion, since DUREZOL® Emulsion is administered topically with minimal systemic absorption, and difluprednate blood levels were not measured in the reproductive animal studies. However, since use of difluprednate during human pregnancy has not been evaluated and cannot rule out the possibility of harm, DUREZOL® Emulsion should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or fetus.

Nursing Mothers

It is not known whether topical ophthalmic administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when DUREZOL® Emulsion is administered to a nursing woman.

Pediatric Use

DUREZOL® Emulsion was evaluated in a 3-month, multicenter, double-masked, trial in 79 pediatric patients. DUREZOL® Emulsion; 40 prednisolone acetate 0.1% for 3 years of age for the treatment of inflammation following cataract surgery. A similar safety profile was observed in pediatric patients comparing DUREZOL® Emulsion to prednisolone acetate ophthalmic suspension, 1%. No significant decrease in growth and development was observed among the patients treated with DUREZOL® Emulsion. Therefore, the safety profile was observed in pediatric patients comparing DUREZOL® Emulsion to prednisolone acetate ophthalmic suspension, 1%. No significant decrease in growth and development was observed among the patients treated with DUREZOL® Emulsion.

Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

Nonclinical Toxicology

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Difluprednate was not genotoxic in vitro in the Ames test, and in cultured mammalian cells CHL/ 10 (a fibroblast; cell line derived from the lungs of newborn female Chinese hamsters). An in vivo micronuclear test of difluprednate in mice was also negative. Treatment of male and female rats with subcutaneous difluprednate up to 10 mcg/kg/day prior to and during mating did not impair fertility in either gender. Long term studies have not been conducted to evaluate the carcinogenic potential of difluprednate.

Animal Toxicology and/or Pharmacology

In multiple studies performed in rodents and non-rodents, subchronic and chronic toxicology tests were consistent between species and ranged from 1-1.25 mcg/kg/day.

Patient Counseling Information

Risk of Contamination

This product is sterile when packaged. Patients should be advised not to allow the dropper tip to touch any surface, as this may contaminate the emulsion. Use of the same bottle for both eyes is not recommended with topical eye drops that are used to contain the emulsion.

Risk of Secondary Infection

If pan dermals, or if redness, itching, or inflammation becomes aggravated, the patient should be advised to consult a physician.

Contact Lens Wear

DUREZOL Emulsion should not be instilled while wearing contact lenses. Patients should be advised to remove contact lenses prior to instillation of DUREZOL® Emulsion. The preservative in DUREZOL® Emulsion may be absorbed by soft contact lenses. Lenses may be reininserted after 10 minutes following administration of DUREZOL® Emulsion.
The lens regrowth hypothesis
Can infant stem cells regenerate human crystalline lens?

By Michael X. Repka, MD, MBA

Dr. Repka is the David L. Guyton, MD, and Fedunick Family Professor of Ophthalmology at the W. I. Brinton Institute, Johns Hopkins University School of Medicine, Baltimore. He has no commercial interests, related or unrelated, in the topic.

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STEM CELLS AND REGENERATIVE medicine are hot topics in biological research, medicine, and ophthalmology. Although scientif- ic and lay press frequently discuss the prom- ise of these therapies for optic nerve and retinal disorders as being just around the corner, real progress has been slow to achieve and often beset by unrealistic expectations and poor results.1

While the introduction of a polymer IOL was revolutionary with many millions implanted annually around the world, the chance to re- place the human crystalline lens with a func- tioning, biologic product has been the dream of many ophthalmologists.

Among many was Charles Kelman, MD, ever a visionary, when he obtained a patent for the removal of cataractous lens protein and refilling the capsular bag with purified soluble or partially fibrillar collagen.2

This biological lens was expected to be engineered with appropriate optical clar- ity and more normal function including accommodation.

More recently, the idea of replacing the lens protein of an infantile cataract by having the body simply regenerate a crystalline lens in place has been discussed.

Following lensctomy in infant eyes, pedi- atric ophthalmologists have noted remarkably clear lens protein expanding the space between the anterior and posterior capsule circular rem- nants, rather than seeing the capsule leaflets fuse together.

NEARING CLINICAL POSSIBILITY

In March 2016, the lens regrowth hypothesis was transformed into a distinct clinical possi- bility. Investigators from China and the United States reported their findings in Nature detail- ing a series of experiments in animals and children up to 2 years of age.3

The researchers initially verified the location of lens epithelial stem/progenitor cells. These cells were distributed beneath the anterior cap- sule to about the lens equator.

They hypothesized if they could disrupt the anterior capsule only minimally during cata- ract surgery, these cells could seal the opening, not cause central fibrosis of the capsule and perhaps regenerate a normal crystalline lens.

The authors designed their “minimally invasive” surgery to include a 1- to 1.5-mm diam- eter anterior capsulotomy as far peripherally as possible followed by aspiration of lens material, while leaving the posterior capsule intact. Then the endogenous lens stem cells would regener- ate the lens.

After refining the technique in rabbits and in non-human primates, they enrolled 12 children with bilateral cataracts into the regeneration arm. The investigational surgery was com- pleted in all 24 eyes.

The capsule was initially collapsed, but re- formed over 3 months, and reached normal lens thickness 8 months after surgery. Average refractive power of the regenerated lenses was 19 D. Lens clarity was judged good in 23 of 24 regenerated lenses and visual acuity was comparable to a comparison group undergo- ing large central capsulotomy surgery. Impressively, the lenses had a mean 2.50 D of accommodation.

The authors appropriately cautioned that their technique does not work for pediatric cataracts with fibrosis involving the capsule, as well as in the presence of other anterior segment abnormalities. They felt that the cur- rent 1.5-mm diameter capsulotomy approach would not be applicable to more mature adult cataracts because of the hard nucleus.

Beyond these limitations, I am concerned about two important issues, one affecting each arm.

For the conventional “group,” I noted that it was not managed with simultaneous posterior

See the Cover Story, “Regrowing the human lens,” for more about the researchers’ findings.

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CHRONIC OPEN-ANGLE GLAUCOMA: A 40-YEAR OPHTHALMIC PERSPECTIVE

FROM THE VIEWPOINT OF a general ophthalmologist—and not from the skewed viewpoint of a glaucoma subspecialist—chronic open-angle glaucoma (in the majority of cases) is a relatively slow-to-progressive, insidious disease with virtually no symptoms and only mild functional interruption of the retinal nerve fiber layer.

Following patients for 35-plus years is an interesting exercise in observational skills. Progression of this group of diseases (with treatment) as a whole seems to be relatively slow, and the risk of blindness in the majority of cases is quite low.

Capsule removal at the time of the lensectomy and as expected nearly every infant needed additional surgery to clear the visual axis. This delay undoubtedly produced more amblyopia in those “control” subjects than would typically be encountered.

For the investigational surgery group, there is an 8-month period required for regeneration of the lens. The refractive blur from aphakia immediately postoperatively until the lens maximally regenerated would likely produce an intense amblyopia, which may not be reversible. This would be an even greater problem with unilateral cataract.

Longer-term follow-up optotype visual acuity is needed to fully address the quality and function of these regenerated lenses.

What I find so exciting in this approach is that the authors were able to use the patient’s own lens stem cells so that they did not need to harvest and transplant tissue at great cost. These stem cells were capable of regenerating pretty normal appearing crystalline lenses.

Also intriguing and worth discussion, is my suspicion that this surgery would likely cost less than current techniques of lensectomy with vitrectomy and IOL placement. ■

‘What evolutionary advantage chronic open-angle glaucoma seemed to give to its recipients remains a mystery for now.’

—Judson P. Smith, MD, PA

There is no question that chronic open-angle glaucoma is a progressive disease, but the rate of progression is slow and even if patients live to be in their mid-to-late 90s, the majority of patients will have adequate functional vision to pursue the tasks that a 90-year-old-plus person needs to perform.

I have seen and am quite aware that there is a subset of about 5% of the glaucoma population with an aggressive form of the disease (especially in African-Americans) that can lead to blindness in several years, if not aggressively treated.

However, in the practice of the general ophthalmologist, these cases are the exception and not the rule.

Medical pharmacologic therapy is usually adequate to control the rate of progression in most cases. Minimally invasive glaucoma surgeries (MIGS) and minimally effective glaucoma surgeries (MEGS)—surgical interventions—remain in the purview of the glaucoma subspecialist, but this was not always the case.

Most of the ophthalmologists who trained in my era (late 1960s to late 1970s) were well trained to perform a single glaucoma-filtering procedure and to deal the complications (of which there were many) in an effective manner.

Fortunately—or unfortunately, depending on your point of view—we did not have to resort to these procedures very often.

Follow-up visits for most patients with chronic open-angle glaucoma were frequently extended from 3 months to 4 months to 6 months depending upon the particular case. Compliance with medications was pretty much unknown other than that patients usually took their drops during the day of the visit to the ophthalmologist.

In spite of all this noncompliance, the disease was still very slow to progressive.

I have only addressed the disease referred to as chronic (simple) open-angle glaucoma [Duke-Elder] and not any of the secondary glaucomas, such as pseudoexfoliation glaucoma, pigmented glaucoma, neovascular glaucoma, uveitic glaucoma, and traumatic angle recession glaucoma (“former golden gloves boxers” glaucoma).

In the final analysis, chronic open-angle glaucoma will be defined in terms of a genetic disease with a wide spectrum of severity. The majority of cases will be in the mild severity category.

What evolutionary advantage chronic open-angle glaucoma seemed to give to its recipients remains a mystery for now.

However, someday, we will learn that having glaucoma was an evolutionary advantageous quirk that has persisted to the present day and is still in the process of evolving.

—Judson P. Smith, MD, PA

Fort Worth, TX

References


LENS REGROWTH

(Continued from page 4)
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En face optical coherence tomography (OCT) is a valuable imaging strategy for anatomic and angiographic viewing of the fundus. The technology is useful for diagnosing and monitoring diseases with layer-specific anatomic abnormalities or microvascular flow alterations, said Philip J. Rosenfeld, MD, PhD.

“The real advantage of en face OCT is the ability to slice and dice the images throughout their entire depth, from the choroid to the vitreous,” said Dr. Rosenfeld, professor of ophthalmology, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami.

“En face OCT imaging became clinically useful with the advent of high-speed, high-density, spectral domain OCT raster-scanning techniques,” Dr. Rosenfeld added. “It has come of age over the past decade, and we can expect its use in clinics will increase with further uptake of faster SD-OCT systems, swept source OCT systems, and developments in OCT angiography.”

En face OCT imaging with defined boundary segmentation was developed and patented by the Bascom Palmer Eye Institute and the University of Miami Miller School of Medicine and then licensed to Carl Zeiss Meditec. This license is now shared with Optovue.

Dr. Rosenfeld said en face OCT imaging has been useful for following disease progression in wet and dry age-related macular degeneration (AMD) and in diseases that disrupt the inner segment/outer segment/ellipsoid zone.

TAKE-HOME

Experience with en face OCT shows its value for following disease progression in wet and dry age-related macular degeneration and in diseases that disrupt the inner segment/outer segment/ellipsoid zone.
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- BEPREVE® is contraindicated in patients with a history of hypersensitivity reactions to bepotastine or any of the other ingredients.
- BEPREVE® is for topical ophthalmic use only. To minimize risk of contamination, do not touch the dropper tip to the eyelids or to any surface. Keep the bottle closed when not in use.
- BEPREVE® should not be used to treat contact lens-related irritation. Remove contact lens prior to instillation of BEPREVE®. Lenses may be reinserted 10 minutes after BEPREVE® administration.
- The most common adverse reaction occurring in approximately 25% of patients was a mild taste following instillation. Other adverse reactions occurring in 2%-5% of patients were eye irritation, headache, and nasopharyngitis.

Please see the accompanying full Prescribing Information for BEPREVE® on the following page.


Made by the respected eye-care specialists at BAUSCH + LOMB

BEPREVE® (bepotastine besilate ophthalmic solution) 1.5%
BEPREVE® (bepotastine besilate ophthalmic solution) 1.5%

HIGHLIGHTS OF PRESCRIBING INFORMATION
The highlights include all the information needed to use BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% safely and effectively. See full prescribing information for BEPREVE®.

WARNINGS AND PRECAUTIONS
To minimize the risk of drop-related conjunctival irritation, touch dropper tip to any surface. Keep bottle tightly closed when not in use. (5.1) BEPREVE® should not be used to treat contact lens-related irritation. (5.2) Contact lenses should not be inserted after instillation of BEPREVE. (5.3)

ADVERSE REACTIONS
The most common adverse reaction occurring in approximately 25% of patients was eye irritation. Other adverse reactions occurring in 2-5% of subjects were eye irritation, headache, and nasopharyngitis. (6)

In a 12-month carcinogenicity study in rats, BEPREVE® was administered at concentrations anticipated for topical ocular use in humans. The no observable effect level was 9.8 mg/kg/day in rats, representing exposure approximating 350 and 200 times that achieved in healthy volunteers in clinical trials conducted in pediatric patients greater than 10 years of age and from adults. BEPREVE® contains 15 mg bepotastine besilate. Bepotastine besilate is designated chemically as (4S,5S)-5-chloro-3-2-pyridylbenzoyl-1-piperidinyl butyric acid monobenzoensulfonate. The chemical structure for bepotastine besilate is:

Bepotastine besilate is a white or pale yellowish crystalline powder. The molecular weight of bepotastine besilate is 547.06 daltons. BEPREVE® ophthalmic solution is supplied as a sterile, aqueous 1.5% solution, with a pH of 6.8. The osmolarity of BEPREVE (bepotastine besilate ophthalmic solution) 1.5% is approximately 292 mOsm/L.

Each mL of BEPREVE (bepotastine besilate ophthalmic solution) 1.5% contains:

Active: Bepotastine besilate 15 mg (equivalent to 12 mg bepotastine)
Preservative: benzalkonium chloride 0.005%
Inactives: monobasic sodium phosphate dibehydrate, sodium chloride, sodium hydroxide to adjust pH, and water for injection, USP

CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Bepotastine is a topically active, direct H1 receptor antagonist and an inhibitor of the release of histamine from mast cells.

12.2 Pharmacokinetics
Absorption: The extent of systemic exposure to bepotastine following topical ocular administration of bepotastine besilate 1% and 1.5% ophthalmic solutions was evaluated in 12 healthy adults. Following one drop of 1% or 1.5% bepotastine besilate ophthalmic solution to both eyes every four times daily for seven days, bepotastine besilate concentrations peaked at approximately one to two hours post-institution. Maximum plasma concentration for the 1% and 1.5% strengths were in the range of 2.7 to 1.8 ng/mL, respectively. Plasma concentration at 24 hours post-institution were below the quantifiable limit (2 ng/mL) in 1/12 subjects in the two dose groups.

Distribution: The protein binding of bepotastine is approximately 55% and independent of bepotastine concentration.

Metabolism: In vitro metabolism studies with human liver microsomes demonstrated that bepotastine is minimally metabolized by CYP450 isozymes. In vitro studies demonstrated that bepotastine besilate does not inhibit the metabolism of various cytochrome P450 substrate via inhibition of CYP3A4, CYP2C9, and CYP2C19. The effect of bepotastine besilate on the drug metabolizing enzymes of CYP2D6 and CYP2C19 and CYP2C19. Excretion: The main route of elimination of bepotastine besilate is urinary excretion (with approximately 75-80% excreted unchanged in urine).

13 NONCLINICAL TOXICITY
13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility
Long-term dietary studies in mice and rats were conducted to evaluate the carcinogenic potential of bepotastine besilate. Bepotastine besilate did not significantly induce neoplasms in mice receiving a nominal dose of up to 230 mg/kg/day for 16 months. Bepotastine besilate was associated with a decrease in the overall incidence of mammary tumors in female rats treated with 1,000 mg/kg/day in a 2-year study. There was no evidence of genotoxicity in the Ames test, in CHO cells (chromosome aberrations), in mouse hepatocytes (unscheduled DNA synthesis), or in the mouse micronucleus test. When oral bepotastine was administered to male and female rats at doses up to 2,000 mg/kg/day, there was a slight reduction in fertility index and surviving fetuses. Infertility was not seen in rats given 200 mg/kg/day oral bepotastine besilate (approximately 3,300 times the systemic concentration anticipated for topical ocular use in humans).

14 CLINICAL STUDIES
Clinical efficacy was evaluated in 2 conjunctival allergen challenge (CACL) studies (237 patients). BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% was more effective than its vehicle for relieving ocular itching induced by a conjunctival allergen challenge, both at a CAC 15 minutes post-dosing and a CAC 8 hours post-dosing of BEPREVE®. The safety of BEPREVE® was evaluated in a randomized clinical study of 861 subjects over a period of 6 months.

16 HOW SUPPLIED/STORAGE AND HANDLING
BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% is supplied in a white low density polyethylene bottle with a white controlled dropper tip and a white polypropylene cap in the following size: 5 mL (NDC 24208-629-62) 10 mL (NDC 24208-629-01) STORAGE: Store at 15°–25°C (59°–77°F).

17 PATIENT COUNSELING INFORMATION
17.1 Topical Ophthalmic Use Only
For topical ophthalmic administration only.

17.2 Steroid or Dropper Tip
Patients should be advised not to touch dropper tip to any surface, as this may contaminate the contents.

17.3 Concomitant Use of Contact Lenses
Patients should be advised not to wear contact lenses prior to instillation of BEPREVE®. The preservative in BEPREVE®, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reininserted after 10 minutes following administration of BEPREVE®.


**REGENERATION**

*Continued from page 1*

capsulorhexis plus a posterior continuous curvilinear capsulorhexis. An IOL was either implanted primarily or the eyes were left aphakic and children were fitted with glasses or contact lenses for refractive correction.

After the minimally invasive procedure, the small capsule opening healed within 1 month and a transparent lens structure formed within 3 months.

During follow-up to 8 months, the lens attained central thickness comparable to a normal lens while refractive power and accommodative amplitude increased.

Achieved visual acuity was comparable in the two surgical groups. However, visual axis opacification occurred in only a single eye that underwent the new procedure (4.2%) versus 42 control eyes (84%). Significantly lower rates of other complications also occurred after the new procedure compared with the standard operation, including corneal edema (8.3% versus 30%), anterior chamber inflammation (16.7% versus 74%), ocular hypertension (0% versus 18%), and a need for additional laser surgery (0% versus 84%).

In addition, the life-long glaucoma risk, which is associated with the current congenital cataract surgery, is expected to be significantly lower due to minimal disruption of the ocular structure, although the investigators noted this needs to be verified.

The accomplishment is notable both because of its implications for overcoming current challenges in managing congenital cataract and because it may signal hope for an exciting new era in regenerative medicine, Dr. Zhang noted.

"Our hypothesis is that, given the proper environment and stimulation, we can regenerate a lens with visual function." Dr. Zhang explained. "However, without an intact lens capsule and proper inductive environment, they won’t form a useful lens."

"Nevertheless, these observations suggest that LECs are stem cells with proliferative potential and the ability to generate mature lens fiber cells," Dr. Zhang said. "Our hypothesis is that, given the proper environment and stimulation, we can regenerate a lens with visual function."

Initial preclinical experiments confirmed a role for LECs in lens regeneration and showed that loss of LEC homeostasis led to cataract formation.

**LECS AS STEM CELLS**

The development of posterior capsule opacification (PCO) and Soemmering ring formation after cataract surgery provided the genesis for the idea of retaining LECs as a means for achieving functional lens regeneration after cataract surgery.

Lens regeneration has been contemplated for many years. However, the new approach overcomes some key difficulties.

"PCO and Soemmering ring formation are well recognized phenomena after cataract surgery and represent disorganized regrowth of LECs," Dr. Zhang explained. "However, without an intact lens capsule and proper inductive environment, they won’t form a useful lens."

"Nevertheless, these observations suggest that LECs are stem cells with proliferative potential and the ability to generate mature lens fiber cells," Dr. Zhang said. "Our hypothesis is that, given the proper environment and stimulation, we can regenerate a lens with visual function."

Initial preclinical experiments confirmed a role for LECs in lens regeneration and showed that loss of LEC homeostasis led to cataract formation.

**TAKE-HOME**

> Functional lens regeneration was achieved in infants undergoing surgery for congenital cataract using a novel minimally invasive technique that maintains lens capsule integrity and preserves lens epithelial stem cells.

**A LOOK AHEAD**

Despite the favorable safety and efficacy outcomes reported in the published paper, Dr. Zhang observed that the new approach does not result in generation of a perfect lens as peripheral cortical changes are seen in some cases.

In addition, it does not address certain underlying causes of cataract, such as genetic mutation, and so the potential for recurrent cataract remains. In fact, opacification is being observed during longer follow-up that ranges up to 18 months in some cases.

"Importantly, however, the visual axis may remain clear during the critical period of vision development so that it would reduce the risk of amblyopia, and buy time while the eye develops to a point where it is possible to implant an IOL powered to provide accurate and long-lasting refractive correction," Dr. Zhang said.

"To date, some children have undergone a second cataract surgery with IOL implantation, and they are doing well during the short-term follow-up," Dr. Zhang said. "So, it appears there is a viable back-up plan if the cataract recurs."

The decision to develop a technique for promoting functional lens regeneration after congenital cataract surgery recognized limitations of the current surgical procedure for that population, both with respect to techniques used for refractive correction and visual rehabilitation and the associated risks and complications, particularly the lifelong risk of glaucoma.

Dr. Zhang said it is tantalizing to think about expanding the project to adult cataract surgery, but challenges exist.

The age-related decline in the regenerative potential of LECs is one obstacle, although Dr. Zhang suggested they are developing techniques and materials that may augment regenerative capability.

A second issue relates to the fact that adult cataract surgery is already a safe and effective procedure that generally produces a rapid return of functional vision.

"Visual recovery that depends on lens regeneration might take 6 months to 1 year in adults, and so patients would need refractive correction during that period," Dr. Zhang said.

"On the other hand, lens regeneration could result in accommodation restoration—thereby providing a solution for the correction of presbyopia, and in a sense, giving a young functional lens back to a patient."

KANG ZHANG, MD, PhD

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Dr. Zhang did not indicate a financial interest in the subject matter.
High myopia: Global pandemic from genetic, environmental factors

Lifestyle factors, computer use, urbanization all are causing increased rates

By Lynda Charters; Reviewed by Jodhbir Mehta, MBBS, PhD

SINGAPORE ::
THE MANNER IN WHICH myopia works has been a mystery until recently when investigators began making inroads into how the disease progresses. This knowledge likely is going to result in lifestyle changes, said Jodhbir Mehta, MBBS, PhD.

“Myopia is the most frequent cause of distance impairment in the world and it is creating an alarming global [pandemic] with deleterious ramifications for the quality of life and economic health of individuals and nations as a whole,” said Dr. Mehta, associate professor, Singapore National Eye Centre, and head of Corneal and External Eye Disease Department. The data are alarming, with almost 22% of the current world population affected. This translates to about 1.5 billion people.

In light of this, Dr. Mehta’s perspective on the disease has changed over time, that is, from his view when he practiced in the United Kingdom that the average degree of myopia of about –3.0 D could be managed with a refractive procedure to recognition of the fact that the average level in Singapore is now –6.0 D. A startling statistic is that almost 80% of the 18-year-olds who enlist in the army in Singapore are myopic.

“My current thinking is that the prevalence of myopia is rising dramatically, i.e., to 60% to 70% in many East Asian countries and 25% to 40% in Western countries,” he said. “It is more concerning that pathological high myopia exceeding –6.0 D ranges from 6.8% to 38% in Asia.”

Myopia has doubled in the United States in the past 30 years and the prevalence of myopia over –8.0 D has increased eightfold, he added.

“In China, 75% of people in the 15- to-24-year age range have myopia and 10% have over –6.0 D,” Dr. Mehta said.

CONCERNS
The concerns with these statistics are the numerous blinding problems that result from myopia.

Though eliminating myopia entirely may be unlikely, it is possible to reduce progression to pathological high myopia that is associated with more severe complications and blindness.

Myopia has doubled in the United States in the past 30 years and the prevalence of myopia over –8.0 D has increased eightfold, he added.

“An automated algorithm currently available on only one proprietary OCT device (Cirrus HD-OCT, Carl Zeiss Meditec) can segment and measure areas of GA,” he said. “With imaging of the photoreceptor/RPE interface, en face OCT is also useful for studying photoreceptor disruption around the edge of GA.”

Dr. Rosenfeld noted this areas of photoreceptor outer segment disruption appear to predict transmission of light into the choroid below Bruch’s membrane in areas devoid of retinal pigment epithelium (RPE).

“En face OCT is also useful for studying photoreceptor disruption around the edge of geographic atrophy.” — Philip J. Rosenfeld, MD, PhD

Similarly, based on the ability to identify outer retinal disruption, progression of macular telangiectasia type 2 has been predicted using en face OCT.

This same outer retinal en face OCT image can also visualize reticular pseudodrusen, which are subretinal drusenoid deposits seen in eyes with AMD. Now, with high-speed, swept-source OCT widefield scans, both the GA and reticular pseudodrusen can be visualized with a high-density, single 12 x 12 mm scan.

Dr. Rosenfeld explained that OCT angiography is a variation of OCT en face imaging. It generates flow images by assembling multiple B scans from specific locations and provides information on flow and intensity.

PHILIP J. ROSENFELD, MD PhD
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This article was adapted from Dr. Rosenfeld’s presentation at Retina 2015 during the American Academy of Ophthalmology. Dr. Rosenfeld receives research grants from Carl Zeiss Meditec.
BACITRACIN OPHTHALMIC OINTMENT USP

Active against 89% to 99% of identified key gram-positive isolates from conjunctivitis and blepharitis from in vitro studies (1993-January 1, 2015)\textsuperscript{1}

In Vitro Susceptibility Data Provided Through the University of Pittsburgh Medical Center. In Vitro Data Should Not Be Considered Representative of Clinical Efficacy\textsuperscript{1}

Established therapeutic utility in blepharitis, conjunctivitis, and other superficial ocular infections caused by Bacitracin-susceptible organisms

- Excellent safety profile—low incidence of adverse events\textsuperscript{2}
- Ointment provides long-lasting ocular surface contact time and greater bioavailability\textsuperscript{3}
- Anti-infective efficacy in a lubricating base\textsuperscript{2}
- Flexible dosing—1 to 3 times daily\textsuperscript{2}
- Tier 1 pharmacy benefit status—on most insurance plans\textsuperscript{4}

Indication

Bacitracin Ophthalmic Ointment is indicated for the treatment of superficial ocular infections involving the conjunctiva and/or cornea caused by Bacitracin susceptible organisms.

Important Safety Information

This product should not be used in patients with a history of hypersensitivity to Bacitracin.

Bacitracin Ophthalmic Ointment should not be used in deep-seated ocular infections or in those that are likely to become systemic.

There is a low incidence of allergenicity exhibited by Bacitracin. If such reactions do occur, therapy should be discontinued.

Please see adjacent page for full prescribing information.

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Ointment

Bacitracin

Rx

STERILE

DESCRIPTION: Each gram of ointment contains 500 units of Bacitracin in a low melting special base containing White Petroleum and Mineral Oil.

CLINICAL PHARMACOLOGY: The antibiotic, Bacitracin, exerts a profound action against many gram-positive pathogens, including the common Streptococci and Staphylococci. It is also destructive for certain gram-negative organisms. It is ineffective against fungi.

INDICATIONS AND USAGE: For the treatment of superficial ocular infections involving the conjunctiva and/or cornea caused by Bacitracin susceptible organisms.

CONTRAINdications: This product should not be used in patients with a history of hypersensitivity to Bacitracin.

PRECAUTIONS: Bacitracin ophthalmic ointment should not be used in deep-seated ocular infections or in those that are likely to become systemic. The prolonged use of antibiotic containing preparations may result in overgrowth of nonsusceptible organisms particularly fungi. If new infections develop during treatment appropriate antibiotic or chemotherapy should be instituted.

ADVERSE REACTIONS: Bacitracin has such a low incidence of allergenicity that for all practical purposes side reactions are practically non-existent. However, if such reaction should occur, therapy should be discontinued.

To report SUSPECTED ADVERSE REACTIONS, contact Perrigo at 1-866-634-9120 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DOSAGE AND ADMINISTRATION: The ointment should be applied directly into the conjunctival sac 1 to 3 times daily. In blepharitis all scales and crusts should be uniformly over the lid margins. Patients should be instructed to take appropriate measures to avoid gross contamination of the ointment when applying the ointment directly to the infected eye.

HOW SUPPLIED: NDC 0574-4022 13 3-1 g sterile tamper evident tubes with ophthalmic tip. NDC 0574-4022 35 3.5 g (1/8 oz) sterile tamper evident tubes with ophthalmic tip.

Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature].

Manufactured For

Perrigo®

Minneapolis, MN 55427

05400 RC J1 Rev 06-13 A


MYOPIA

(Continued from page 12)

opias, which are associated with high levels of the disease. These blinding disorders are increasing worldwide—not just in Asia.

The economic impact of this global pandemic is considerable, Dr. Mehta related.

Problems for individuals with high myopia, he said, include:

- Unsuitable jobs for those with uncorrected refractive errors
- The cost of treatment with optical devices or refractive procedures
- The need for frequent long-term follow-up
- The compromised quality of vision even among those without a myopia-related pathology

Dr. Mehta explained further that the earlier that myopia starts, the greater the burden.

“We are seeing a shift to a younger onset of myopia, which is especially concerning because younger eyes have more rapid progression of myopia,” he said.

ANALYZING THE CAUSES AND PREVENTION

There is, of course, a genetic component to myopia that is uncontrollable. In Asia, this carries an odds ratio of greater than 11 times; the risk also increases by 2% to 5% in children with two myopic parents. Monozygotic twins also have a higher risk than dizygotic twins.

Environmental causes of myopia are being recognized as having a secondary role in disease development, with excessive near work activity (studying and use of electronic devices) and too little outdoor activity. In fact, increasing outdoor activity exerts a protective effect against the development and progression of myopia, possibly because of an effect of light intensity, possibly the ultraviolet spectrum, and vitamin D.

Dr. Mehta advises parents to monitor how their children read, that is, by keeping books 30 cm away, using sufficient lighting, sitting back from the computer, taking regular breaks, and increasing outdoor activities.

“These interventions can actually reduce the rate of myopia development,” he said. “However, the rate of myopic progression is not affected.”

The most effective way to reduce myopic progression is instillation of an anti-muscarinic topical medication, such as atropine.

However, the drawbacks to this approach are considerable: light sensitivity, near blur, and preclude use of these medications, in addition to the fact that they are not commercially available or FDA approved. A recent Singapore National Eye Center study of three doses of atropine showed that a low dose (0.01%) may slow myopic progression by about 50% to 60% and was associated with fewer side effects compared with the 1% dose.

‘We are seeing a shift to a younger onset of myopia, which is especially concerning.’

— Jodhbir Mehta, MBBS, PhD

TREATMENT OPTIONS

Orthokeratology contact lenses that are worn overnight are an effective treatment option, with recent results showing the elongation of axial length slowing down 40% to 50%. The disadvantages are cost and risk of infection.

Dual-focus contact lenses that are worn during day are another effective option that is associated with decreased myopic progression of 30% to 40%, Dr. Mehta explained.

“Myopia is becoming a global [pandemic], with rates increasing in Asia and the West,” Dr. Mehta said. “Lifestyle factors, computer use, and urbanization are causing the increasing rates.

“It is unlikely that it will be possible to eliminate myopia, but it is possible to reduce progression to pathological high myopia that is associated with more severe complications and blindness,” he added. “A recent study seemed to advocate use of low-dose 0.01% atropine to reduce progression with minimal side effects.”

JODHBIr MEHTA, MBBS, PhD

jodhbir.s.mehta@snec.com.sg

Dr. Mehta did not indicate any financial interest in the subject matter.
ALREX®: TREATS THE ITCH AND MORE.

SHORT-TERM TREATMENT FOR THE FULL SPECTRUM OF SAC* SIGNS AND SYMPTOMS1-3

INDICATION
ALREX® (loteprednol etabonate ophthalmic suspension) is indicated for the temporary relief of the signs and symptoms of seasonal allergic conjunctivitis.

IMPORTANT SAFETY INFORMATION
ALREX® is contraindicated in most viral diseases of the cornea and conjunctiva, including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of the ocular structures. ALREX® is also contraindicated in individuals with known or suspected hypersensitivity to any of the ingredients of this preparation and to other corticosteroids.

Prolonged use of ALREX® is associated with several warnings and precautions, including glaucoma with optic nerve damage, defects in visual acuity, cataract formation, secondary ocular infections, and exacerbation or prolongation of viral ocular infections (including herpes simplex).

If this product is used for 10 days or longer, intraocular pressure should be monitored. The initial prescription and renewal of the medication order beyond 14 days should be made by a physician only after reexamination of the patient with the aid of magnification. Fungal infections of the cornea may develop with prolonged use of corticosteroids.

Ocular adverse reactions occurring in 5-15% of patients treated with loteprednol etabonate ophthalmic suspension (0.2%-0.5%) in clinical studies included abnormal vision/blurring, burning on instillation, chemosis, discharge, dry eyes, epiphora, foreign body sensation, itching, infection, and photophobia.

Please see brief summary of full Prescribing Information on the following page.


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**BRIEF SUMMARY OF PRESCRIBING INFORMATION**

This Brief Summary does not include all the information needed to use Alrex® (loteprednol etabonate ophthalmic suspension 0.2%) safely and effectively. See full prescribing information for Alrex.

**Alrex®**
loteprednol etabonate ophthalmic suspension 0.2%

**Sterile Ophthalmic Suspension**

**Rx only**

**INDICATIONS AND USAGE**

Alrex Ophthalmic Suspension is indicated for the temporary relief of the signs and symptoms of seasonal allergic conjunctivitis.

**CONTRAINDICATIONS**

Alrex, as with other ophthalmic corticosteroids, is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures. Alrex is also contraindicated in individuals with known or suspected hypersensitivity to any of the ingredients of this preparation and to other corticosteroids.

**WARNINGS**

Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision, and in posterior subcapsular cataract formation. Steroids should be used with caution in the presence of glaucoma.

Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection.

Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).

Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution.

**PRECAUTIONS**

**General:** For ophthalmic use only. The initial prescription and renewal of the medication order beyond 14 days should be made by a physician only after examination of the patient with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

If signs and symptoms fail to improve after two days, the patient should be re-evaluated.

If this product is used for 10 days or longer, intraocular pressure should be monitored.

Fungal infections of the cornea are particularly prone to develop coincidently with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal cultures should be taken when appropriate.

**Information for Patients:** This product is sterile when packaged. Patients should be advised not to allow the dropper tip to touch any surface, as this may contaminate the suspension. If redness or itching becomes aggravated, the patient should be advised to consult a physician.

Patients should be advised not to wear a contact lens if their eye is red. Alrex should not be used to treat contact lens related irritation. The preservative in Alrex, benzalkonium chloride, may be absorbed by soft contact lenses. Patients who wear soft contact lenses and whose eyes are not red, should be instructed to wait at least ten minutes after instilling Alrex before they insert their contact lenses.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic in vitro in the Ames test, the mouse lymphoma tk assay, or in a chromosome aberration test in human lymphocytes, or in vivo in the single dose mouse micronucleus assay. Treatment of male and female rats with up to 50 mg/kg/day and 25 mg/kg/day of loteprednol etabonate, respectively, (1500 and 750 times the maximum clinical dose, respectively) prior to and during mating did not impair fertility in either gender.

**Pregnancy:** Teratogenic effects: Pregnancy Category C. Loteprednol etabonate has been shown to be embryotoxic (delayed ossification) and teratogenic (increased incidence of meningocoele, abnormal left common carotid artery, and limb flexures) when administered orally to rabbits during organogenesis at a dose of 3 mg/kg/day (85 times the maximum daily clinical dose), a dose which caused no maternal toxicity. The no-observed-effect-level (NOEL) for these effects was 0.5 mg/kg/day (15 times the maximum daily clinical dose). Oral treatment of rats during organogenesis resulted in teratogenicity (absent innominate artery at ≥5 mg/kg/day doses, and cleft palate and umbilical hernia at ≥50 mg/kg/day) and embryotoxicity (increased postimplantation losses at 100 mg/kg/day and decreased fetal body weight and skeletal ossification with ≥50 mg/kg/day). Treatment of rats with 0.5 mg/kg/day (15 times the maximum clinical dose) during organogenesis did not result in any reproductive toxicity. Loteprednol etabonate was maternally toxic (significantly reduced body weight gain during treatment) when administered to pregnant rats during organogenesis at doses of ≥5 mg/kg/day.

Oral exposure of female rats to 50 mg/kg/day of loteprednol etabonate from the start of the fetal period through the end of lactation, a maternally toxic treatment regimen (significantly decreased body weight gain), gave rise to decreased growth and survival, and retarded development in the offspring during lactation; the NOEL for these effects was 5 mg/kg/day. Loteprednol etabonate had no effect on the duration of gestation or parturition when administered orally to pregnant rats at doses up to 50 mg/kg/day during the fetal period. There are no adequate and well controlled studies in pregnant women. Alrex Ophthalmic Suspension should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers:** It is not known whether topical ophthalmic administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Systemic steroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when Alrex is administered to a nursing woman.

**Pediatric Use:** Safety and effectiveness in pediatric patients have not been established.

**ADVERSE REACTIONS**

Reactions associated with ophthalmic steroids include elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

Ocular adverse reactions occurring in 5-15% of patients treated with loteprednol etabonate ophthalmic suspension (0.2% - 0.5%) in clinical studies included abnormal vision/blurring, burning on instillation, chemosis, discharge, dry eyes, epithora, foreign body sensation, itching, injection, and photophobia. Other ocular adverse reactions occurring in less than 5% of patients include conjunctivitis, corneal abnormalities, eyelid erythema, keratoconjunctivitis, ocular irritation/pain/discomfort, papillae, and uveitis. Some of these events were similar to the underlying ocular disease being studied.

Non-ocular adverse reactions occurred in less than 15% of patients. These include headache, rhinitis and pharyngitis.

In a summation of controlled, randomized studies of individuals treated for 28 days or longer with loteprednol etabonate, the incidence of significant elevation of intraocular pressure (≥10 mm Hg) was 2% (15/901) among patients receiving loteprednol etabonate, 7% (11/164) among patients receiving 1% prednisolone acetate and 0.5% (3/583) among patients receiving 0.5% loteprednol etabonate. The incidence of significant elevation of intraocular pressure (≥10 mm Hg) was 15% (11/73) among patients receiving placebo. Among the smaller group of patients who were studied with Alrex, the incidence of clinically significant increases in IOP (≥10 mm Hg) was 1% (1/133) with Alrex and 1% (1/135) with placebo.

**DOSAGE AND ADMINISTRATION**

SHARE VIGOROUSLY BEFORE USING. One drop instilled into the affected eye(s) four times daily.

Revised: August 2013.

Bausch & Lomb Incorporated, Tampa, Florida 33637

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Based on 9007904-9005504

US/ALX/15/0005 Issued: 02/2015
Cataract surgery an option for some PAC, PACG patients
EAGLE study aims to explore certain scenarios in which early lens extraction is best suited

By Lynda Charters; Reviewed by Anjali M. Bhorade, MD

ST. LOUIS ::

There might be a role for lens extraction in certain scenarios for patients with primary angle-closure (PAC) or primary angle-closure glaucoma (PACG). This question is being addressed in the effectiveness of early lens extraction with IOL implantation for the treatment of PACG in the EAGLE study, said Anjali M. Bhorade, MD. “In such patients, the lens plays a major role in the pathogenesis of PAC and PACG,” said Dr. Bhorade, associate professor of ophthalmology, Department of Ophthalmology and Visual Sciences, Washington University School of Medicine, St. Louis. “Those with the former have thicker lenses that are positioned more anteriorly and a decreased anterior chamber angle.”

However, she pointed out that current studies of angle closure and cataract surgery are limited in that few patients were included, many studies were nonrandomized, and the methodologies varied greatly, making comparisons among the studies extremely difficult.

In her attempt to determine if cataract surgery is beneficial in this patient population, she wanted to evaluate patients based on whether their cataracts were visually relevant, she explained. Those with visually relevant cataracts typically undergo a laser peripheral iridotomy (LPI) and if the IOP is controlled medically, the patients are monitored.

**Visually Relevant Cataracts**

However, there is a question about the appropriateness of managing these patients with phaco-trabeculectomy or phacoemulsification. Dr. Bhorade recounted a study conducted by Tham and colleagues (Ophthalmology 2008; 115:1267-1273) in which 72 eyes with medically controlled IOP and a visually relevant cataract following a LPI were randomly assigned to phacoemulsification or a phaco-trabeculectomy. The results showed that the IOP decreased in both groups, but the difference between them did not reach statistical significance. The group with the combination therapy had fewer IOP medications but more postoperative complications compared with phacoemulsification alone.

“If there are patients with a visually significant cataract whose IOP is medically controlled but they would like to decrease their medications, phacoemulsification might be a good choice,” she said.

If the IOP is medically uncontrolled after an LPI, Dr. Bhorade considers the same treatment scenario for these patients. Dr. Tham and colleagues also performed a study (Ophthalmology 2009;116:725-731) that included 51 eyes with uncontrolled IOP despite medical therapy and a visually relevant cataract. In this group, the combination therapy significantly lowered the IOP compared with the phacoemulsification group.

However, the result was the same as in the previously described group. Fewer IOP medications were needed postoperatively, but there were more postoperative complications.

The results showed that the IOP decreased in both groups, but the difference between them did not reach statistical significance. The group with the combination therapy had fewer IOP medications but more postoperative complications compared with phacoemulsification alone.

“...continues on page 18: Managing IOP..."
MANAGING IOP

(Continued from page 17)

“It appears that initial cataract surgery in patients with visually significant cataracts may be an appropriate treatment.” — Anjali M. Bhorade, MD

“Cataract surgery alone might be indicated in these patients,” she said.

Another therapeutic course to consider is cataract surgery versus LPI as the initial treatment. In two previous studies, eyes were randomly assigned to one of the treatments. In one study (Ophthalmology 2008;115:1134-1140), the mean IOP was lower in the phacoemulsification group than in the LPI group; in the second study (Ophthalmology 2012;119:2274-2281), the 2-year cumulative survival rate was 89.5% in the phacoemulsification group compared with 61.1% in the LPI group.

“It appears that initial cataract surgery in patients with visually significant cataracts might be an appropriate treatment,” Dr. Bhorade said.

NONVISUALLY RELEVANT CATARACTS

This management scenario—in which patients have nonvisually relevant cataracts and medically uncontrolled IOP after a LPI—is less clear. A 2013 study (Ophthalmology 2013;120:62-67) by Tham and colleagues looked at the results in patients who were randomly assigned to phacoemulsification or trabeculectomy. The patients in both groups had similar IOP reductions before and after surgery.

Results with trabeculectomy, as reported previously, showed the need for fewer medications but more complications developed. One-third of patients developed a visually relevant cataract. Patients with visually significant cataracts might be an appropriate treatment.

“When an LPI, cataract surgery in a patient with nonvisually significant cataract with uncontrolled IOPs might be an appropriate approach.” — Anjali M. Bhorade, MD

The participating patients were 50 years or older with newly diagnosed PACG or PAC and IOPs over 30 mm Hg. The angle closure was 180° or more and patients had a nonvisually significant cataract.

“The participating patients were 50 years or older with newly diagnosed PACG or PAC and IOPs over 30 mm Hg. The angle closure was 180° or more and patients had a nonvisually significant cataract. Patients were randomly assigned to lens extraction or a LPI and followed for 3 years. The primary outcomes were the patient-centered health status determined by the EQ-5D questionnaire, the IOP at 3 years, and the incremental cost per quality-adjusted life year gained. Results are forthcoming.” — Anjali M. Bhorade, MD

“The 31-site, randomized EAGLE Study (Trials 2011;12:133. DOI: 10.1186/1745-6215-12-133) evaluated if patients with PAC or PACG benefited from early lens extraction by analyzing if the patient reports, clinical measures, or cost effectiveness improved.

Finally, a Cochrane review of retrospective and prospective studies indicated that there was a lack of evidence from any highly qualified, randomized clinical trials to support if early lens extraction is superior to other treatments (Cochrane Database Syst Rev 2006;3:CD005555. DOI: 10.1002/14651858.CD005555.pub2).

THE EAGLE STUDY

The 31-site, randomized EAGLE Study (Trials 2011;12:133. DOI: 10.1186/1745-6215-12-133) evaluated if patients with PAC or PACG benefited from early lens extraction by analyzing if the patient reports, clinical measures, or cost effectiveness improved.

The participating patients were 50 years or older with newly diagnosed PACG or PAC and IOPs over 30 mm Hg. The angle closure was 180° or more and patients had a nonvisually relevant cataract. Patients were randomly assigned to lens extraction or a LPI and followed for 3 years. The primary outcomes were the patient-centered health status determined by the EQ-5D questionnaire, the IOP at 3 years, and the incremental cost per quality-adjusted life year gained. Results are forthcoming.

Dr. Bhorade summarized, “Based on what is known thus far about cataract surgery and its appropriateness for patients with PAC and PACG . . . some studies have suggested that cataract surgery may be an appropriate treatment to lower IOP in patients with a visually significant cataract.”

For patients with a nonvisually significant cataract, she continued, cataract surgery may be an appropriate option after an LPI and the IOP remains uncontrolled.

“However, the role of cataract surgery as an initial treatment for PAC/PACG in a patient with a nonvisually significant cataract remains unclear,” she concluded. “Results from the EAGLE study may help clarify this answer.” — Anjali M. Bhorade, MD

This article was adapted from Dr. Bhorade’s presentation at the 2016 meeting of the American Glaucoma Society. Dr. Bhorade has no financial interest in the subject matter.
Looking deeper
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**IOL platform designs: Achieving quality of vision**

Extended range of focus increases patients’ options, satisfaction following implantation

By David Teenan, FRCS(Ed), FRCOphth; Reviewed by Albert Augustin, MD

**Editor’s Note:** This article first appeared in sister publication, Ophthalmology Times Europe.

A primary unintended consequence of lens platforms offering vision correction in multiple vision zones is the incidence of visual dysphotopsias. Glare and halos after implantation of a multifocal IOL are highly variable.

In controlled clinical trials with the Tecnis IOLs (Abbott Medical Optics [AMO]), the incidence of moderate halos was 6% and severe halo occurred in 5%. In studies of the AcrySof multifocal lens (Alcon Laboratories), 2.7% reported severe glare and 11% severe halos.

Fundamentally, design considerations may explain these differences. However, additional factors such as residual refractive error, wavefront anomalies, IOL decentering, posterior capsular opacification and dry eye disease may also induce postoperative photic phenomena.

Thus, although lens design is integral to reducing the potential for postoperative visual disturbances, the surgeon must still pay careful attention to optimizing the ocular surface and performing meticulous surgery.

It is hoped that a new-design lens will lower incidence of glare and halo via elongation of the focal zone. The Tecnis Symfony IOL (AMO) may also provide improvements in chromatic aberration, providing patients with sharper vision.

A recently completed patient satisfaction survey demonstrated that these design considerations translate to improved performance.

**COMPETING VISION ZONES**

Traditional multifocal lenses are constructed using diffractive optics, which split light into multiple zones for vision at near, intermediate, and distance. The lens options on the market employ different design considerations to provide vision at different distances without compromising quality of vision.

The AcrySof IOL utilizes apodized optics to spread light distribution across the surface of the IOL based on the size of the pupil and vision demand. That is, more light is theoretically available in the near-distance zone when the focus is near.

These lenses are available in two models, +2.5 and +3.0, with the former intended to provide greater distance vision and the latter intended to provide equal vision across all three distances.

However, an inescapable fact of such a design is that light diffracted through multiple vision zones at the optical surface results in competing images on the retina, which is the basis for visual phenomena such as halo and glare.

The Tecnis family of IOLs employ a slightly different mechanism, with a wavefront-designed aspheric surface and a posterior diffractive surface.

Three different lens options are offered to permit customization of the lens to a patient’s individual vision needs: the +4.0 model has a theoretical reading distance of 33 cm, the +3.25 lens a theoretical reading distance of 42 cm and the +2.75 model a theoretical reading distance of 50 cm. The aspheric surface is intended to reduce contrast sensitivity, and may affect the path of light transmitted through the posterior diffractive zone.

However, again, a design fundamental of the Tecnis family is that the diffractive optics split light to

**Defocus Curve: 3-Month Adjusted Data Bilaterally Implanted Subjects**

![Defocus Curve](image)

(Figure 1) The Tecnis Symfony IOL is designed with a diffractive echelette that creates a novel diffraction pattern to elongate the depth of focus. Though light comes from distinct points, the elongated focus brings the light to a similar point on the retina. (Image courtesy of Abbott Medical Optics)

**Take-Home**

- **Patient satisfaction is high following implant of the Symfony IOL, which is designed with an elongated focal zone in an attempt to minimize visual compromises and avoid visual dysphotopsias.**

Continues on page 23: Extended
Indication
ZIRGAN® (ganciclovir ophthalmic gel) 0.15% is a topical ophthalmic antiviral that is indicated for the treatment of acute herpetic keratitis (dendritic ulcers).

Important Safety Information about ZIRGAN®

- ZIRGAN® is indicated for topical ophthalmic use only.
- Patients should not wear contact lenses if they have signs or symptoms of herpetic keratitis or during the course of therapy with ZIRGAN®.
- Most common adverse reactions reported in patients were blurred vision (60%), eye irritation (20%), punctate keratitis (5%), and conjunctival hyperemia (5%).
- Safety and efficacy in pediatric patients below the age of 2 years have not been established.

Please see brief summary of Prescribing Information on the adjacent page.

BRIEF SUMMARY OF PRESCRIBING INFORMATION
This Brief Summary does not include all the information needed to use Zirgan safely and effectively. See full prescribing information for Zirgan.

Zirgan ganciclovir ophthalmic gel 0.15%
Initial U.S. Approval: 1989

1 INDICATIONS AND USAGE
ZIRGAN (ganciclovir ophthalmic gel) 0.15% is indicated for the treatment of acute herpetic keratitis (dendritic ulcers).

2 DOSAGE AND ADMINISTRATION
The recommended dosing regimen for ZIRGAN is 1 drop in the affected eye 5 times per day (approximately every 3 hours while awake) until the corneal ulcer heals, and then 1 drop 3 times per day for 7 days.

3 DOSAGE FORMS AND STRENGTHS
ZIRGAN contains 0.15% of ganciclovir in a sterile preserved topical ophthalmic gel.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Topical Ophthalmic Use Only
ZIRGAN is indicated for topical ophthalmic use only.

5.2 Avoidance of Contact Lenses
Patients should not wear contact lenses if they have signs or symptoms of herpetic keratitis or during the course of therapy with ZIRGAN.

6 ADVERSE REACTIONS
Most common adverse reactions reported in patients were blurred vision (60%), eye irritation (20%), punctate keratitis (5%), and conjunctival hyperemia (5%).

7 USE IN SPECIFIC POPULATIONS
7.1 Pregnancy: Teratogenic Effects
Pregnancy Category C: Ganciclovir has been shown to be embryotoxic in rabbits and mice following intravenous administration and teratogenic in rabbits. Fetal resorptions were present in at least 85% of rabbits and mice administered 60 mg/kg/day and 108 mg/kg/day (approximately 10,000x and 17,000x the human ocular dose of 0.25 mcg/kg/day, respectively), assuming complete absorption. Effects observed in rabbits included: fetal growth retardation, embryolethality, teratogenicity, and/or maternal toxicity. Teratogenic changes included cleft palate, anophthalmia/microphthalmia, aplastic organs (kidney and pancreas), hydrocephaly, and brachygnathia. In mice, effects observed were maternal/fetal toxicity and embryolethality. Daily intravenous doses of 90 mg/kg/day (14,000x the human ocular dose) administered to female mice prior to mating, during gestation, and during lactation caused hypoplasia of the testes and seminal vesicles in the month-old male offspring, as well as pathologic changes in the nonglandular region of the stomach (see Carcinogenesis, Mutagenesis, and Impairment of Fertility). There are no adequate and well-controlled studies in pregnant women. ZIRGAN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

7.3 Nursing Mothers
It is not known whether topical ophthalmic ganciclovir administration could result in sufficient systemic absorption to produce detectable quantities in breast milk. Caution should be exercised when ZIRGAN is administered to nursing mothers.

7.4 Pediatric Use
Safety and efficacy in pediatric patients below the age of 2 years have not been established.

7.5 Geriatric Use
No overall differences in safety or effectiveness have been observed between elderly and younger patients.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
ZIRGAN (ganciclovir ophthalmic gel) 0.15% contains the active ingredient, ganciclovir, which is a guanosine derivative that, upon phosphorylation, inhibits DNA replication by herpes simplex viruses (HSV). Ganciclovir is transformed by viral and cellular thymidine kinases (TK) to ganciclovir triphosphate, which works as an antiviral agent by inhibiting the synthesis of viral DNA in 2 ways: competitive inhibition of viral DNA-polymerase and direct incorporation into viral primer strand DNA, resulting in DNA chain termination and prevention of replication.

12.2 Pharmacokinetics
The estimated maximum daily dose of ganciclovir administered as 1 drop, 5 times per day is 0.375 mg. Compared to maintenance doses of systemically administered ganciclovir of 900 mg (oral valganciclovir) and 5 mg/kg (IV ganciclovir), the ophthalmically administered daily dose is approximately 0.04% and 0.1% of the oral dose and IV doses, respectively, thus minimal systemic exposure is expected.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility
Ganciclovir was carcinogenic in the mouse at oral doses of 20 and 1000 mg/kg/day (approximately 3,000x and 160,000x the human ocular dose of 0.25 mcg/kg/day, assuming complete absorption). At the dose of 1,000 mg/kg/day there was a significant increase in the incidence of tumors of the preputial gland in males, forestomach (nonglandular mucosa) in males and females, and reproductive tissues (ovaries, uterus, mammary gland, clitoral gland, and vagina) and liver in females. At the dose of 60 mg/kg/day, a slightly increased incidence of tumors was noted in the preputial and hardier glands in males, forestomach in males and females, and liver in females. No carcinogenic effect was observed in mice administered ganciclovir at 1 mg/kg/day (160x the human ocular dose). Except for histocytic sarcoma of the liver, ganciclovir-induced tumors were generally of epithelial or vascular origin. Although the preputial and clitoral glands, forestomach and hardier glands of mice do not have human counterparts, ganciclovir should be considered a potential carcinogen in humans. Ganciclovir increased mutations in mouse lymphoma cells and DNA damage in human lymphocytes in vitro at concentrations between 50 to 500 and 250 to 2,000 mcg/mL, respectively. In the mouse micronucleus assay, ganciclovir was clastogenic at doses of 150 and 500 mcg/kg (IV) (24,000x to 80,000x the human ocular dose) but not 50 mg/kg (8,000x human ocular dose). Ganciclovir was not mutagenic in the Ames Salmonella assay at concentrations of 500 to 5,000 mcg/mL. Ganciclovir caused decreased mating behavior, decreased fertility, and an increased incidence of embryolethality in female mice following intravenous doses of 90 mg/kg/day (approximately 14,000x the human ocular dose of 0.25 mcg/kg/day). Ganciclovir caused decreased fertility in male mice and hypospermatogenesis in mice and dogs following daily oral or intravenous administration of doses ranging from 0.2 to 10 mg/kg (30x to 1,000x the human ocular dose).

14 CLINICAL STUDIES
In one open-label, randomized, controlled, multicenter clinical trial which enrolled 164 patients with herpetic keratitis, ZIRGAN was non-inferior to acyclovir ophthalmic ointment, 3% in patients with dendritic ulcers. Clinical resolution (healed ulcers) at Day 7 was achieved in 77% (55/71) for ZIRGAN versus 72% (48/67) for acyclovir 3% (difference 5.8%, 95% CI -9.6%-18.3%). In three randomized, single-masked, controlled, multicenter clinical trials which enrolled 213 total patients, ZIRGAN was non-inferior to acyclovir ophthalmic ointment 3% in patients with dendritic ulcers. Clinical resolution at Day 7 was achieved in 72% (41/57) for ZIRGAN versus 69% (34/49) for acyclovir (difference 2.5%, 95% CI -15.6%-20.9%).

17 PATIENT COUNSELING INFORMATION
This product is sterile when packaged. Patients should be advised not to allow the dropper tip to touch any surface, as this may contaminate the gel. If pain develops, or if redness, itching, or inflammation becomes aggravated, the patient should be advised to consult a physician. Patients should be advised not to wear contact lenses when using ZIRGAN.

Revised: April 2014

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US/ZGN/15/0005
Based on 9224702 (flat)-9224802 (folded)
different foci, which has the potential to cause dysphotopsias.

Another lens option corrects vision across the multiple viewing ranges via pseudoaccommodation (CrystaLens, Bausch + Lomb).

Postmarketing evidence suggests that, although these lenses provide good distance vision, patients may require glasses for near demands, and so the lens may not supply the full range of vision of other IOL technologies.

**EXTENDED RANGE OF VISION**

The Tecnis Symfony IOL is designed with a diffractive echelette that creates a novel diffraction pattern to elongate the depth of focus (Figure 1).

Even though light comes from distinct points, the elongated focus brings the light to a similar point on the retina. Correspondingly, this increased depth of focus relative to monofocal and other multifocal platforms creates a mechanism to ensure less defocus in the visual plane—in other words, less light that is out of focus. Because halos and glare result from defocused images in the viewing plane along the z-axis, the Symfony’s elongated depth of focus yields the ideal solution to reduce dysphotopsias.

Such an effect is demonstrated in defocus curves demonstrating 20/20 or better mean visual acuity from distance to 1.5 D of defocus, 20/40 or better mean visual acuity from distance to 2.5 D of defocus and a 1.0 D increase in depth of focus throughout the defocus curve.4 (Figure 2)

Furthermore, the Symfony is constructed with achromatic technology intended to reduce wavelength-dependent defocus. Chromatic aberration results from certain wavelengths of light stopping short of the point of focus (the macula), resulting in blur and reductions in contrast. Studies suggest that the average eye has around 2.0 D of chromatic aberration between 400 and 700 nm and 0.8 D between 500 and 640 nm.5

The achromatic technology in the Symfony platform yields sharper focus, in effect bringing the focal point of each wavelength closer to the macula, thereby resulting in sharper vision less given to chromatic variance. Because it is coupled with correction of spherical aberration, the resulting vision does not sacrifice depth of focus.6,7 (Figure 3)

**PATIENT SATISFACTION SURVEY**

I recently completed a patient satisfaction survey in my clinic, assessing visual outcomes after implantation with the Tecnis Symfony IOL in a population of 160 eyes of 80 patients undergoing refractive lens exchange. This was a retrospective review with the primary objectives of measuring uncorrected distance visual acuity (UCDVA), uncorrected near visual acuity (UCNVA), patient satisfaction and complications.

One month after surgery, UCDVA was 20/32 or better in 93% of patients while UCNVA was 20/50 in 88%. In the questionnaire, 83% of patients reported being satisfied or very satisfied and 90% of patients said they would recommend the procedure. Severe difficulty with glare, haloes and ghosting was reported by only 7%, 6% and 1% of patients, respectively. Little or no difficulty with driving at night was reported by 72% of patients reported. There were no reported intra- or postoperative complications.

**CONCLUSION**

Many variables affect presbyopic patients’ ability to see at multiple distances after implantation of a phakic IOL.

Thus, even with new designs on the market, such as the Symfony, it remains critically important to understand the individual vision demands and desires of the patient, as well as what he or she is willing to compromise to achieve the desired refractive outcome.

The level of compromise the patient is willing to accept will direct the lens choice. If the patient wants good reading, perhaps a higher add multifocal lens would be appropriate, assuming there is an understanding that there may be some issues with quality of vision.

In contrast, a patient who drives a lot might be happier with a low-add multifocal, with the caveat that some distance acuity may be lost.

Ultimately, then, what the Symfony technology offers by way of an extended range of focus is another lens option to match to patients’ specific needs. There is less chance of a visual compromise at any given distance, and an improved chance that visual dysphotopsias can be avoided.

Lastly, studies demonstrate that the proprietary features of the lens allow it to transmit light with achromatic correction in order to deliver the best overall quality of vision. Studies demonstrating that Symfony offers optimal modal translation function are not simply data emanating from the laboratory.

The conclusions are reinforced by surveys demonstrating that patients are able to perceive the differences in quality of vision at all distances, and, in turn, are extremely satisfied with the vision the lens provides.8

**References**

4. 166 Data on File. Extended Range of Vision IOL 3-Month Study Results (NQ).

**DAVID TEENAN, FRCS(ED), FRCOPHTH**

Dr. Teenan is the U.K. medical director of the Optical Express International Medical Advisory Board (IMAB) and is registered with the General Medical Council (GMC) and the Irish Medical Council (IMC). He did not declare a financial interest in the subject matter.
Consider latest excimer laser applications for presbyopic patients

Key to successful technique is to center treatment on visual axis, not on pupil

By Fred Gebhart; Reviewed by Gustavo E. Tamayo, MD

The key to successful presbyopia treatment is to center treatment on the visual axis, not on the pupil. The visual symptoms and the poor visual outcomes of any presbyopia treatment are the result of decentration due to centering treatment on the center of the pupil rather than on the visual axis.

It is not possible to capture the precise visual axis using current technology. Dr. Tamayo added, but centering treatment on the Purkinje image is a useful surrogate for the visual axis.

The procedure itself creates a multifocal cornea with different powers at different points along the surface of the cornea. The surgeon creates a peripheral knee on the cornea, which creates distinct areas of negative spherical aberration and a central area of positive spherical aberration. It is this combination of positive spherical aberrations with negative spherical aberrations that creates the increase in depth of focus and improves near vision.

Correcting presbyopia by altering the cornea is not a perfect solution.

Dr. Tamayo cautioned that normal aging processes mean that presbyopia will continue to progress over time. Laser correction needs to be repeated after about seven years for most patients. In addition, the correction can be tweaked or even reversed as needed for patients in whom the procedure is not successful.

Excimer laser device manufacturers have long recognized the potential for presbyLASIK procedures, he said.

One key advantage from the ophthalmologist’s perspective is that almost any current excimer laser device can be used to correct presbyopia with a simple software upgrade.

Dr. Tamayo presented a prospective study of excimer laser presbyopia treatment of 121 eyes in 66 patients who were followed for 38 to 66 months. The mean preoperative sphere was 0.180 ± 2.2 D (-5.0 to + 5 D) and the mean preop cylinder was -0.736 ± 0.97 (-6.5 to 0 D). Most of the patients, 57.9%, were hyperopic, 14% were myopic myopia and 10.7% were emmetropic. Within the study group, 86.8% received presbyLASIK, 13.2% presbyLASEK and 9.9% were being re-treated.

After surgery, 97.5% had 20/40 or better uncorrected distance binocular vision and 85.9% had 20/40 or better uncorrected monocular vision. With correction, 100% of patients had 20/25 or better distance binocular vision and 96.8% had 20/25 or better monocular vision.

Near vision results were similar. A total of 95.9% had uncorrected near binocular vision of 20/25 or better and 79.4% had 20/25 or better uncorrected near monocular vision. All of the patients with emmetropia or myopia had 20/25 or better uncorrected near visual acuity compared to 78.3% of patients with hyperopia.

Patients were quite satisfied with the procedure. A total of 92.6% of patients reported they did not need to wear glasses at any time after surgery, 93.5% said they will repeat surgery when needed and 100% said surgery produced a significant positive change in their lives.

“These new techniques give us another way to correct presbyopia using noninvasive surgery that is completely reversible,” Dr. Tamayo said. “This may be the most flexible and the most successful solution we can offer to our younger patients with some accommodation present.”

Bogota, Colombia ::

Presbyopia can be confounding for patients who do not want to wear glasses or contact lenses. Though corneal inlays or IOLs may be standard procedures, the latter is a definitive surgical procedure with the potential for significant complications.

Advances in technology now offer a third alternative, excimer laser ablations to the cornea (PresbyLASIK) to create a multifocal cornea, said Gustavo E. Tamayo.

“This is surgery completely outside the eye,” said Dr. Tamayo, founder and partner, Bogota Laser Refractive Institute, Bogota, Colombia. “It is a variation on the LASIK, LASEK, or PRK procedures that most of us are already familiar with. And with wavefront-guided instruments, the excimer laser treatment is both reversible and repeatable.”

NEW APPLICATION OF FAMILIAR TECHNOLOGY

Using excimer laser energy to treat presbyopia is not a new concept, Dr. Tamayo noted. In general practice, about 93% of ophthalmologists who opt for surgical treatment of presbyopia opt for excimer laser monovision and 7% choose an IOL.

But earlier excimer techniques did not always produce optimal results. Patients complained of visual symptoms, such as halos and flairs. Visual acuity did not always reach target.

“Improvements in wavefront technology, better understanding of ocular aberrations, improvements in the excimer laser itself, and the advent of femtosecond lasers to help create flaps have made this the right time to consider this technique,” he said. “It is particularly useful for younger patients with presbyopia, especially those between about 40 and 55 who are years away from needing cataract surgery.”

The key to successful presbyopia treatment is to center treatment on the visual axis, not on the pupil, he continued.

Nearly all of the patient complaints of visual symptoms and the poor visual outcomes of any presbyopia treatment are the result of decentration due to centering treatment on the center of the pupil rather than on the visual axis.

Prospective Study

Dr. Tamayo presented a prospective study of excimer laser presbyopia treatment of 121 eyes in 66 patients who were followed for 38 to 66 months. The mean preoperative sphere was 0.180 ± 2.2 D (-5.0 to + 5 D) and the mean preop cylinder was -0.736 ± 0.97 (-6.5 to 0 D). Most of the patients, 57.9%, were hyperopic, 14% were myopic myopia and 10.7% were emmetropic. Within the study group, 86.8% received presbyLASIK, 13.2% presbyLASEK and 9.9% were being re-treated.

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Patients were quite satisfied with the procedure. A total of 92.6% of patients reported they did not need to wear glasses at any time after surgery, 93.5% said they will repeat surgery when needed and 100% said surgery produced a significant positive change in their lives.

“These new techniques give us another way to correct presbyopia using noninvasive surgery that is completely reversible,” Dr. Tamayo said. “This may be the most flexible and the most successful solution we can offer to our younger patients with some accommodation present.”

Take-home

Excimer laser ablation to the cornea (PresbyLASIK) to create a multifocal cornea may be an alternative treatment for patients with presbyopia.
BESIVANCE® (besifloxacin ophthalmic suspension) 0.6%: A Powerful Option for the Treatment of Bacterial Conjunctivitis

Penny A. Asbell, MD, FACS, MBA

ABSTRACT  Treatment of bacterial conjunctivitis can shorten the clinical course of disease, reduce symptoms, and abbreviate the period of contagion.1,2 Introduced in 2009, BESIVANCE® (besifloxacin ophthalmic suspension) 0.6% is a broad-spectrum, topical fluoroquinolone with high potency and balanced affinity for bacterial DNA gyrase and topoisomerase IV.3,5

In vitro studies have found that common bacterial conjunctivitis pathogens, including several antibiotic-resistant strains, are susceptible to besifloxacin; and, in clinical trials, BESIVANCE® has an established safety profile and robust efficacy against typical bacterial conjunctivitis pathogens.6,7

BESIVANCE® is indicated for the treatment of bacterial conjunctivitis caused by susceptible isolates of the following bacteria: *Aerococcus viridans*, CDC coryneform group G, *Corynebacterium pseudodiphtheriticum*, *Corynebacterium striatum*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Moraxella lacunata*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus hominis*, *Staphylococcus lugdunensis*, *Staphylococcus warneri*, *Streptococcus mitis* group, *Streptococcus oralis*, *Streptococcus pneumoniae*, *Streptococcus salivarius*.8

*Efficacy for this organism was studied in fewer than 10 infections.8

Use of a mucoadhesive polymer in the BESIVANCE® formulation impacts the duration of the antimicrobial on the ocular surface and contributes to its pharmacokinetic/pharmacodynamic profile.9 Formulated for use only as a topical ophthalmic antibiotic, besifloxacin has not been used in internal medicine or agriculture, which may decrease selection pressure for resistance to the drug.10,11

See Important Safety Information about BESIVANCE®

Introduction

Approximately 4 million cases of bacterial conjunctivitis are estimated to occur in the US annually, and many of them seek medical attention.11 An estimated 1% to 4% of primary care consultations are for acute red eye, and there is evidence that the majority of those cases are caused by bacterial conjunctivitis.11,12

In a published review of clinical studies, it was found that most cases of acute conjunctivitis in children were bacterial in origin.1,13 Interestingly, physicians have been found to underestimate the prevalence of bacterial conjunctivitis.1

Patients with acute bacterial conjunctivitis characteristically experience tearing, ocular surface irritation, marked redness, and the presence of mucopurulent discharge that can be copious and lead to matting of the lash cilia. To prevent spreading the infection to others, patients are frequently required to stay home from work or school. While the prognosis is generally favorable—60% of cases resolve spontaneously within 2 weeks—bacterial conjunctivitis carries a small (but not zero) risk of progressing to keratitis, particularly in patients carrying large numbers of bacteria and/or an epithelial defect.13 Furthermore, infection with a difficult-to-treat pathogen such as *Pseudomonas aeruginosa* (Figure 1) carries a higher risk for adverse outcomes.2

Important Safety Information for BESIVANCE®

- **BESIVANCE®** is for topical ophthalmic use only, and should not be injected subconjunctivally, nor should it be introduced directly into the anterior chamber of the eye.
- As with other anti-infectives, prolonged use of BESIVANCE® may result in overgrowth of non-susceptible organisms, including fungi. If super-infection occurs, discontinue use and institute alternative therapy.
- Patients should not wear contact lenses if they have signs or symptoms of bacterial conjunctivitis or during the course of therapy with BESIVANCE®.
- The most common adverse event reported in 2% of patients treated with BESIVANCE® was conjunctival redness. Other adverse events reported in patients receiving BESIVANCE® occurring in approximately 1–2% of patients included: blurred vision, eye pain, eye irritation, eye pruritus and headache.
- **BESIVANCE®** is not intended to be administered systemically. Quinolones administered systemically have been associated with hypersensitivity reactions, even following a single dose. Patients should be advised to discontinue use immediately and contact their physician at the first sign of a rash or allergic reaction.
- Safety and effectiveness in infants below one year of age have not been established.

In vitro studies demonstrated cross-resistance between besifloxacin and some fluoroquinolones.
Microbiology

Since bacterial conjunctivitis is typically treated without culturing the eye, selection of an appropriate treatment requires knowledge of the most likely etiologic agents and their susceptibilities. Pathogens commonly implicated in bacterial conjunctivitis include the following typical commensal flora of the skin and nasopharynx: gram-positive organisms *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Streptococcus pneumoniae*; and gram negatives *Moraxella catarrhalis* and *Haemophilus influenzae*.10

*P. aeruginosa* is of special concern, especially for contact lens wearers.2

An important challenge in the management of bacterial conjunctivitis is antimicrobial resistance.

Resistance

Clinicians who treat external ocular disease have been somewhat protected from problems associated with antibiotic resistance due to the unique pharmacokinetics of topically administered ophthalmic drugs—which can typically achieve concentrations at the site of infection greater than systemic drugs.

However, even among ocular infections, rates of in vitro resistance to commonly used antibiotics are increasing rapidly; and resistant pathogens have been identified as a potential cause of treatment failure.15 It is therefore important that ophthalmologists keep abreast of the changing status of antibiotic resistance.

The study-designated Ocular TRUST (for Tracking Resistance in the US Today) reported nationwide antibiotic susceptibility patterns of three key ocular pathogens—*S. aureus*, *S. pneumoniae*, and *H. influenzae*—to multiple classes of ophthalmic antibiotics.14 Ocular TRUST found that, despite widespread use of fluoroquinolones in medicine and veterinary settings, and consequently high resistance selection pressure, the antibiotics remained a consistently active class of antibiotic against *S. pneumoniae*, *H. influenzae*, and methicillin-susceptible *S. aureus* (MSSA) ocular isolates.15 Of particular concern, however, is the increasing emergence of multidrug resistant gram-positive pathogens, including methicillin-resistant *S. aureus* (MRSA) and methicillin-resistant *S. epidermidis* (MRSE). According to the Ocular TRUST study, MRSA is becoming increasingly resistant to multiple antibiotics.14 Ocular isolates from the 2009 ARMOR (Antibiotic Resistance Monitoring in Ocular microoRganisms) surveillance showed similar patterns of multidrug resistance among MRSA.15 ARMOR also revealed high rates of resistance among ocular MRSE isolates, and concerning levels of multidrug resistance among other staphylococci and *Pseudomonas* strains.15

Potency

Antibiotic potency is typically quantified in terms of the minimum inhibitory concentration (MIC), the lowest concentration of a drug able to inhibit the growth of a bacterial isolate.16 To describe the potency of a drug against a bacterial species, we use the MIC50 and MIC90, the concentrations of antibiotic necessary to inhibit the growth of 50% and 90%, respectively, of different bacterial isolates of the same species. While low MIC values indicate that low concentrations of drug will be required to effect bacterial inhibition, the clinical significance of in vitro data has not been established.16

Three large clinical studies of BESIVANCE® for the treatment of bacterial conjunctivitis demonstrated low MICs against the 1324 bacterial pathogens collected (MIC50 = 0.06 and MIC90 = 0.25 μg/mL).16 The clinical significance of in vitro data has not been established.

A randomized, double-masked, vehicle controlled parallel-

A 42-year-old man requested an emergency ophthalmology visit due to symptoms of “pink eye.” The patient reported a 2-day history of redness, irritation, and a thickened discharge from his right eye. Upon awakening, his eyelid was matted shut. His left eye felt normal and seemed to be unaffected. He reported no contact with anyone who had pink eye at home or work. He wore glasses for distance; otherwise he had no significant ocular or medical history.

Examination of his right eye revealed a best corrected visual acuity of 20/30. Slit lamp examination showed trace lid swelling, 2+ conjunctival injection, and mucopurulent discharge. The eye tested negative for the presence of adenovirus. The cornea and anterior segment appeared normal. The left eye was correctable to 20/20, and slit lamp exam was normal.

The patient was diagnosed with acute bacterial conjunctivitis in the right eye. BESIVANCE® (besifloxacin ophthalmic solution) 0.6% was prescribed and the patient instructed to instill one drop in the affected eye 3 times a day (4 to 12 hours apart) for 7 days. Seen 3 days later, the patient was significantly improved. He was instructed to continue BESIVANCE® to the end of the initial 7-day period and then discontinue.
group study in which patients (N=957) with acute bacterial conjunctivitis were treated with either BESIVANCE® (n=475) or vehicle (n=482; 0.01% benzalkonium chloride) TID for 5 days was conducted. The overall microbial eradication rate at day 5 was 91% for BESIVANCE® vs 60% for vehicle (P<0.0001). The overall clinical resolution rate was 45% for BESIVANCE® vs 33% for vehicle (P=0.0084). Clinical resolution was defined as the absence of both ocular discharge and bulbar conjunctival injection. Indeed, clinical research has demonstrated microbial eradication at day 5 by besifloxacin in cases of bacterial conjunctivitis culture-positive for MRSA and MRSE. In this study, 1,317 cases of bacterial conjunctivitis were reviewed and those caused by MRSA (n=35), MRSE (n=81), and P. aeruginosa (n=9) were pooled from 4 multicenter, double-masked, randomized clinical trials; 3 studies (2 vehicle controlled and 1 active controlled) administered BESIVANCE® TID for 5 days, and one vehicle-controlled study administered BESIVANCE® BID for 3 days. This study found that the bacterial eradication rate at day 5 of MRSA or MRSE was 81.2% (40/49) for BESIVANCE® vs 57.1% (20/35) for vehicle, while the clinical resolution rate at day 5 was 49.0% (24/49) for BESIVANCE® vs 51.4% (18/35) for vehicle. Clinical resolution was defined as the absence of both ocular discharge and bulbar conjunctival injection. This study also found that the MIC₅₀ values for besifloxacin were 4 μg/mL for both ciprofloxacin-resistant MRSA and ciprofloxacin-resistant MRSE. Microbial eradication does not always correlate with clinical outcomes in anti-infective trials.

The Besifloxacin Molecule

The besifloxacin molecule is part of the topical ocular fluoroquinolone family. Fluoroquinolones work by binding 2 enzymes critical for DNA bacterial replication: DNA gyrase (topoisomerase II) and topoisomerase IV. The original quinolones predominantly targeted DNA gyrase, which gave them good activity against replication of gram-negative organisms. Subsequent generations have had better activity against topoisomerase IV, which expanded the spectrum of coverage against gram-positive organisms.

Besifloxacin has 2 halogen atoms on the quinoline backbone: a fluorine (common to all fluoroquinolones) and a chlorine at carbon 8. This contributes to a balanced and increased affinity for both DNA gyrase and topoisomerase IV, enhancing besifloxacin’s overall in vitro potency. Targeting both enzymes relatively equally also means that 2 mutations would be required for the development of substantial resistance. The clinical significance of in vitro data has not been established. In vitro studies demonstrated cross-resistance between besifloxacin and some fluoroquinolones.

Treating Bacterial Conjunctivitis

Since suspected bacterial conjunctivitis cases are not routinely cultured, empirical therapy should be broad-spectrum, covering as many as possible of the common gram-positive and gram-negative pathogens known to cause bacterial conjunctivitis. BESIVANCE® has a broad spectrum of coverage that includes gram-positive and gram-negative pathogens that commonly cause bacterial conjunctivitis. BESIVANCE® has demonstrated potency against worrisome pathogens such as MRSA, MRSE, and P. aeruginosa. BESIVANCE® is also formulated with a mucoadhesive polymer. Studies have shown that this suspension allows for prolonged surface contact with the eye compared to antibiotics formulated in aqeous solutions.

Finally, BESIVANCE® has an established safety profile and is a potent agent for the treatment of bacterial conjunctivitis.

Penny A. Asbell, MD, FACS, MBA, is professor of ophthalmology, director of cornea and refractive services, and cornea fellowship director in the department of ophthalmology of the Mount Sinai School of Medicine in New York, NY.

References

BESIFLOXACIN TECHNICAL PAPER

Besivance® (besifloxacin ophthalmic suspension) 0.6%

5 WARNINGS AND PRECAUTIONS

5.1 Topical Ophthalmic Use Only

Besivance is for topical ophthalmic use only, and should not be introduced directly into the anterior chamber of the eye. Use should be limited to 1 application per eye per day. If more than one topical ophthalmic medication is used, the order of application is important and should be followed. Instill one drop in the affected eye(s) 3 times a day (16 doses total). Following the first and second daily doses, the maximum plasma concentrations were 1.15 mcg/mL on day 1 and 0.43 ng/mL on day 6. The average elimination half-life for besifloxacin was estimated to be 2.5 hours following multiple dosing was estimated to be 7 hours.

12.4 Microbiology

Besivance is an 8-chloro fluoroquinolone with the potency and some fluoroquinolones.

12.3 Pharmacokinetics

Besivance did not induce unscheduled DNA synthesis in CHO cells

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Besifloxacin is an 8-chloro fluoroquinolone with a white tail yellowish-white powder.

5.4.1 Special Characteristics

Connective tissue disorder, including Besifloxacin is an 8-chloro fluoroquinolone with a white tail yellowish-white powder.

5.4.2 Inhibition of Drug Metabolism

Besifloxacin has been shown to be active against MC-1 and 0.43 ng/mL on day 6. The average elimination half-life for besifloxacin was estimated to be 2.5 hours following multiple dosing was estimated to be 7 hours.

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Controlling postoperative pain in pediatric strabismus surgery
Multimodal approach is likely best; sub-Tenon’s bupivacaine may help lower pain levels

By Michelle Dalton, ELS

BUPIVACAINE CAN REDUCE PAIN
in children undergoing strabismus surgery, said Laura B. Enyedi, MD. She and her two co-authors, David K. Wallace, MD, MPH, and Guy de Lisle Dear, MBCHIR, discussed off-label use of anesthetic drugs in the pediatric population.

In one study on strabismus surgery, Dr. Enyedi said upward of 50% of pediatric patients “experience clinically significant pain” in the postoperative period.

“Pain is bad for the patient, for the healthcare system, and for the doctor,” said Dr. Enyedi, associate professor of ophthalmology and associate professor in pediatrics, Duke University School of Medicine, Durham, NC.

“It’s associated with discharge delays, contact after discharge, patient and parental dissatisfaction, as well as long-term postoperative behavioral changes.”

The best pain control is a multimodal approach that consists of narcotics and non-narcotic pain relievers including non-steroidal anti-inflammatory, acetaminophen, and local anesthetics, she said.

Previous randomized studies on the pediatric population have evaluated everything from anesthetic drugs to delivery methods and used a variety of outcome measures. But with conflicting results, no clinical consensus has emerged to determine what benefit—if any—can be gleaned with local anesthetics on pain control.

Dr. Enyedi’s group evaluated whether local anesthetics—either topical or sub-Tenon’s—given at the end of strabismus surgery, reduce postoperative pain in children of ages 1 year to under 8 years.

The randomized, double-masked study enrolled 50 patients already scheduled for strabismus surgery at the Duke Eye Center. Patients were randomly assigned to one of three groups: sub-Tenon’s control with topical anesthetic, sub-Tenon’s anesthetic with topical control, and a sub-Tenon’s control with a topical control. Wounds were both fornix- and limbal-based.

“Our drugs included a topical anesthetic, which is lidocaine hydrochloride 3.5%, acti gel, a sub-Tenon’s anesthetic, bupivacaine 0.5%, and two controls, a topical control, hypromellose 0.3%, which is Genteal Severe Dry Eye Relief, and the sub-Tenon’s control was balanced salt solution,” she said. “All patients received the sub-Tenon’s clear liquid via a blunt cannula through the surgical wound at the end of surgery and a topical clear gel applied to the surface of the eye at the end of surgery.”

Researchers assessed pain at multiple points: every 5 minutes postoperatively for the first 30 minutes; then every 15 minutes for the next 2 hours; then hourly until patient discharge.

Using the Children’s Hospital Eastern Ontario Pain Scale (CHEOPS)—an objective pain scale that assesses pain in young children by looking at several items including the cry, the facial expression, and body position—scores ranged from 4 to more than 14.

“A score of greater than 4 on this scale is considered an indication of pain,” she said. Nonetheless, there was a statistically significant difference with the sub-Tenon’s bupivacaine group having a lower pain score than the control group in the first 30 minutes. The bupivacaine group also had lower pain scores than the lidocaine group, but the difference did not reach statistical significance, she said.

A re-assessment of pain scores in the bilateral group dissipated the statistical differences between the control and bupivacaine groups, she said.

For the first 30 minutes, Dr. Enyedi’s group found the bupivacaine group had lower pain scores than the control group. The primary outcome in this study was the average pain score over the first 30 minutes, Dr. Enyedi said, with secondary pain outcomes including the peak pain score in the same timeframe, the total average pain score over the entire assessed period until discharge, and the number of times the pain score was above 6. Other secondary outcomes included total narcotic use, postoperative nausea, time to discharge, and negative postoperative behaviors.

Baseline characteristics for the three groups were similar in terms of age, gender, number of muscles operated on, number of incisions, as well as limbal-versus-fornix incisions.

“There was a difference in the distribution of bilateral cases, with the sub-Tenon’s bupivacaine group having fewer bilateral cases than either the topical lidocaine or control groups,” she said, adding that bilaterality might be a factor associated with pain.

LAURA B. ENYEDI, MD
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This article was adapted from Dr. Enyedi’s presentation at the 2015 meeting of American Academy of Ophthalmology. Dr. Enyedi received grant support from the Pediatric Eye Disease Investigator Group. She reported no other financial disclosures.
Ganciclovir gel is effective for herpes simplex epithelial keratitis, and emerging evidence shows it also can be used to treat other corneal disease.

Take-home

There is good evidence that topical ganciclovir gel (Zirgan, Bausch + Lomb) can help treat herpes simplex epithelial keratitis, said Kristin Hammersmith, MD.

There is also emerging evidence about the gel’s role in the treatment of other herpes viruses, including varicella zoster, cytomegalovirus, and adenovirus, according to Dr. Hammersmith, fellowship director, Cornea Service, Wills Eye Hospital, and associate professor, Thomas Jefferson University, Philadelphia.

The addition of ganciclovir gel to the armamentarium in 2009 after FDA approval was welcome by ophthalmologists because of side effects associated with other treatments, Dr. Hammersmith said. Previous treatments have been associated with some risk for conjunctival inflammation and corneal erosion rates (shown in images above).

Ganciclovir works similarly as acyclovir. The agent is phosphorylated, contributes to less toxicity and is generally well tolerated. It also has a similar toxicity to tears and a long and stable shelf life. The approved use is five times a day until the dendrite is healed and then three times a day for 7 days. However, there is still plenty of room to explore how well it works to treat various herpes-related problems, Dr. Hammersmith noted.

The treatment appears effective for epithelial keratitis, Dr. Hammersmith said, citing evidence from four multicenter trials that looked at ganciclovir and acyclovir that found equal rates of recovery and healing times.

A Cochrane review article published last year analyzed 137 studies with more than 8,000 patients and found 29 studies that specifically used topical ganciclovir. Although the investigators concluded that ganciclovir was at least as effective as acyclovir for the treatment of epithelial keratitis, they added that any potential advantage was mitigated by study heterogeneity and possible publication bias.

Effect after PK

There is also some evidence to measure the effect of ganciclovir after penetrating keratoplasty (PK).

Dr. Hammersmith discussed a 2005 prospective study from Tabbara with six patients, half of whom were post-PK. Ganciclovir 0.15% was used twice a day for a year. There were no recurrences in the group with prophylaxis; the recurrence rate was 30% in the untreated group. “It may be helpful in prophylaxis with or without PK,” she said. “This is small evidence, but it’s interesting.”

There is also small-but-growing evidence for ganciclovir to treat other types of herpes and adenovirus. Ganciclovir gel may be helpful to treat pseudodendrites associated with varicella zoster keratitis. There is limited positive evidence for its use in treating adenovirus, a common problem with few treatment options. “There are lots of areas of opportunity for research to enhance our understanding of [ganciclovir gel’s] utility in other applications,” Dr. Hammersmith said.

References


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This article was adapted from Dr. Hammersmith’s presentation during Cornea Subspecialty Day at the 2015 meeting of the American Academy of Ophthalmology.
Dr. Hammersmith has no financial interests related to her comments. Her presentation addresses some off-label uses of ganciclovir gel.
Addressing clinical challenges of Acanthamoeba keratitis cases

Recognition, specific diagnosis, aggressive therapy are critical steps in management

By Lynda Charters; Reviewed by Elmer Y. Tu, MD

GLENVIEW, IL ::

ACANTHAMOEBA KERATITIS might be a rare corneal disease, but its deleterious impact on vision and incapacitation of the patient cannot be over-emphasized.

The potential for severe visual loss, substantial associated pain, and lengthy period of therapy exists.

However, timely recognition, establishment of a specific diagnosis, and rapid aggressive therapy are keys to the best possible outcomes in this patient population, said Elmer Y. Tu, MD.

Delayed recognition is the most common controllable factor leading to a poor outcome, said Dr. Tu, professor of clinical ophthalmology, University of Illinois Eye and Ear Infirmary, Glenview, IL.

Recognition often is delayed, Dr. Tu pointed out, because Acanthamoeba is rarely acute, but rather presents as a subacute or chronic parasitic infection that primarily affects the cornea, mimicking closely the presentation of noninfectious disorders, such as dry eye and non-specific epitheliopathies, or other subacute infections like fungi, microsporidia, and herpes.

“Most patients are treated first for other diagnoses, which delays recognition and appropriate treatment for weeks or even months,” Dr. Tu said.

‘It is critical that physicians understand the risk factors associated with Acanthamoeba keratitis, because it can look like anything else.’ — Elmer Y. Tu, MD

Continues on page 28 : Keratitis
**Keratitis**

(Continued from page 27)

“It is critical that physicians understand the risk factors associated with *Acanthamoeba* keratitis, because it can look like anything else.”

**Incidence Rates**

Importantly, most cases of *Acanthamoeba* keratitis develop in patients who wear contact lenses, with the incidence rates the same between hard and soft lenses, and 7% to 11% of patients can have bilateral disease, Dr. Tu said.

Interestingly, the risk of development of *Acanthamoeba* keratitis in the United States has increased significantly over the past 10 years.

“The reason that recognition is so important was demonstrated in our 2007 study in which the main prognostic factor that determines the visual outcome is the anatomic level of the disease,” Dr. Tu said.

He and his colleagues reported in *Ophthalmology* (2008;115:1998-2003) that the disease likely the first things that physicians will look at. Specific microbiologic methods that are not part of standard corneal culturing techniques for suspected infectious keratitis include use of charcoal yeast or nonnutrient agar with an *Entero-bacter aerogenes* overlay, histologic stains, corneal biopsy, and polymerase chain reaction detection.

Confocal microscopy, Dr. Tu said, is highly predictive of the presence of the pathogen regardless of the use of culturing and/or microbial methods, with good positive and negative and predictive values in their hands. Some studies have reported lower than desired sensitivity and specificity values, but he commented that these values might reflect the operator- and interpreter-dependent nature of the technology.

**Medical Therapy**

The therapeutic choices depend on the complexity of the case, according to Dr. Tu.

“Our standard practice is debridement,” he said. “We usually provide a combination of medications including propamidine and biguanides, either polyhexamethylene biguanide or chlorhexidine, that are instilled hourly until some improvement is seen.”

Patients might receive systemic medications if needed. In addition, steroids are stopped or curtailed when *Acanthamoeba* keratitis is suspected or diagnosed.

He cautioned physicians to be alert to the possibility of drug adverse effects that can worsen the patients’ pain especially with the diamidines, propamidine, and hexamidine.

**Visual Outcomes**

Dr. Tu reported that the overall visual results tend to be “quite good.” In patients with epithelial disease, their chances of achieving 20/25 or better vision are good.

However, despite therapy, as many as 5% of patients can continue to test culture positive for the pathogen.

In such patients, physicians can increase the dosage of the topical drugs by increasing the concentrations, adding medications, or changing medications. Therapies can fail because of drug resistance, polymicrobial infection, infectious and noninfectious inflammatory sequelae, neurotrophic epithelial disease, and require surgical management.

Secondary drugs include voriconazole, pentamidine and, potentially, benzalconium chloride (BAK)-containing compounds. Voriconazole is an anti-fungal agent that targets the cell wall of the *Acanthamoeba* cyst, and the drug might be beneficial for some patients when administered topically and systemically as adjunctive therapy in patients unresponsive to normal therapy.

Other agents include, miltefosine, approved in 2014 by the FDA for treating leishmaniasis, has anti-*Acanthamoeba* activity, as does pentamidine when administered intravenously to reduce the risk of recurrence of *Acanthamoeba* in patients undergoing corneal transplantation.

Administration of other antimicrobial drugs might be beneficial in some patients who harbor co-pathogens, such as herpes simplex, fungal or bacterial pathogens, or other protozoa, Dr. Tu noted.

“If use of an anti-bacterial drug is desired, we recommend one that uses BAK,” he said.

“Based on our studies, the fluoroquinolones, by themselves, do not have a substantial anti-*Acanthamoeba* effect, but BAK does.”

**Surgical Therapy**

Corneal transplantation can be effective for these patients, with increasing availability of medical anti-*Acanthamoeba* therapy. Collagen crosslinking is a potential option as an adjunctive therapy in very selected cases, but more needs to be learned about its effectiveness and role in treating *Acanthamoeba* keratitis.

“Acanthamoeba keratitis is the best characterized form of ocular parasitic infection,” Dr. Tu said. “Contact lens wear is the primary risk factor, but is not an exclusive disease of contact lens wearers. Regardless, any contact lens-related keratitis that responds poorly to standard antibacterial therapy should be considered a possible case of *Acanthamoeba* keratitis.”

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**“Any contact lens-related keratitis that responds poorly to standard antibacterial therapy should be considered a possible case of *Acanthamoeba* keratitis.”**

— Elmer Y. Tu, MD
**INDICATIONS AND USAGE**

ZYLET® (loteprednol etabonate 0.5% and tobramycin 0.3% ophthalmic suspension) is a topical anti-infective and corticosteroid combination for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superfi cial bacterial ocular infection or a risk of bacterial ocular infection exists.

Ocular steroids are indicated in infl ammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the eye and fungal diseases of ocular structures. The use of a combination drug with an anti-infective component is indicated where the risk of superfi cial ocular infection is high or where there is an expectation that potentially dangerous numbers of bacteria will be present in the eye.

The particular anti-infective drug in this product (tobramycin) is active against the following common bacterial eye pathogens: Staphylococci, Streptococci (coagulase-positive and coagulase-negative), including penicillin-resistant strains. Streptococci, including some of the Group A-beta-hemolytic species, some nonhemolytic species, and some Strepptococcus pneumoniae, Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Enterobacter aerogenes, Proteus mirabilis, Morganella morgani, most Proteus vulgaris strains, Haemophilus infl uenzae, and H. aegyptius, Moraxella lacunata, Acinetobacter calcoaceticus and some Neisseria species.

**IMPORTANT SAFETY INFORMATION**

- **ZYLET®** is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.

**IMPORTANT SAFETY INFORMATION (continued)**

- Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. If this product is used for 10 days or longer, intraocular pressure should be monitored.
- Use of corticosteroids may result in posterior subcapsular cataract formation.
- The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnifi cation such as a slit lamp biomicroscopy and, where appropriate, fl uorescein staining.
- Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infections. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.
- Employment of corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and exacerbate the severity of many viral infections of the eye (including herpes simplex).
- Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use.
- Most common adverse reactions reported in patients were injection and superfi cial punctate keratitis, increased intraocular pressure, burning and stinging upon instillation.

Please see Brief Summary of Prescribing Information for ZYLET® on adjacent page.
BRIEF SUMMARY OF PRESCRIBING INFORMATION
This Brief Summary does not include all the information needed to use Zylet safely and effectively. See full prescribing information for Zylet.

Zylet®
(loteprednol etabonate 0.5% and tobramycin 0.3% ophthalmic suspension)
Initial U.S. Approval: 2004

DOSEAGE AND ADMINISTRATION

2.1 Recommended Dosing
Apply one or two drops of Zylet into the conjunctival sac of the affected eye every four to six hours. During the initial 24 to 48 hours, the dosing may be increased, to every one to two hours. Frequency should be decreased gradually as warranted by improvement in clinical signs. Care should be taken not to discontinue therapy prematurely.

2.2 Prescription Guideline
Not more than 20 mL should be prescribed initially and the prescription should not be refilled without further evaluation (see Warnings and Precautions (5.3)).

CONTRAINDICATIONS

4.1 Nonbacterial Etiology
Zylet, as with other steroid anti-infective ophthalmic combination drugs, is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpetic keratitis, vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.

WARNINGS AND PRECAUTIONS

5.1 Intracocular Pressure (IOP) Increase
Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma.

If this product is used for 10 days or longer, intraocular pressure should be monitored.

5.2 Cataracts
Use of corticosteroids may result in posterior subcapsular cataract formation.

5.3 Delayed Healing
The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification such as a slit lamp biomicroscopy and, where appropriate, fluorescein staining.

5.4 Bacterial Infections
Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary bacterial infections. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.

5.5 Viral Infections
Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).

5.6 Fungal Infections
Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungal invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal cultures should be taken when appropriate.

5.7 Aminoglycoside Hypersensitivity
Sensitivity to topically applied aminoglycosides may occur in some patients. If hypersensitivity develops with this product, discontinue use and institute appropriate therapy.

ADVERSE REACTIONS

Adverse reactions have occurred with steroid/anti-infective combination drugs which can be attributed to the steroid component, the anti-infective component, or the combination.

Zylet:
In a 42 day safety study comparing Zylet to placebo, ocular adverse reactions included injection (approximately 20%) and superficial punctate keratitis (approximately 15%). Increased intraocular pressure was reported in 10% (Zylet) and 4% (placebo) of subjects. Nine percent (9%) of Zylet subjects reported burning and stinging upon instillation.

Ocular reactions reported with an incidence less than 4% include vision disorders, discharge, itching, lacrimation disorder, photophobia, corneal deposits, ocular discomfort, eyelid disorder, and other unspecified eye disorders.

The incidence of non-ocular reactions reported in approximately 14% of subjects was headache; all other non-ocular reactions had an incidence of less than 3%.

Loteprednol etabonate ophthalmic suspension 0.2% - 0.5%.
Reactions associated with ophthalmic steroids include increased intraocular pressure, which may be associated with infrequent optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, delayed wound healing and secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

In a summation of controlled, randomized studies of individuals treated for 28 days or longer with loteprednol etabonate, the incidence of significant elevation of intraocular pressure (≥10 mm Hg) was 2% (15/901) among patients receiving loteprednol etabonate, 7% (11/164) among patients receiving 1% prednisolone acetate and 0.5% (3/593) among patients receiving placebo.

Tobramycin ophthalmic solution 0.3%:
The most frequent adverse reactions to topical tobramycin are hypersensitivity and localized ocular toxicity, including lid itching and swelling and conjunctival erythema. These reactions occur in less than 4% of patients. Similar reactions may occur with the topical use of other aminoglycoside antibiotics.

Secondary Infection:
The development of secondary infection has occurred after use of combinations containing steroids and antimicrobials. Fungal infections of the cornea are particularly prone to develop coincidentally with long-term applications of steroids.

The possibility of fungal invasion must be considered in any persistent corneal ulceration where steroid treatment has been used.

SECONDARY INFECTION:

USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Teratogenic effects: Pregnancy Category C. Loteprednol etabonate has been shown to be embryotoxic (delayed ossification) and teratogenic (increased incidence of meningocoele, absence of common carotid artery, and limb fusions) when administered orally to rabbits during organogenesis at a dose of 3 mg/kg/day (35 times the maximum daily clinical dose), a dose which caused no maternal toxicity. The no-observed-effect-level (NOEL) for these effects was 0.5 mg/kg/day (6 times the maximum daily clinical dose). Oral treatment of rats during organogenesis resulted in teratogenicity (absent innominate artery at ≥5 mg/kg/day doses, and cleft palate and umbilical hernia at ≥50 mg/kg/day) and embryotoxicity (increased post-implantation losses at 100 mg/kg/day and decreased fetal body weight and skeletal ossification with ≥50 mg/kg/day). Treatment of rats at 0.5 mg/kg/day (6 times the maximum daily clinical dose) during organogenesis did not result in any reproductive toxicity. Loteprednol etabonate was maternally toxic (significantly reduced body weight gain during treatment) when administered to pregnant rats during organogenesis at doses of ≥5 mg/kg/day.

Oral exposure of female rats to 50 mg/kg/day of loteprednol etabonate from the start through the fetal period through day 21 of lactation, a maternally toxic treatment regimen (significantly decreased body weight gain), gave rise to decreased growth and survival and retarded development in the offspring during lactation; the NOEL for these effects was 5 mg/kg/day. Loteprednol etabonate had no effect on the duration of gestation or parturition when administered orally to pregnant rats at doses up to 50 mg/kg/day during the fetal period.

Reproductive studies have been performed in rats and rabbits with tobramycin at doses up to 100 mg/kg/day parenterally and have revealed no evidence of impaired fertility or harm to the fetus. There are no adequate and well controlled studies in pregnant women. Zylet should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers
It is not known whether topical ophthalmic administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Systemic steroids that appear in human milk could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when Zylet is administered to a nursing woman.

8.4 Pediatric Use
Two trials were conducted to evaluate the safety and efficacy of Zylet® (loteprednol etabonate and tobramycin ophthalmic suspension) in pediatric subjects age zero to six years; one was in subjects with lid inflammation and the other was in subjects with blepharconjunctivitis.

In the lid inflammation trial, Zylet with warm compresses did not demonstrate efficacy compared to vehicle with warm compresses. Patients received warm compress lid treatment plus Zylet or vehicle for 7 days. The majority of patients in both treatment groups showed reduced lid inflammation.

In the blepharconjunctivitis trial, Zylet did not demonstrate efficacy compared to vehicle, loteprednol etabonate ophthalmic suspension, or tobramycin ophthalmic solution.

There was no difference between treatment groups in mean change from baseline blepharconjunctivitis score at Day 15.

There were no differences in safety assessments between the treatment groups in either trial.

8.5 Geriatric Use
No overall differences in safety and effectiveness have been observed between elderly and younger patients.

NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate or tobramycin.

Loteprednol etabonate was not genotoxic in vitro or in vivo. The mouse lymphoma TK assay, a chromosome aberration test in human lymphocytes, or in an in vivo mouse micronucleus assay.

Oral treatment of male and female rats at 50 mg/kg/day and 25 mg/kg/day of loteprednol etabonate, respectively, (500 and 250 times the maximum daily clinical dose, respectively) prior to and during mating did not impair fertility in either gender. No impairment of fertility was noted in studies of subcutaneous tobramycin in rats at 100 mg/kg/day (1700 times the maximum daily clinical dose).

PATIENT COUNSELING INFORMATION
This product is sterile when packaged. Patients should be advised not to drop the dropper tip to touch any surface, as this may contaminate the suspension. If pain develops, redness, itching or inflammation becomes aggravated, the patient should be advised to consult a physician. As with all ophthalmic preparations containing benzalkonium chloride, patients should be advised not to wear soft contact lenses when using Zylet.

MANUFACTURER INFORMATION
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Based on 9007705-9004405 Revised 08/2013 US/ZYL/15/0014
Fungal infections after keratoplasty: Research reaffirms upswing in cases

Consider pearls for better management; weigh risk/benefit of surgical intervention

By Vanessa Caceres; Reviewed by Anthony Aldave, MD

LOS ANGELES ::

INFECTIONS AFTER keratoplasty—particularly Descemet stripping endothelial keratoplasty (DSEK)—are on the rise, with the majority of cases being fungal, said Anthony Aldave, MD.

A report from the Eye Bank Association of America (EBAA) identified an increasing trend in the incidence of fungal infections after corneal transplantation between 2005 and 2010. 1

In addition, a recently conducted follow-up study has confirmed a significant increase in the incidence of post-keratoplasty fungal infection.

“The risk is significantly higher following DSEK than penetrating keratoplasty [PK],” said Dr. Aldave, professor of ophthalmology, Wallon Li Chair in Cornea and Uveitis, chief, Cornea and Uveitis Division, and director, Cornea and Refractive Surgery Fellowship, Stein Eye Institute, University of California, Los Angeles.

Research from the EBAA found that two-thirds of all infections were due to fungi, and almost all of those were Candida species.

The diagnosis of post-keratoplasty interface infections most often occurs 3 to 16 weeks after surgery. The usual signs are focal interface opacities that slowly increase in size and number, Dr. Aldave said.

“Imaging with confocal microscopy to identify the presence of fungi can be very helpful to diagnose the cause,” he said.

An anterior chamber tap can be performed as well, but would likely be negative if the organisms are confined to the donor-host interface following DSEK or Descemet membrane endothelial keratoplasty (DMEK).

Biopsy is another option, although excision of a portion of the donor cornea is probably easier with cases of DMEK than DSEK, he added.

In terms of management, corneal rim cultures that are positive can be helpful to guide therapy, Dr. Aldave advised.

Surgeons should also find out about the mate cornea (the fellow eye donor cornea) to determine if donor corneal rim cultures were performed and whether the recipient developed an infection.

INFERILATES AS FACTOR

Management also will depend on the number of infiltrates.

“In the case of a post DSEK or DMEK infection, if the infection looks like it involves the host stroma, removing the donor graft will not eradicate infection,” he said.

A review of literature on post DSEK and DMEK interface infections shows only a small number of case reports or case series, including a total of 23 patients, Dr. Aldave said.

A small percentage had a positive donor corneal rim culture; 15 were negative. All reported organisms were Candida.

Recipient cultures were performed in 18 of the 23 cases, and all were culture positive.

“The majority of those were Candida, but there were also Staph species and Nocardia. Sometimes, you have to consider a bacterial organism as the cause,” he said.

Among the 23 patients, those treated with topical, intracameral and/or oral antifungal therapy eventually required PK.

However, two patients who received antifungal injections into the interface did not require PK.

POSTKERATOPLASTY INTERFACE INFECTIONS

As the infection resolved following PK in each of the 10 eyes in which it was performed, Dr. Aldave concluded that a PK appears to be the definitive means to manage an interface keratitis following DSEK.

“If you perform a PK, trephinate a larger diameter than the graft itself so you can excise the host and donor together,” Dr. Aldave said.

Reference


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This article was adapted from Dr. Aldave’s presentation at Cornea Subspecialty Day during the 2015 meeting of the American Academy of Ophthalmology. Dr. Aldave did not indicate any proprietary interest in the subject matter.
SAN FRANCISCO ::

**DIAGNOSES** of mosquito-borne forms of uveitis are occurring more often in developed countries, in addition to developing-world countries where diagnosis is often expected—largely because of extensive global air travel and easy interconnectivity among the world's countries.

Mosquitos are the culprits in the spread of some of these diseases—specifically, West Nile virus, Dengue fever, and Chikungunya.

Though the three diseases can appear similar, there are some characteristics that can help physicians distinguish among them, said Emmett T. Cunningham, MD, PhD, MPH.

"West Nile virus infection tends to be less severe than either Dengue fever or Chikungunya infection," said Dr. Cunningham, director, The Uveitis Service, California Pacific Medical Center; research associate, The Francis I. Proctor Foundation, University of California-San Francisco; and adjunct clinical professor of ophthalmology, Stanford University School of Medicine, all in the San Francisco Bay Area.

**WEST NILE VIRUS**

West Nile virus is a flavivirus of about 12 kilodaltons in size that was first identified in 1937 in Uganda. The virus's natural reservoirs are birds, which, in turn, transmit the virus to mosquitos that then pass it to mammals.

The infection entered the United States in 1999, and the incidence has grown since that time, making the disease a global disorder. The incidence is less than one case per 100,000 people, according to Dr. Cunningham.

West Nile virus appears cyclically and seasonally, with outbreaks more often in summer and fall.

The virus has a neurologic component, and most cases of neurologic disease are severe and occur in elderly patients and/or diabetics. These neuroinvasive cases—characterized by central nervous system involvement, severe headache, nausea, and vomiting—tend to be the ones in which there are ocular manifestations.

The typical presentations in symptomatic patients—who account for about 15% of affected patients with West Nile virus—are systemic in nature (i.e., fever, headache, myalgia, arthralgia, nausea, vomiting, skin rash, and pharyngitis).

"The virus generally has incubation periods ranging from 2 to 14 days and the fever is self-limited and lasts about 1 week. Most patients (80%) are asymptomatic. At the other end of the spectrum are 5% of patients with encephalitis who have severe headaches, meningismus, confusion, stupor/coma, tremors, convulsions, and paralysis. Ocular manifestations can vary among patients and included anterior chamber and vitreous inflammation, retinal vasculitis, retinitis, choroiditis (the most common finding), and multifocal chorioretinitis in a curvilinear pattern.

The early retinal lesions are deep yellow-white. Fluorescein and indocyanine green angiography (ICGA) are valuable for identifying these types of lesions.

**DENGUE FEVER**

Dengue fever is similar to West Nile virus in that it also is a flavivirus, about the same size as West Nile virus at 11 kilodaltons, the incubation period ranges from 2 to 14 days, and the disease has a worldwide distribution.

Dengue fever tends to be limited to tropical environs, where it is endemic and occurs less often than West Nile virus. An estimate is that 50...
to 100 million new cases develop each year. Cases do appear in the United States, largely in Florida and Texas, and these represent most of the cases. However, some are imported, i.e., acquired during travel, Dr. Cunningham explained.

Patients with Dengue fever also are affected systemically. Classic Dengue fever is characterized by high fever, severe headache, myalgia, arthralgia, malaise, nausea, vomiting, and a maculopapular skin rash. Ten percent of patients may develop cutaneous, subconjunctival, or retinal hemorrhages. This form is referred to as Dengue hemorrhagic fever.

The ocular disease is bilateral in 75% of patients. In addition to subconjunctival and retinal hemorrhages, findings include anterior chamber and vitreous inflammation, retinal vasculitis, and vascular occlusion, retinitis, deep retinal spots/foveolitis, retinal pigment epithelial mottling, serous retinal detachment, and choroiditis.

Hemorrhage, yellow-white lesions, and vasculitis are seen most often, Dr. Cunningham noted.

“Interestingly, the clinical fundus picture in these patients does not look nearly as bad as the vascular leakage on fluorescein angiography,” he said. “A great deal of leakage is present in these patients and it can be seen on ICGA images as well. Typically, retinal vasculitis does not leak on ICGA, but it can in patients with Dengue fever.”

**CHIKUNGUNYA**

Chikungunya, an alphavirus and also a worldwide pathogen, was first reported in 1953 in East Africa in Tanzania and Mozambique. The disease now tends to be found mostly in Africa and East Asia, but recently it has extended to South America, Caribbean nations, and in the Southeastern United States. The name—which means “to walk bent over”—is characterized by severe arthritis.

The incubation period ranges from 2 to 14 days. The systemic manifestations in acute cases are similar—with patients complaining of fever, headache, low back pain, severe joint pain, myalgia, malaise, nausea, and vomiting. Patients who are severely affected suffer multiorgan failure, central nervous system involvement, and death.

The ocular manifestations include anterior chamber and vitreous inflammation with high intraocular pressure, retinal hemorrhage, retinal vasculitis, retinal vascular occlusion, retinitis, neuroretinitis, serous retinal detachments, and choroiditis.

Dr. Cunningham described a case of Chikungunya with focal areas of retinitis, such as are seen sometimes in patients with necrotizing retinitis due to syphilis or herpes virus infection. The patients tend to have panuveitis.

Because these mosquito-borne diseases can have similar appearances upon presentation, Dengue fever may be hard to differentiate from Chikungunya. He advised placing the diseases in the context of their endemic areas, areas of patient travel, and systemic symptoms.

“Hemorrhages would suggest that the patient has Dengue fever, and profound arthritis suggests Chikungunya if the patients have been to areas that have those disorders,” Dr. Cunningham said. “If they have been to South America, the chances of them having contracted Chikungunya are much lower.”

**Editor’s Note:** Although not discussed in Dr. Cunningham’s AAO lecture last November, Zika Virus is a related mosquito-borne flavivirus of increasing prevalence and importance—particularly in South America and the Caribbean.

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**CLINICIANS SHOULD**

**RECOGNIZE THE SYMPTOMS OF WEST NILE VIRUS, DENGUE FEVER, AND CHIKUNGUNYA THAT ARE SPREAD BY MOSQUITOS AND CAN HAVE OCULAR MANIFESTATIONS.**

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This article was adapted from Dr. Cunningham’s presentation at the 2015 meeting of the American Academy of Ophthalmology. Dr. Cunningham has no financial interest in the subject matter.

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**JUNE 1, 2016 :: Ophthalmology Times**
Special Report  )  CONVENTIONAL & UNCONVENTIONAL APPROACHES TO OCULAR INFECTION

PK-related infections require careful vigilance, regardless of etiology
Case study highlights risks in contact lens-related Pseudomonas corneal ulcer

By Vanessa Caceres; Reviewed by Bennie H. Jeng, MD

Baltimore ::

Infections associated with penetrating keratoplasty (PK) require careful monitoring and an examination into the cause of the infection, according to Bennie H. Jeng, MD.

Specific types of infection include microbial keratitis, endophthalmitis, recurrence of viral infection, and transmission of infections from the donor, said Dr. Jeng, professor and chair man, Department of Ophthalmology and Visual Sciences, University of Maryland School of Medicine, Baltimore.

Dr. Jeng shared the case of a 53-year-old woman treated for a contact lens-related Pseudomonas corneal ulcer in the right eye. After the infection cleared, the patient developed a new infiltrate that the referring ophthalmologist thought looked a little different.

Although culturing identified it as fungus, its specific species could not be pinpointed. She was started on hourly voriconazole 1% and natamycin for recalcitrant infection.

The infection still progressed, and a deep anterior lamellar keratoplasty was performed to debulk the infection. Postoperatively, she was started on prednisolone acetate 1% and gatifloxacin.

Still, the patient’s infection persisted, and she was referred to the office of Dr. Jeng and colleagues. Despite aggressive therapy including topical, intracameral, and oral antifungal agents, therapeutic PK was required to treat the infection.

“Unfortunately, the patient had started herself on topical steroids immediately postope ratively,” Dr. Jeng said. “So, as you’d expect, there was recurrence of the infection by day six.”

The infection still was not controlled with intracameral injections of antifungals. Five days later, a limbus-to-limbus PK was performed along with irrigation of the anterior chamber with antifungals.

Postoperatively, the patient was put on oral antifungals.

The infection was “surprisingly sensitive” to voriconazole and amphotericin, Dr. Jeng said. “I think the infection was hiding deep in the cornea.”

The limbus-to-limbus graft eventually failed, and a 7-mm PK and cataract extraction was performed. Ultimately, she was regrafted once more, but at 4 years after original presentation, the patient’s best spectacle-corrected visual acuity was 20/25.

The causes of infections associated with penetrating keratoplasty are evolving, but no matter what the etiology, these infections consistently require vigilance and aggressive treatment.

Take-home

Touching upon the risks

Dr. Jeng said that his case touched upon a series of risks associated with infection in the setting of PK.

Microbial keratitis can arise from a contaminated donor button, although Dr. Jeng said that is happening much less frequently.

However, surgeons should also be aware of the increasing risk of fungal infections (some transmitted from the donor) compared with bacterial infections, based on data from the Eye Bank Association of America, Dr. Jeng said.

“One possible reason for the rise in fungal infections is that endothelial keratoplasty is on the rise, and fungus love living in that interface because they are protected,” he said.

Something that he does see more often is the recurrence of a host infection, which could be modulated by the use of certain postoperative medications like steroids. Late infections could be caused by suture-related problems, persistent epithelial defects, chronic use of bandage contact lenses, ocular surface disease, and eyelid and adnexal abnormalities.

“We need to identify these infections very early on and culture them,” Dr. Jeng said. “Any small infection in the graft needs to be treated aggressively.”

He prefers to use fortified antibiotics because of the risk of graft wound dehiscence if the infection progresses.

“I’ll decrease steroids if they’re on it,” Dr. Jeng said. “If a suture is involved, I’ll remove it. If it’s necessary to regraft, I’ll do it.”

Although there is less risk nowadays for viral infections, it still is possible for patients to get a recurrent or new onset herpetic infection transmitted from the donor, Dr. Jeng said.

There were previous reported cases of hepatitis B transmission, but with stringent eye bank screening in the last few decades, this infection seems to be a thing of the past. There have been no documented cases of HIV transmission via a graft to date, Dr. Jeng said.

Bennie H. Jeng, MD

This article was adapted from Dr. Jeng’s presentation at the 2015 meeting of the American Academy of Ophthalmology. Dr. Jeng did not indicate any proprietary interest in the subject matter.

Zika babies at risk for additional, newly reported eye disorders

Researchers have reported additional eye problems discovered in babies with the Zika virus (bit.ly/1WPPqKJ). Studying three Brazilian infants born in late 2015 to mothers with suspected Zika virus, researchers from Stanford University found that babies born with Zika are also at risk for other eye problems, such as hemorrhagic retinopathy, abnormal blood vessel development, and torpedo maculopathy. The infants in this study also exhibited previously published disorders such as eye lesions, optic nerve problems, and microcephaly.

Though a small study with limited data, experts continue to encourage that babies with microcephaly be examined by an ophthalmologist.
Severe corneal infections necessitate prompt attention for management

Patients must be monitored closely, referred to specialist if no improvement

By Fred Gebhart; Reviewed by Christopher N. Ta, MD

PALO ALTO, CA ::

**CORNEAL INFECTIONS ARE** among the most serious reasons for ophthalmologic visits and require immediate attention.

“Early and accurate diagnosis is important for a favorable outcome for a patient with a severe infection of the cornea,” said Christopher N. Ta, MD.

“It is the infection that can cause severe, irreversible loss of vision,” said Dr. Ta, professor of ophthalmology, Byers Eye Institute, Stanford University School of Medicine, Palo Alto, CA. “Infection is the number one thing to diagnose and the number one thing to treat.”

But infections differ. Different etiologies, different organisms, different susceptibility profiles, different diagnostic and treatment resources, and other factors all play roles in clinical decision making.

Diagnosis and treatment are relatively straightforward in academic centers and larger cornea specialty clinics. Take a history, perform an examination and take scrapings from the cornea, send the scrapings for culture, identification, and susceptibility testing—and treat as indicated by the results.

“That’s the ideal, but we all recognize that immediate laboratory support may not be available in every ophthalmology clinic,” Dr. Ta noted. “A good history and a careful exam can usually lead you to the right diagnosis and treatment.”

**IDENTIFY RISK FACTORS**

Bacteria are the most common infectious agents affecting the cornea, he continued.

Contact lens wear is by far the most common cause of corneal infection, most often secondary to *Pseudomonas aeruginosa*. Progression is typically rapid.

Other common risk factors for corneal infection include trauma to the eye and postoperative infections. Following ocular injury, Gram-positive bacteria, including various strep and staph species are common, as are fungal infections.

*Streptococcus pneumonia* infections tend to produce deep central ulcers with hypopyon. Progression is rapid and the risk of corneal perforation is high. *Staphylococcus aureus* infections may be treatement-resistant to various antibiotics, including methicillin-resistant *Staphylococcus aureus* (MRSA).

Less common risk factors include sutures or other foreign bodies in the eye, neurotropic keratopathy, autoimmune disorders, dry eye, and eyelid abnormalities.

Other infectious agents include herpes virus and *Acanthamoeba*. Herpes infections are usually recurrent and present in the setting of a neurotrophic cornea and vascularization. *Acanthamoeba* infections are usually associated with contact lens wear.

The first step in any evaluation is a complete history to help identify potential causes and organisms. If laboratory identification is available, use a spatula to scrape the base of the ulcer. The scrapings are inoculated directly onto culture media.

Bacteria are the most likely agent in eye infections and scrapings can be inoculated onto blood agar, chocolate agar, and a broth media. Brain-heart infusion or Sebaroud’s media are used to isolate fungal infections.

If a herpes infection is suspected, scrapings can be sent for polymerase chain reaction (PCR) analysis of viral DNA fragments. *Acanthamoeba* testing requires a special media with live bacterial cultures, such as non-nutrient agar with *E. coli* overlay. A confocal microscopy is also sometimes used to identify fungal and *Acanthamoeba* infections.

Because bacteria are the most common infectious agents affecting the cornea, it is usually appropriate to begin empiric treatment with topical broad-spectrum antibiotic. If the ulcer is small, peripheral, and does not threaten vision, hourly application of a commercially available fluoroquinolone is a good first step. Typical agents include besifloxacin and moxifloxacin.

“If it is a large, deep, central corneal ulcer that threatens vision, some of us will advocate a fortified antibiotic that covers both gram positive and gram negative bacteria,” Dr. Ta added. “I would begin with a commercially available agent until you can get fortified antibiotics compounded.”

**ROLE OF COMPOUNDING PHARMACY**

Ophthalmologists should know a local compounding pharmacy, he continued.

For infections that require agents, such as cefazolin, tobramycin or vancomycin, the compounding pharmacy converts an intravenous formulation to a fortified ophthalmic formulation.

“If you have a patient with a MRSA infection of the cornea that is also resistant to fluoroquinolones, one of the very few antibiotics that could eliminate those organisms is vancomycin,” Dr. Ta said. “But vancomycin is not commercially available in an ophthalmic formulation. That’s when you need a compounding pharmacy to make it for you.”

If there is a high level of suspicion for fungal infection, it may be reasonable to begin treatment with both a broad spectrum antibiotic and topical natamycin, a broad spectrum antifungal. Treatment can be adjusted depending on culture and susceptibility testing.

Patients who have a history of chronic topical steroids are also at risk for herpes keratitis. Antiviral agents such as topical ganciclovir or oral acyclovir, valacyclovir or famciclovir are effective treatment for herpes keratitis.

“Most cases of corneal ulcers are caused by bacteria and can be treated empirically with broad-spectrum antibiotics,” Dr. Ta said. “However, these patients need to be monitored very closely and if they don’t improve, referral to specialist care is very important.”

**CONVENTIONAL & UNCONVENTIONAL APPROACHES TO OCULAR INFECTION**

**take-home**

- Conducting a good history and a careful exam can usually lead clinicians to the right diagnosis and treatment in cases of severe microbial keratitis.

This article was adapted from Dr. Ta’s presentation at the 2015 meeting of the American Academy of Ophthalmology. Dr. Ta did not indicate any proprietary interest in the subject matter.
Novel dual agonist leads to notable IOP lowering

Safety, tolerability reasonable for new medication regardless of a.m. or p.m. dosing

By Vanessa Caceres; Reviewed by Eydie G. Miller-Ellis, MD

In a group of 123 patients, the drug ONO-9054 showed a greater reduction in IOP and a longer duration of IOP reduction compared with latanoprost (Xalatan, Pfizer), said Eydie G. Miller-Ellis, MD.

ONO-9054 is a highly selective and potent dual EP3 and FP prostanoi receptor agonist.

“It’s hypothesized that agonist activity against EP3 and FP receptors might provide more sustained reduction in IOP than the FP agonist latanoprost,” said Dr. Miller-Ellis, chief, glaucoma service, and professor of clinical ophthalmology, Perelman School of Medicine, University of Pennsylvania, Philadelphia.

Two previous clinical trials have shown that ONO-9054 both increases uveoscleral and trabecular outflow in animals and that it is safe and well tolerated in healthy normotensive adults and subjects with open-angle glaucoma (OAG) and ocular hypertension.

The previous research has found IOP reductions both from single and repeated doses. The IOP reductions extended to 33 hours post-dose.

“There are clinically relevant reductions in IOP regardless of a.m. or p.m. dosing,” Dr. Miller-Ellis said.

In the latest research with ONO-9054, a double-masked, parallel group, active comparator study, ONO-9054 was compared against latanoprost using once-daily doses at 10 p.m. for 28 days. All subjects had either ocular hypertension or mild-to-moderate OAG. Investigators measured IOP at 8, 10, and 12 o’clock every day as well as 4 and 8 o’clock at 1 and 29 days. The primary comparison measure was change from baseline to day 29 in terms of mean IOP at all time points.

The secondary measure was safety and tolerability, Dr. Miller-Ellis said.

Investigators found a similar baseline of 24 mm Hg in both treatment groups. Although both ONO-9054 and latanoprost had a significant IOP reduction compared with the untreated baseline, ONO-9054 patients had a more significant drop in IOP, Dr. Miller-Ellis said. This drop was particularly noticeable later in the day.

“On day 29, the odds of a more than 25%, 30%, and 35% reduction in IOP were 2.39, 2.37, and 4.85 more with ONO-9054 than the odds for latanoprost,” Dr. Miller-Ellis said. This drop was particularly noticeable later in the day.

“At Day 29, the odds of a mean IOP reduction of ≤-25%, ≤-30% and ≤-35% for ONO-9054 were 2.39, 2.37, and 4.85 more with ONO-9054 than the odds for latanoprost [p < 0.05, post hoc analysis] The odds were up to 4.69 times more at individual time points on Day 29 [p < 0.05, prospective analysis] The odds of an IOP reduction of ≤-30% and ≤-40% for ONO-9054 subjects were 1.9 and 2.4 times more, respectively, across all 13 timepoints from Days 8, 15, and 29 combined (p < 0.001, post hoc analysis).

There was also a greater change in IOP than the untreated baseline, ONO-9054 patients had a more significant drop in IOP, Dr. Miller-Ellis said. This drop was particularly noticeable later in the day.

At Day 29, the odds of a mean IOP reduction of ≤-25%, ≤-30% and ≤-35% for ONO-9054 were 2.39, 2.37, and 4.85 times more, respectively, than the odds for latanoprost (p < 0.05, post hoc analysis).

Safety and tolerability were similar between the two medications. The only adverse events were ocular in nature and mild or moderate in severity.

Eydie G. Miller-Ellis, MD
eydie.miller-ellis@uphs.upenn.edu
This article was adapted from Dr. Miller-Ellis’ presentation at the 2015 meeting of the American Academy of Ophthalmology. Dr. Miller-Ellis is a consultant for ONO Pharmaceutical.

Responders on Day 29: Percent change from baseline

(08:00, 10:00, 12:00, 16:00, 20:00)

At Day 29, the odds of a mean IOP reduction of ≤-25%, ≤-30% and ≤-35% for ONO-9054 were 2.39, 2.37, and 4.85 times more, respectively, than the odds for latanoprost (p < 0.05, post hoc analysis).

The odds were up to 4.69 times more at individual time points on Day 29 (p < 0.05, prospective analysis).

The odds of an IOP reduction of ≤-30% and ≤-40% for ONO-9054 subjects were 1.9 and 2.4 times more, respectively, across all 13 timepoints from Days 8, 15, and 29 combined (p < 0.001, post hoc analysis).

For the responders on Day 29, 4.69 times was for the ≤-40% response. (Figures courtesy of Eydie G. Miller-Ellis, MD)

Mean IOP mm Hg on Day 29

This figure highlights the 1-mm Hg difference for 10:00 to 20:00 timepoints.
Considering value-based medicine: Quality of life with DME therapies

Protocol T tracking efficacy of various agents, average number of injections for patients

By Vanessa Caceres; Reviewed by Bryan K. Hong, MD

TAKING HOME

In DME patients with worse baseline visual acuity, aflibercept and ranibizumab provided more of a quality-of-life improvement—yet, aflibercept had an associated higher cost.

What is Value-Based Medicine (VBM)?

The practice of medicine based upon

- Patient Value Gain
- Financial Value Gain

conferred by healthcare interventions

Patient-value gain is based on standardized cost-utility analysis. (Tables courtesy of Bryan K. Hong, MD)

Dr. Hong is a vitreoretinal fellow at the Wills Eye Hospital, Thomas Jefferson University, Philadelphia.

Dr. Hong’s work is based on methodology developed by Gary Brown, MD, and Melissa Brown, MD, of Thomas Jefferson University, who were able to assign time-trade off utilities to specific visual acuity levels, thereby allowing the comparison of value-based efficacy across medical specialties in a way that is understandable to the public.  

Comparative Value Gain by Treatment

<table>
<thead>
<tr>
<th>SSRI for Depression</th>
<th>21.6%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cataract Surgery</td>
<td>20.8%</td>
</tr>
<tr>
<td>Glaucoma, Timolol Rx</td>
<td>19.9%</td>
</tr>
<tr>
<td>Anti-hypertensives</td>
<td>6% to 9%</td>
</tr>
<tr>
<td>Statins</td>
<td>4% to 6%</td>
</tr>
<tr>
<td>Osteoporosis Drugs</td>
<td>1%</td>
</tr>
</tbody>
</table>

Although aflibercept demonstrated QOL gains for the worse VA group, that also came at a higher cost of $63,223. That compared with $2,528 for bevacizumab and $40,364 for ranibizumab.

The study concluded that aflibercept and ranibizumab are both cost-effective over 17 years in the treatment of DME and yield comparable gains in QOL. Ranibizumab is more cost-effective due to its lower cost.

“The conclusions of studies like this one are easily misinterpreted by policy makers,” Dr. Hong pointed out in a joint statement with Gary Brown, MD. “It is important to understand that the ‘most cost-effective’ treatment is not necessarily what is best for the patient. The treatment that affords the highest patient-value should be the preferred treatment, and only when two treatments appear to be comparable should a cost-utility analysis be used to decide which is more economical for third party payer with limited resources.”

References

LEARNING METHOD AND MEDIUM
This educational activity consists of a case discussion and study questions. The participant should, in order, read the learning objectives at the beginning of this case discussion, read the case discussion, answer all questions in the post test, and complete the Activity Evaluation/Credit Request form, to receive credit for this activity. Please visit http://www.tinyurl.com/EyeOnCataract-6 and follow the instructions provided on the post test and Activity Evaluation/Credit Request form.

CONTENT SOURCE
This continuing medical education (CME) activity captures content from an expert roundtable discussion held in San Diego, California, on April 16, 2015.

ACTIVITY DESCRIPTION
Cataract surgery is the most commonly performed surgery among adults in the United States, and the number of patients undergoing this procedure is continuing to increase. For patients who are identified as candidates for cataract surgery, optimization of the ocular surface is critical for obtaining optimal patient outcomes. A host of new tools can help cataract surgeons with their preoperative evaluations. Among these are several tests that are useful adjuncts for diagnosing dry eye/meibomian gland dysfunction. The purpose of this activity is to update ophthalmologists on recent advances in the care of patients with cataracts.

TARGET AUDIENCE
This activity is intended for ophthalmologists.

LEARNING OBJECTIVES
Upon completion of this activity, participants will be better able to:
• Manage preoperative ocular surface conditions, with the potential to affect surgical outcomes in patients with cataracts
• Demonstrate appropriate IOL selection, knowledge of appropriate refractive targets, and understanding of strategies for achieving intended goals
• Discuss the risks and benefits of cataract surgery with patients
• Describe the benefits of new diagnostic and surgical technologies with applications in cataract surgery

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Patient with Keratoconus

This Month’s Case

With Keratoconus

New York Eye and Ear Infirmary of Mount Sinai

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Cataract Surgery in A Patient With Keratoconus

This Month’s Case

New York Eye and Ear Infirmary of Mount Sinai

ORiGInAL ReLeASE: June 1, 2016 • lAsT ReViEW: April 22, 2016 • ExpIration: June 30, 2017
A 51-year-old man with a 20-year history of keratoconus presents with complaints of glare and decreased vision. The glare first developed approximately 1 year ago and is now severe. He needs rigid gas permeable (RGP) contact lenses for vision correction and has been wearing them successfully for 12 years. He has progressive posterior subcapsular cataracts (PSCs) OU, which were first diagnosed 3 years ago. His history also includes seasonal allergic rhinoconjunctivitis, for which he has been using intranasal fluticasone and oral loratadine. In addition, he has hypertension that is being treated with a thiazide diuretic.

On examination, his best corrected visual acuity (measured while wearing RGP contact lenses) is 20/40 OD and 20/50 OS, 20/60 OD and 20/100 OS on manifest refraction, and 20/100 OD and > 20/400 OS with glare (brightness acuity testing). His intraocular pressure is 11 mm Hg OD and 10 mm Hg OS. Digital contact pachymetry measurements are 428 µm OD and 388 µm OS.

Endothelial cell counts by specular microscopy are 1800 cells/mm² OD and 1500 cells/mm² OS. Tear osmolarity is elevated at 308 mOsm/L OD and 317 mOsm/L OS. The matrix metalloproteinase-9 assay is negative OU.

Eversion of the superior lids reveals 2+ tarsal papillae OU. Slit-lamp examination shows 1+ corneal striae OD and an early corneal scar OS (Figure 1), along with 1+ PSC OU. Despite corneal scarring only in the left eye, the patient is more bothered by his vision in the right eye because of dominance. His posterior segment examination is normal.

On slit-lamp topography, done 1 month after the patient stopped wearing his RGP contact lenses, sim K values (Kmax/Kmin) are 46.8/44.3 D OD and 51.6/44.2 D OS (Figure 2). Corneal pachymetry measured by optical low-coherence reflectometry (OLCR) is 490 µm OD and 473 µm OS. Wavefront aberrometry shows significantly more total

Figure 1. Vertical deep stromal Vogt striae OD (A) and moderate diffuse apical stromal scarring OS (B), which are classic for moderately advanced keratoconus

Figure 2. Topography reveals steeper keratometry, more distortion in the central 3- and 5-mm zones, thinner central pachymetry, and accentuated steepening of the posterior float in the left eye (B) compared with the right eye (A). This asymmetry is consistent with the topographic picture that is classically seen in most patients with keratoconus.

Figure 3. Intracocular lens calculator reveals anisometropia of approximately 5 D. The biometry shows steeper keratometry, more astigmatism, and a longer axial length in the left eye than in the right eye. The biometry is consistent with moderate keratoconus OD and advanced keratoconus OS.

Images Courtesy of John Sheppard, MD, MMSc
corneal higher-order aberration OS than OD (0.878 µm vs 0.299 µm) and particularly higher total coma OS than OD (0.790 µm vs 0.017 µm).

Astigmatism measurements obtained with 4 different methods (manual keratometry, automated keratometry, topography, and OLCR) are fairly consistent in the right eye for magnitude (range, 2.57-3.5 D) and axis (117°-123°), but the range of magnitude values is wider in the left eye (7.5-9.26 D).

Intraocular lens (IOL) calculations (Figure 3) performed using the OLCR IOL calculator with a target refraction of 0.00 D generates spherical power values of 15.5 or 16.0 D OD using different formulas and recommends a toric IOL with 3.75 D cylinder power at the IOL plane. The recommended spherical powers for the left eye range from 9.5 to 11.5 D, and even with implantation of a toric IOL with 6.0 D cylinder, the patient is left with 5 D of residual astigmatism.

A variety of issues necessitates particular attention when patients with keratoconus need cataract surgery. These pertain to the challenges of IOL calculations, correction of astigmatism, long-term biometric stability, and need for concurrent or future management of the keratoconus. **Intraocular Lens Considerations**

Predictability of IOL power selection in eyes with keratoconus is limited by the difficulty in accurately determining corneal power and obtaining accurate astigmatic axis measurements if a toric IOL is considered. Regardless of the type of IOL chosen, it is important to allow for reversal of contact lens-induced corneal warpage prior to obtaining measurements that will be used for the IOL power calculation.

No established guidelines on the length of time to wait after discontinuation of contact lens wear exist. The interval is longer for RGP contact lenses than for soft contact lenses because RGP lenses than for soft contact lenses because RGP contact lens washout period for RGP contact lenses.

Several groups have analyzed their refractive results using various strategies to determine IOL power in eyes with keratoconus. One small study reported better refractive predictability was achieved using the SRK-II formula than the SRK-T or SRK formulas, but found poorer predictability overall in eyes with moderate or severe keratoconus vs those with only mild disease.2

Another paper reviewing refractive outcomes after cataract surgery in eyes with keratoconus reported good results using actual keratometry (K) values and targeting low myopia in eyes with mild (n = 35) or moderate (n = 40) keratoconus.3 Use of actual K values with a mean target refraction of -5.4 D in 8 of 17 eyes with severe keratoconus (defined as mean K > 55 D) resulted in a large hyperopic biometry prediction error (mean, +6.8 D). For the remaining eyes with severe keratoconus, use of a standard K value of 43.25 D and a mean target refraction of -1.8 D yielded much better results (mean biometry predicted error, +0.6 D).

In a study including 23 eyes, surgeons evaluating outcomes with toric IOL implantation reported the best results were achieved using (1) corneal topography-derived K values and the SRK7 formula in eyes with mild and moderate keratoconus and (2) K values from corneal topography and manual keratometry using the SRK7 and SRK II formulas in those with severe keratoconus.4 Although toric IOLs are generally recommended for cylinder reduction in eyes with regular astigmatism, good refractive and functional outcomes were achieved with toric IOL implantation in those patients with stable keratoconus.

Similarly, others have reported favorable results with toric IOL implantation in eyes with stable keratoconus.5-7 Therefore, it appears that a toric IOL might be a reasonable choice if, preoperatively, there is good congruity of the axis using multiple methods of measurement. However, a toric IOL should only be considered to correct astigmatism if the patient will not be using RGP contact lenses postoperatively. In addition, for patients with keratoconus who have been happy wearing RGP contact lenses, and particularly if they would be left with significant astigmatism after toric IOL implantation, a monofocal IOL with an RGP contact lens for astigmatism correction may be the preferred option because it will likely provide the best overall quality of vision.

If it seems probable that the keratoconus will progress to necessitate corneal transplantation, any astigmatic correction rendered at the time of earlier cataract surgery would be irrelevant, an unnecessary expense, and possibly counterproductive because it may contribute to excessive cylinder error postkeratoplasty. Thus, IOL selection is more complicated in the setting of a younger patient whose keratoconus may be progressing or in patients with significant corneal scarring because these individuals may become candidates for keratoplasty. A low-power IOL will be needed in an eye with keratoconus undergoing cataract surgery because of the steepness of the keratoconic cornea. If keratoplasty is performed in the future, the eye will be left with a significant refractive error due to a reduction in the K value after the transplant. When future keratoplasty is a possibility and the patient is willing to continue RGP contact lens wear after cataract surgery, consideration can be given to using the predicted postkeratoplasty K value in IOL power calculations. As a general guide, in eyes with axial myopia, which constitute most patients with keratoconus, keratoplasty with a 0.25-mm donor-host diameter disparity will induce an additional 2 to 4 D of myopia.8 Use of the same size donor and host trephination significantly flattens the keratometry and induces significantly less myopia than use of disparate donors.9

**KERATOCONUS MANAGEMENT**

Corneal cross-linking (CXL) can be performed to stabilize mild-to-moderate keratoconus. When CXL is performed prior to cataract surgery, surgeons should ideally wait at least 6 months for the topography to stabilize before obtaining measurements for IOL power calculation, although stabilization may occur earlier in some patients. Because change in refraction after CXL can continue for years, patients should be counseled that continued contact lens use may be likely even after successful, uncomplicated cataract surgery. Corneal cross-linking performed after cataract surgery is well tolerated and often induces minimal spherical shift. Once again, however, individual responses are variable, and refraction can continue to change long-term. Considering the potential for CXL to cause a hyperopic shift, which is usually approximately 1 D after 1 year,10 surgeons may wish to target at least 1 to 2 D of myopia in a patient who is anticipated to undergo CXL after cataract surgery.

**ALLERGY MANAGEMENT AND OCULAR SURFACE OPTIMIZATION**

This case is a reminder that ocular allergies, including allergic conjunctivitis and vernal keratoconjunctivitis, are often associated with keratoconus.10,11 Thus, clinicians managing patients with keratoconus should attend to preventive and therapeutic measures for allergy management and ocular surface optimization prior to any surgical planning. In a patient with keratoconus, optimizing the condition of the ocular surface may also be important for enabling successful RGP contact lens wear postoperatively.
The patient in this case presents with several issues that can be affecting the condition of his ocular surface, including long-term contact lens wear, use of medications that can cause ocular dryness (an oral antihistamine and an oral diuretic), and allergic conjunctivitis. When there is concern about the effects of any systemic medication on dry eye, the ophthalmologist should speak to the prescribing physician about finding an alternative treatment or safe dosage reduction.

Oral antihistamines used to treat an allergy are well-substantiated risk factors for dry eye.15 Options for managing significant allergic rhinitis that do not cause ocular dryness include an intranasal corticosteroid, an intranasal antihistamine, and the oral leukotriene receptor antagonist montelukast. Although intranasal corticosteroids are generally considered to have a better ocular safety profile than ophthalmic or systemic corticosteroids, they have been associated with the development of a PSC.14,15 As the bottom line, however, any corticosteroid used in or around the eye may have ocular side effects, so ophthalmologists need to carefully monitor all patients being treated with these medications. Allergen avoidance, when possible, is one of the most effective interventions for controlling allergic disease. Allergy testing can now be performed in the ophthalmologist’s office with a US Food and Drug Administration–approved skin test for 60 common allergens, and patients often appreciate the convenience of this testing.18,19

Surgical Decision

This patient urgently needed to have cataract surgery to continue functioning in his daily activities and drive safely at night. Thus, it was decided that performing CXL for the keratoconus in his right eye would not meet his needs. The patient was offered cataract surgery with a toric IOL for the more symptomatic dominant right eye. A toric IOL was deemed acceptable in the context of his having reliably reproduced keratometric axis measurements from 4 different devices and a normal healthy endothelium with minimal corneal scarring. First, however, the patient was treated to rehabilitate his ocular surface. He underwent allergy skin testing and, on the basis of the findings, practiced allergen avoidance, which, together with use of topical antiallergy medications, resulted in an improvement of his allergy signs and symptoms. He was able to discontinue the oral antihistamine.

Furthermore, his dry eye improved with modification of his oral antihypertensive medication and an aggressive dry eye management regimen that included topical loteprednol, punctal plugs, and an oral nutritional supplement containing omega fatty acids, antioxidants, and other nutrients. His tear osmolality decreased to 300 mOsm/L OD and 299 mOsm/L OS. His topographic parameters after ocular surface rehabilitation did not change. One week after undergoing uneventful phacoemulsification with implantation of a 15.5 D single piece hydrophobic acrylic aspheric IOL with 2.57 D cylinder power at the corneal plane (3.75 D cylinder power at the IOL plane) at 121°, the patient was pleased to see 20/25-2 uncorrected OD. With his improved vision, the patient was able to function without his RGP contact lens OD whenever convenience dictated and binocularity was not required. Most of the time, however, he continued wearing his RGP contact lens OU because they provided better overall binocularity. The patient eventually underwent successful monofocal IOL implantation OS with a target of -2.0 D myopia.

For more information on ocular surface management, see a Patient With Mixed Aqueous Deficiency/Evaporative Dry Eye Disease at http://medicus.com/downloads/Eye_on_Cataract_Monograph.pdf.

Summary

Cataract surgery will eventually be required in some eyes with keratoconus, and the presence of PSCs at a relatively young age in this patient and other patients with keratoconus may be associated with the use of corticosteroid medications to control allergic disease. The decision of whether to perform cataract surgery alone or combined with CXL or keratoplasty will need to be individualized, taking into account the keratoconus stage and topographic stability, along with the patient’s goals and preferences. Cataract surgeons must recognize the complexities of IOL power selection in eyes with keratoconus, along with the benefits and limitations of correcting astigmatism with a toric IOL, and discuss these issues with patients for shared decision making. As in all patients undergoing cataract surgery, optimization of the ocular surface prior to obtaining preoperative biometry is mandatory for maximizing the refractive outcome and patient satisfaction. Control of the ocular surface disease and allergy should be initiated prior to biometry and throughout the perioperative period, and then with adequate maintenance doses indefinitely thereafter.

References


Visit http://www.tinyurl.com/EyeOnCataract-6 for online testing and instant CME certificate or scan QR code
Exploring keratoconic experience in long-arc ICRS

Minimally invasive surgery appealing; implants can be removed or repositioned if needed

By Delso Bonfante, MD, and Fernando Bonfante, MD

Editor’s Note: This article first appeared in sister publication, Ophthalmology Times Europe.

Until recently, patients with keratoconus faced a somewhat bleak future. Patients whose vision could no longer be managed with spectacles and rigid contact lenses typically faced highly invasive penetrating or lamellar keratoplasty and the side effects and postoperative complications associated with these procedures.

This is no longer the case. There are now several treatment options available including toric phakic IOLs, collagen corneal cross-linking, topo-guided photorefractive keratectomy (PRK) and intrastromal corneal ring segments (ICRS).

Although some patients may still eventually require a corneal transplant, these treatment modalities can at least delay, if not negate, the need for keratoplasty.

APPEALING TO PHYSICIANS, PATIENTS

In patients with early-stage keratoconus, ICRS implantation can help to improve visual acuity by decreasing irregular astigmatism and reducing corneal steepening. ICRS implantation is appealing to both surgeons and patients because the surgery required is minimally invasive and because the implants can be removed or repositioned if necessary.

In addition, the approach can be successfully combined with other treatments, such as corneal crosslinking and PRK, in patients with more advanced keratoconus, which can optimize the effects of the ICRS.

Though ICRS implantation may be associated with complications, such as incomplete channel creation and postoperative segment migration, the approach may be regarded as a core treatment in keratoconus management.

‘Data from both of these studies are consistent with the findings from [our] own retrospective analysis.’

There are numerous commercially available ICRS. These include the Intacs (Addition Technology), the Ferrara ring (Ferrara Ophthalmics), and the Keraring (Mediphacos).

ICRS selection depends largely on surgeon preference. In our practice, the Keraring is regularly used because it is available in two models (SI-5 and SI-6) for implantation in 5.0, 5.5 and 6.0 mm optical zones, and in a variety of thicknesses (from 150 μm to 350 μm) and arc lengths (from 90° to 355°), allowing for precise tailor treatment according to patient’s needs.

Also, the Keraring was specifically designed for corneal ectatic disorders and incorporates a unique prismatic design that helps to reduce the incidence of glare and halos. The newer, longer arc lengths (340° and 355°) were designed to aid central corneal flattening; they are mainly used in patients with central (nipple-type) keratoconus. Because the 340° and 355° Kerarings have become available only recently, there are few published data describing refractive and topographic outcomes in patients implanted with these longer arc lengths.

(FIGURE 1) Keratometry values before and after Keraring implantation. (Images courtesy of Delso Bonfante, MD)
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Duties will include providing clinical care to ophthalmology patients, teaching the principles of ophthalmology to medical students and undergraduate students in Allied Health programs, developing basic and/or clinical research, and performing additional departmental and/or sectional administrative duties as assigned by the Chair of the Department of Surgery.

The University is especially interested in candidates who can contribute to the diversity and excellence of the academic community through their research, teaching, and/or service. Applicants are requested to include in their cover letter information about how they will further this goal. The University of Vermont is an Affirmative Action/Equal Opportunity Employer. Applications from women, people with disabilities, veterans and people of diverse racial, ethnic and cultural backgrounds are encouraged. Applications will be accepted until the positions are filled.

Interested individuals should electronically submit their curriculum vitae with a cover letter and contact information for four references electronically to Brian Kim, MD c/o Emily Nuse at Emily.Nuse@uvmhealth.org or apply on-line at https://www.uvmjobs.com

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We recently performed a retrospective analysis to evaluate the visual and refractive outcomes following femtosecond-laser-assisted Keraring 340° (300 μm or 200 μm thickness) implantation in patients with keratoconus. Forty-eight eyes of 38 patients (mean age 25.6 years [range 14–43 years]) were evaluated.

All types of keratoconus—not only nipple-type keratoconus—were included in the analysis.

Outcome measures included uncorrected visual acuity (UCVA), best-corrected visual acuity (BCVA), manifest refraction sphere, cylinder, keratometry and corneal topography.

At an average follow-up of 6 months (range 3–18 months), mean UCVA and mean BCVA (LogMAR) were 0.65 and 0.32, respectively, versus preoperative values of 1.19 and 0.55. There were also marked reductions in mean sphere (−1.95 preoperatively versus −5.17 postoperatively) and cylinder (−2.46 preoperatively versus −4.68 postoperatively).

There was a reduction in all keratometry values. The mean K value was reduced from 49.18 D preoperatively to 44.74 D postoperatively, indicating a mean reduction of 4.44 D after Keraring implantation. Reductions in mean K1 and K2 were also noted.

**Comparative Findings**

As noted earlier, because the Keraring 340° has been available only for a short time, there are few other studies describing outcomes following implantation of this ICRS.

A prospective 11-eye study by Efekan Coskunseven, MD, in patients with advanced central or paracentral zone keratoconus who were implanted with the Keraring 340° also showed improvements in UCVA, BCVA, cylindrical refraction, spherical equivalent and mean K.

Similarly, in a 12-eye study by Rodrigo Teixeira Santos, MD, there was a statistically significant improvement in uncorrected distance visual acuity and a (non-statistically significant) improvement in corrected distance visual acuity after 6 months.

Dr Santos’ study also showed statistically significant improvements in sphere, cylinder and spherical equivalent and keratometry values (mean K, K1 and K2) at 6 and 12 months. Significant improvements in mean astigmatism and asphericity were also noted at both follow-up visits (unpublished data).

Overall, data from both of these studies are consistent with the findings from my own retrospective analysis. It is clear that larger studies with long-term follow-up across a spectrum of keratoconus patients are needed.

**References**


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Debo Bantante, MD, is the founder and clinical director of Clínica de Olhos Delso Bonfante, Campinas, Brazil. Fernando Bonfante, MD, is a corneal specialist at the medical school of the Holy House of São Paulo, Brazil. Drs Delso and Fernando Bonfante state that they have no financial interests in Mediphacos Ltda.
Remember enduring those seemingly endless years of residency and fellowship training? The grueling pattern of long hours and clinicals is something most surgeons compare with an ophthalmic version of boot camp. “Usually people who did not know me in training are shocked that I survived,” said Sonia Rana, MD. That’s because Dr. Rana not only earned her badge of honor while being Chief Resident at Kresge Eye Institute, Wayne State University, Detroit, but she also completed it while having two children, and still managed to graduate on time.

“I think there’s never really a good time to have kids,” said Dr. Rana, who is now a glaucoma and cataract specialist at Lansing Ophthalmology, East Lansing, MI.

Dr. Rana had her first child in 2011 while in her residency, and her second in 2014, the week before her fellowship began.

“I took three and a half weeks off each time,” she explained, adding that she pooled her vacation time for the rest of the year in order to take time off for the births of her daughters.

Balancing it all

Though she could have taken maternity leave, she didn’t want to risk her standing in her training programs. “It’s the law,” Dr. Rana said, referring to how she could have legally taken off 6 to 8 weeks, and possibly longer, with maternity leave, “but they can punish you in other ways,” such as delaying her graduation.

Because the application process for the training programs was so extensive and time consuming, she wanted to avoid the reapplication process at all costs by graduating on time.

Dr. Rana credits the support of her husband, parents, and friends for helping her get through training and her pregnancies.

“Those people who knew me in training were very supportive of my pregnancy,” she said. “A lot of that may have had to do with the fact that I continued to ‘pull my weight’ and made my pregnancies something I dealt with out of my clinical responsibilities.”

Dr. Rana’s peers also voted her best resident teacher, granting her the Golden Apple Award when she graduated.

“I don’t think it needs to be taboo,” she said, referring to having a child during training. “We are smart, capable people.”

That same goal-oriented mindset has stuck with Dr. Rana.

“One of my internal goals was to drop off or pick the kids up from school,” she explained, adding that she drives the kids to school every morning before work.

She also has a routine of biking with her children everyday after dinner. Her older daughter rides a scooter, while Dr. Rana rides a bike with a carriage attached for her younger daughter to sit in.

“It’s a way to work in exercise and family time,” she said, citing that having enjoyable activities outside of work is a key way to be an effective employee. It’s likely you won’t be as effective of an employee “if you’re always at work or your brain is always at work.”

Dr. Rana said she hopes her drive to reach her goals will inspire her daughters. “I am doing my best for my family while still trying to pursue my own dreams and I hope one day that teaches my daughters great lessons about following their own ambitions,” she said.

“I knew I wasn’t cut out to be a stay at home mom and I love doing what I do so I know even though it’s hard, it is definitely worth it,” she concluded. “I’m helping people see, saving their vision, or preventing their blindness. [It] can’t get much more meaningful than that!”

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**Ophthalmic Superwoman**

Resident, fellow, and mother of two

Sonia Rana, MD, with her husband and two daughters. Dr. Rana hopes her drive to reach her dreams will inspire her children to do the same.

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