EyeWorld
The News Magazine of the American Society of Cataract & Refractive Surgery

Fall 2004 Review

EyeWorld Supplement — October 2004

A fall update on the advantages of fourth-generation fluoroquinolones

"We now have at our disposal a new generation of antibiotics that maximize potency, penetration and safety."

Stephen S. Lane, MD

The development of topical antibiotics for use in ophthalmology has an evolutionary history characterized by continued change and incremental improvement.

Potency, penetration, and safety are the cornerstone attributes of any antibiotic, and have become the yardstick not only in measuring the effectiveness of the various available antibiotics, but also in comparing one agent to another.

More than ever it is critical that clinicians be well versed in these concepts so that informed decisions can be made about the most appropriate agents to use.

Fortunately, we now have at our disposal a new generation of antibiotics that maximize potency, penetration and safety. These fourth-generation fluoroquinolones, moxifloxacin (Vigamox, Alcon, Fort Worth, Texas) and gatifloxacin (Zymar, Allergan, Irvine, Calif.), offer an improved spectrum of pharmacodynamics, broader spectrum of coverage, and better resistance to bacteria than their predecessors. As a consequence, they are now the most popular and frequently used antibiotics by ophthalmologists in the United States.

Despite the power of these fourth-generation fluoroquinolones, differences do exist between the two agents currently available.

The following information will provide clinical evidence on the benefits of moving to the fourth-generation fluoroquinolones. In addition, the data will challenge the reader to determine if the differences between these agents translate to differences in therapeutic value. Finally, you will be treated to firsthand insight from some of the leading cataract and refractive surgeons in the country. I think you will enjoy the dialogue.

Stephen S. Lane, M.D.

Fourth-generation fluoroquinolones are effective against MRSA

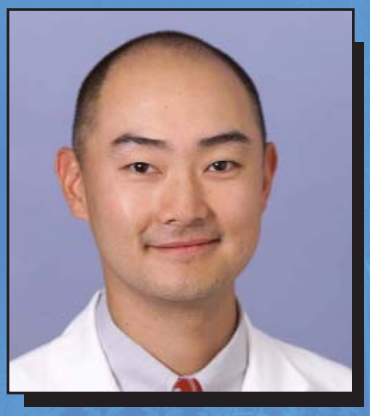
by Francis S. Mah, M.D.

Fourth-generation fluoroquinolones have increased potency and better penetration than all previously available topical antibiotics, making them able to eradicate the increasingly reported resistant bacteria. Methicillin-resistant *Staphylococcus species* strikes fear in all that treat infections. Although it is difficult, it is possible to successfully treat methicillin-resistant infectious keratitis. (Figure 1)

Figure 1

At ASCRS 2004 we reported on a study we conducted to determine the clinical relevance of *in vitro* methicillin resistance in ocular infections by comparing the clinical response of infectious keratitis caused by methicillin-resistant *Staphylococcus aureus* (MRSA) or methicillin-resistant *Staphylococcus epidermidis* (MRSE) to methicillin-sensitive *Staphylococcus aureus* (MSSA) or methicillin-sensitive *Staphylococcus epidermidis* (MSSE).[1]

This information contains a non-FDA-approved use. Please see full prescribing information.



"In terms of MICs, moxifloxacin definitely had lower MICs than gatifloxacin. Since this is statistically significant, by definition, moxifloxacin would be described as being more potent for these isolates."

Francis S. Mah, M.D.

In the systemic world, it is well documented that patients with MRSA infections do worse than patients with MSSA. We wanted to determine whether this was true in ophthalmology, because what happens in the systemic world doesn't always predict what happens in the ophthalmic world.

The *in vitro* aspect of this study looked at the minimum inhibitory concentrations (MICs) of 90 recent keratitis isolates determined using E-tests. Susceptibility was determined by comparing the MICs to the NCCLS standards for each antibiotic. NCCLS standards are based on safe, achievable concentrations of antibiotic in serum. Unfortunately for eyecare specialists, there are no standards for topical ocular therapy in terms of susceptibility and resistance breakpoints. Therefore, we must use the systemic standards as a guide.

Clinically, our study retrospectively reviewed the charts of all *Staphylococcus sp.* (aureus and epidermidis) keratitis patients during the eight-year period from August 1996 through August 2003. Twenty cases of MRSA and three cases of MRSE were compared to 15 cases of MSSA and seven cases of MSSE. Thirteen men and 10 women had MR infections, and these patients ranged in age from 18 to 96 years. Eleven men and 11 women had MS infections, and they ranged in age from 15 to 84 years.

Time to resolution

Resolution of keratitis was calculated by time to corneal re-epithelialization and time to disappearance of cornea infiltrate. Additionally, we evaluated adverse events.

The time range for re-epithelialization was one to 88 days for MRSA infections, with a mean of 23 days. MRSE infections had a time range of two to 30 days for re-epithelialization, with a mean of four days.

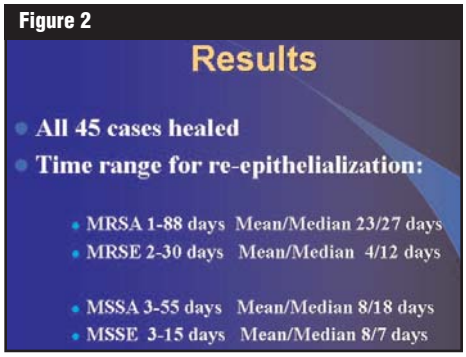
The time range for re-epithelialization was three to 55 days for MSSA infections, with a mean of eight days, and three to 15 days for MSSE infections, with a mean of eight days. (Figure 2)

The time range for infiltrate resolution was one to 124 days for MRSA infections, with a mean of 19 days, and 11 to 18 days for MRSE infections with a mean of 14.5 days. The time range for infiltrate resolution for MSSA infections was six to 93 days, with a mean of 19 days, and the time range for infiltrate resolution for MSSE infections was three to 22 days, with a mean of seven days. No adverse events occurred.

We found that there was a longer length of time to epithelialization, but no increase in infiltrate resolution of MRSA infections compared to MSSA infections, but it was not statistically significant. In terms of the eye, there doesn't seem to be a huge difference between MRSA and MSSA.

We then compared the effectiveness of newer fluoroquinolone agents in treating these infections. In terms of MICs, moxifloxacin definitely had lower MICs than gatifloxacin. Since this is statistically significant, by definition, moxifloxacin would be described as being more potent for these isolates. We also compared the effectiveness of other drugs and found that cefazolin and bacitracin were somewhat effective. Obviously, vancomycin was 100% effective.

Figure 2



One problematic note, however, is that resistance to moxifloxacin and gatifloxacin has been reported with MRSA and MRSE. This is occurring more with MRSE than with MRSA.

However, the issue of resistance should be kept in perspective. This resistance is *in vitro* resistance as compared to systemic standards. These standards are from the systemic world, and topically we can dose higher and get more drug into the eye than the systemic world can get into the blood. The systemic world is limited by toxicity of medication and the bioavailability of these medications orally or intravenously. In ophthalmology, these issues are of little concern.

The toxicity is so minimal that we can dose extremely frequently, and we are going to have fewer clinical failures because we can get so much drug into the eye with these newer fluoroquinolones.

In a separate study (presented at ARVO 2004) we used MRSA and a fourth-generation agent in our rabbit keratitis model, and we found that we can overcome resistance by dosing at a high frequency.[2] There is probably some resistance that can't be overcome, but we can definitely overcome low to moderate resistance with high dosing of these agents. But we need to follow patients carefully if we are considering this strategy because clinically this is unknown territory.

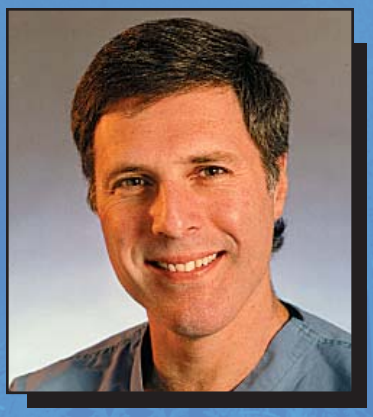
Fourth-generation advantages

Fourth-generation fluoroquinolones have advantages over previous generations in treating gram-positive organisms because they have the C-8 methoxy group which improves gram-positive activity. Additionally, moxifloxacin has a larger C-7 side chain as compared to gatifloxacin, which actually will decrease resistance as well as the likelihood of developing resistance.

[1] Silk MW, Mah FS, Kowalski RP, Clinical Response of MRSA and MRSE Infectious Keratitis to Conventional Antibiotic Therapy. Presented at ASCRS 2004, San Diego, CA.

[2] Kowalski RP, Mah FS, Romanowski KA, Yates Y, Gordon J, Gatifloxacin (Zymar™) Can Be Effective In Comparison to Vancomycin and Cefazolin for Treating Gatifloxacin-Related Staphylococcus aureus Keratitis in a NZW Rabbit Model. Presented at ARVO 2004, Ft. Lauderdale, FL

Francis S. Mah, M.D., is co-director of the Charles T. Campbell Eye Microbiology Lab at the University of Pittsburgh.



"Unlike the other fourth-generation fluoroquinolone, gatifloxacin, moxifloxacin is considered to be a biphasic molecule. Therefore, moxifloxacin is soluble in both lipid and aqueous solutions."

Harold R. Katz, M.D.

Vigamox safely treats corneal ulcers

by Harold R. Katz, M.D.

Vigamox (Alcon) is ideal for treating corneal ulcers for several reasons. It has broad-spectrum coverage, especially against gram-positive organisms. In fact, it is eight to 16 times more potent against gram-positive organisms than previous generation fluoroquinolones. It also is active against resistant organisms that are resistant to the earlier-generation fluoroquinolones.

Vigamox has activity against methicillin-resistant *Staphylococcus aureus* (MRSA). My colleagues and I conducted a study in rabbits that found Vigamox is as effective as vancomycin in the treatment of MRSA. Since vancomycin is the drug of choice for MRSA, this is important and exciting information.

Additionally, it has excellent activity against gram-negative organisms, and it has good activity against *Pseudomonas aeruginosa*. Traditionally, the fluoroquinolone of choice for the treatment of pseudomonas has been ciprofloxacin. However, ciprofloxacin does not penetrate very well into the cornea, whereas Vigamox does.

In our rabbit study, we induced corneal ulcers with MRSA in one group. In the other group, we induced ulcers using *Pseudomonas aeruginosa*. In the pseudomonas group, we showed that Vigamox was as good as ciprofloxacin in the treatment of *Pseudomonas aeruginosa* corneal ulcers in rabbits.

Based on animal models and *in vitro* data, it would appear that Vigamox is an excellent choice for the treatment of corneal ulcers. (Figure 1)

Excellent penetration

Human and animal studies have shown that topical moxifloxacin penetrates at very high levels into ocular tissues including the tear film, cornea, anterior chamber, and ciliary body.

There are a number of theories as to why moxifloxacin has such good penetration. Unlike the other fourth-generation fluoroquinolone, gatifloxacin, moxifloxacin is considered to be a biphasic molecule.

Therefore, moxifloxacin is soluble in both lipid and aqueous solutions. This is important when a molecule has to penetrate into different ocular tissues because different tissues of the eye are permeable to lipid-soluble molecules while other tissues are soluble to aqueous-soluble molecules. If a molecule has both lipid and aqueous solubility it can achieve very high concentrations in the eye.

Research has shown that moxifloxacin penetrates at higher levels into the cornea than gatifloxacin. Additionally, it has been shown that moxifloxacin has better penetration into the anterior chamber than gatifloxacin.

Figure 1

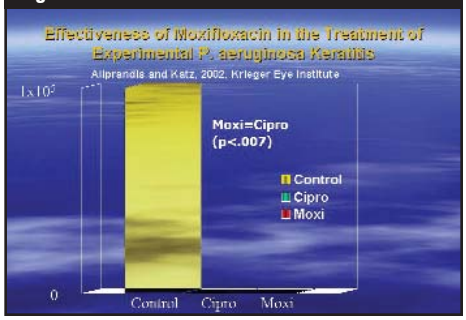
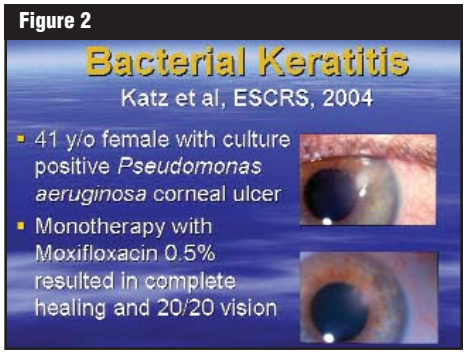


Figure 2



My colleagues and I also conducted a study to evaluate the ocular absorption of moxifloxacin by determining the concentration of moxifloxacin in the aqueous humor of patients undergoing cataract surgery.[1]

The study included 60 patients that received one of two different topical dosing regimens of moxifloxacin. In the first dosing regimen group, the operative eye was treated with one drop every 15 minutes for four doses on day of surgery. In the other group, the operative eye was treated with one drop four times daily on the day prior to surgery, and with one drop every 15 minutes for four doses on the day of surgery.

The study found that administration of Vigamox prior to cataract surgery had no effect on postoperative corneal and conjunctival healing. Moxifloxacin demonstrated rapid and extensive ocular absorption. The aqueous humor maximum concentration was 25- to 30-fold above the median MICs for *S. aureus* and *S. epidermidis* isolates from clinical cases of endophthalmitis. There was no statistically significant difference in aqueous humor maximum concentration between the one- and two-day regimens.

We also conducted a case study (to be presented at ESCRS, 2004) of a patient with a *Pseudomonas aeruginosa* corneal ulcer who was successfully treated with topical Vigamox. This patient was treated soon after Vigamox was approved by the FDA, and the patient recovered 20/20 vision. (Figure 2) Since then, I have successfully treated several other patients with pseudomonas ulcers.

[1] Katz HR, Masket S, Lane SS, Sall K, Orr SC, McCue BA, Faulkner RD, Dahlin DC, ARVO 2004.

Harold R. Katz, M.D., is director of cornea and refractive surgery at the Krieger Eye Institute in Baltimore.

> ***"We concluded that moxifloxacin in commercial Vigamox penetrates into the aqueous humor with four times daily dosing to therapeutic effective kill levels, where gatifloxacin in Zymar does not."***
>
> **James P. McCulley, M.D.**

Moxifloxacin effectively penetrates into the aqueous humor

by James P. McCulley, M.D., F.A.C.S.

Due to the shortcomings of second- or third-generation fluoroquinolones, new ophthalmic antibiotics were needed. It was hoped that the next generation of fluoroquinolones would have better gram-positive coverage, especially against streptococcus; that they would be effective against resistant organisms, especially against resistant staphylococcus; that they would be effective against atypical mycobacteria; that they would have better penetration into the anterior chamber with four times daily dosing; and that they would slow the development of resistance.

When the fourth-generation fluoroquinolones became available my colleagues and I conducted a study to directly compare penetration of the two fourth-generation fluoroquinolones into aqueous humor in humans after topical application and to published levels for second- and third-generation fluoroquinolones.[1]

Forty patients scheduled for routine phacoemulsification and IOL insertion that were otherwise without ocular disease were given, in a double-masked fashion, either moxifloxacin 0.5% or gatifloxacin 0.3% to use four times daily on the day before surgery and one hour prior to the surgical entry into the anterior chamber on the day of surgery.

Aqueous humor samples were taken and chromatographically analyzed by HPLC. Aqueous humor fluoroquinolone concentration was calculated by peak comparison to the known concentration peak for ciprofloxacin (which was run as an internal standard). (Figure 1)

This preoperative dosing was used as a surrogate for what postoperative dosing would be.

Aqueous humor concentration

The study found that moxifloxacin penetrated significantly better than gatifloxacin.

Both fourth-generation fluoroquinolones achieved superior aqueous humor concentrations after four times daily dosing compared to prior generation fluoroquinolones.

Bactericidal concentration

When a drug has a maximum fluid/tissue concentration that is 10 times the MIC for an organism, one can be confident of kill and that the concentration will predictably prevent the development of mutations or resistance. Moxifloxacin exceeded 10 times the MICs for all of the bacteria that are sensitive to fluoroquinolones, while gatifloxacin did not. (Figure 2)

For the bacteria that are resistant to prior generations of fluoroquinolones, moxifloxacin exceeded the MIC, but did not necessarily reach 10 times the MIC. Gatifloxacin did not achieve concentrations above the MICs of resistant organisms.

We concluded that moxifloxacin in commercial Vigamox penetrates into the aqueous humor with four times daily dosing to therapeutic effective kill levels, where gatifloxacin in Zymar does not.

Moxifloxacin was able to reach a mutation prevention concentration and a kill concentration for all of the susceptible bugs, and it achieved a concentration above the MIC of resistant bugs. Gatifloxacin did not reach 10 times the MIC for susceptible organisms, and it did not reach the MIC of resistant organisms.

Figure 1

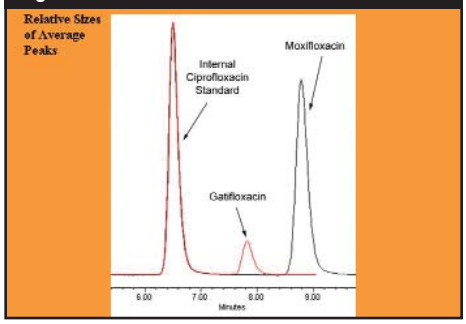
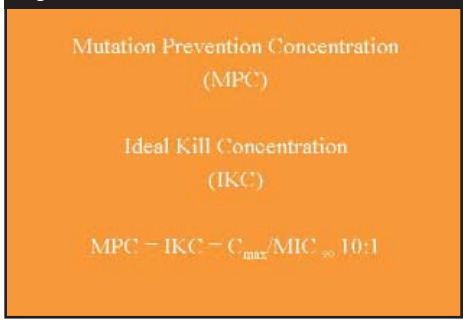


Figure 2

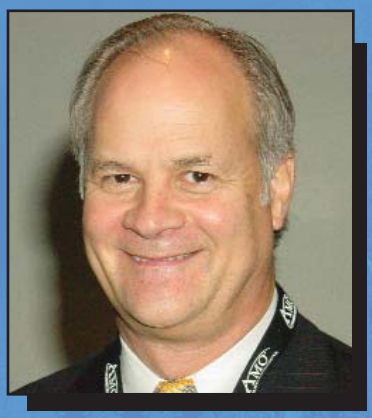


[1] McCulley JP, Surratt G, Shine W, 4th Generation Fluoroquinolone Penetration into Aqueous Humor in Humans, Invest. Ophthalmol. Vis. Sci. 44:E Abstract 4927-B251 Vol 2.

James P. McCulley, M.D., F.A.C.S., is professor and chairman of the Department of Ophthalmology at the University of Texas Southwestern Medical School in Dallas.

Fourth-generation fluoroquinolone use in LASIK patients

by Daniel S. Durrie, M.D.



"Personally, I have made the decision to use Vigamox because I like not having an added preservative, and I like the pH closer to 7."

Daniel S. Durrie, M.D.

The ideal antibiotic for refractive surgery would be safe, effective, non-toxic, well tolerated, and well accepted as the standard in refractive surgery. Fourth-generation fluoroquinolones have all but possibly the last criterion.

New antibiotics are normally evaluated based on kill rates, penetration into the cornea and anterior chamber, and the sensitivity of certain bacteria to these antibiotics.

However, no clinical studies for fourth-generation fluoroquinolones were conducted on LASIK patients, so there were no data to assure me of the safety of the use of fourth-generation fluoroquinolones in LASIK patients.

LASIK presents a unique risk because it creates a space for potential microorganism sequestration and proliferation deep within stroma. Additionally, there is the uncoupling of natural defense mechanisms with temporary denervation and alteration of tear film dynamics.

Because the fourth-generation fluoroquinolones fit the profile of the ideal antibiotic, my colleagues and I wanted to determine whether they would be safe to use in LASIK patients. We also wanted to determine whether there was a difference between the two fourth-generation fluoroquinolones: Vigamox and Zymar.

Our goal was to see if there was anything unusual with the healing profile compared to what had been seen previously in the clinical trial that used TobraDex (Alcon). I had used all three of the third-generation fluoroquinolones for the past three or four years and had never had an infection. All three of these fluoroquinolones were very well tolerated.

However, resistance to these fluoroquinolones was starting to develop. Between 1993 and 2001, the number of resistant strains increased, especially in endophthalmitis. (Figure 1)

LASIK surgeons needed to consider moving to the fourth-generation fluoroquinolones. We needed an antibiotic that would be well tolerated by patients and that would provide the broadest spectrum of coverage.

Assessing safety

Our research center conducted a clinical trial designed to assess the overall safety of Vigamox and Zymar in humans undergoing LASIK. This prospective, randomized, double-masked, single-center clinical trial included 60 eyes in 30 patients. One eye of each patient received Vigamox and the other received Zymar. Subjective and objective outcome measures were analyzed for comparisons.

Our study evaluated the following measures:

- Pupil size
- Visual acuity
- SPK
- Edema
- Glare
- Haze
- Halos
- Sharpness and clarity
- Overall vision
- Sandy, gritty, or scratchy feeling
- Itching
- Ease of use
- Redness
- Overall irritation
- Overall comfort
- Speed of recovery

We found no significant differences between Vigamox and Zymar in outcome measures or patient responses. Both were found to be safe and well tolerated in the LASIK setting. We found no difference compared to third-generation fluoroquinolones, and we found no difference between Vigamox and Zymar.

This was great news for LASIK surgeons because they could now make the decision to use fourth-generation fluoroquinolones in LASIK patients. Since LASIK is an elective procedure you want patients to be comfortable. If one fluoroquinolone had been better tolerated than the other, it would have been an important consideration when choosing an antibiotic.

Other considerations

Although our study found no differences between Vigamox and Zymar, there are inherent differences.

Moxifloxacin has a more natural pH of 6.8, compared to Zymar's pH of 6.0. The theory is that moxifloxacin may feel better when it is instilled in the eye, and it may penetrate better. (Figure 2)

Additionally, Vigamox is self-preserved. It does not contain BAK, and BAK and other preservatives have been found to be toxic to epithelial cells.

Personally, I have made the decision to use Vigamox because I like not having an added preservative, and I like the pH closer to 7.

I use Vigamox in my LASIK patients, and I've also started using it for PRK, LASEK, CK, and refractive lensectomy patients.

For LASIK patients, I use Vigamox 30 minutes prior to surgery, followed by Alphagan P (Allergan) and proparacaine, one drop before the prep.

During surgery, I use tetracaine after inserting the speculum. I also use Vigamox immediately following surgery and in conjunction with a steroid four times a day for a week.

Figure 1

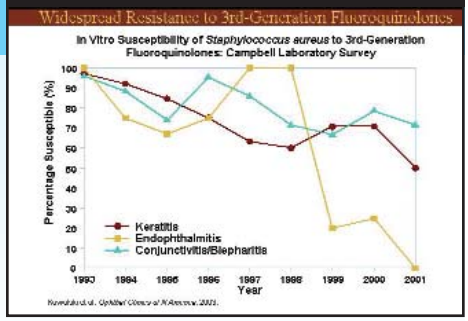
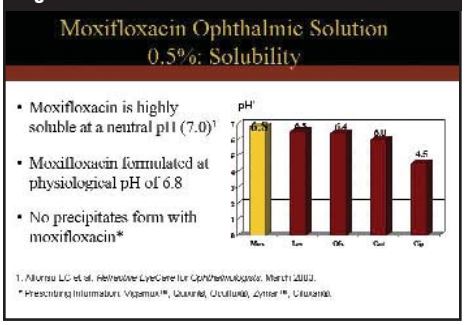


Figure 2



Daniel S. Durrie, M.D., is director of refractive surgery at Durrie Vision in Kansas City, and clinical associate professor of ophthalmology at the University of Kansas School of Medicine.

"The time to corneal epithelial healing following LASEK surgery was similar for the Vigamox and Zymar regimens. The range of time to healing was four to seven days for the Vigamox regimen and four to eight days for the Zymar regimen."

William Trattler, M.D.

Fourth-generation fluoroquinolones' effect on LASEK

by William Trattler, M.D.

Advanced surface ablation procedures, including PRK and LASEK, have regained popularity over the past few years. Surface ablation procedures have the advantage of avoiding flap-related intraoperative and postoperative complications as well as the potential for providing better quality of vision. The main downsides of advanced surface ablation are increased amounts of postoperative discomfort and a longer time to improved vision.

The amount of time required for the epithelium to heal is a key factor in the success of advanced surface ablation procedures. The faster the epithelium heals, the sooner the vision will recover and the faster the discomfort will end for the patient. It is, therefore, critical to take steps to maximize the ability of the corneal epithelium to heal. During the preoperative exam, dry eye testing will identify patients with poor tear function. These patients can benefit from preoperative treatment of their dry eye, which will help them heal faster. Another key issue is the postoperative medication regimen.

LASEK study

I recently conducted a study which measured whether there was a difference between the effects of Vigamox and Zymar on corneal re-epithelialization after LASEK surgery.

My colleagues and I at Miami's Center for Excellence in Eye Care conducted a prospective, randomized, investigator-masked, single-center trial involving 30 patients.[1] The LASEK procedures were performed using dilute alcohol to loosen the epithelium, and the hinge was placed superiorly. The ablation diameter was 8 mm in 29 out of 30 cases, and 9 mm in one case.

Following the laser treatment, the epithelium was replaced, and a bandage contact lens was placed. Patients were instructed to administer a four-times-daily regimen that included Vigamox and other Alcon medications to one eye. The other randomized eye of each patient received a four-times-daily regimen that contained Zymar and other Allergan medications. The primary outcome measure was a physician's assessment of complete corneal re-epithelialization.

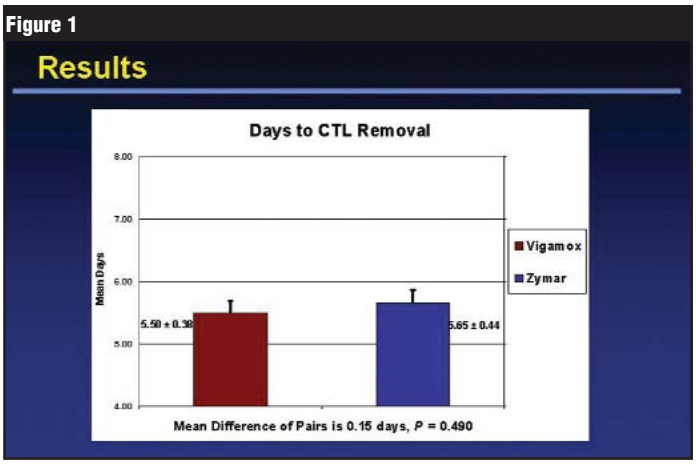
Time to healing

The time to corneal epithelial healing following LASEK surgery was similar for the Vigamox and Zymar regimens. The contact lens was kept in place until the epithelium had completely regenerated and the epithelium had smoothed over. The range of time to healing was four to seven days for the Vigamox regimen and four to eight days for the Zymar regimen.

Time to contact lens removal was 5.50 ± 0.38 days for Vigamox and 5.65 ± 0.44 days for Zymar. All patients had excellent improvement in their vision following surgery, and there were no postoperative complications. (Figure 1)

We concluded that after LASEK surgery, a regimen containing Vigamox produced an equivalent rate of corneal re-epithelialization to a regimen containing Zymar.

Figure 1



[1] Trattler W. Fourth-Generation Fluoroquinolones' Effects on Epithelial Healing Following LASEK. Paper presented at Refractive Surgery Subsection of the Florida Society of Ophthalmology Annual Meeting; August 2004; Orlando, FL.

William Trattler, M.D., is from the Center for Excellence in Eye Care in Miami.

This supplement was produced by EYEWORLD under an educational grant from Alcon Laboratories Inc. The views expressed herein do not necessarily represent the views of Alcon, ASCRS, or the publisher and editorial board of EYEWORLD and in no way imply endorsement by EyeWorld or ASCRS.

Copyright 2004 ASCRS Ophthalmic Corporation. All rights reserved.
VIGAMOX™ (moxifloxacin HCl ophthalmic solution) 0.5% as base and TOBRADEX® (tobramycin and dexamethasone ophthalmic suspension) Sterile are trademarks of Alcon Laboratories, Inc. ZYMAR and Alphagan P are trademarks of Allergan, Inc.