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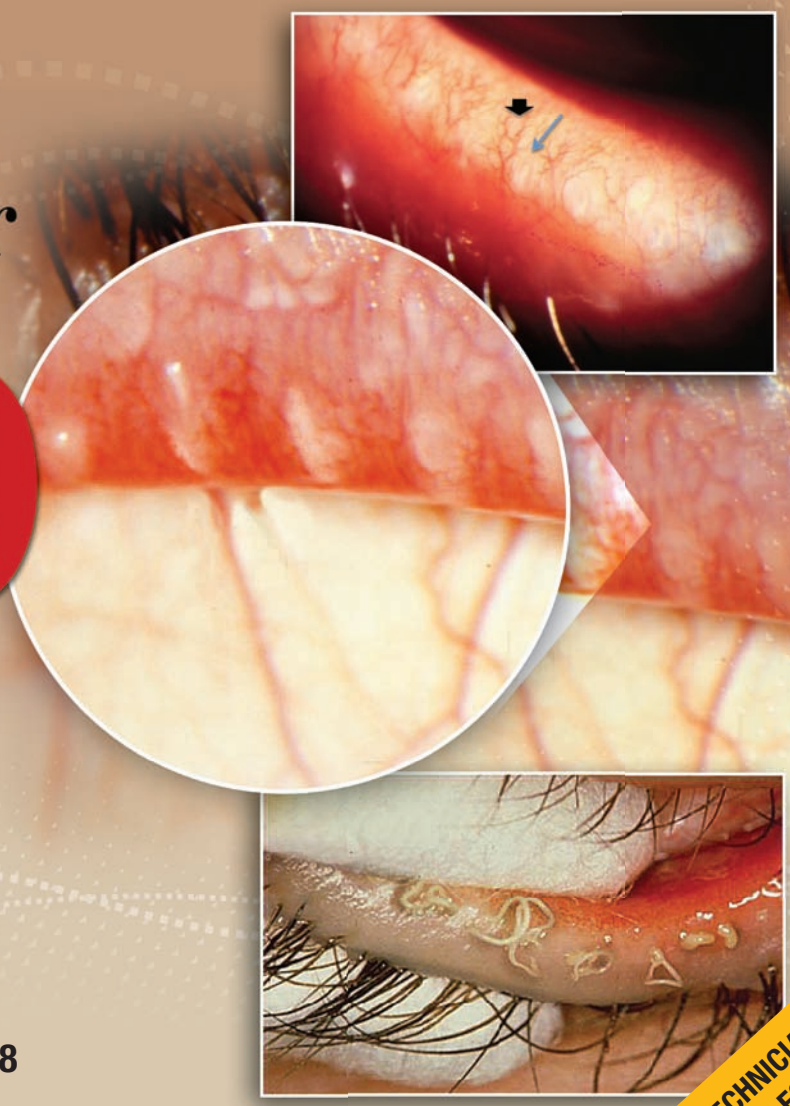

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REVIEW NEWS
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Regeneron's Eylea Approved for Macular Edema Following CRVO

In September, the Food and Drug Administration approved Regeneron Pharmaceuticals' Eylea (aflibercept) injection for the treatment of macular edema following central retinal vein occlusion. The recommended dose for Eylea is 2 mg every four weeks.

The approval of Eylea for macular edema following CRVO was based on data from the Phase III COPERNICUS and GALILEO studies. In both studies, the primary efficacy end point was the proportion of patients who gained at least 15 letters of best-corrected visual acuity at 24 weeks compared to baseline as measured by ETDRS. Results for the Eylea 2-mg monthly group were superior to those for the sham control group for the primary endpoint.

The safety and efficacy of Eylea in the treatment of macular edema following CRVO were assessed in two randomized, multicenter, double-masked, sham-controlled studies: COPERNICUS and GALILEO. A total of 358 patients were treated and evaluable for efficacy (217 with Eylea) in the two studies. In both, patients were randomly assigned in a 3:2 ratio to either 2 mg Eylea administered every four weeks, or sham injections (control group) administered every four weeks for a total of six injections. After six monthly injections, patients continued to receive Eylea treatment during weeks 24 to 52 only if they met pre-specified retreatment criteria (PRN), except for patients in the sham control group in the GALILEO study who continued to receive sham injections through week 52. Patients ranged in age from 22 to 89 years with a mean of 64 years.

In the COPERNICUS study, after six months, 56 percent of patients receiving Eylea 2 mg monthly gained at least 15 letters of BCVA from baseline, as measured by ETDRS, compared to 12 percent of patients receiving sham injections ($p<0.01$), the primary endpoint of the study. Patients receiving Eylea 2 mg monthly gained, on average, 17.3 letters of vision compared to a mean loss of 4.0 letters with sham control injections ($p<0.01$), a secondary endpoint.

In the GALILEO study, after six months, 60 percent of patients receiving EYLEA 2 mg monthly for the first six months, gained at least 15 letters of BCVA from baseline, compared to 22 percent of patients receiving sham injections ($p<0.01$) during this time, the primary endpoint of the study. Patients receiving Eylea 2 mg monthly gained, on average, 18 letters of vision compared to a mean gain of 3.3 letters with sham control injections ($p<0.01$), a secondary endpoint.

UK Group: 'Major Breakthrough' in Dry AMD

University of Kentucky researchers, led by Jayakrishna Ambati, MD, have made an exciting finding in the dry form of age-related macular degeneration. Geographic atrophy causes blindness in millions of individuals due to death of retinal pigment epithelial cells. The paper, "ERK1/2 Activation is a Therapeutic Target in Age-Related Macular Degeneration" appears in the Aug. 21 online issue of the *Proceedings of the National Academy of Sciences*.

Dr. Ambati, a professor of physiology, and professor and vice chair of ophthalmology and visual sciences at UK, is a leader in the field of macular degeneration research. Previous research from the Ambati laboratory published in the journal *Nature* showed that in human eyes with geographic atrophy there is a deficiency of the enzyme DICER1, leading to accumulation of toxic Alu RNA molecules in the retinal pigmented epithelium. Another paper published in the journal *Cell* showed that when these RNAs build up in the eye they trigger activation of an immune complex known as the NLRP3 inflammasome. In turn, this leads to the production of a molecule known as IL-18, which causes death of retinal pigmented epithelial cells and vision loss by activating a critical protein known as MyD88.

Importantly, Dr. Ambati and colleagues found evidence that activity of the inflammasome, IL-18, and MyD88 were all increased in human eyes with GA. They then showed that blocking any of these components could prevent retinal degeneration in multiple disease models. The researchers are

Expanded Labeling for B + L's Besivance

The Food and Drug Administration has granted additional labeling indications to Bausch + Lomb for its Besivance (besifloxacin ophthalmic suspension) 0.6% eye drop, including an indication to treat bacterial conjunctivitis infections caused by susceptible isolates of *Pseudomonas aeruginosa*, a rare but potentially virulent pathogen that can be associated with serious eye conditions, such as corneal ulcers and blindness. Three other significant ocular pathogens added to the indications granted for the Besivance eye drop include *Aerococcus viridians*, *Moraxella catarrhis* and *Staphylococcus warneri*.

Besivance suspension has been approved in the United States for the treatment of bacterial conjunctivitis since 2009 and is the first and only dual-halogenated chlorofluoroquinolone in topical ophthalmic use. It has demonstrated potent activity and high rates of eradication against problematic multi-drug resistant Gram-positive organisms, such as Methicillin-resistant *S. aureus* (MRSA)/Methicillin-resistant *S. epidermidis* (MRSE), and Gram-negative pathogens, such as *P. aeruginosa*, that can cause serious eye infections.

"Many eye-care physicians consider *Pseudomonas aeruginosa* as a more serious threat to ocular health than MRSA," said Terrence P. O'Brien, MD, professor of ophthalmolofy at Bascom Palmer Eye Institute of the University of Miami, Fla. "With the additional indication of *Pseudomonas aeruginosa* as well as the other important ocular pathogens covered by besifloxacin 0.6%, physicians now have a potent, broad-spectrum, branded prescription eye drop to rapidly treat bacterial conjunctivitis caused by the most common serious sight-threatening pathogens."

excited that blocking these pathways could herald a new potential therapy for GA, for which there is no approved treatment.

In the current paper, the authors show that Alu RNA, which increases following DICER1 deficit, activates a family of enzymes known as extracellular-signal-regulated kinases (ERK) 1/2. ERK 1/2, which are also known as classical mitogen-activated protein kinases (MAPKs), were found to be increased in the RPE of human eyes with GA and shown to be key mediators of RPE cell death. This work further defines the mechanisms of cell death in human GA and identifies a new therapeutic target for the dry form of AMD.

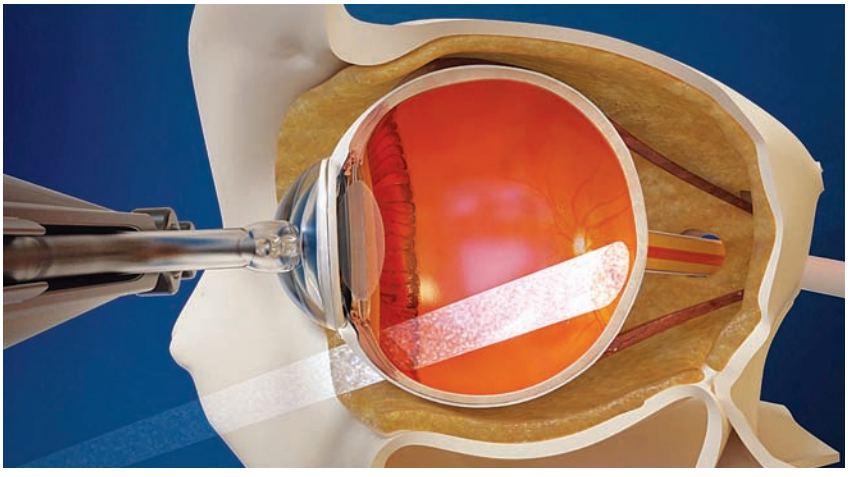
Oraya INTREPID Study Achieves Primary Endpoint

During the 12th EURETINA Congress in Milan, Italy, Oraya Therapeutics announced that its INTREPID trial of radiation therapy for wet age-related macular degeneration achieved its primary end point. The INTREPID study is the first sham-controlled, double-masked trial to evaluate the effectiveness and safety of a one-time radiation therapy in conjunction with as-needed anti-VEGF injections for the treatment of wet AMD. A total of 21 sites in five European countries participated in the trial with a total enrollment of 230 subjects.

Timothy L. Jackson, PhD, FRCOphth, King's College Hospital, London, lead investigator for the trial, presented the results on September 8. He reported that the trial demonstrated a statistically significant reduction in as-needed injections after one year. The actively treated patients required approximately 35 percent fewer injections than the sham group with similar or in some cases, better visual acuity outcomes. No radiation-related adverse events were experienced at the one-year end point, including 60 subjects already at two-year follow-up. In addition, a defined population sub-group comprising roughly half of the study participants experienced even lower injection rates, while exhibiting meaningful vision benefit compared to sham.

Dr. Jackson stated that, "the year-one results of the INTREPID trial are very encouraging for people with wet AMD—the prospect of fewer eye injections will appeal to all those receiving anti-VEGF therapy, and for certain subsets there is the added advantage of an improved visual outcome. Whilst it will be important to monitor safety over a longer period, the results so far suggest a favorable safety profile."

"We are very pleased that the re-



An illustration of Oraya Therapeutic's iRay radiotherapy system, which is being tested in conjunction with anti-VEGF injections to treat wet age-related macular degeneration.

sults of the INTREPID trial have validated the benefits of the Oraya Therapy for patients, clinicians and health care providers," stated Jim Taylor, CEO of Oraya Therapeutics. "It is rare to have a new therapy that demonstrates improved patient outcomes while simultaneously offering the potential to significantly reduce treatment burden and costs. To have these benefits validated in a rigorous clinical trial is very rewarding, and we are exceptionally grateful to the patients and clinicians who participated in this important study. In the coming weeks, we will be introducing the therapy on a commercial basis in several European markets, and we look forward to the opportunity to make a significant positive impact on the treatment of wet AMD in the months and years ahead."

24-Hour IOP Monitoring Shows Some Promise

Continuous 24-hour intraocular pressure monitoring with a contact lens sensor demonstrated good safety and tolerability in a recent *Archives of Ophthalmology* study published online on Aug. 13, 2012. Forty patients with or suspected of having glaucoma participated in two 24-hour IOP monitoring sessions at a one-week interval. Patients pursued daily activities, and sleep behavior was not controlled. Incidence of adverse events and tolerability (visual analog scale score) were assessed. Reproducibility of signal patterns was assessed using Pearson correlations.

The recorded IOP patterns showed fair to good reproducibility, suggesting that data from continuous 24-hour IOP monitoring may be useful in the management of patients with glaucoma, the authors conclude. REVIEW

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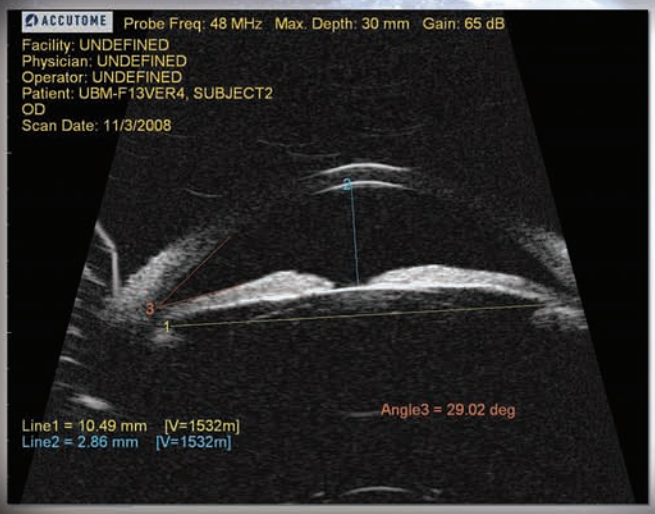

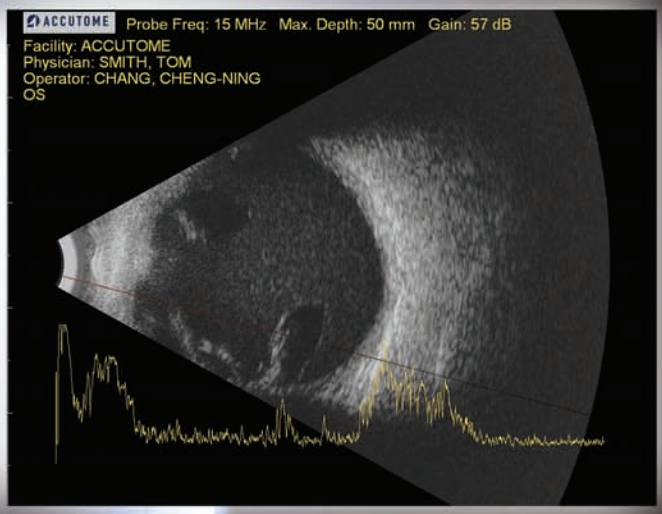

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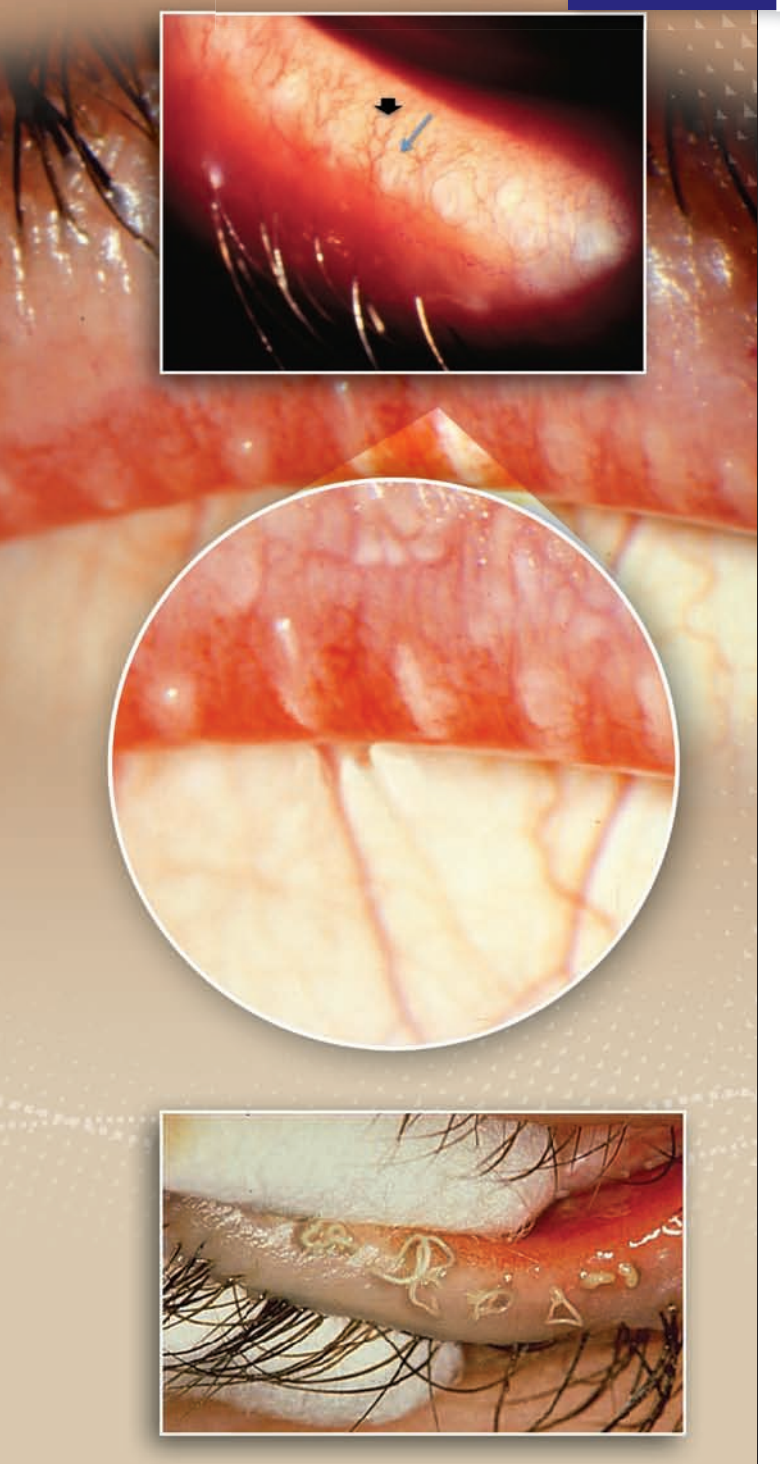

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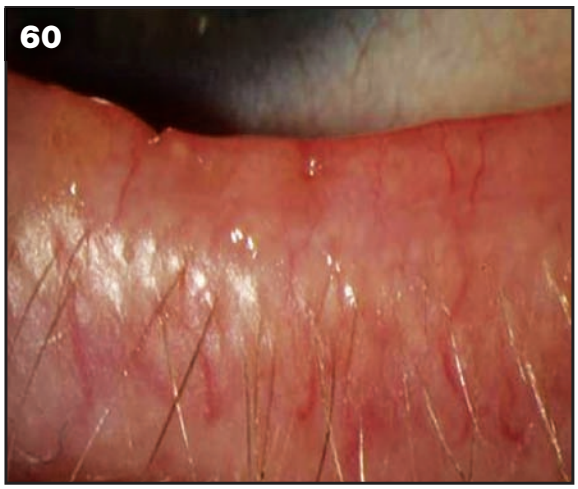

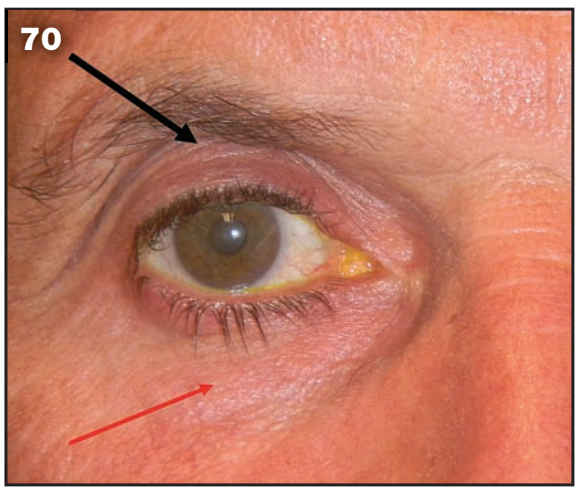

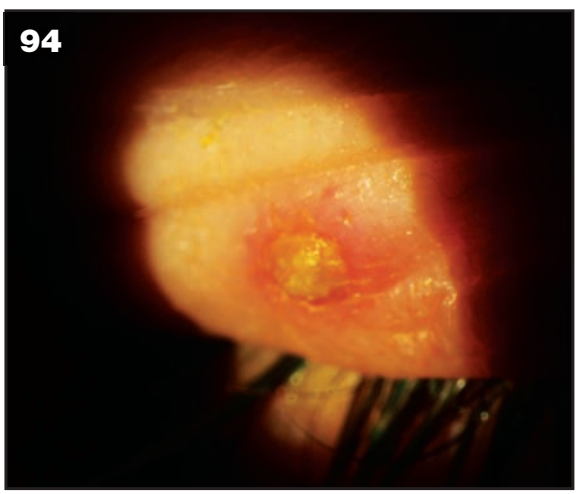

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ADVERSE REACTIONS: Bacitracin has such a low incidence of allergenicity that for all practical purposes side reactions are practically non-existent. However, if such reaction should occur, therapy should be discontinued.

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 carefully removed and the ointment then spread 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.

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REVIEW Editor's Page

Christopher Glenn, Editor in Chief

The Carrot, the Stick & the Dismal Science

It's been a bleak month for those who follow health-care economics. (And yes, they're probably all bleak if that's what you do for a living.) A widely reported study by the Institute of Medicine found that waste in the system accounted for $750 billion in unnecessary services, excessive administrative costs, fraud and other problems, some 30 percent of the total expenditure. Even to someone who went into editing because they said there's no math involved, 30 percent waste is a pretty astonishing figure.

A couple of less-publicized news reports highlight different approaches to wasted health-care dollars. One sees opportunity, one sees something less benign.

Reuters reports, "In one sign of the growing importance of healthcare to the economy, S&P Dow Jones Indices added health insurer UnitedHealthcare to the Dow Jones industrial average, replacing Kraft Foods." The article adds, " ... the race to cut costs is creating profits in parts of the industry."

A slightly different take on waste came in a report from the Washington-based Center for Public Integrity. Over the last decade, a study by the group suggests that cases of potential "upcoding" by thousands of physicians and hospitals, in part aided by the use of EMRs, "have added $11 billion or more to their fees ... signaling a possible rise in medical billing abuse."

Among the investigation's key findings:

"Doctors steadily billed Medicare for longer and more complex office visits between 2001 and the end of the decade even though there's little hard evidence they spent more time with patients or that their patients were sicker and required more complicated, and time-consuming, care. The higher codes for routine office visits alone cost taxpayers an estimated $6.6 billion over the decade.

"More than 7,500 physicians billed the two top paying codes for three out of four office visits in 2008, a sharp rise from the numbers of doctors who did so at the start of the decade.

"The most lucrative codes are billed two to three times more often in some cities than in others, costly variations government officials said they could not explain or justify. In some instances, higher billing rates appear to be associated with the burgeoning use of electronic medical records and billing software."

Medical societies dispute the suggestion of increased fraud, and the study cites CMS officials who say that most doctors and hospitals are "honest and try to bill Medicare correctly ... ." Still the report implies that after years of failing to correctly code for all that they do, some physicians are simply recouping money that they previously failed to collect. "I'm not sure it's malicious. It's a fact a life," says one industry consultant.

On one hand, the carrot of profit-driven cost-cutters. On the other, the stick of fraud-seeking government regulators. No wonder they call it dismal.


A Catalys for Change In Cataract Surgery

Surgeons describe the inner workings of OptiMedica's Catalys femtosecond laser and discuss its role in cataract surgery.

Walter Bethke, Managing Editor

In early September, the OptiMedica Catalys Precision Laser System was approved to perform corneal incisions by the Food and Drug Administration, meaning U.S. surgeons can now get reimbursed for using it, since astigmatic keratotomy is currently the only aspect of femtosecond cataract surgery surgeons can charge separately for. In this article, surgeons well-versed in the use of the Catalys give you an idea of what to expect if you decide to start using it.

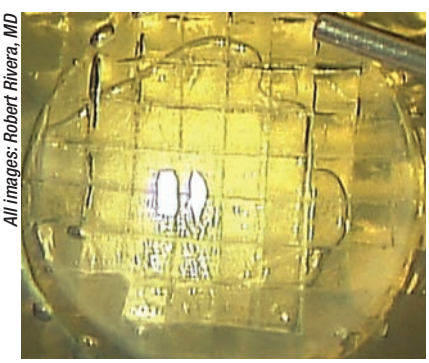
The Docking Step

Surgeons who perform femtosecond surgery, either for cornea or cataract applications, say that the initial docking of the device with the eye is critical. Here are surgeons' impressions of the Catalys' approach to this key step.

"The laser's Liquid Patient Interface functions as a little immersion system," explains William Culbertson, MD, head of OptiMedica's medical advisory board. (Dr. Culbertson has a financial interest in the device.) "The part that couples to the eye is a little reservoir into which we pour balanced salt solution. We then bring down the focusing cone that's connected to the laser and couple it with the patient interface/water bath. In this way, the laser doesn't distort the cornea by pressing it up against a cone or plate. This lets the laser focus its treatment more accurately. What's more, the patient interface operates under low vacuum, only raising the patient's intraocular pressure by 8 mmHg. It also allows us to treat out to 11 mm diameter, such as when creating relaxing incisions."

The laser also has a force-sensing function that will try to compensate for any forces exerted against the patient interface, such as patient movement from breathing.

All images: Robert Rivera, MD



Dividing the nucleus into dozens of square column-like segments can be an efficient way to aid nuclear removal, say surgeons.

Placing the Treatment

To place the femtosecond treatment, the laser uses a high-definition 3D optical coherence tomographer and a feature called the Integral Guidance System.

"The 3D optical coherence tomographer gives a precise image of such features as the anterior and posterior corneal surfaces, the iris plane and the pupil," says Robert Rivera, MD, a Catalys user from Salt Lake City. "You get an axial and sagittal view of the structures so, in the case of lens tilt, the laser automatically adjusts for the tilt and tilts the anterior capsulotomy treatment. It also automatically creates a 500-µm safe zone to keep the treatment away from the posterior capsule." Once the laser finds the center of the pupil, the center of the limbus and the recess of the capsular bag, the surgeon can use the system's Integral Guidance and touch screen to make fine adjustments to where the treatment will be laid down.

Surgeons say the liquid interface aids in the capsulotomy creation.

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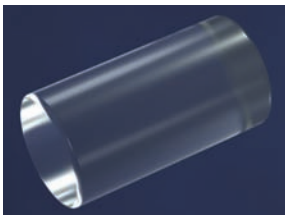

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Bridgewater, NJ 08807 LAC102-0512ROPH

A free-floating anterior capsulotomy, rather than one that requires manual tearing, is the ideal endpoint for laser capsulotomy, say surgeons.

"When we had a fixed-curved applanation plate, we were getting too many incomplete capsulotomies, with the attendant risks of radial tears, and which were difficult to advance due to the problem of folds and distortion created by coupling a fixed cone to the cornea," explains Dr. Culbertson. "You'd get these uncut places on the anterior capsule that corresponded exactly to the location of the corneal fold on applanation. This is why we switched to the immersion interface."

Bochum, Germany, cataract surgeon Burkhard Dick, who consults for OptiMedica, says the capsulotomy creation has been consistent, and in many cases the laser completely dissects the capsular circle without the need for manual tearing afterward. "With around 960 cases with the Catalys, the incidence of free [floating] capsules is more than 99 percent," he avers. "Where it may not be free is a mature cataract, which is a little different."

For nuclear softening, the laser allows the surgeon to choose a pattern, such as two intersecting lines creating four quadrants or three lines creating six segments. Then, within those segments, the laser will create smaller segments. "In the treatment that I use, it creates a series of square columns throughout the lens similar in shape to French fries," says Dr. Rivera. "I then use a Chang chopper to feed the segments into the I/A port. I'd estimate that, on average, I use two-thirds less phaco energy in removing the nucleus than I did before."

Dr. Culbertson says that the device has been able to treat pediatric cases under general anesthesia, small pupil cases with Malyugin rings, lenses with very limited capsular support, traumatic cataracts; and opaque, mature lenses. The last category requires more phaco energy than the average case.

AK Incisions

In addition to allowing surgeons to charge extra for the use of the Catalys in conjunction with cataract surgery, the FDA approval of the creation of corneal incisions also means that users can create more consistent incisions, say surgeons.

"With a standard manual astigmatic keratotomy incision, there's some inconsistency as the blade 'porpoises' up and down in the cornea as you drag it

across, so you're not exactly sure how deep you're cutting, how long it is or what bevel you've made it at," says Dr. Culbertson. "But these variables are precisely made with the laser. I presented a paper at the 2012 meeting of the European Society of Cataract and Refractive Surgeons that found when we made Catalys incisions in plastic, animal models and in clinical cases, the accuracy of the incision length was within 1 degree of the intended arc, the optical zone was within 0.1 mm of intended and the depth was within 20 µm." Dr. Culbertson adds that after the AK incisions are made, there's very little effect from them until you open them with a blunt instrument. "So you can use an intraoperative aberrometer or topographer to monitor the incisions as you slowly open them on the table until you get the exact effect you want," he says. The laser is also capable of creating intrastromal incisions. Though intrastromal AK can only treat up to about 1.5 D of cylinder, says Dr. Culbertson, they cause less pain than full-thickness wounds and there's no risk of infection.

Experienced users say you'll have to adjust your current AK nomogram to compensate for the laser's increased power. "You get more effect from a laser incision due to the uniformity of the depth created by the laser," Dr. Culbertson explains. "We adjust our AK nomograms down by 30 percent. So, if we have 1 D of astigmatism to correct, we subtract 30 percent, or 0.3 D, and treat for 0.7 D."

Dr. Culbertson says a reliable AK nomogram will come in time. "We haven't done enough incisions to develop a nomogram for it yet," he says. "We're working off of our existing nomograms right now. Factors such as age and the orientation of the astigmatism will have to be derived empirically by simply doing a lot of cases." REVIEW

Dr. Rivera has no financial interest in the Catalys.

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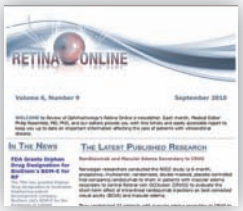

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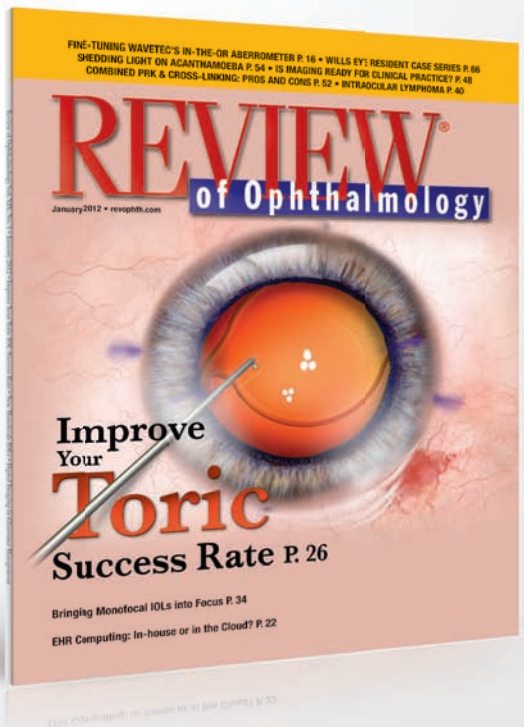

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Considerations, Options For Retirement Funds

A look at some of the basic principles of retirement saving, and the choices related to tax decisions on your nest egg.

Jon C. Ylinen, Madison, Wis.

By far, the most common question from physicians at my talks and meetings is: "What should I be saving to retire comfortably at close to my current lifestyle?" In this installment of Financial Focus, I will highlight some general principles on retirement saving, and then look at how to allot your savings in various pre-tax and post-tax options.

Variables and Budget Analysis

There is no one-size-fits-all answer to this question. A retirement analysis can be done by using an equation that takes into account the following variables: your (and your spouse's) age; your monthly retirement savings; dollars needed (present value) for your current lifestyle; annual inflation (currently 3.43 percent per year, according to inflationdata.com); your current retirement portfolio's value; and the potential rate of return.

What you are looking for is whether the potential expected return on your current retirement savings, combined with your monthly additions to retirement accounts, equal what you need to keep your current lifestyle with inflation up until (and beyond) your life expectancy.

A key error to avoid is underestimating the power of inflation. For example, to replace the purchasing power of $10,000 a month in today's dollars using the current inflation rate, you would need $13,546 a month in 10 years; $18,979 a month in 20 years; and $26,592 a month in 30 years.

Take a good look at your budget and begin to identify: the expenses that will remain in your budget as you make the transition from your career to retirement (property taxes, insurance, groceries, utilities, etc.); those that will leave the budget (mortgage, student loans, kids, saving for retirement, etc.); and the expenses that will be added (increased travel, more golf, classes). This will yield a good starting figure to multiply by an estimated inflation number to serve as a goal.

As with any equation, if you tweak just one variable you may have quite a different outcome. Also, since many variables are not guaranteed, actual results will generally differ. This may seem complicated, but most financial advisors should have a tool that they use to help narrow this down.

If you find that you are behind on your current retirement effort, you may need to do one or several of the following: increase your monthly savings; push back your retirement age; lower your lifestyle expectations for retirement; or seek a higher rate of return on your invested assets. However, note that investments with a higher rate of return potential will generally be accompanied by higher risk.

Due to the fluctuation of this equation, I suggest that this should be calculated at least once per year to make sure you are on track with your personal retirement goal.

Pre-Tax vs. Post-Tax Savings

There are two major buckets for retirees to withdraw income from at retirement: pre-tax and post-tax buckets. To give you the most options and choices at retirement, you should consider stashing your nest egg in both buckets. A rough guideline, which can vary immensely from family to family depending on their specific savings patterns and goals, is to put roughly two-thirds of your money into a pre-tax account and one-third of your intended retire-

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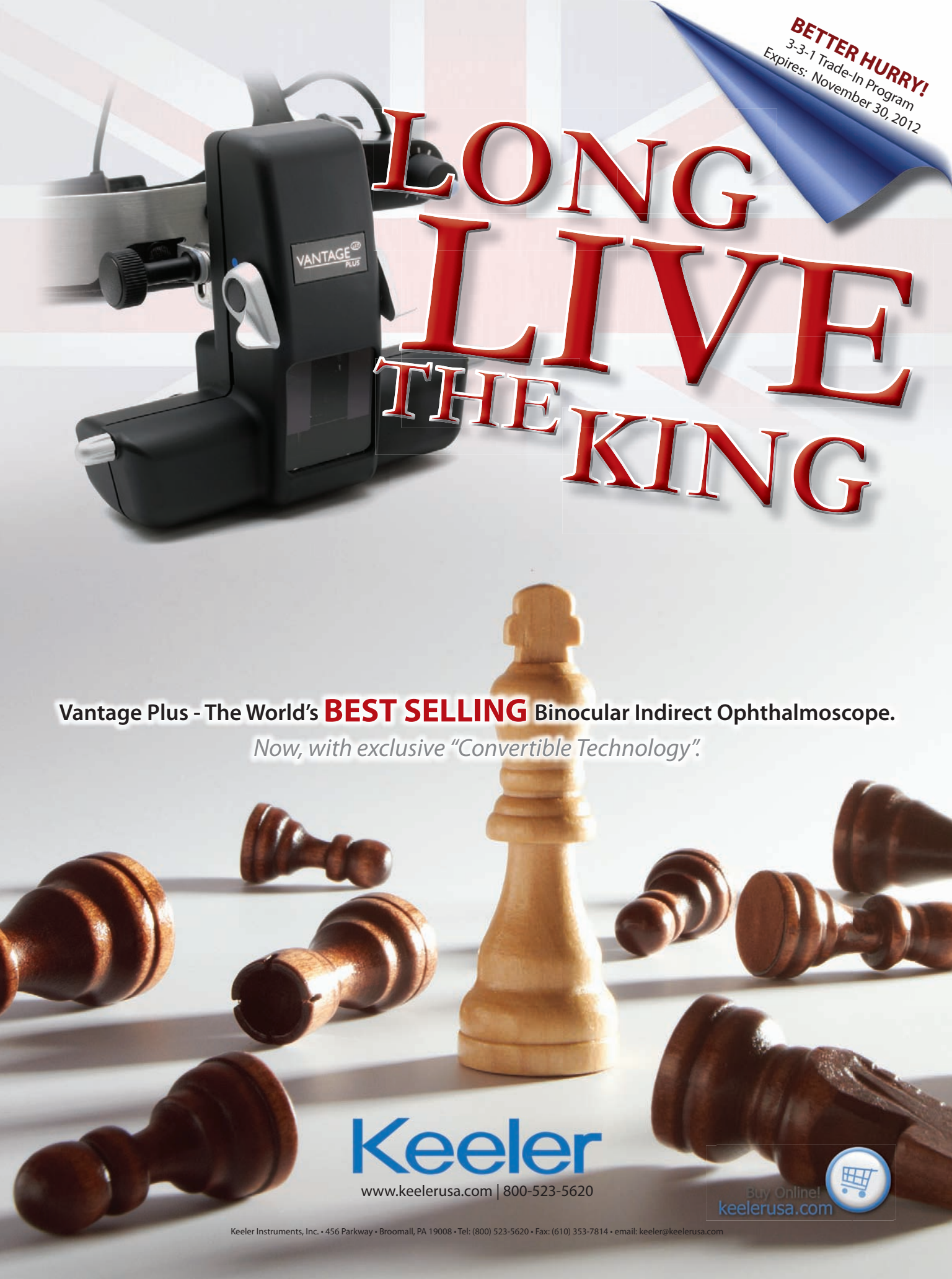
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ment money into a post-tax vehicle.

Pre-tax accounts (401k, 403b, 457 plans, traditional IRAs, etc.) are advantageous because you get a tax break in the year that you contribute to these accounts. (You do not have to pay tax on the income you put into these accounts in the year that you contribute, and the growth is completely tax-deferred, meaning you are not taxed on any growth as it accrues in the accounts. The disadvantage is that you are taxed at 100 percent on all withdrawals past age 59 and a half as ordinary income.

Post-Tax accounts (Roth IRAs, Roth 403bs, Roth 401ks) are advantageous because you are not taxed on a single penny that comes out of these accounts when you withdraw, as long as the withdrawal is qualified. For a withdrawal to be qualified, funds must be in the Roth IRA for five years and the account owner must be 59 and a half. Roth IRAs also grow on a tax-deferred basis. The disadvantage is that you do not get a tax break in the year that you contribute.

The big-picture thinking on a retirement strategy and the tax issues that surround them is that you want to defer taxes when you are at a higher bracket and pay the taxes at a lower bracket. Of course, we don't know where tax brackets will be in five, 10 and 20-plus years from now, and we cannot predict exactly how much we will have to pay Uncle Sam out of our nest egg.

Because of the progressive nature of our tax system, we want to pull money from pre-tax accounts in the lower brackets (currently the 10 percent and 15 percent brackets) and then avoid paying a quarter (or more) in taxes on every dollar we pull out by taking out the money needed in retirement above the lower tax bracket thresholds from our Roth vehicles.

The complicated part of this strategy is that there are income phase-out ranges and limits that exclude many physicians from putting money directly into a Roth IRA. (You cannot contribute to these accounts at all when your adjusted gross income is more than $183,000 if you are married, filing jointly, and more than $125,000 if you are single; and the contribution is limited to $5,000 per person annually). Most physicians are over these limits.

But on January 1, 2010 income limits on who could convert money into a Roth IRA were lifted. So, almost every physician can do a non-deductible IRA, and then convert it to a Roth IRA the next day. You should plan to convert it the next day because that minimizes the growth on that account that you would be liable to pay taxes on, as the conversion creates a taxable event on any earnings. This can be a bit of a paperwork nightmare for some, but there are many financial advisors who

can help navigate these steps efficiently on your behalf, and this may be well worth the hassle when you have tax-favored accounts.

Also, more and more employers (currently about a third) are offering Roth versions of their 401k and 403b options, so you can put post-tax contributions away under the current limits of $17,000 per year as well.

For a Roth IRA, earnings withdrawn prior to reaching age 59 and a half and/or not meeting the five-year holding period may be subject to a 10-percent penalty in addition to income tax. After-tax contribution amounts are generally returned income-tax free; however, for Roth conversions, if converted amounts are not held for the five-year period, distributions may be subject to a 10-percent penalty.

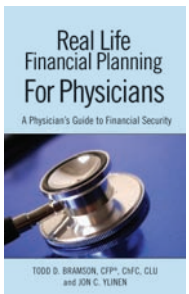
Investors' anticipated tax bracket in retirement will determine whether or not a Roth IRA versus a traditional one will provide more money in retirement. Generally, investors who are in a higher tax bracket at retirement relative to their current tax bracket while making contributions to a Roth IRA benefit more than an investor who is in a lower tax bracket at retirement.

If you do not have access to a Roth account through an employer and you want to supplement your retirement assets, another option to consider is the cash value of a life insurance policy. These types of vehicles are very complicated and should be carefully contemplated. Talk with your advisor. And, keep in mind that the primary reason to purchase a life insurance product is the death benefit, not for tax benefits. Life insurance products contain fees, such as mortality and expense charges, and may contain restrictions, such as surrender charges. Policy loans and withdrawals may create an adverse tax result in the event of a lapse or policy surrender, and will reduce both the cash value and death benefit. REVIEW

This should not be considered as tax or legal advice. Please consult a tax or legal professional for information regarding your specific situation.

Mr. Ylinen is a financial advisor with North Star Resource Group. He co-authored the book Real Life Financial Planning for Physicians. *He maintains a national comprehensive financial planning practice that caters almost exclusively to physicians.*

For information on this topic or any other financial matter, direct your inquiries to his website, askjonylinen.com.



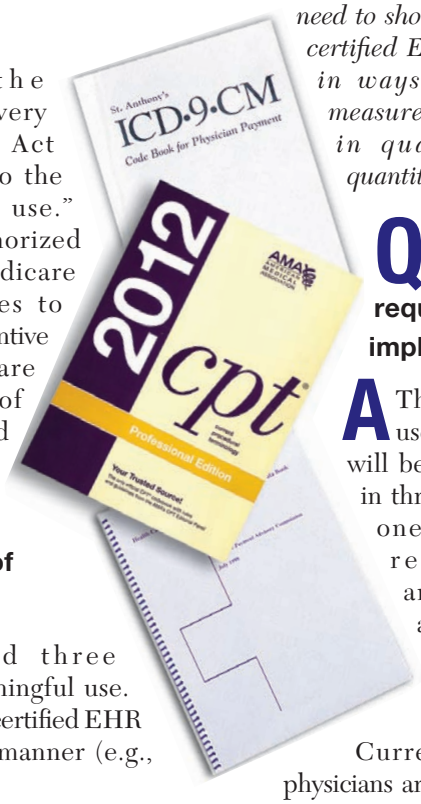
Donna McCune, CCS-P, COE

The Fundamentals of Meaningful Use

A look at the Medicare requirements and incentives for becoming a "meaningful user" of electronic health records.

Q Where did the phrase "meaningful use" first appear?

A In 2009, the American Recovery and Reinvestment Act first introduced us to the phrase "meaningful use." This legislation authorized the Centers for Medicare & Medicaid Services to provide a financial incentive to physicians who are "meaningful users" of electronic health record technology.



Q What are the fundamentals of meaningful use?

A ARRA defined three elements of meaningful use. They required use of a certified EHR

1. in a meaningful manner (e.g., e-prescribing);
2. for electronic exchange of health information with the objective of improving the quality of health care; and
3. to submit clinical quality and other measures.

The CMS final rule on the topic published July 13, 2010, states: "*meaningful use means providers need to show they're using certified EHR technology in ways that can be measured significantly in quality and in quantity.*"

Q How will these requirements be implemented?

A The meaningful use requirements will be implemented in three stages, each one adding new requirements and increasing accountability for some established requirements. Currently, eligible physicians are being held to Stage 1 requirements. Stage 2 requirements have been proposed but are not finalized.

Q Is there a financial incentive to be a meaningful user of EHR?

A Yes. The Health Information Technology bonus program began in 2011. Separate programs exist for Medicare and Medicaid, and the programs will continue through 2016. However, to qualify for an incentive payment, physician participation must begin no later than 2014.

Q How does a physician qualify for the Medicare HIT bonus?

A Physicians qualify for the incentive bonus payment by demonstrating that they meet the meaningful use requirements. The Medicare incentive program requires successful demonstration of meaningful use each consecutive year of participation.

Q Are bonus payments made to individual physicians?

A Yes and no. Bonus payments are made for each eligible professional; this means that each eligible provider in a group may qualify for the bonus. However, the bonus payments are made to the holder of the tax ID number of the group.

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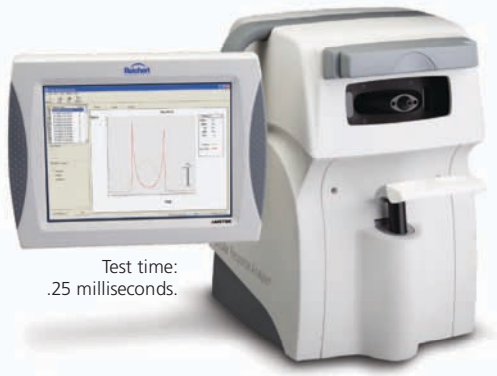

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Q What is the maximum incentive payment for the bonus programs?

A The maximum incentive payment in the Medicare program is $44,000 and $63,750 for the Medicaid incentive program. Physicians may not participate in both the Medicare and Medicaid programs concurrently, and must choose one to participate in. However, physicians may make a one-time switch between programs.

Q Will I be penalized if I do not adopt EHR and meet meaningful use requirements?

A Yes. To avoid being penalized by CMS, you must attest to meaningful use by October 3, 2014. The penalties (reduction to your Medicare fee schedule) will be a reduction of 1 percent in 2015, 2 percent in 2016, 3 percent in 2017 and up to 5 percent beyond 2017.

Q What steps should I take to achieve meaningful use?

A Your first step is to partner with a certified EHR software vendor. The vendor of a certified system provides assurance that the EHR technology is capable of meeting meaningful use requirements. At the present time, there are approximately 1,300 Certified Health IT Products; however the number of certified programs changes frequently. For a current list visit: http://oncchpl.force.com/ehrcert/CHPLHome.

Q What are the general requirements for Stage 1 meaningful use?

A For Stage 1, eligible professionals (such as ophthalmologists) must report all 15 of the Core Set Objectives and Measures in sufficient number to meet or exceed specific threshold requirements. In addition, eligible professionals must report five of 10 Menu Set Objectives and Measures. At least one of the five measures must address public health. Lastly, you are required to report six Clinical Quality Measures.

Further details on these measures can be found at: http://www.cms.gov/Regulations-and-Guidance/Legislation/EHRIncentivePrograms.

Q If I have EHR and want to participate in the Medicare bonus program, how do I start the process to report meaningful use?

A In order to receive your incentive bonus, eligible professionals will need to register in the Medicare

EHR Incentive Program. You may register at any time. Registration does not hold you accountable to attestation, but you cannot attest to meaningful use if you are not registered. You can learn more about the registration process at the following CMS link: http://www.cms.gov/Regulations-and-Guidance/Legislation/EHRIncentivePrograms/RegistrationandAttestation.html.

Q If I have met the requirements for meaningful use, Stage 1, how do I inform CMS?

A After you have satisfied the requirements for Stage 1 meaningful use, you can attest to it on the CMS website. The attestation process requires providers to enter numerators and denominators for the various measure ratios and CQMs, as well as applicable exclusions, and to legally attest that meaningful use was successfully achieved. Once your data is submitted, you will see a summary of the data and whether or not it was successful.

Q Am I required to have met meaningful use for the entire year?

A No. In the first reporting period, for Stage 1 criteria, eligible professionals must attest to 90 continuous days of meaningful use. Subsequent reporting periods require a full year's participation. If you are not successful with your first attempt at attestation, you can select a different 90-day reporting period and try again.

Q When can we expect to be held accountable for Stage 2 and Stage 3 requirements?

A The proposed Stage 2 requirements were finalized on August 23, 2012. CMS pushed back the start date for Stage 2 compliance to January 1, 2014. There is only sketchy information about Stage 3 at this time. Physicians will be held to the requirements for each stage for two successive years.

Q How much bonus money has been paid to physicians for the Medicare EHR incentive program?

A According to CMS, as of May 2012, $994,883,305 has been paid to a total of 58,530 Medicare eligible professionals under the EHR Incentive Program. REVIEW

Ms. McCune is vice president of the Corcoran Consulting Group. Contact her at DMcCune@corcoranccg.com.

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REFERENCES

1. BROMDAY [package insert]. Irvine, CA: ISTA Pharmaceuticals, Inc. 2010. **2.** Catizone CA, ed. *Survey of Pharmacy Law 2011*. Mt. Prospect, IL: National Association of Boards of Pharmacy; 2010.

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*Inclusion of BMN required only for certain states, as listed in the National Association of Boards of Pharmacy's *Survey of Pharmacy Law*.[2]

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Bromday™ (bromfenac ophthalmic solution) 0.09%

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Bromday (bromfenac ophthalmic solution) 0.09% safely and effectively. See full prescribing information for Bromday.

Bromday (bromfenac ophthalmic solution) 0.09%
Initial U.S. Approval: 1997

----------INDICATIONS AND USAGE----------

Bromday is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract extraction (1).

----------DOSAGE AND ADMINISTRATION----------

Instill one drop into the affected eye(s) once daily beginning 1 day prior to surgery, continued on the day of surgery and through the first 14 days post-surgery (2.1).

---------DOSAGE FORMS AND STRENGTHS---------

Topical ophthalmic solution: bromfenac 0.09% (3)

----------WARNINGS AND PRECAUTIONS----------

· Sulfite Allergic Reactions (5.1)
· Slow or Delayed Healing (5.2)
· Potential for cross-sensitivity (5.3)
· Increase bleeding of ocular tissues (5.4)
· Corneal effects including keratitis (5.5)
· Contact Lens Wear (5.6)

----------ADVERSE REACTIONS----------

The most commonly reported adverse reactions in 2-7% of patients were abnormal sensation in eye, conjunctival hyperemia and eye irritation (including burning/stinging) (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact ISTA Pharmaceuticals, Inc. at 1-877-788-2020, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION
Revised: 8/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

Bromday (bromfenac ophthalmic solution) 0.09% is indicated for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery.

2. DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

For the treatment of postoperative inflammation in patients who have undergone cataract extraction, one drop of Bromday ophthalmic solution should be applied to the affected eye(s) once daily beginning 1 day prior to cataract surgery, continued on the day of surgery, and through the first 14 days of the postoperative period.

2.2 Use with Other Topical Ophthalmic Medications

Bromday ophthalmic solution may be administered in conjunction with other topical ophthalmic medications such as alpha-agonists, beta-blockers, carbonic anhydrase inhibitors, cycloplegics, and mydriatics. Drops should be administered at least 5 minutes apart.

3. DOSAGE FORMS AND STRENGTHS

Topical ophthalmic solution: bromfenac 0.09%.

4. CONTRAINDICATIONS

None.

5. WARNINGS AND PRECAUTIONS

5.1 Sulfite Allergic Reactions

Contains sodium sulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

5.2 Slow or Delayed Healing

All topical nonsteroidal anti-inflammatory drugs (NSAIDs) may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

5.3 Potential for Cross-Sensitivity

There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

5.4 Increased Bleeding Time

With some NSAIDs, there exists the potential for increased bleeding time due to interference with platelet aggregation. There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

It is recommended that Bromday ophthalmic solution be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

5.5 Keratitis and Corneal Reactions

Use of topical NSAIDs may result in keratitis.

In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs and should be closely monitored for corneal health.

Post-marketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Post-marketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days post surgery may increase patient risk for the occurrence and severity of corneal adverse events.

5.6 Contact Lens Wear

Bromday should not be administered while wearing contact lenses

6. ADVERSE REACTIONS

6.1 Clinical Trial Experience

The most commonly reported adverse experiences reported following use of bromfenac after cataract surgery include: abnormal sensation in eye, conjunctival hyperemia, eye irritation (including burning/stinging), eye pain, eye pruritus, eye redness, headache, and iritis. These events were reported in 2-7% of patients.

6.2 Post-Marketing Experience

The following events have been identified during post-marketing use of bromfenac ophthalmic solution 0.09% in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to topical bromfenac ophthalmic solution 0.09% or a combination of these factors, include corneal erosion, corneal perforation, corneal thinning, and epithelial breakdown. [see Warnings and Precautions (5)]

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C.

Reproduction studies performed in rats at oral doses up to 0.9 mg/kg/day (1300 times the recommended human ophthalmic dose [RHOD]) and in rabbits at oral doses up to 7.5 mg/kg/day (11,000 times RHOD) revealed no evidence of teratogenicity due to bromfenac. However, 0.9 mg/kg/day in rats caused embryo-fetal lethality, increased neonatal mortality, and reduced postnatal growth. Pregnant rabbits treated with 7.5 mg/kg/day caused increased post-implantation loss.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects:

Because of the known effects of prostaglandin biosynthesis-inhibiting drugs on the fetal cardiovascular system (closure of ductus arteriosus), the use of Bromday ophthalmic solution during late pregnancy should be avoided.

8.3 Nursing Mothers

Caution should be exercised when Bromday is administered to a nursing woman.

8.4 Pediatric Use

Safety and efficacy in pediatric patients below the age of 18 have not been established.

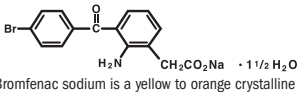
8.5 Geriatric Use

There is no evidence that the efficacy or safety profiles for Bromday differ in patients 65 years of age and older compared to younger adult patients.

11. DESCRIPTION

Bromday (bromfenac ophthalmic solution) 0.09% is a sterile, topical, nonsteroidal anti inflammatory drug (NSAID) for ophthalmic use. Each mL of Bromday contains 1.035 mg bromfenac sodium (equivalent to 0.9 mg bromfenac free acid).

Bromfenac sodium is designated chemically as sodium 2-amino-3-(4-bromobenzoyl) phenylacetate sesquihydrate, with an empirical formula of $C_{15}H_{11}BrNNaO_3 \cdot 1\frac{1}{2}H_2O$. The structural formula for bromfenac sodium is:



Bromfenac sodium is a yellow to orange crystalline powder. The molecular weight of bromfenac sodium is 383.17. Bromday ophthalmic solution is supplied as a sterile aqueous 0.09% solution, with a pH of 8.3. The osmolality of Bromday ophthalmic solution is approximately 300 mOsmol/kg.

Each mL of Bromday ophthalmic solution contains:

Active: bromfenac sodium hydrate 0.1035%
Preservative: benzalkonium chloride (0.05 mg/mL)
Inactives: boric acid, disodium edetate (0.2 mg/mL), polysorbate 80 (1.5 mg/mL), povidone (20 mg/mL), sodium borate, sodium sulfite anhydrous (2 mg/mL), sodium hydroxide to adjust pH and water for injection, USP.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Bromfenac is a nonsteroidal anti-inflammatory drug (NSAID) that has anti-inflammatory activity. The mechanism of its action is thought to be due to its ability to block prostaglandin synthesis by inhibiting cyclooxygenase 1 and 2.

Prostaglandins have been shown in many animal models to be mediators of certain kinds of intraocular inflammation. In studies performed in animal eyes, prostaglandins have been shown to produce disruption of the blood-aqueous humor barrier, vasodilation, increased vascular permeability, leukocytosis, and increased intraocular pressure.

12.3 Pharmacokinetics

The plasma concentration of bromfenac following ocular administration of 0.09% Bromday (bromfenac ophthalmic solution) in humans is unknown. Based on the maximum proposed dose of one drop to the eye (0.045 mg) and PK information from other routes of administration, the systemic concentration of bromfenac is estimated to be below the limit of quantification (50 ng/mL) at steady-state in humans.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility

Long-term carcinogenicity studies in rats and mice given oral doses of bromfenac up to 0.6 mg/kg/day (900 times the recommended human ophthalmic dose [RHOD] of 1.67 mcg/kg in 60 kg person on a mg/kg/basis, assuming 100% absorbed) and 5 mg/kg/day (7500 times RHOD), respectively revealed no significant increases in tumor incidence.

Bromfenac did not show mutagenic potential in various mutagenicity studies, including the reverse mutation, chromosomal aberration, and micronucleus tests.

Bromfenac did not impair fertility when administered orally to male and female rats at doses up to 0.9 mg/kg/day and 0.3 mg/kg/day, respectively (1300 and 450 times RHOD, respectively).

14. CLINICAL STUDIES

14.1 Ocular inflammation and pain following cataract surgery

Clinical efficacy was evaluated in three randomized, double-masked, placebo-controlled trials in which subjects requiring cataract surgery were assigned to Bromday or placebo. Patients were dosed with one drop per eye starting the day before surgery and continuing for 14 days. The primary endpoint was clearing of ocular inflammation by day 15. An additional efficacy endpoint was the number of patients who were pain free on day 1 after cataract surgery.

In 2 of the 3 studies, Bromday ophthalmic solution had statistically significant higher incidence of completely clearing inflammation (46-47% vs. 25-29%) and also had a statistically significant higher incidence of subjects that were pain free at day 1 post cataract surgery (83-89% vs. 51-71%).

16. HOW SUPPLIED/STORAGE AND HANDLING

Bromday (bromfenac ophthalmic solution) 0.09% is supplied in a white LDPE plastic squeeze bottle with a 15 mm LDPE white dropper-tip and 15 mm polypropylene gray cap as follows:

1.7 mL in 7.5 mL container (NDC 67425-999-17)
1.7mL in 7.5mL container as a Twin Pack (2 bottles) (NDC 67425-999-34)

STORAGE Store at 15° – 25°C (59° – 77°F).

17. PATIENT COUNSELING INFORMATION

17.1 Slowed or Delayed Healing

Patients should be advised of the possibility that slow or delayed healing may occur while using NSAIDs.

17.2 Sterility of Dropper Tip

Patients should be advised to not touch dropper tip to any surface, as this may contaminate the contents.

17.3 Concomitant Use of Contact Lenses

Contact lenses should not be worn during the use of this product.

17.4 Concomitant Topical Ocular Therapy

If more than one topical ophthalmic medication is being used, the medicines should be administered at least 5 minutes apart

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OTC Drops: Telling the Tears Apart

Michelle Stephenson, Contributing Editor

When choosing an over-the-counter artificial tear for your dry-eye patient, consider severity of disease and form of dry eye.

Artificial tears are a mainstay in the management of dry-eye symptoms, and there are numerous over-the-counter artificial tear products on the market today. Patients are often overwhelmed by the choices and do not understand the differences between them. When helping patients choose a tear, the most important considerations are the underlying cause of the dry eye and how often the patient is instilling drops.

"Self-selection of medications is not a good idea," says John Sheppard, MD, professor of ophthalmology, microbiology and molecular biology at Eastern Virginia Medical School. "Invariably, when patients bring in their drops, they will be the Wal-Mart or Safeway brand of tears, which are by far the most inferior tears on the market. Or, worse yet, they will use a topical vasoconstrictor like Visine, which induces vascular fragility, rebound vasodilation and dependence upon the vasoconstrictor to maintain a quiet, white-looking eye. Many times, patients will present using drops every 30 minutes or every hour, and this has a deleterious effect on lifestyle and well-being."

When choosing an artificial tear for patients, experts generally consider three questions: Based on disease severity and dosing, is the optimum artificial tear for this patient preserved or not preserved? Does the patient have more of an aqueous deficiency, mixed disease or an evaporative form of dry eye? How severe is it?

Preservatives

In recent years, there has been debate about whether the preservatives used in artificial tears are safe. While there are obvious advantages to the use of preservatives, several recent studies have highlighted the toxic effects of benzalkonium chloride. For example, a recent study conducted at the University of Illinois at Chicago found that topical application of BAK to the eye causes corneal neurotoxicity, inflammation and reduced aqueous tear production.[1]

In this study on mouse eyes that were topically treated with vehicle or BAK (0.01% or 0.1%), BAK-treated corneas had significantly reduced nerve fiber density and aqueous tear production, and increased inflammatory cell infiltration and fluorescein staining. Changes were most significant after treatment with 0.1% BAK. Sequential *in vivo* imaging of corneas showed both reversible neurotoxicity characterized by axonopathy and recovery and irreversible neurotoxicity characterized by nerve degeneration

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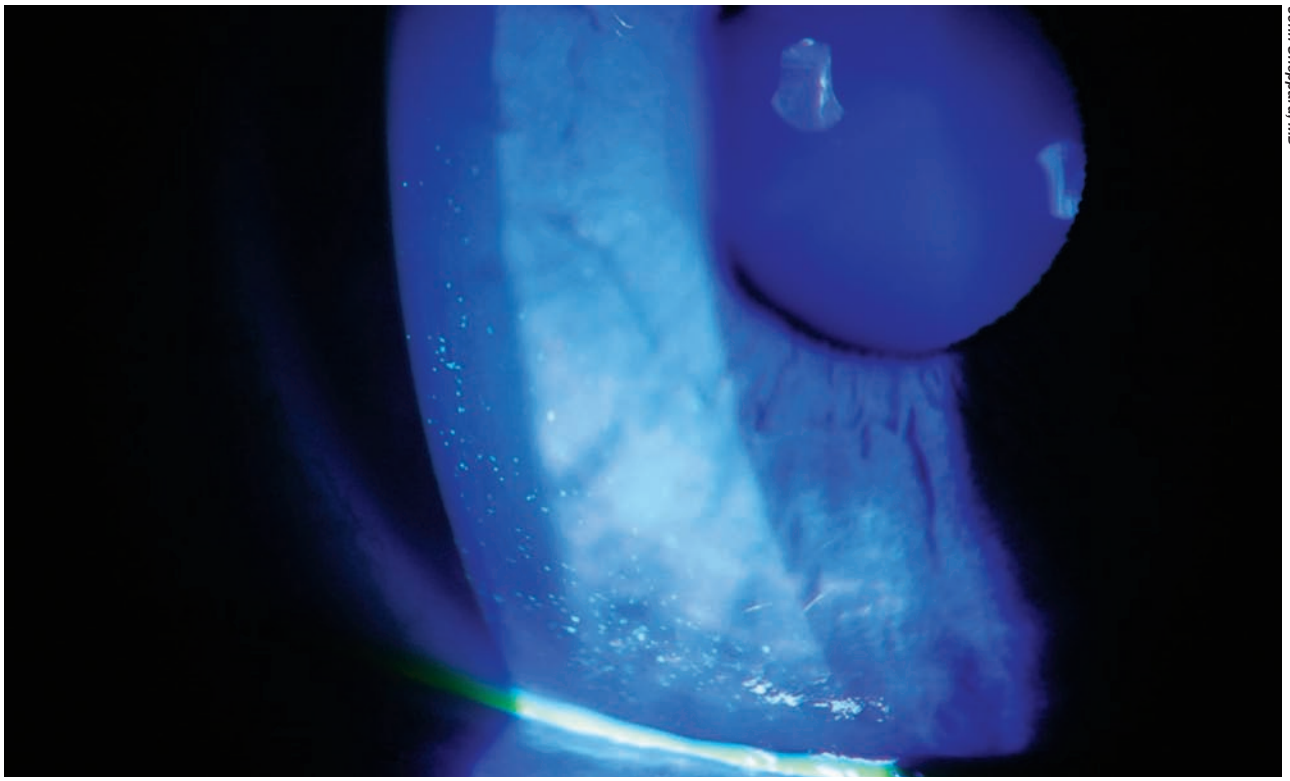

John Sheppard, MD

Figure 1. Inferior superficial punctate keratopathy in mild dry eye.

and regeneration. Both doses of BAK reduced nerve fiber length; however, the reduction was significantly more with the higher dose.

Fortunately, patients with severe dry eye or patients who are hypersensitive to preservatives now have excellent choices of a totally preservative-free drop, according to Dr. Sheppard. "There are good choices from a wide variety of manufacturers, and they come in a single-dose unit (SDU) with a twist-off cap," he says. "In theory, you take one dose, and you dispose of it. Careful handling of the SDU will allow multiple uses because many are re-cappable, and as long as you don't contaminate the tip by touching your fingers, eyelids or eyelashes, then it can be reused at least over the course of one day. However, I don't recommend that practice to unreliable patients," he says.

If a patient requires a preservative-free preparation, Dr. Sheppard notes that a few good choices are Refresh (Allergan), TheraTears, Soothe (Bausch + Lomb) and Systane (Alcon). "You can never go wrong with these. It's just a little more expensive and a little more time-consuming to apply the drops," he adds.

Another choice is formulations containing vanishing preservatives. The preservatives basically turn into water or a non-toxic chemical when they are exposed to air or mix with the tear film. "The first vanishing preservative (sodium perchlorate) was introduced in the Genteal brand by Novartis, which is still available. Another brand of vanishing preservative is sodium chlorite or Purite from Allergan, which is found in a wide variety of their products, including all of their multi-dose preparations of the Refresh Optive brand of tears," Dr. Sheppard explains.

Robert Latkany, MD, notes that cost can also play a role in artificial tear choice. "The preservative-free products can be double the cost of the preserved ones," he says. "There have been studies showing that these preservatives are destroying the ocular surface, but I think it's overstated and overhyped. If I can save some money for a particular patient and have him or her use Refresh Liquigel with a disappearing preservative rather than Refresh Celluvisc because they are using these products forever, numerous times a day, then I will take that into consideration. Many of these people see me every two to four weeks, so I can monitor the situation. If there is ever an issue with an artificial tear product, I pick up on it quickly," says Dr. Latkany, founder of New York Eye and Ear Infirmary's Dry Eye Clinic.

The choice between a tear with a preservative and a preservative-free tear comes down to the number of drops instilled in the eye daily. According to Stephen Pflugfelder, MD, director of the Ocular Surface Center at Baylor College of Medicine in Houston, it would be best for patients who

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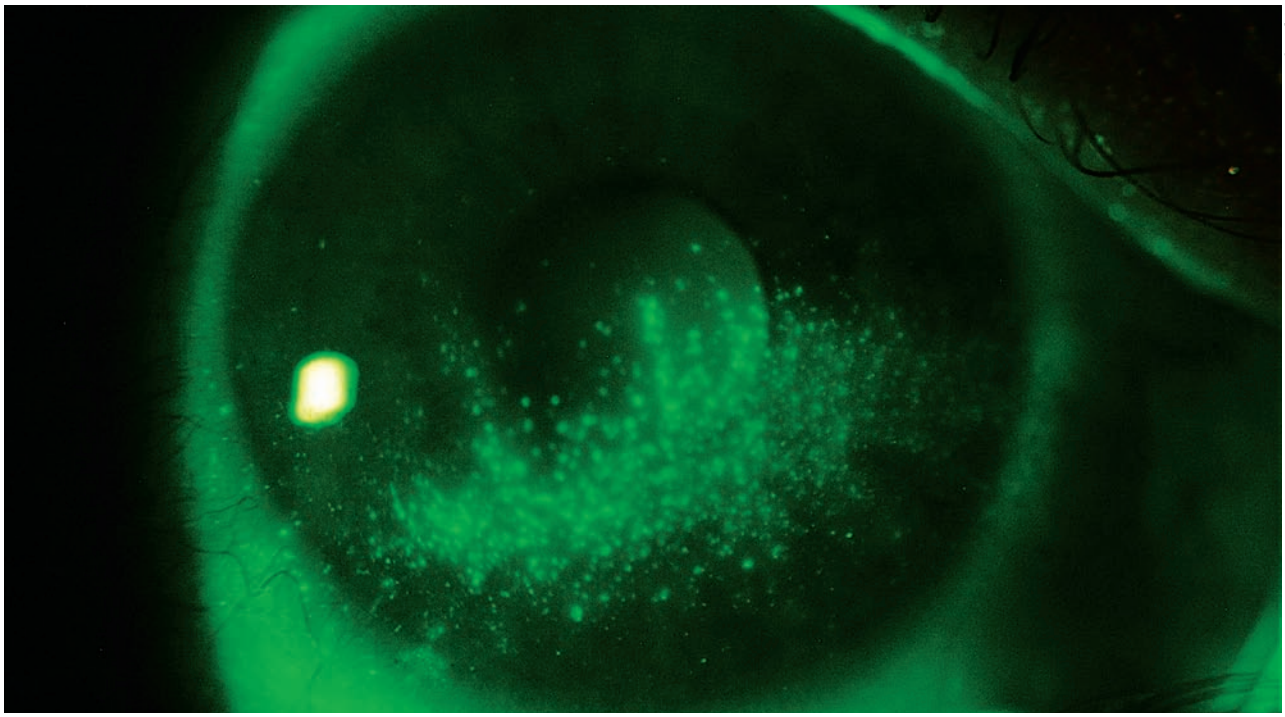

Jay Pepose, MD, PhD.

Figure 2. Moderate stippling of the corneal surface with fluorescein, as typically seen in patients with dry eye.

use tears more than four times a day or who have severe dry eye to use a preservative-free unit-dose artificial tear.

Lipids

Another important approach to providing an excellent over-the-counter tear preparation is to attempt to mimic the biphasic nature of tears by providing a lipid and an aqueous component to the tear, Dr. Sheppard says. "The guar in Systane provides an excellent matrix for the aqueous component of the tear. Refresh Optive Advance as well as Soothe from Bausch + Lomb provide a lipid substitute to better stabilize the tear film. Another valuable additive to over-the-counter tears is hyaluronic acid, which can be found in Blink tears from Abbott," he explains.

Viscosity

Another factor to consider when recommending drops is viscosity. Patients with mild dry eye may prefer a watery drop, while those with more severe dry eye may prefer a thicker drop that stays on the cornea longer.

"For more severe dry-eye patients and for patients who have many erosions on their corneal surface, I would prefer a thicker, more viscous drop, such as Refresh Celluvisc or Systane Ultra preservative-free," Dr. Latkany says. "The problem with the more viscous drops is that they tend to blur the vision because they are gooey and sticky. They leave more residual foreign particles in the eye. As the product sits on the lash, it hardens, forming crust. Also, the gooey nature of the drop allows allergens and other chemicals to stick to the tear film. However, there are also problems with watery drops like Refresh Plus. While I think they are the best drops, I have found that they really don't last much longer than three to four minutes. Patients will be putting a lot of drops in their eyes if they have to use them every three to four minutes."

Dr. Pflugfelder agrees that transient blurring can be a problem with more viscous drops. "Although the more viscous tears may decrease friction in the eye and lubricate the eye better, they do come with the side effect of being more blurry. In some cases, if someone can't close his or her eye because he or she has Bell's palsy, and a whole section of the inferior cornea is drying out, I definitely would recommend a thicker tear or a gel or even an ointment, knowing that although it may blur the patient's vision, it would probably protect the eye better. People who have good vision and can blink normally don't tend to like very viscous artificial tears. Some people use them at night, but you can even have blurred vision for an hour or so after you wake up in the morning," he adds.

Osmolarity

Another differentiating feature among the drops is osmolarity. "Some tears have lower osmolarity," Dr. Pflugfelder says. "There are some studies that show that lower osmolarity tears may have a better effect on the ocular surface. There are some tears

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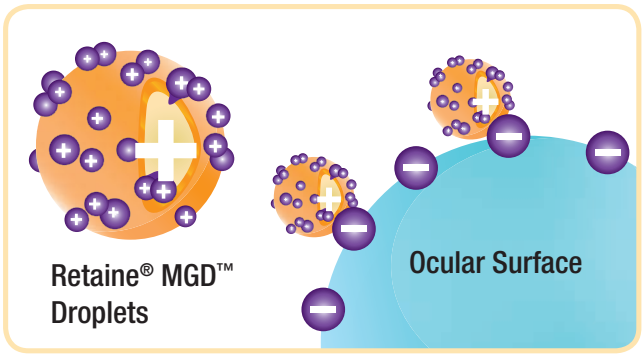

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that have ingredients that are called osmoprotectants. They are taken up by cells, and they blunt the response of the epithelial cells on the surface of the eye to high osmolarity in the tears. The Optive tears have osmoprotectants; some of those are found in sports drinks also because people can lose a lot of fluid and their blood may be a higher osmolarity. There is pretty good scientific evidence that they do help to protect cells."

For example, a study conducted by Dr. Pflugfelder and his colleagues at Baylor found that the osmoprotectants L-carnitine and erythritol, alone or in combination, protect against stress activation of corneal epithelial cells cultured in hyperosmolar media.[2]

After a patient starts on an artificial tear, she needs frequent follow-up to determine whether the drop is relieving symptoms. "They may need to use the drop for a month or two before they can determine whether it will work for them," says Dr. Sheppard.

Jay Pepose, MD, PhD, medical director of Pepose Vision Institute and president of the Lifelong Vision Institute, St. Louis, relies on a combination of symptoms and tear osmolarity to assess the efficacy of treatment. "I test patients' tear osmolarity before I initiate treatment, and then I ask them not to use any tears or put anything in their eye for at least 30 minutes, but preferably for at least an hour, before they come in for follow-up, and then I re-test their tear osmolarity after they have been on a product for a few weeks," he says. "Changes in tear osmolarity, along with vital staining and tear breakup time and reduction in symptoms, help me to decide whether patients are using the appropriate product or if we may need to switch tears, supplement treatment with cyclosporine, consider doxycycline or punctal plugs or add omega-3s."

Dr. Latkany notes that artificial tears are helpful as adjunctive agents, but that they are not the answer for dry-eye patients. "None of these can come close to the complexity of our natural tears," he says. "I am not in love with any of them, but we are improving the options. I think the marketing campaigns from the pharmaceutical companies make these products appear very attractive and very complex and to appear to be the answer to all dry-eye patients, but that is far from the truth, and we have a long way to go." REVIEW

1. Sarkar J, Chaudhary, Namavari A, et al. Corneal neurotoxicity due to topical benzalkonium chloride. Invest Ophthalmol Vis Sci 2012;53(4):1792-1802.
2. Corrales RM, Luo L, Chang EY, Pflugfelder SC. Effects of osmoprotectants on hyperosmolar stress in cultured human corneal epithelial cells. Cornea 2008;27:574-579.

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Dry-Eye Disease By the Numbers

Walter Bethke, Managing Editor

Adding a quantifiable element to diagnosis may help clinicians catch and treat dry eye.

The Irish physicist and engineer Lord Kelvin famously said, "To measure is to know," and used this attitude of scientific rigor to advance research in a number of fields. Dry-eye researchers are beginning to appreciate the power of quantifiable values as well, as new devices for measuring aspects of tears begin to work their way into practice. Here is a look at the research behind these new instruments and experts' opinions on their ability to aid diagnosis and treatment by adding a quantifiable dimension to the process.

LipiView

LipiView is the diagnostic half of a treatment system for meibomian gland dysfunction developed by TearScience (Morrisville, N.C.). The idea is to use LipiView to determine the extent of MGD and then employ the LipiFlow device to treat it. *(For a discussion of the LipiFlow, see "Managing and Making Sense of MGD" on p. 48.)*

The LipiView interferometer aims to detect patients suffering from dry eye due to meibomian gland dysfunction.

LipiView uses interferometry to measure the lipid layer's thickness between blinks, and gives a quantitative assessment in interferometric color units, which the company says are close to, but not exactly, nanometers. One study of lipid layer thickness found a connection between a patient's lipid layer thickness and his dry-eye symptoms. In the study, researchers had 137 consecutive patients complete the Standard Patient Evaluation of Eye Dryness questionnaire, and then measured their lipid layers with interferometry. For patients with severe dry-eye symptoms (a SPEED score of 10 or greater), 74 percent also had LLT of 60 nm or less. On the other end of the spectrum, 72 percent of patients with no symptoms (SPEED score of zero) had a LLT of 75 nm or thicker. When the researchers performed a linear regression analysis, there was a statistically significant relationship between LLT and symptom score, and as LLT increased, symptom score

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1. DEWS Report, The Ocular Surface, April 2007: 164,86
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Take a Systematic Approach to Eye Care

decreased (p=0.0014).[1]

"I've seen patients with signs and symptoms of evaporative dry eye who come in and undergo LipiView, confirming a deficient lipid layer," says Duke surgeon Alan Carlson, who consults for TearScience and has been using the LipiView/LipiFlow system for 11 months. "It's not uncommon for a patient to have, for example, 28 to 35 ICU values measured by LipiView that improve after a LipiFlow treatment and a regimen to get the glands functioning again. They may even double or triple their lipid layer. And this often correlates with a notable improvement in their symptoms. Dry-eye patients are heterogeneous and complex, and are dealing with a chronic disease process. The duration and severity of disease can cloud the patient's own assessment and measure of improvement. LipiView testing that shows a two- to threefold increase in lipid layer thickness in addition to the improvements seen on examination can further encourage the patient with respect to progress and prognosis."

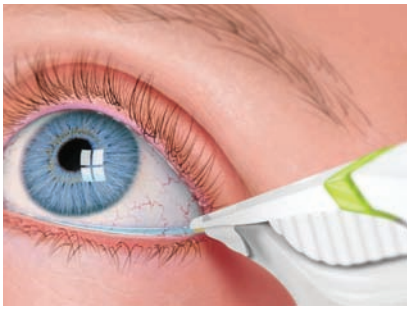
Dr. Carlson says LipiView has worked its way into the set of tests he administers. "I perform a meticulous slit lamp exam, assessing blink, lid margin, the meibomian glands and gland orifices," he explains. "Then I look at staining patterns, tear film stability, LipiView and meibography. This combination of testing helps us sort out the root cause. We're finding that it is a minority of patients who have dry eye whose primary cause is deficient tear production, while the majority of patients with tear-film instability [evaporative dry eye] have issues related to meibomian gland dysfunction and gland obstruction."

Though the LipiView system is approved and in use, physicians and the company are still learning the best ways to use it in a clinical setting. "We haven't been able to precisely correlate LipiView in every case with outcomes and perceived patient response," says Dr. Carlson. "We'd like to be able to. There is a company-sponsored study looking at this as well as looking at the test's correlation with other dry-eye findings and tests, and the data is still being gathered. While we look forward to improving our ability to better define the magnitude and duration of response to LipiFlow based on a multitude of findings—including LipiView—it's remarkable to reflect on the progress we've made in a single year with respect to diagnosing and understanding the treatment needed for dry-eye patients who have their condition on the basis of MGD leading to deficient tear-film stability rather than inadequate tear production."

TearLab Osmolarity Testing

The TearLab system uses a small sample of a patient's tears to test the concentration of electrolytes in the tear film, which gives an osmolarity reading. Patients with higher levels of osmolarity, especially within certain ranges, are likely to have dry-eye disease.

"In the 1980s and 1990s, tear osmolarity was thought to be the gold standard in dry-eye testing, but it wasn't a practical tool at that time because you frequently couldn't get a large enough sample. It had to be collected and then transferred to another measuring chamber, and there was often evaporative loss of the sample during the transfer process," explains Michael Lemp, MD, who consults for TearLab. "Therefore, it was mainly a research tool. The current TearLab test is different, and has been available since 2008. It only needs a small amount of tears, 50 nl. The technology is based on electrical impedance, and the collecting system is such that as soon as the tip of the collecting pen touches the inferior margin tear strip, the user hears an audible beep notifying that the collection is complete. Within three seconds, the sample is measured. You then put the pen in a receiving reader on the device and you receive a reading of the osmolarity."



The TearLab collects a tear sample for analysis from the inferior margin tear strip.

When the measurement is returned, the physician can identify a dry-eye patient in one of two ways: one of the eyes has an osmolarity of 308 mOsm or higher; or there is a difference between the two eyes of 8 mOsm or greater, since tear-film instability between eyes is also a hallmark of the disease. The device itself has a variability of 1.5 percent, which Dr. Lemp says translates into about 5 mOsm. "In addition, we've found that a reading of 316 mOsm is a good cutoff between mild and moderate dry-eye disease," he adds.

Dr. Lemp says assigning a value to the patient's ocular surface helps ferret out patients who might otherwise go undiagnosed. "We know that in mild to moderate dry-eye disease, less than half of the patients have any corneal staining," he says. "Yet many doctors might think if a patient doesn't have staining he doesn't have disease, and would miss 50 percent of patients with mild to moderate disease. Also, up to 40 percent of patients with clear objective evidence of dry eye are asymptomatic."

Dr. Lemp says that there have been some articles published that question TearLab's utility. A poster presented at the annual meeting of

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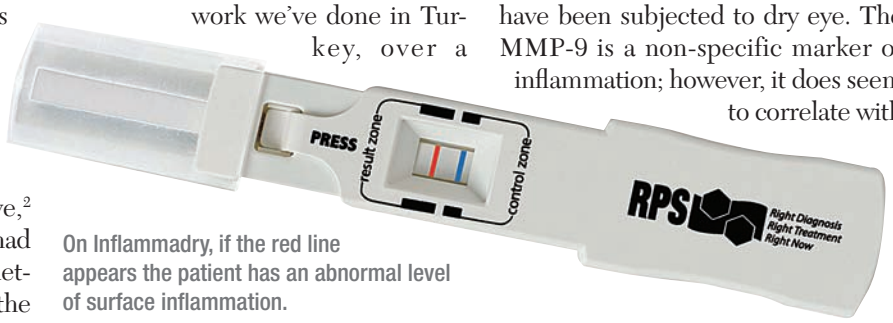
RELIANCE INTERNATIONAL

the Association for Research in Vision and Ophthalmology found no correlation between signs and symptoms of dry eye, including tear osmolarity. *(Sullivan BD, et al. IOVS 2012;53:ARVO E-Abstract 550)* The researchers noted, though, that the "clinical presentation of dry eye is multifactorial, with each test contributing different information, thus correlation between different tests should not be expected."

A recent study from Hungary reported that tear osmolarity wasn't able to distinguish between normals and patients with dry eye,[2] but Dr. Lemp says that the study had issues, and is drafting a response letter to the journal. "In that study, the researchers tested only one eye rather than two, so they didn't understand about variability," he avers. "And the study is guilty of selection bias, in that they qualified people for inclusion in the study by using the results of Schirmer's, tear-film breakup time and corneal staining, but not osmolarity testing. Then, during the study, the researchers asked how well the first three tests correlated in each patient, and found that the tests correlated well. This is no surprise, though, because these initial tests all needed to be positive in order for the subjects to enter the study. The researchers then reported that tear osmolarity didn't correlate well, but this wouldn't be unusual because it wasn't one of the entry criteria like the others."

Other studies, meanwhile, have found good reliability from tear osmolarity measurements.[3,4] One multicenter study performed by Dr. Lemp and several colleagues analyzed 314 patients to see how well six major dry-eye tests (including osmolarity, Schirmer's and tear-film breakup time) correlated to the increasing severity of dry-eye disease. The researchers say that, using a cutoff of 312 mOsm/L, tear hyperosmolarity exhibited 73-percent sensitivity and 92-percent specificity. They say that the other tests exhibited either poor sensitivity or poor specificity. Also, inter-eye differences in osmolarity were found to correlate with increasing disease severity (r^2 = 0.32).

Dr. Lemp says they're always learning more about the disease and what osmolarity can tell them about it. "In work we've done in Turkey, over a three-month period of treatment with cyclosporine in bona fide cases of dry eye, it took two months before we saw a profound lowering of osmolarity," he says. "However, the symptoms didn't go down by a statistically significant amount until three months. This lag is understandable, because even though the surface has gotten better at two months, it hadn't gotten better to the point where the patient could perceive it. We've learned it takes some reparative time before that occurs."



On Inflammadry, if the red line appears the patient has an abnormal level of surface inflammation.

Inflammadry

Inflammadry (Rapid Pathogen Screening, Sarasota, Fla.) is a test similar to an at-home pregnancy test that takes a sample of a patient's tears and gives a positive (ocular surface disease) or negative (no ocular surface disease) result. Users say that, though it doesn't give a numerical result, the test's reading is actually based on a quantifiable value of the amount of matrix metalloproteinase-9 in the tears. "If the test is positive, then basically that means there's over 40 ng/ml for the level of MMP-9," says Ottawa's Bruce Jackson, MD, who has done studies with Inflammadry but has no financial interest in the device. "The company has looked at the levels in a normal eye, and found 40 ng/ml to be the upper range of normal.

"MMP-9 is a proteolytic enzyme that comes from stressed epithelial cells on the ocular surface," Dr. Jackson continues. "So, these are cells that have been subjected to dry eye. The MMP-9 is a non-specific marker of inflammation; however, it does seem to correlate with dry eye, ocular surface disease and some of the clinical findings."

To perform the test, the clinician takes a sample of tears from the inside lining of the lower lid. Ten minutes later, if a red line appears in the result window of the detector, that indicates elevated MMP-9. There isn't a lot of independent research on Inflammadry at the moment, but in RPS studies, the company found the test to have 85-percent sensitivity and 94-percent specificity.[5]

Dr. Jackson says that, using the Dry Eye Workshop levels of tear dysfunction, patients ranked as "mild" are more in the normal range of Inflammadry, "but you start to pick up abnormal levels at level two, three and four," he says. "And, the stronger the red line, the higher level. It goes up in both Sjögren's and MGD, so it can give you a really good idea of whether there are inflammatory mediators in the tears."

Inflammadry isn't approved in the United States and, though it's approved in Canada, it currently has no distributor there, so Dr. Jackson can only use it for research projects at the moment. "When it's available, though," he says, "I'll combine it with

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the use of the TearLab osmolarity test and get a better idea of where it fits in the clinic."

Anterior-segment OCT

A system currently more in the research realm than the everyday practice is anterior-segment optical coherence tomography (coupled with custom-made, third-party image processing software) for the measurement of tear characteristics. Here's a look at what researchers are finding with these systems.

In one study of 48 aqueous-deficient patients and 47 controls, researchers found clues for diagnosing dry eye on OCT: They reported that the cutoff value for an abnormal lower tear meniscus radius was 182 µm and the value for a an abnormal lower tear meniscus height was 164 µm. They added that the LTMR diagnostic sensitivity and specificity were 0.92 and 0.87, respectively, and that the LTMH diagnostic sensitivity and specificity were 0.92 and 0.90. The tear meniscus was smaller in aqueous-deficient patients than in healthy subjects.[6]

Looking at treatment, researchers used OCT to image the upper and lower tear menisci in 14 consecutive dry-eye patients. They then started the treatment group on daily cyclosporine administration and repeated the measurements at one and two months.

They found that, in the treatment group, measurements showed significant increases of both upper (p=0.003) and lower (p=0.0003) tear menisci heights, after a month of cyclosporine. The tear meniscus volumes in the treatment group after one month of treatment showed significant increases of both upper (p=0.007) and lower (p=0.007) tear menisci. At two months, the increase in the tear meniscus was still evident (p<0.05).[7]

Though the expense of acquiring a high-res OCT, and the intricacies of dealing with third-party custom software for image management prohibit OCT tear measurement from being widespread, researchers say that the rapid, noninvasive, and detailed images from OCT can often provide them with helpful insights about the presence of dry eye and the effectiveness of therapies. REVIEW

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Anton Willerscheidt, MD
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Confidence is a vital part of ophthalmic surgery, both for the surgeon and the patient. A surgeon's confidence is something that patients instinctively perceive, so the more assurance that the doctor exudes, the more comfortable the patient will be. For surgeons, having faith in your equipment and your surgical team can be a key component of your overall demeanor. For more than a decade now, my practice has been working with Sightpath Medical to utilize its mobile refractive and cataract surgery services, an arrangement that has helped me feel my most confident.

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We have found this arrangement very reassuring, particularly when there is a change in technology or a new procedure. We have recently converted from utilizing a keratome to the IntraLase FS 60 Laser System, and our Sightpath Medical technician's extensive experience has helped make our transition and the learning curve as smooth as possible.

Sightpath Medical provided us with a way to lease the necessary equipment and bring in experienced technicians to help us conduct surgeries. With this arrangement, there is no capital outlay necessary, nor are there ongoing costs for maintenance and supplies.

Today's patients are becoming increasingly educated on the technologies available in refractive surgery, and many inquire specifically about the IntraLase method.

For us, it was important to be able to transition to this cutting-edge technology without worries about how to finance the change or train staff to use it efficiently, and Sightpath Medical has helped us achieve that.

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Transitioning from one technology to another can sometimes be stressful, but my experience with the IntraLase has highlighted just how smooth a transition can be when the right support is in place.

Transitioning from one technology to another can sometimes be stressful, but my experience with the IntraLase has highlighted just how smooth a transition can be when the right support is in place. My practice's long relationship with Sightpath Medical has helped us not only offer the cutting edge technologies that patients demand, but also implement and utilize them with maximum efficiency, giving us added confidence in our services.

Managing and Making Sense of MGD

Christopher Kent, Senior Editor

Meibomian gland dysfunction has become a topic of increasing interest, but many questions remain unanswered.

Thanks in large part to the 2011 report from the International Workshop on Meibomian Gland Dysfunction, sponsored by the Tear Film and Ocular Surface Society, interest in the connection between meibomian gland dysfunction and dry eye has increased noticeably. The report, which took more than two years to complete and involved input from more than 50 dry-eye experts around the world, attempted to correct several perceived oversights in this area. Among other things, despite the worldwide prevalence of meibomian gland dysfunction, there was no commonly accepted definition of the disease or agreement about diagnosis, classification or therapy.

The workshop offered the following as a formal definition of meibomian gland dysfunction: "a chronic, diffuse abnormality of the meibomian glands, commonly characterized by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion." Although low or absent delivery of the secretions is most commonly seen, the report notes that excess secretion can also occur. In either case, the result of these changes can be alterations of the tear film, symptoms of eye irritation, inflammation of the ocular surface and dry eye. (Links to summaries of the report, as well as the full report, can be found at tearfilm.org.)

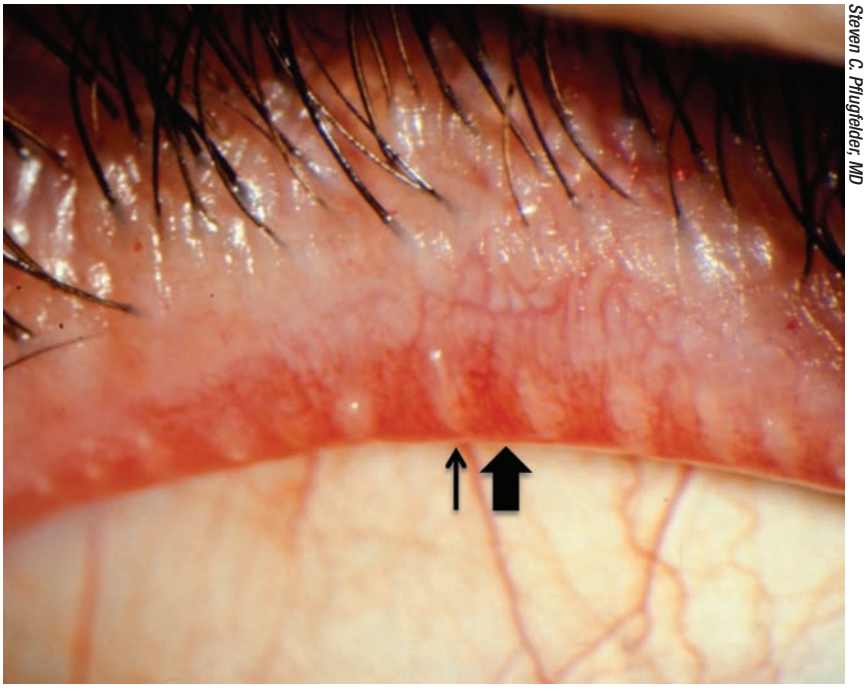
Shifting Clinical Focus

Penny A. Asbell, MD, FACS, MBA, professor of ophthalmology and director of cornea and refractive surgery at the Mount Sinai School of Medicine in New York, believes the report represents a paradigm shift in the treatment of dry eye. "Health professionals have now been alerted that lid disease can be a major contributing factor in ocular surface disease," she points out. "As a result of this report, ophthalmologists are now evaluating the lids more carefully and more often when seeing patients with dry-eye complaints."

Dr. Asbell notes that in the past, doctors were thinking more about an abnormal tear film, primarily relating to low tear volume from aqueous-deficient dry eye. "Their primary concern was increasing the volume or quality of the tears," she says. "This is still perfectly reasonable and important to consider in someone with ocular surface disease, but a lot of the problem with the tear film may actually stem from lid disease rather than simple aqueous deficiency. It isn't a new idea, but the report coalesces the data to support that line of thinking.

This article has no commercial sponsorship.

"In the past, there's been a lack of data on meibomian gland disease, reflecting a general lack of interest in this area," she continues. "For example, when we did the study of cyclosporine that led to Restasis eye drops, we looked at the lids as part of the clinical trial, but only briefly and not with a lot of intense interest," she says. "It wasn't a focus of the trial. That's one reason there's not as much data about meibomian gland disease as we'd like; most previous studies didn't worry much about analyzing lid findings, and very few trials have looked at lid disease directly. So, we're still at the beginning of the process of understanding meibomian gland disease, and seeing what, if anything, helps to improve it. Hopefully, going forward, the new level of interest generated by the report will result in new data about the natural history of the disease, how common it is, and how and when to treat it."



Steven C. Pflugfelder, MD

Examining the lids is an important part of any exam. This patient has severe metaplasia and posterior migration of meibomian gland orifices (small arrow) with lid margin hyperemia (large arrow). Findings like these indicate that the glands are obstructed and that lid therapy (warm compresses, massage or LipiFlow) is unlikely to work. They also indicate the presence of lid and ocular surface inflammation that should be treated.

The Nature of the Disease

"Inspissation of the meibomian glands is very common in the United States, although studies suggest that it may be even more common in some Asian populations," notes Jay S. Pepose, MD, PhD, medical director of the Pepose Vision Institute and professor of clinical ophthalmology at Washington University School of Medicine and Barnes-Jewish Hospital. "Meibomian gland disease is probably the main cause of dry eye—certainly of evaporative dry eye. Of course, dry eye can be a mixed disease, where you have some aqueous deficiency component and some evaporative component."

Regarding what percentage of dry eye might be attributable to meibomian gland disease, Dr. Asbell says existing studies haven't provided a clear answer. "However, some of the data suggests that as much as 60 percent of dry eye may be attributable to MGD," she notes. "It could also be a big part of contact lens intolerance. It may be that lid disease contributes to an abnormal tear film, which in turn produces a less-than-comfortable contact lens fit. That's another group of patients for whom we may have been overlooking a major source of problems. However, we don't yet know for sure whether there's a connection."

"You can look at meibomian gland disease from two perspectives," says Steven C. Pflugfelder, MD, professor and director of the Ocular Surface Center at Baylor College of Medicine's Cullen Eye Institute. "One is that it's an eyelid problem. There are people whose lids become inflamed as a result of meibomian gland disease. However, not a whole lot of people come in complaining about that. Most people who have meibomian gland disease—or those in whom it appears to be the cause of their problem—come in because they have a tear dysfunction and they're starting to get corneal or conjunctival disease. The nerves on their corneas are being stimulated, so they're sensing irritation, or their vision is getting blurred. In that case, it's more of a tear dysfunction problem."

Dr. Pflugfelder adds that when meibomian gland disease is present, it does seem to affect tear stability. "In many people it appears to cause conjunctival redness, irritation and corneal epitheliopathy—particularly in the lower cornea," he says. "We know that the eye gets inflamed, because if you sample the tears at the ocular surface there are higher levels of inflammatory mediators and proteases in many of those patients. And there are probably a lot of other things going on that we don't know about."

As for what causes the meibomian glands to malfunction, Dr. Pepose says multiple factors may be to blame. "Some people think androgens like

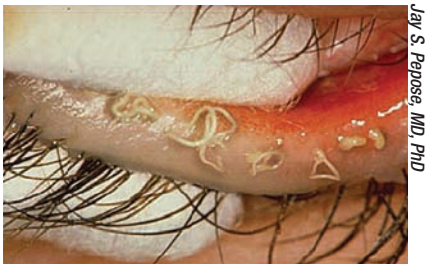
testosterone play a role in maintaining normal meibomian gland function," he notes. "I'm sure that fatty acid metabolism plays a role, not just in maintaining the gland function, but also in altering the constituents of the secretion. The proper balance of elements like polar lipids and waxy esters in the secretion help to keep the tears from evaporating."

Conducting the Exam

A number of strategies during the examination process can help ensure an accurate diagnosis:

• ***Always examine the eyelids and express the glands.*** "I think examining the eyelids is a requisite part of any examination," says Dr. Pepose. "If you don't express the lids, you're not getting the information you need: Does the patient have inspissated or functioning meibomian glands? If you manually express the glands, you can judge or grade their ability to secrete meibum. You could find a clear secretion, which is normal, or an opaque secretion, which is not normal. *(See example, above.)* Or, the glands could be completely blocked—no secretion at all. So there are different stages of meibomian gland disease."

Dr. Asbell says that when a patient presents with complaints that sound like ocular surface disease, in addition to doing a Schirmer's test, ocular surface staining with fluorescein and lissamine, and checking tear-film breakup time, she does a thorough lid evaluation. "Evaluating the lids means more than just looking at them at the slit lamp," she says. "It means putting a little pressure on them to see whether the meibum that's secreted is normal or abnormal. Doctors are starting to make this part of their regular exam and making decisions based on those findings. That's actually a big change; for many clinicians this was not routine before the report came out. People weren't looking at the lids too closely, unless the patient had a real complaint or there was obvious inflammation."



Jay S. Pepose, MD, PhD

Thick, toothpaste-like meibum expressed upon applying maximum pressure in a patient with obstructive meibomian gland disease.

Dr. Asbell notes that to examine the lids you need to pull them back using your finger or a tool such as a Q-Tip. "The edges of the lids where the orifices for the meibomian glands are located point toward the ceiling or floor, so to get a look at them you have to pull the lids away from the eye a little," she says. "You then turn the edges toward you by everting the lids a little bit. This is important because the lids may look normal, but when you put some pressure on them you may discover that the meibum looks quite abnormal. This is what Donald Korb, OD, FAAO, describes in the workshop report as 'non-obvious MGD.' "

Dr. Asbell adds that there's no easy way to distinguish between minimal production of meibum and blockage of the outflow channels. "That's a subtle distinction, because the glands are within the lids," she points out. "All we can do is check to see whether meibum is coming out. As the glands make meibum, it's normally pushed out to the surface. If a gland becomes obstructed so the meibum can't get out, the gland tends to degenerate and stop functioning altogether, leading to minimal or nonexistent production."

• ***Remember that hypersecretion can be equally problematic.*** Dr. Asbell notes that one way a meibomian gland problem can manifest is through hypersecretion. "You sometimes see people with a sort of foam along the edge of the lids, indicative of increased meibum secretion," she says. "On the other hand, you see people who don't produce any meibum at all, even with increased pressure from your finger or a Q-Tip. Are these different stages of the same disease, or different etiologies leading to different endpoints? I'm not sure we know the answers."

• ***Check for aqueous deficiency.*** "When examining these patients, my primary interest is in determining whether there's an aqueous deficiency or normal aqueous production and volume," says Dr. Pflugfelder. "If there's an aqueous deficiency, that might require a different treatment approach than if I find a normal amount of aqueous production. I'd say that 95 percent of patients who come in having trouble, but with normal aqueous, have meibomian gland disease."

• ***Use retroillumination to check the number of glands.*** "It's possible to see the glands by using retroillumination during the lid exam," notes Dr. Asbell. "There are 30 or 40 glands in the upper lid and 20 to 30 in the lower lid. If a patient has severe meibomian gland disease, you can actually see that some of the glands are no longer present. Losing one or two probably isn't significant, but losing a lot of them can be."

• ***Don't assume patients will voluntarily mention their symptoms.*** "I'm more proactive and aggressive about assessing the meibomian glands if a patient is symptomatic," says Dr. Pepose. "But patients sometimes don't volunteer their symptoms. You may have to elicit this information from them using directed questions. It may be that they've reached a point where they are hypesthetic, or the symptoms are so chronic that they think they're normal findings. If you

ask a patient, 'Are you having problems?' he may say, 'I'm fine.' But if you ask whether he has fluctuating vision during the day, he may say yes. He may admit that his eyes feel irritated, that he has a foreign body sensation, or that his eyes often feel dry—if you ask him directly."

• ***Ask whether the symptoms are worse in the morning or evening.*** "Many patients with meibomian gland disease say that their eyes feel worse when they first wake up," notes Dr. Pepose. "That's different from patients with aqueous deficiency dry eye, where they almost always get worse as the day goes on."

• ***Consider having new patients fill out a dry-eye survey.*** "Because we're a specialty practice focusing on cornea, refractive surgery, external disease and cataract, we routinely give new patients a dry-eye survey," Dr. Pepose says. "That tells us right away if the patient is symptomatic; it helps us to direct the exam."

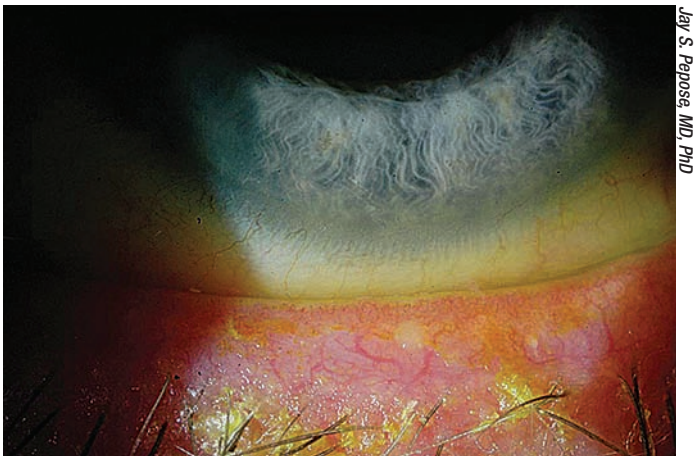
• ***Consider checking tear osmolarity.*** "I think tear osmolarity is important because it's a consequence of having a lipid deficiency," Dr. Pepose says. "If your tears are evaporating, your tear film will become hyperosmolar. Testing osmolarity provides another important clue.

"Imagine being an internist and trying to determine whether someone is diabetic without being able to measure his glucose or hemoglobin," he continues. "You'd have to base your diagnosis on signs and symptoms. You'd say, 'Are you thirsty? Tired? Do you urinate a lot?' That would be the level of management. In my mind, that's where we were before tear osmolarity. At least now we have an objective marker that we can use to determine: A) Does the patient really have dry eye? and B) If we start treating, will it get better? Will the osmolarity drop?

"Of course, hyperosmolarity doesn't tell you if the patient has meibomian

gland disease or an aqueous problem, because osmolarity is elevated in all forms of dry eye," he adds. "But it's unusual to find a patient with normal tear osmolarity who has a dry-eye problem. If osmolarity is normal, you're probably safe focusing your attention elsewhere."

Dr. Pflugfelder notes that the new tests that measure matrix metalloprotease 9 and osmolarity of the tear film could both be useful when trying to measure meibomian gland disease. "Both factors increase when meibomian gland disease is present, so these tests might help us in the clinic," he says. "For example, doxycycline is a potent inhibitor of MMP-9. So it makes sense that if people have high levels of MMP-9, they might be candidates for doxycycline. Corticosteroids also inhibit MMP-9 production." (The Inflammadry test to measure MMP-9, produced by Rapid Pathogen Screening in Sarasota, Fla., has not been approved by the Food and Drug Administration.) Other devices designed to quantify the tear film as an aid to dry-eye diagnosis include the LipiView Ocular Surface Interferometer from TearScience (Morrisville, N.C.). (For more on these instruments, see the article on p. 38.)



Jay S. Pepose, MD, PhD

A patient with meibomian gland disease, telangiectasia and inflammation of the lid margin.

Treating MGD

Options for treatment remain limited, but each one seems to help some subset of patients:

• ***Warm compresses, massage and hygiene.*** Dr. Asbell says her primary treatment for MGD is still mainly lid hygiene. "That consists of warmth applied to the lids to loosen up the meibum, along with lid scrubs," she explains. "The lid scrubs may be prepackaged, but in some cases patients prefer to create their own lid scrub using baby shampoo with a cotton ball or something along those lines."

Dr. Pflugfelder notes that many of the patients he sees are beyond the point of no return. "They don't have any glands left, or the ones they have aren't functioning," he says. "For them I believe heating and massaging won't do anything. There will be a subset of people who still have functioning glands, and heating and massaging will cause some glandular secretion to make it onto the ocular surface. At least, I think so. We need a rigorous clinical trial to confirm that this actually happens."

• ***Lipid-based artificial tears.*** "If the patient has significant shortening of the tear breakup time, meaning the tear layer is not uniformly covering the ocular surface, then I'll add an artificial tear as well," says Dr. Asbell. "Some artificial tears are now targeted toward managing meibomian gland dysfunction; they're made with a more lipid base to replace factors that may not be being produced sufficiently by diseased meibomian glands."

• ***Antibacterials and nutritional supplements.*** Dr. Asbell notes that one factor that may contribute to pathology is normal bacteria such as staphylococcus breaking down the fatty components of the meibum into free fatty acids. "Free fatty acids can contribute to lid irritation and changes in the ocular surface," she points out. "Systemic doxycycline can interfere with the lipases that break down some of the fatty components. So, after I try lid hygiene and artificial tears, if the patient is still symptomatic I may switch the patient to a systemic product such as doxycycline or tetracycline.

"Doxycycline has been used successfully for treating skin problems such as acne and rosacea for years," she points out. "I might also consider using a topical antibiotic such as bacitracin as a way to reduce the overall volume of bacteria. The idea is not that this constitutes an infection, because there are always bacteria on the lid. There may just be too many microbes, or the type of microbe present may lead to more fatty acid breakdown."

Dr. Pflugfelder notes that doxycycline, topical steroids and nutritional supplements like fish oil and gamma-linolenic acid may all help some patients. "Doxycycline hasn't had a masked clinical trial, as far as I know, but corticosteroids have been tested, as have the nutritional supplements," he says. "Those do show improvement at least in symptoms and maybe in signs. Because there's some evidence-based validity to prescribing those three therapies, I tend to favor them. And I have seen some improvement in eyelid redness with these treatments. I've also seen improvement with topical azythromycin, although it hasn't been subjected to a randomized clinical trial. However, I can't honestly say that the meibomian glands function any better as a result

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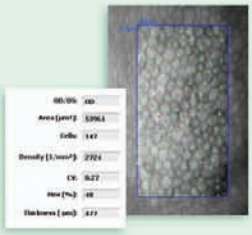

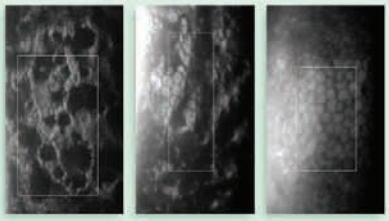

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of these treatments.

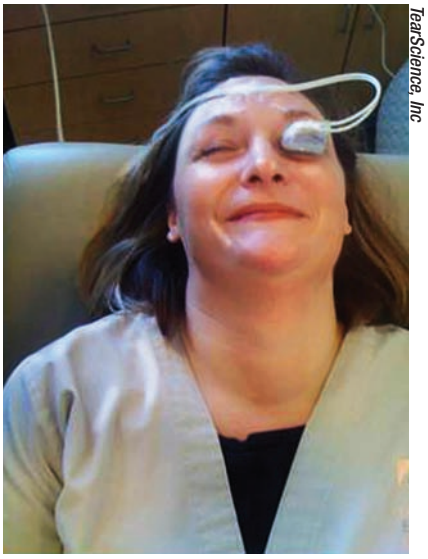
"Unfortunately, at this point, my treatment is still geared to decreasing inflammation on the eye, because I don't have any treatments that will really improve the meibomian gland disease," he adds. "I'm not even convinced that improving meibomian gland function will help these patients that much."

The High-tech Approach

As more attention has been devoted to meibomian gland dysfunction, new approaches to treatment have begun to appear. "The company TearScience in North Carolina has developed the LipiFlow device, which covers the lids and heats and massages them, with the goal of making them function more normally for some period of time," Dr. Asbell notes. "The procedure is FDA-approved, but insurance doesn't cover it, and it's expensive; the device costs about $100,000 and the disposable eye cups for each use cost about $650 a pair. At this time, the patient has to pay out of pocket. I have minimal experience with it, but I know some ophthalmologists swear by it. I think it's too early to know how this will end up fitting into the treatment picture."

Dr. Pepose has used the device for about 10 months, and has a favorable opinion of it. "The LipiFlow system has been shown in studies to be efficacious in about 86 percent of patients who have inspissation of the meibomian glands," he says. "Many people have been treated with oral agents such as tetracycline or doxycycline and tried using warm compresses without getting relief.

"Warm compresses apply heat to the outside of the eyelid, the opposite side from the meibomian glands—and you have a vascular structure on the outer lid that picks up some of that heat and carries it away," he continues. "With the LipiFlow system, the heat starts on the inside. The interface locks around the eyelid, with the heating element on the inner aspect, closer to where the meibomian glands are. The device heats up the meibum and then mechanically massages open the glands.



TearScience, Inc

TearScience's LipiFlow device is designed to apply heat and massage directly to meibomian glands to stimulate flow.

"Ultimately, of course, you have to select the right patients," he notes. "This device can be very useful, particularly in individuals in whom the secretion resembles toothpaste. They have to have some glands that are expressing. I wouldn't treat patients who are not symptomatic and have no complaints, or patients at the opposite end of the spectrum, where you put pressure on the meibomian glands and there's no expression at all. But I think there is a role for LipiFlow in the patients who still have some secretion from the glands."

Dr. Pepose admits there are limits to what the device can accomplish. "Like any treatment, I don't get a 100-percent response," he says. "And I have to explain to people that it's not a forever treatment; it seems to be effective for nine to 12 months, maybe a little beyond in some patients. So they probably will require retreatment, because we're not addressing the underlying cause of the problem. Also, the system may reduce but doesn't necessarily eliminate the problem in patients who have been suffering for many years, so we explain to patients that this is an adjunct; they may still need to use other approaches, such as occasional drops. And cost is a barrier for many patients. It's an expensive device, and every time you use the device you have to pay for the interface. Unfortunately, at this point in time it's not a covered service.

"On the other hand, many of these patients have been on tetracycline; they've tried warm compresses; they're already taking omega-3s and using tear drops with lipid substitutes or serum tears," he notes. "They've gone full spectrum and they're still unhappy. Many of them feel that the opportunity to improve their quality of life is worth paying for the treatment. And in my experience, the vast majority of patients do respond to this. A lot of patients have told us that, unlike anything they've tried before, this gave them some relief. People have told us that for the first time in months they could go through the day without thinking about their eyes. For them it was worth it."

Dr. Pflugfelder is more skeptical regarding how helpful this kind of approach is, high-tech or not. "Even when the meibomian glands aren't good and I recommend warm compresses and lid massage, at best that leads to a 30- to 50-percent improvement," he says. "Many patients aren't helped at all, and it's a lot of effort on their part. In fact, a lot of the support for using warmth and massage is anecdotal."

Asked about the studies showing the LipiFlow device was efficacious in 86 percent of MGD patients, he notes that those studies were limited in their scope. "There are no controlled, randomized clinical trials proving that this approach is superior to placebo," he says. "I'm sure it does help some

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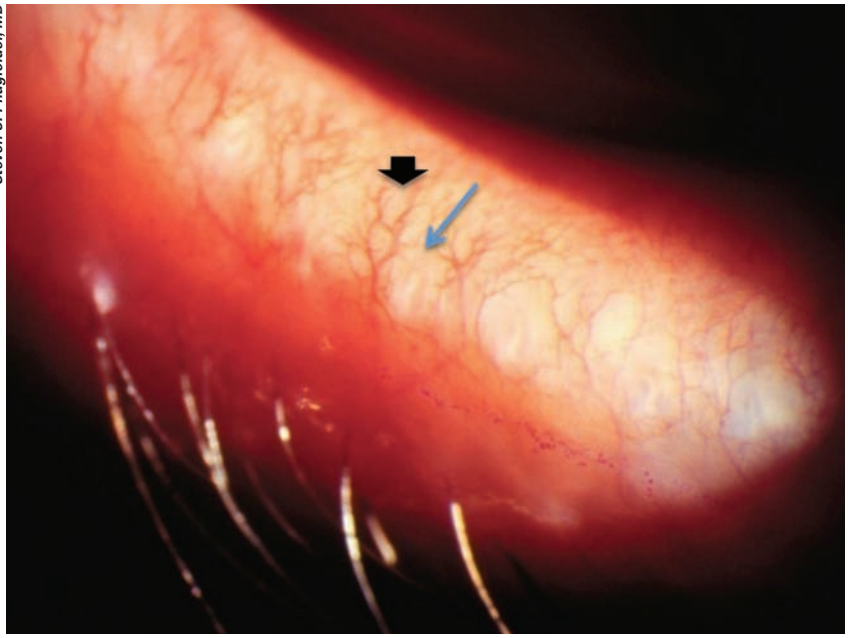

Steven C. Pflugfelder, MD

Severe metaplasia and posterior migration of meibomian gland orifices (small arrow) with lid margin telangiectasia (large arrow). This is another case in which the glands are obstructed and lid therapy is unlikely to work, although lid and ocular surface inflammation is present and needs to be treated.

patients, but the clinical data showing which patients it helps is lacking. In the meantime, many of these patients are very uncomfortable and desperate for relief, so they're often game to try anything."

The Asymptomatic Factor

Dr. Asbell notes that there are a host of questions about meibomian gland dysfunction that remain unanswered. "Many patients seem to develop meibomian gland disease as they age, so it may be partly an age-related phenomenon," she says. "We also don't always find a direct correlation between a meibomian gland problem and patient symptoms. Some of these patients clearly have meibomian gland disease, but they're not symptomatic at all.

"Most of us occasionally see a patient with very dry eyes—at least from our perspective—who says he uses drops once in a while but not every day because it doesn't bother him that much," she continues. "To us, it looks like his condition should be really painful. Then there are patients who are very symptomatic, but the exam reveals almost no sign of a problem. The reason for that disconnect in some patients is still a mystery."

Dr. Pepose agrees. "Thirty percent of dry-eye patients don't have any symptoms but have some sign," he points out. "We don't know the reason. Maybe they're chronically inflamed and they've reached a point at which they have less sensation on the ocular surface. In any case, it's not uncommon to have a discordance between signs and symptoms, and that's been one of the big problems getting treatments approved for dry eye. The FDA in the past has required that a drug be effective in reduction of both symptoms and signs. But here we have a disease where the symptoms and signs rarely ever correlate well. How can we expect a treatment to fix both, when they don't correlate to begin with? In fact, the drier you get, the more variation there is in all of these tests. So it's not surprising that we haven't seen many dry-eye treatment approvals."

"Even after years of doing research in this area, I still don't really know how much of dry-eye disease is directly attributable to meibomian gland dysfunction," notes Dr. Pflugfelder. "There's no question that many people with an unstable tear film but normal tear production volume have evidence of meibomian gland disease. At the same time, a lot of people have meibomian gland disease without manifesting any symptoms.

"It may be a disease that requires two problems in order to be clinically manifest," he says. "For example, it may require some age-related changes on the ocular surface or in the tear film. Maybe decreased capacity for reflex tearing causes the disease to become more obvious to the doctor and patient. I think it's still an area that's evolving."

Mysteries to Solve

For now, we seem to have more questions regarding meibomian gland disease than answers. "When it comes to meibomian gland dysfunction, there are still many things we don't know enough about," she says. "Why is MGD symptomatic in some patients but not others? Which patients do we need to treat? What's the best way to treat? Hopefully, the workshop report will inspire much more interest in this disease, leading to new studies and data that will answer some of these key questions."

"To have success treating meibomian gland disease, we may need to identify patients at an early stage when the glands are still salvageable," notes Dr. Pflugfelder. "But that would require better diagnostic methods; either imaging or molecular markers of lipid function, something that would be simple for doctors to

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use. There are researchers who are looking at lipid profiles from normal and diseased glands and trying to make sense of it, and they are seeing differences in the lipids. Maybe what they learn will eventually filter down to the clinician. But right now you'd have to have a degree in biochemistry to really understand it."

In the final analysis, when it comes to diagnosis Dr. Asbell notes that it's not a yes or no situation regarding whether an ocular surface problem is being caused by meibomian gland disease or aqueous deficiency. "Many patients look like they have a combination of problems," she says. "In fact, it's possible that there's a sort of crossover between multiple problems. Abnormality in the meibum could affect the tear film and tear production; you could end up with both aqueous deficiency and MGD, with both of them contributing to abnormality of the tear film and ocular surface symptoms."

Dr. Pepose agrees that our understanding of dry eye is evolving, and notes that doctors are starting to focus more on an etiological assessment. "We're trying to determine at the outset whether a patient really does have dry eye, with increasing help from objective testing," he says. "I'm a proponent of that. However, it's important to remember that even the best objective test isn't a substitute for examining the patient. Doctors looking for diabetes can't use blood sugar levels alone; they have to ask whether the patient has diabetic neuropathy or diabetic retinopathy. The same is true with dry eye. Testing factors such as osmolarity is important, but you still have to look at the lids. Is this more of an aqueous problem? Is it meibomian gland disease? Is it mixed? Then you can start appropriate treatment and monitor the results." REVIEW

Drs. Asbell, Pflugfelder and Pepose have no financial ties to TearScience or any of the products discussed.

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Staying Local with Blepharitis Treatment

Ways to diagnose and categorize the disease, and thoughts on the best way to treat it when it occurs.

Mark B. Abelson, MD, CM, FRCSC, FARVO, Aron Shapiro and Caroline Tobey, Andover, Mass.

Blepharitis is a condition that involves the eyelids and associated structures, so why do we treat a blepharitis-affected lid by putting a topical steroid or antibiotic drops in the eye along with some lid scrubbing? We see the eye as our patient, and we don't want to waste our therapeutic efforts by sending drugs to far-off places such as the liver or the kidneys; instead, it makes much more sense to deliver an effective treatment straight to the source of discomfort, which in this case is the lid.

This month we'll go over the basics of blepharitis, explore the ins and outs of drug delivery, and consider how current delivery methods may be falling short when it comes to this common ocular disorder. What should become clear is that the eyelids and conjunctiva, while geographically close, may require very different treatment applications, and the course of therapy for blepharitis should be administered accordingly.

The ABCs of Blepharitis

Blepharitis is a multifactorial ocular surface disorder that can consist of an inflammation of the eyelid margin, including the lid and its dermis; the eyelashes, the tarsal conjunctiva, the mucocutaneous junction; and the meibomian glands. The condition is typically chronic and characterized by intermittent, acute flare-ups. Blepharitis can also be associated with a variety of systemic diseases like dermatitis, as well as ocular surface diseases such as dry eye, conjunctivitis or keratitis.[1] Signs and symptoms of blepharitis include swelling, thickening, scaling and/or crusting of the eyelids, redness of the lid margins, bulbar and palpebral hyperemia, gritty eyes and itchy eyelids. Staphylococcal blepharitis patients frequently exhibit mild adhesion of the lids, thickened lid margins, and missing and misdirected eyelashes; seborrheic blepharitis appears as greasy flakes or scales around the base of the eyelashes and a mild redness of the eyelids.[2]

We, too, have gotten involved in the classification of blepharitis, and in 2006 we created a classification system known as the Ora Calibra Blepharitis Scales, which consist of standardized, photo-validated scales for blepharitis and meibomitis based on anatomical descriptors. These validated scales have been used in previous clinical trials in order to accurately assess factors such as:

- lid margin redness;
- palpebral conjunctival redness;
- lid-edge shape;
- keratinization;
- lash folliculitis and debris;
- meibomian gland alignment, secretion viscosity and secretion color;
- perigland redness, and
- lash loss.

To construct the scales, a panel of clinicians ranked digital images from least severe to most severe, and they selected representative images to generate a scale of 0 to 3 (normal to severe). A lid margin evaluation was also performed, analyzing regional lid edge redness (temporal, medial and nasal) as well as lash folliculitis, lid hyperkeratinization, lash madarosis, cross-sectional posterior lid edge shape and lash debris. Additionally, Ora's direct meibomian gland tracking technology system is able to track and observe meibomian gland secretion's viscosity, color and thickness over time.

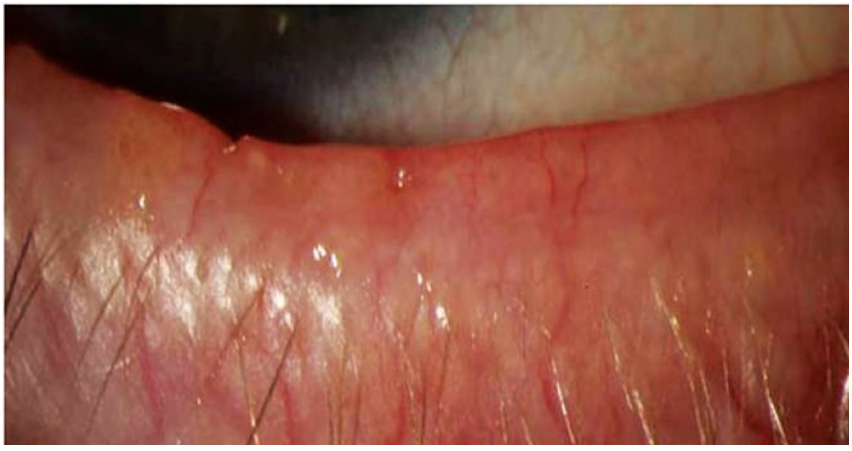
These scales have been used in

This article has no commercial sponsorship.

multiple studies conducted for the treatment of blepharitis, and have become a standard for blepharitis disease classification.[3-5] One such study (supported by Allergan in collaboration with Schepens Eye Research Institute) compared testosterone 0.03% ophthalmic with a placebo, and showed that testosterone was effective in relieving symptoms of blepharitis as measured by the Ora Calibra scales. This result was anticipated based upon the known role of androgens in regulation of the meibomian glands and formation of the tear film's lipid layer.[3,6]

The scales were also used in a multicenter, randomized, investigator-masked, and active-controlled, 15-day study evaluating the clinical efficacy and safety of tobramycin 0.3%/dexamethasone 0.05% (TobraDex ST) ophthalmic suspension compared to azithromycin 1% (AzaSite) ophthalmic solution in the treatment of moderate to severe blepharitis or blepharo-conjunctivitis. This study demonstrated a statistically significant improvement (decrease, p=0.0002) in mean global score in subjects treated with tobramycin/dexamethasone compared to subjects treated with azithromycin.[4]

The standard treatment regimen for blepharitis has historically consisted of localized lid hygiene, including the use of warm compresses and eyelid scrubs. These treatment modalities may have limited efficacy for many patients, however, especially those with more severe cases of the disease. Topical antibiotics are recommended to decrease the bacterial load, and topical corticosteroids may help in cases of severe inflammation. However, a bacterial etiology for blepharitis and the efficacy of treating it with an antibiotic have yet to be fully proven, and the only recent placebo-controlled study failed to show efficacy.[7] There isn't one approved yet, but a localized, prescription-grade anti-inflammatory formula applied directly to the lid would be an improved approach for blepharitis treatment.



The inflammation involved in blepharitis, if not addressed by treatment, can result in a significant amount of lid notching and scarring.

For the treatment of blepharitis, the American Academy of Ophthalmology also recommends the use of lid scrubs,[2] as they serve as a maintenance regimen for chronic circumstances. Lid scrubs are also recommended as a background standard of care in investigational clinical trials. Traditionally, however, patients' compliance with lid scrubs is limited due to the labor-intensive and messy nature of the treatment. Additionally, while foaming lid cleansers and premoistened pads are available, there is no universally accepted regimen for lid hygiene and lid scrubs.

Blepharitis also has an inflammatory component and, if left untreated, it can result in significant lid notching and scarring. This is very uncomfortable for the patient and can also lead to reduced effectiveness of the lid in performing its natural function of spreading the tears across the ocular surface to keep the surface hydrated.

The Problem with Drops

When a drop hits the eye, three parts of the anterior segment—the cornea, conjunctiva, and sclera—act as routes for the drug's absorption, though the cornea is the primary route for ocular penetration. There is a reason that topical drops have become the delivery method of choice for eye-care practitioners. For one, drops have significant advantages over other methods, including the minimization of adverse systemic effects as well as the avoidance of first-pass metabolism, which restricts the concentration of drug that ultimately reaches its target tissue.[8]

However, drops do have a few shortcomings, as well. First, they can be particularly difficult to physically manage for some patients, especially the elderly. Additionally, there is an array of physical and physiological barriers that protect the eye and significantly diminish the amount of drug being delivered. The cornea acts as a powerful protective wall, due to its relatively small surface area and low permeability.[9] These natural ocular barriers, like the blinking reflex and tear turnover, equip the eye with an effective removal system for foreign bodies, including eye drops.[9] Epithelial tight junctions also avert the diffusion of larger molecules and act as a barrier for smaller molecules.[10]

The eye's rapid turnover of tears creates quite a problem for an ocular drop. The tear film is typically only about 7 µL in volume, whereas one

eye drop is about 30 to 50 µL, depending on the surface tension characteristics of the drug.[11] Thus, approximately only 1 to 3 percent of a topical drop penetrates to the intended target tissues in the eye.[12] The remainder of the drop drains from the tear film by way of the nasolacrimal system and is then either deposited on the eyelids or metabolized by enzymes in the tears and surface tissues. As a result, at least 80 percent of the applied topical solution disappears due to drainage and does not enter the eye.[13] The subsequent reflex blinking that occurs when a drop hits the eye also decreases bioavailability.[14] Additionally, the contact time of a drug with the ocular tissues it's trying to access is only around one minute, due to the constant production of lacrimal fluid (0.5 to 2.2 µl/min.).[15]

In addition to the physical and physiological roadblocks the eye innately creates for a drop, tear flow is also very different from person to person, making an appropriate treatment course all the more difficult. For example, one study showed that dry-eye patients, who already have a compromised tear film, may undergo enhanced drug absorption because the barrier functions mentioned above aren't working adequately.[10]

Certain factors in a drug's formulation can modify its ability to penetrate these delicate yet robustly protective ocular tissues. These factors include the drug's general physiological mechanism of action, as well as the tissue concentrations of the active ingredient over time. However, there are methods that increase a drug's dwell time on the affected eye. For example, various compounds like high-viscosity solutions can be added to topically administered ophthalmic drugs in order to enhance corneal absorption, either by increasing corneal residence time or corneal penetration. These types of solutions yield an increased dwell time on the ocular surface, which allows for longer absorption time.[9] One such example of a drug with an added absorption component is the ocular steroid Tobradex, which was reformulated as Tobradex ST to reflect a decrease in the amount of steroid (from 0.1% to 0.05%) as well as the addition of an inactive agent (xanthan gum), to stabilize the combination and increase contact time. Despite a reduced drug concentration, pharmacokinetic bioequivalence studies showed equivalent anterior chamber concentrations of dexamethasone following dosing of Tobradex and Tobradex ST.[4]

An Optimal Vehicle

Ideally, treating the lid directly may circumvent problems of topical drug delivery. An optimal vehicle would provide a means for prolonging residence time at the site of application and improving tissue penetration.[16] Surprisingly, despite the number of eye drops used to treat ocular surface disease, no products have been developed for local delivery to the lid for blepharitis, although we have found time to develop topical products for the cosmetic treatment of our eyelashes. Latisse (Allergan), bimatoprost 0.03% solution, is approved for increasing eyelash length, thickness and darkness in patients with hypotrichosis of the eyelashes. Latisse was repurposed from the glaucoma medication Lumigan, after the medication was found to cause patients' eyelashes to grow thicker. Latisse is applied topically, directly to the lashes with a sterile brush, rather than in Lumigan's original form of an eye drop. And perhaps there's something we can learn from the success of a product such as Latisse: When you want to treat a local condition, the more local the delivery, the better the result will be. What better example of this need is there than the delivery of therapeutics for blepharitis directly to the affected lids?

By now, it should be clear that we feel improvements in blepharitis therapies are needed, and that these ought to include enhancements in the localized delivery of drugs such as topical steroids. By zeroing in on the local nature of this condition, it's reasonable to presume that treatment success can also be brought into sharper focus. REVIEW

Dr. Abelson is a clinical professor of ophthalmology at Harvard Medical School and senior clinical scientist at the Schepens Eye Research Institute. Mr. Shapiro is vice president of anti-infectives and anti-inflammatories and Ms. Tobey is a medical writer at Ora Inc., in Andover.

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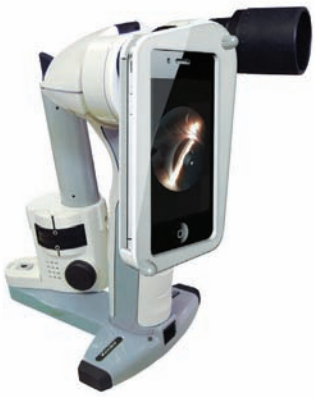

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Dry AMD: the Role of Complement

The complement system is implicated in the pathogenesis of dry AMD and, potentially, in its treatment.

By Omar S. Punjabi, MD, and Peter K. Kaiser, MD, Cleveland

The complement system consists of a series of soluble proteins derived from the liver that play a key role in eradication of foreign invaders. Activation of the system results in the production of the cytolytic membrane attack complex (MAC), leading to death of targeted cells via cell lysis. This system plays a key role in the prevention of infection by being involved in the recognition, opsonization and lysis of microorganisms and foreign pathogens. Complement activation can occur by one of three pathways: classical, lectin and alternate pathways.

The classical pathway is initiated when C1q (a pattern recognition molecule) binds to immunoglobulin in immune complexes, to C-reactive protein on self or microbial surfaces, or directly to molecules expressed on microbial membranes. This complex activates C1r, which becomes enzymatically active and cleaves C1s. C1s then activates C2 and C4, releasing C2a, C2b, C4a, and C4b. C2b and C4b become joined to form C3 convertase, C4b2b. C2 is similar (and related) to complement factor B (CFB), while C4 is similar (and related) to C3. The C4b2b molecule is functionally similar to C3bBb. C5 is the fifth component of complement, which plays an important role in inflammatory and cell killing processes. This protein is composed of alpha and beta polypeptide chains that are linked by a disulfide bridge. An activation peptide, C5a, which is an anaphylatoxin that possesses potent spasmogenic and chemotactic activity, is derived from the alpha polypeptide via cleavage with a convertase. The C5b macromolecular cleavage product can form a complex with the C6 complement component, and this complex is the basis for formation of the membrane attack complex, which includes additional complement components. The C5 convertase cleaves C5 into its two active components C5a and C5b. The result of this cleavage is the release of a C5a fragment, a potent inflammatory molecule, and activation of C5b, which initiates the MAC.

The MAC is initiated when the complement protein C5 convertase cleaves C5 into C5a and C5b. Another complement protein, C6, binds to C5b. The C5bC6 complex is bound by C7 and finally C8C8 alpha-gamma induces the polymerization of 10 to 16 molecules of C9 into the complex called MAC.

Initiation of the lectin pathway occurs when pattern recognition molecules (any of mannose-binding lectin (MBL), L-ficolin, H-ficolin, or M-ficolin) bind to the exterior surfaces of bacteria.

The alternative pathway is continuously activated by spontaneous hydrolysis of the internal thioester bond in C3 to form C3(H20). This molecule, although not cleaved, can fulfill the same role as C3b in C3 convertase. C3(H20) binds to CFB, and this complex is cleaved by the complement serine protease factor D (CFD), resulting in splitting of the CFB protein into Ba and Bb fragments. C3(H20)Bb is a C3 convertase, which splits C3 into C3a and C3b. Once produced by these means, C3b perpetuates the positive feedback loop described above, joining CFB to form more convertase enzyme. Newly cleaved C3b is also deposited on nearby surfaces. C3(H20)Bb is a less efficient enzyme than C3bBb, but is less easily inac-

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tivated by complement factor H (CFH) and its cofactor complement factor I (CFI).

Tight regulation of the complement cascade is necessary to prevent immune mediated disease and off-target damage of non-infected host cells. The balance between complement activation and inhibition is mediated by a series of regulatory proteins. CFH is critical inhibitor of the complement pathway that ensures the system targets foreign rather than host cells by neutralizing activated complement proteins that adhere to normal host cells.

AMD and Complement

The leading cause of vision loss in industrialized countries is age-related macular degeneration and its prevalence is increasing with the aging of the population.[1,2] The defect in AMD is thought to lie in the outer retina and retinal pigment epithelium, and genetic predisposition, age, ischemia and environmental factors may play a role in its development.[3,4]

Several recent studies have reported an association between AMD and key proteins in the complement cascade. For example, a variation in the gene encoding CFH, the key inhibitor of complement mediated damage to non-pathologic cells, produces a nearly fivefold increase in the risk of AMD for individuals who harbor the Y402H polymorphism.[5-8] The products of complement activation have been detected in blood in AMD patients. Hendrik P. N. Scholl and colleagues found that C3d, CFB and CFD were significantly increased in patients with AMD.[9] The presence of activation products in circulating blood indicates that the inflammation found in AMD is not limited to the retina, but is systemic. The extent of this systemic complement activation in AMD is currently unknown.

Mutations in complement-related genes including CFB, C2 and C3 have been associated with AMD.[10] However, mutations in the CFH gene appear to have the greatest link to AMD.[5-8] The CFH gene forms part of the RCA (regulators of complement activation) gene cluster located in the 1q32 chromosomal region of the human genome. The Y402H genetic variant of CFH gene is commonly associated with AMD. Genetic studies suggest that there may be further variants in the region associated with altered risk that have not yet been uncovered.

Local complement system in the human RPE-choroid complex has also been described. Cells within the neural retina, RPE and choroid demonstrated gene expression profiles consistent with replication of the complete cohort of complement components and regulatory proteins associated with both the classical and alternative pathways.[11] Components of the complement system have also been identified in drusen.[12,13] Druse in AMD contain almost all alternative complement pathway proteins, including CFH, C3, and the products of its activation and degradation, as well as the terminal pathway proteins C5, C6, C7, C8, C9, separately and in combination as the MAC. An implication of this hypothesis relates to the finding that homozygous individuals for the most common CFH risk allele (Y402H) tend to concurrently manifest raised levels of choroidal C-reactive protein, a serum biomarker for inflammation,[14] and in patients with both problems an increased risk of AMD progression.[15] Thus, since dysfunction of the local complement system is associated with AMD, the RPE-choroid complex is a potential location for the delivery of novel therapeutic agents that target the complement cascade.

Current Role of Complement-Based Therapies

A number of AMD therapies are being developed to target specific components of the complement cascade. Complement therapies also have the potential to work at an earlier stage in the disease process, preventing progression to late AMD. However, modulation of the

Current Medications in the Pipeline for the Management of Dry Age-related Macular Degeneration

Drug	Mechanism of action	Sponsor	Clinical study phase
POT-4 (Compstatin)	C3 inhibitor	Alcon	Phase II
ARC 1905	Aptamer-based C5 inhibitor	Ophthotech	Phase I completed
Eculizumab (Soliris)	C5 Antibody	Alexion Pharmaceuticals	Phase III
FCFD4514S	Anti-factor D antibody	Genentech	Phase II
TA106	CFB inhibitor	Taligen Therapeutics, Alexion Pharmaceuticals	Pre-clinical development
JSM-7717 and JPE-1375	Peptidomimetic C5a receptor inhibitors	EvaluatePharma and Jerini AG respectively	Pre-clinical development

complement cascade may adversely affect the body's defense mechanisms. Hence, any new therapeutic modality must affect AMD without adversely affecting the body's immunological function. The use of local complement component inhibitors minimizes potential systemic side effects of complement inhibition. However, local inhibition of complement via intravitreal injections may have a shorter half-life and more local adverse effects, and may not be feasible in a life-long disease such as AMD.

Some companies are evaluating nucleic acid aptamers that are synthetically derived and demonstrate desirable therapeutic properties largely owing to their three-dimensional structure, high target specificity, and high binding affinity. Others are using monoclonal antibodies that are laboratory-engineered clones of immunoglobulins designed to bind to specific target cell surfaces. They inhibit specific molecules or activate the immune system. Monoclonal antibody-based complement inhibitors exhibit similar molecular recognition characteristics, but they also have the potential to provoke an immunogenic response, which does not occur with aptamer compounds.

Some of the medications that are on the horizon and show potential in the management of AMD include:

• Eculizumab (Soliris, Alexion Pharmaceuticals, Cheshire, Conn.) is an orphan drug that is marketed for intravenous treatment of paroxysmal nocturnal hemoglobinuria (PNH), and received FDA approval in 2007 as the only licensed monoclonal antibody that targets the complement system. The molecule has been humanized to minimize immunogenicity and increase drug half-life, but was originally derived from a murine C5 antibody. This drug binds to C5 and prevents downstream activation and formation of MAC. The drug is administered intravenously over six months; weekly dosing during the initial induction period followed by two weekly maintenance doses. The COMPLETE (Complement inhibition of systemic Eculizumab for the treatment of Non-Exudative Age-Related Macular Degeneration) study at Bascom Palmer *(Yehoshua Z, et al IOVS 2012;53:ARVO E-Abstract 2046)* is one of the first to study the use of systemic complement inhibition for the treatment of dry AMD. *(See Retinal Insider, September 2012 for more on the COMPLETE Trial.)* Their results involving 30 eyes of 30 patients at six months showed that systemic treatment with eclizumab did not decrease drusen volume. In the same study, systemic use of eclizumab did not decrease the growth rate of geographic atrophy. Their explanations for lack of treatment effect for GA in this population included the possibility that complement activation may have no role in growth of GA; or the study duration was too short; or a higher drug dose was needed; inadequate penetration into the eye; different complement target needed; or that they used an inappropriate endpoint. These results were from a single study and involved administering systemic medication in just 30 eyes of 30 patients, and the power of the study may not be adequate to appropriately assess the role of C5 inhibition in dry AMD. Further studies are indicated in assessing the role of eclizumab in dry AMD.

• POT-4 (Alcon), a derivative of compstatin, is a potent C3 inhibitor that suppresses complement activation by preventing the formation of key elements within the proteolytic cascade, thus impeding local inflammation, upregulation of angiogenic factors and subsequent tissue damage. POT-4 is administered intravitreally, which may limit possible unwanted systemic effects. Early results of POT-4 suggest that it manifests a good safety profile and drug tolerability. *(Kaushal S, et al IOVS 2009;50:ARVO e-abstract 5010.)* It is currently in Phase II clinical trials.

• ARC1905 (Ophthotech, New York, N.Y.) is an aptamer-based C5 inhibitor, blocking the cleavage of C5 into C5a and C5b fragments and is another intravitreally adminis-

tered complement inhibitor being evaluated in AMD. Like POT-4, it is similarly selective for a centrally positioned component within the cascade, although exerting its effect further downstream.

• FCFD4514S (Genentech) is an anti-factor D antibody being studied for the treatment of dry AMD. Blockage of the complement factors (such as factor D) that moderate the production of these end-products serves to attenuate complement activation, rather than shutting the system down completely. Anti-factor D is administered intravitreously and selectively inhibits CFD which is a key component of the amplification step of the alternatve pathway. It is currently in Phase II testing for dry AMD.

• TA106 (Taligen Therapeutics; Alexion Pharmaceuticals, Cheshire, Conn.) is a CFB inhibitor, still in pre-clinical development, that is primarily being investigated as an inhaled formulation in the treatment of severe, chronic asthma refractory to current therapies and is recently being studied for macular degeneration.[16]

• JSM-7717 (EvaluatePharma) and JPE-1375 (Jerini AG; Berlin, Germany) are two peptidomimetic C5a receptor (which is pro-inflammatory) antagonists currently in preclinical assessment for AMD.[17] Receptor antagonists competitively bind to the C5a receptor neutralizing interaction, and hence such drugs have the potential to suppress the inflammatory response without adversely affecting complement-related immunity and are being used in pre-clinical studies.[18]

• Intravenous administration of CR2-fH, a recombinant form of CFH, was associated with a reduction in CNV size and the physiological sequelea of CNV on retinal function. The effectiveness of this approach in a mouse model of laser-induced AMD was recently elucidated.[19] This strategy involves the supplementation of wild-type CFH with a recombinant "protective" form of the protein in high-risk variant cases. In theory, such augmentation should be helpful in re-instituting homeostatic regulation of the alternative pathway of the complement system. This drug is being studied in animal models and is part of ongoing pre-clinical experiments.

• C1INH (ViroPharma Inc., Exton, Pa.) received FDA approval for the treatment of hereditary angioneurotic edema in 2008. Mutations in the gene that encodes SERPING1, a C1-inhibitor (C1INH) may similarly play a role in the development of AMD.[20] A recent study showed that C1INH is present in the human retina and choroid, and AMD affection status was correlated with increased levels of the protein in the choroid.[20] This drug, although not being used clinically, has the potential to be used in AMD.

Thus, there is substantial evidence now that the complement system plays a role in the pathogenesis of AMD, but its exact role is uncertain. A number of drugs are being developed that target various components of the complement cascade, predominantly the alternate complement pathway. The complement cascade remains as one of the many therapeutic targets in AMD, and our understanding of its role in AMD is still primitive. However, emerging drugs that target the complement cascade are promising and may play a vital role in the prevention and management of this condition in the future. REVIEW

Dr. Kaiser is a consultant to Alcon, Novartis, Genentech, Ophthotech, Allegra, Bayer, Regeneron and ArcticDx; he reports a financial interest in SKS Ocular, LLC. Contact him at Cole Eye Institute, 9500 Euclid Ave., Desk i3. Cleveland, Ohio 44195. Phone: (216) 444-6702, e-mail: pkkaiser@aol.com.

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PAP: New Concerns for Prostaglandin Use

These popular drugs are causing previously unnoticed cosmetic changes that can be problematic for patients—and doctors.

by Stanley J. Berke, MD, FACS, Garden City, N.Y.

Prostaglandin analogues have become a mainstay of glaucoma treatment, for good reason; they're quite effective at lowering intraocular pressure and don't require multiple applications each day. Until recently, it seemed like the downsides of this class of drug were minimal, making it a good choice for many patients.

Now, however, it's become known that another side effect has been staring us in the face—literally—all along. Apparently, for biochemical reasons, there's an affinity between the prostaglandin drugs and periorbital cells, in particular the fat cells. Exposure to the prostaglandin affects their metabolism, causing them to shrink. The shrinkage of the fat cells surrounding the eye causes enophthalmos—the eye becomes more sunken-in. The result is a deepening of the superior eye lid sulcus, while periorbital fat tissue seems to melt away. The cosmetic change—once you know to look for it—is actually quite striking, especially when a patient is using a prostaglandin unilaterally, which ends up causing asymmetry between the eyes.

The effects produced by the use of a topical prostaglandin include upper lid ptosis; deepening of the upper lid sulcus; involution of dermatocholasis; periorbital fat atrophy; mild enophthalmos; inferior scleral show; increased prominence of lid vessels; and tight eyelids. This constellation of findings has been called prostaglandin-associated periorbitopathy, or PAP. Technically, you could probably include all the other known side effects (e.g., lengthening of lashes and increased pigmentation of the iris and periorbital skin) under that umbrella, but this is of interest precisely because it's gone unnoticed for so long.

It's important to note that exposure to prostaglandins doesn't kill fat cells or reduce their number. In fact, people have the same number of fat cells in their bodies their entire adult lives. When a person becomes fat, the fat cells have simply gotten fatter, and when a person becomes thinner, the fat cells have shrunk. So the change is caused by an alteration of the fat cells, not by their elimination.

Hiding in Plain Sight

The first patient that brought this to my attention was using a prostaglandin in one eye only; he asked me why his lid on that side was drooping. When I looked closely I realized it was only drooping a little bit, but his eyes displayed a lot of asymmetry because the lid sulcus was so much deeper in that eye. I was able to measure and photograph that he had enophthalmos, which suggested that this was an issue of fat atrophy.

This got my attention, and to my amazement, when I began looking for it in my patients who use prostaglandin eye drops for treatment of glaucoma, I found the effect almost 100 percent of the time. Once you know to look for it, it's very apparent. In a typical day I may see 40 patients; 20 or 25 have glaucoma and 10 or 15 of those patients are using prostaglandins. I started looking at those patients, and I noted this PAP effect in nearly everyone—especially if they were using a prostaglandin unilaterally.

Once I became aware of the phenomenon, I started taking photographs before initiating treatment. When a patient is trying a prostaglandin for the first time I usually do a monocular trial to test the efficacy of the drug.

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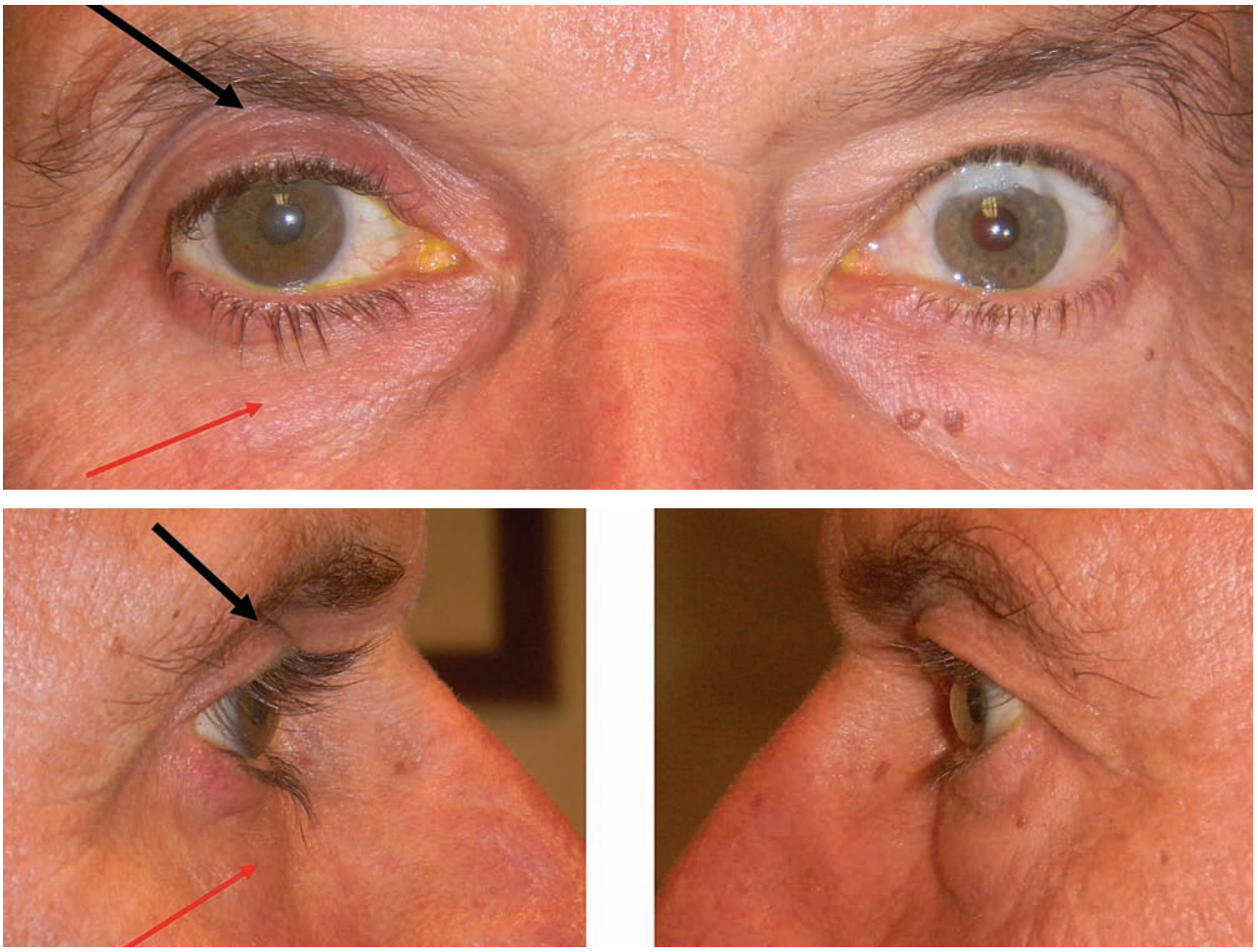


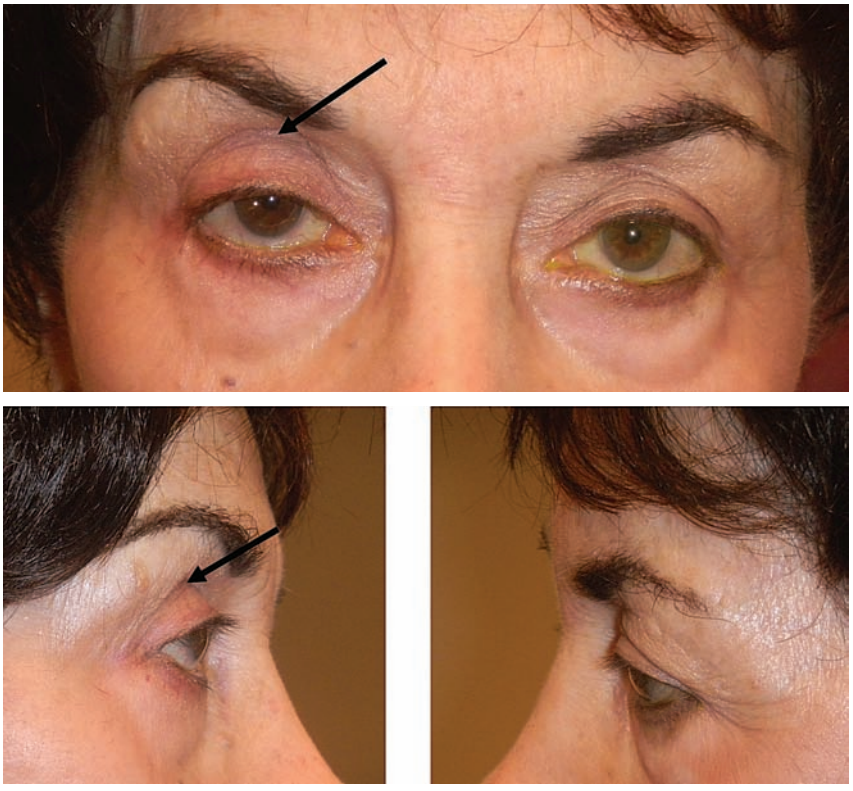
A 71-year-old male who had a trabeculectomy in the left eye but has used prostaglandin drops for seven years in the right eye, resulting in 3+ prostaglandin-associated periorbitopathy OD. Note the sunkenness of the eye OD and appearance of the surrounding tissues.

When these patients came back three weeks later, I could already see, and was able to document, full-blown PAP. That amazed me; I thought it would take months or years before you'd see these changes. Then, if I told the patient to stop the drops and return in three weeks, the PAP was completely resolved. Again, I was really surprised. Based on what I've seen, however, I suspect that if someone uses a prostaglandin for several years, even if they stop the drug they may not get total resolution. Some of the changes may be permanent.

Searching the Literature

Initially, I thought I was the first to notice this effect. I couldn't find any mention of it in the package inserts, on company websites or in any of the journals I read. Eventually, though, I discovered that several articles had previously been published documenting this phenomenon. The earliest article was published in an optometry journal in 2004[1]; the authors reported observing two cases of eyes becoming deep-set after using bimatoprost (Lumigan 0.03%). Other articles later appeared in journals published in other countries. The first report of this made by an American ophthalmologist was an article published in *Ophthalmic Plastic and Reconstructive Surgery* in 2008 by Louis Pasquale, MD, chief of glaucoma services at Massachusetts Eye & Ear Infirmary, and his colleagues, including lead author Theodoros Filippopoulos, MD, who was a glaucoma fellow with Dr. Pasquale at the time.[2] They observed this problem as a side effect of bimatoprost.

All of the early articles reported cases involving bimatoprost, which might lead one to conclude that the problem is limited to that drug. It wasn't until the fifth article in 2009, from Japan, that travaprost (Travatan) was reported as causing two cases.[3] Meanwhile, in my own patients I found that this change was occurring in those using any prostaglandin, so I believe it's safe to say that it's an



This 86-year-old female used travoprost OD for one year. Signs of PAP are readily visible, causing the eyes to look assymetric.

issue with the entire class of drugs rather than being unique to any one of them. Of course, there could be differences in how this side effect occurs within the class; it may be a more prominent effect with one drug than another. I have patients who are only on latanoprost (Xalatan) who have full-blown PAP. Hopefully, future studies will determine whether significant differences exist between the prostaglandins. (Dr. Pasquale and his colleagues at MEEI have recently completed a longitudinal, cross-sectional study of PAP that will be presented as a poster at the American Academy of Ophthalmology meeting this year.)

How Did We Miss It?

How is it that such a readily visible phenomenon escaped our attention for so long? Most of us are very observant, so that was one of the first questions that occurred to me: How could this have gone unrecognized for so long?

As ophthalmologists and glaucoma specialists, it may be that we're not focusing as much on what the patient's eyelids look like. We put drops in, sit the patient at the slit lamp, check the pressure, look at the eye and check the optic nerve under the microscope. We do imaging studies of the back of the eye where the damage is. And until now, we were not aware that there was a problem at the level of the eyelids, so we weren't focusing our attention on it.

Another point is that the majority of these patients use these drops bilaterally. When a patient uses a prostaglandin bilaterally, asymmetry doesn't develop, and changes that occur over time are more easily missed or blamed on factors such as aging. And of course, we don't see most of these patients every day, so small changes in appearance are easy to overlook. Even when the changes are noticeable—and in some cases they are—if you have no reason to believe the changes are connected to your treatment, you're unlikely to make the connection.

Now, of course, I look for PAP in all patients and include it as part of my findings. If someone is on a prostaglandin drug, I'll grade the PAP that exists just as I would any other clinical finding. For example, I might note "3+ PAP, left eye," or "mild PAP OS," in the chart.

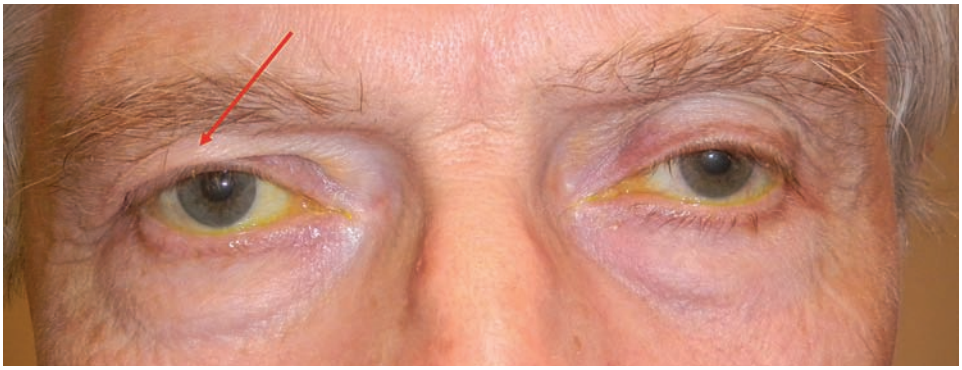
Consequences of PAP

Obviously, altering someone's appearance—potentially in a negative way—is not an insignificant thing. For that reason, being aware of this issue has definitely affected the way I choose a first-line, pressure-lowering drug. In the past, when I was not aware of this issue, I would almost always opt for a prostaglandin as the first-line drug for most patients. Today, I'm less likely to use a prostaglandin if a patient only needs to be treated in one eye, because of concerns about unwanted cosmetic changes. Not only is the patient likely to have longer lashes and darker skin unilaterally, but the treated eye will become more deep-set and the appearance of the lids will become asymmetrical. If a patient uses a prostaglandin bilaterally, at least it will affect both eyes so the patient won't end up with an asymmetric appearance.

There are other potential negative consequences as well. For one thing, making the eye more sunken can make it harder to examine. Deep-set eyes are much more of a challenge, so this side effect may put us at a disadvantage in our efforts to help the patient.

In addition, asymmetrical appearance can trigger unnecessary medical testing by other doctors.

If an individual is using a prostaglandin in one eye only, the resulting asymmetry may lead other doctors to question the reason for it. Those doctors might reasonably believe that one eye is bulging more than the other (even though the prostaglandin eye is actually becoming more sunken in). In theory, a bulging eye could imply a thyroid disorder or a tumor behind the eye. This could instigate a whole line of questioning and a medical workup, which has in fact happened; patients have undergone CAT scans and MRIs as doctors tried to determine why the eyes were asymmetric. If doctors were aware that this can be a consequence of using a prostaglandin in only one eye, many patients—and the health-care system—could be spared unnecessary testing.



Discontinuing use of prostaglandins seems to result in reversal of PAP. This 70-year-old male used travoprost in both eyes for four years; the photograph was taken eight months after the drops were discontinued OD.

It's also important to realize that this effect will occur even when the drug is only being used for cosmetic purposes, as when it's prescribed as Latisse (bimatoprost 0.03%). Beyond the desired effect of lengthening the lashes, the eyes may become more sunken; some patients may look better, but some may look worse. I've seen lectures promoting Latisse given by doctors who were not aware of this side effect. Clearly, any time a medical professional prescribes a drug, knowing all of the side effects is crucial. And, as already noted, even doctors who don't prescribe the drug need to know about this to prevent unnecessary testing and scans in search of an explanation for the asymmetry.

Of course, there is a potential upside to PAP. Usually, when we talk about a side effect we assume it's a negative, but that's not always true. Making your eyelashes longer and thicker is an example of a good side effect—it's something people like. The same thing is true here: If an individual has loose, puffy, baggy lids with fat prolapse and loose skin before treatment, this drug can make him look better. *(For example, see the photos on p. 74.)* For some patients who might be candidates for plastic surgery, this could be thought of as a "blepharoplasty in a bottle." You can tell those patients that this drop will not only lower their pressure, it will make their lids look better.

However, if patients don't have loose, puffy skin and their eyes are fairly deep-set to begin with, their eyes may become even more deep-set. Young people, for example, tend not to have a problem with puffy skin and may already have deep-set eyes. If you give these drops to young people, their eyes may go from being deep-set to being very deep set. This effect, along with darkening of the periorbital skin, can give them a "zombie" look.

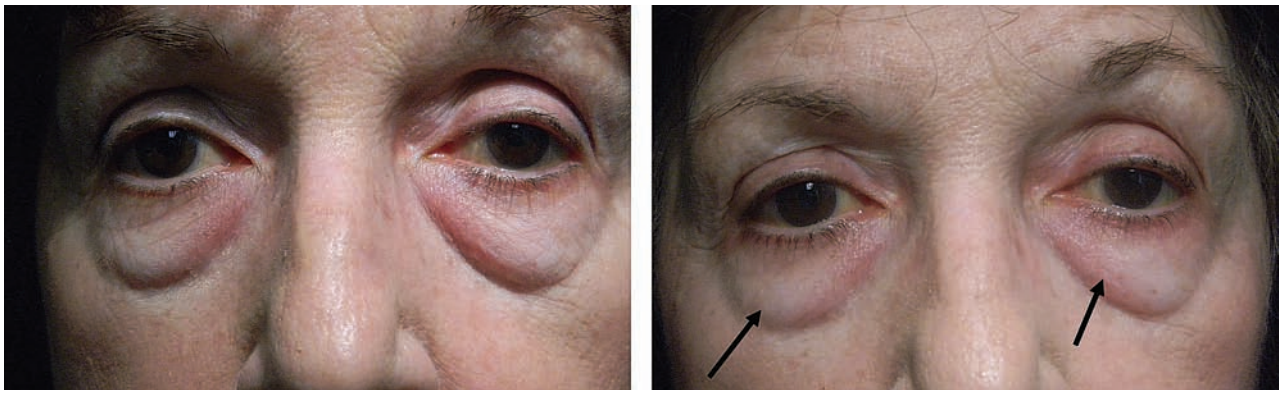
Manufacturer Response

Based on suggestions from myself, Dr. Pasquale, and Dr. Wiley Chambers from the Food and Drug Administration, most manufacturers have added a sentence to their package inserts in the post-marketing experience section. For example, most inserts for topical prostaglandin drops now mention "reports of periorbital and lid changes associated with a deepening of the eyelid sulcus." They don't list this under the adverse reaction or side effects sections, because this was not officially noted during any of the clinical studies performed for the FDA.

Despite the mention in package inserts, the inclusion of this important piece of information is inconsistent in other places. In full-page ads placed in journals and other magazines, it is often not listed. I have recommended, and continue to recommend, the consistent inclusion of this important side effect in all written and verbal information about these drugs. I have also suggested that the companies send a mailing to all medical professionals informing them about this.

Interestingly, some early animal studies showed that the drug had a much higher concentration in the periorbital tissue than in the anterior chamber—which is where the drug needs to go in order to be effective. However, the drug companies say they have received very few reports of the PAP side effect, even though the drug has been available for 10 years and is the number one drug used to treat glaucoma in the world. This may explain why PAP was not listed as a side effect earlier.

Of course, this "downside" to prostaglandins could also have a monumental upside. This property of the



The periorbital fat atrophy caused by PAP can improve cosmesis in some patients. Left: A 74-year-old woman before treatment. Right: After using travaprost in both eyes for two months.

drug could lead to an entirely new, potentially even more lucrative use for the drug: shrinking fat cells not only around the eyes, but in other parts of the body as well. I have already made this suggestion to several of my patients being treated for glaucoma bilaterally with prostaglandin drops: Rub any excess drop that exits the eye into the upper and lower lids, and improved cosmesis will start to occur within weeks. I offer the opposite advice for patients with deep-set eyes: Be vigilant about absorbing the excess prostaglandin drop with a tissue, to avoid absorption by the periocular fat cells.

Implications for the Clinic

In terms of using this information in the clinic, probably the most important piece of advice I can offer is to simply be aware of the problem when you're deciding what to prescribe. Look at the state of the patient's lids and take that into consideration when choosing an option. Should you use a prostaglandin first in this patient, or a different class of drug? Should you consider not using a drug at all, perhaps opting for selective laser trabeculoplasty or surgery instead?

Clearly this is especially important if you're planning to treat unilaterally, which may cause the patient to develop an asymmetrical appearance. (That can be a problem even if the overall effect makes the eye look better.) Patients should be aware of this possibility, just as they should know that the drug might change their eye color—an effect that some patients don't mind, but others do. If the patient will use the drug in both eyes, you should still have the discussion, even though asymmetry won't be an issue. Both eyelids will look less puffy and more deep-set, which may or may not be a good thing, depending on how the eyes look pre-treatment.

If you really want to monitor changes, the best way is with photography. Taking photographs at the outset is an option and is easy to do, though it's certainly not mandatory. When I was first noticing this, I was very interested in it, and I took lots of external photographs. (Bear in mind that the patient must give written consent for medical photography—especially if you want to use the images for presentation or publication.)

In terms of patients who are already on treatment, I think doctors should be trying to observe whatever changes are taking, or have taken, place. Document the effect either by describing and grading or by photography, and note it in the medical record. Patients who develop PAP may elect to continue or discontinue the drug. Those who have cosmetically-bothersome orbital fat atrophy may wish to consult with an orbital plastic surgeon. (There are some treatments available, and this is an active area of investigation in the field.)

Now You See It…

The bottom line here is that although this has been very sparsely published, this effect is real, it's common, and it's associated with all the drugs in the class, including the generics. It's now listed in the package inserts. And it can have significant cosmetic and structural effects that we should be aware of, should look for, should document, and should discuss with the patient, just as we would with any side effect of any drug. REVIEW

Dr. Berke is associate clinical professor of ophthalmology at Hofstra North Shore-LIJ School of Medicine in Hempstead, N.Y., and chief of the Glaucoma Service at Nassau University Medical Center in East Meadow, N.Y.

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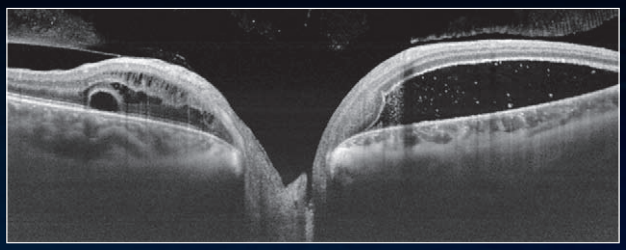

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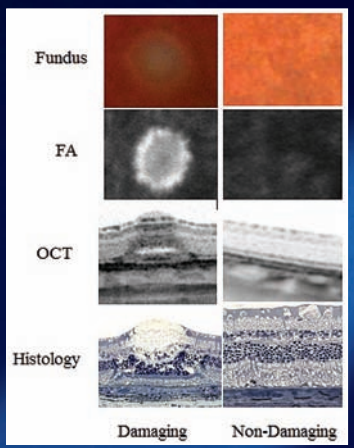

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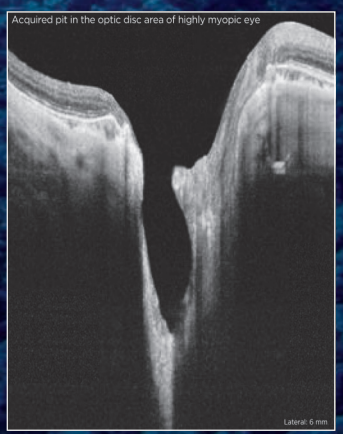

Courtesy: Department of Ophthalmology, Tokyo Medical and Dental University

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Don't Get Lost in The Shifting Sands

How to treat the various stages of diffuse lamellar keratitis and crucial tips on differentiating it from central toxic keratopathy.

Walter Bethke, Managing Editor

Diffuse lamellar keratitis, also called the Sands of Sahara syndrome, is a complication of LASIK in which inflammatory cells appear in the interface. Though it's rare, when it does occur surgeons say quick recognition and treatment can mean the difference between a good outcome and a drawn-out battle that could potentially leave the eye with a refractive error. Here's a look at the defining characteristics of DLK and how to differentiate it from central toxic keratopathy, a condition that some surgeons say DLK can be mistaken for.

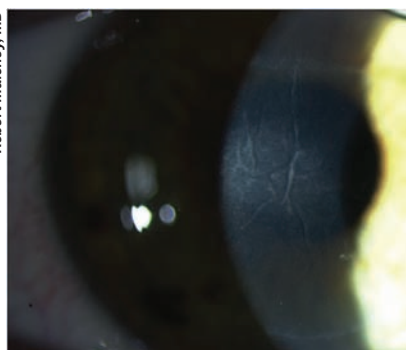
Early Stages of DLK

Many surgeons use the DLK classification scheme proposed by San Diego surgeon Eric Linebarger in 2000 while he was at the Phillips Eye Institute in Minneapolis.[1]

"In stage one, there are cells in the interface in the periphery of the flap," explains Minneapolis surgeon Elizabeth Davis. "They're usually very fine. At this point, it's pretty mild and we just advocate increasing the steroids to hourly and checking the patient in one to two days. If DLK is going to occur, it's almost always present on day one, and it doesn't just suddenly appear a week later."

The hallmark of stage-two DLK is that the cells have crossed the pupillary axis and are more diffuse across the interface, say surgeons. "The treatment is hourly steroids, and some surgeons will add a steroid ointment for use at bedtime," says Dr. Davis. "We check the patient in one or two days."

"At stage three you start to see clumping of cells with surrounding clear areas," says Dr. Davis. Surgeons say this agglomeration can sometimes lead to a decrease in visual acuity.[2] "If it is severe, I irrigate under the flap," says Los Angeles surgeon Robert Maloney. If DLK reaches the third stage, many surgeons agree that removing the cells is important along with concomitant steroid treatment, which may include oral steroids.



Robert Maloney, MD

Surgeons say central toxic keratopathy, shown here, is non-inflammatory while DLK is an inflammatory condition.

In terms of differential diagnosis, Dr. Maloney says there are two other entities to rule out. "On slit-lamp exam, DLK is diffuse and confined to the interface," he says. "Infectious keratitis, though, tends to extend anterior and posterior to the interface as the microorganisms spread through the stroma, and is associated with inflammation, redness and pain. The other entity to differentiate DLK from is central toxic keratopathy, also called stage four DLK [discussed below]."

Later Stage DLK vs. CTK

Some controversy exists over whether the entity some surgeons diagnose as stage four DLK is actually a different disease altogether, called central toxic keratopathy. Since the

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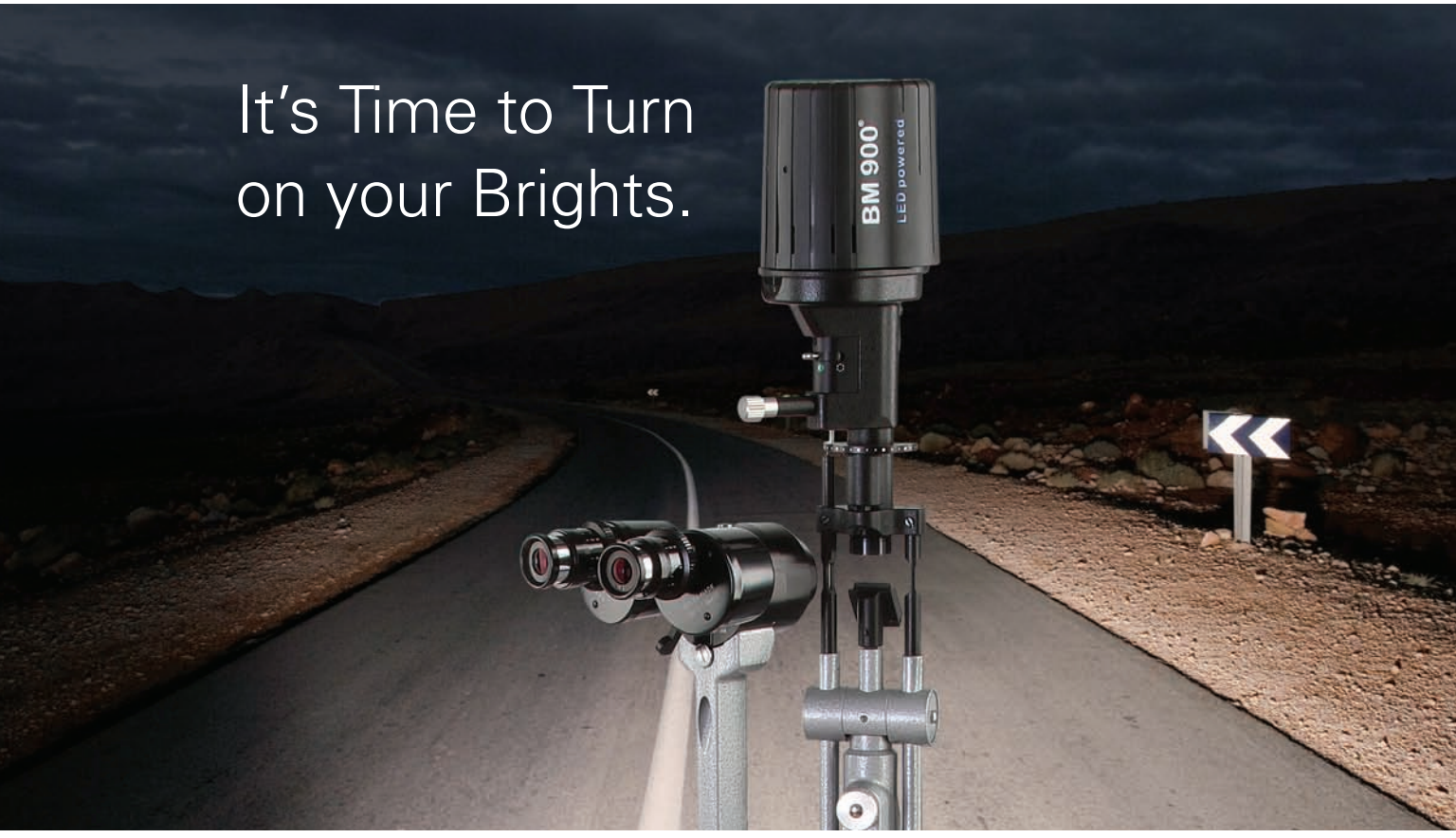

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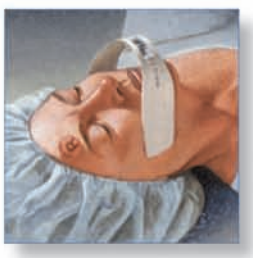

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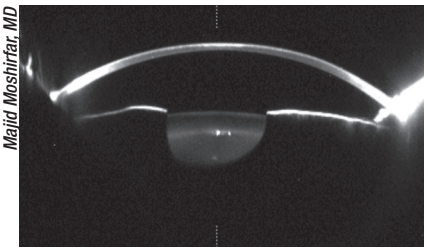
treatment for CTK is different from that for DLK, surgeons say it pays to look for certain diagnostic clues.

Dr. Maloney says some cases of DLK can progress to CTK. "CTK presents as an opacification in the cornea, associated with striae, that's either anterior or posterior to the flap," he says. "There is no significant inflammation. It seems to be a collapse of the collagen structure because patients tend to get quite hyperopic. The difference between infectious keratitis and CTK is that there is inflammation with infection, and the difference between DLK and the other two entities is whether it's confined to the interface or not."

Majid Moshirfar, MD, of the University of Utah's Moran Eye Center, agrees that CTK needs a different treatment approach, but also thinks it is actually separate from DLK. Dr. Moshirfar believes what is graded as stage-4 DLK is simply the aftermath of an intensive round of treatment for stages one through three, leaving a "burned out" cornea that has a "mudcrack" appearance. For a stage-four DLK like this, Dr. Moshirfar stops the steroid and allows the cornea, often hyperopic at this point, to remodel and heal itself over a period of 18 to 24 months. An enhancement may be required at that point to correct the refractive error.

Dr. Moshirfar says once you see the entity CTK, you will most likely see that it's different from DLK, and says the time course is usually a key to diagnosis also, since CTK doesn't present immediately after surgery. "Day one, the patient will be fine," he says. "Then, on day three or four, he'll call you and you'll have him come in. On examination, you'll see this opacified, almost nebulous, gelatinous shape located either centrally or paracentrally. It looks almost like a disciform herpetic keratitis, and is usually 4 to 5 mm in diameter. You can tell that it comes out of the interface, and involves both the flap and the posterior stromal bed." He says that CTK apparently involves a tissue necrosis that is destroying the collagen. He adds that, to add to the potential confusion, there is sometimes low-grade DLK in the periphery of the CTK cornea.


Majid Moshirfar, MD

On OCT, CTK will be visible extending outside the flap interface, in contrast to DLK, which stays within the interface.

To treat CTK, surgeons advocate backing off the anti-inflammatories rather than ramping them up. "The focus is not to use the steroid," says Dr. Moshirfar. "If something is killing the keratocytes in the cornea, then we won't have any more keratocytes to lay down more collagen, so we should treat that. That's why I put CTK patients on antioxidants in the form of multivitamins, co-enzyme q10, doxycycline 200 mg b.i.d., and 2,000 to 4,000 mg of vitamin C daily. Vitamin C, I think, is useful in a condition such as this because it has properties that help promote collagen, and the doxycycline helps prevent matrix metalloproteinases from destroying more corneal collagen."

Dr. Moshirfar won't discontinue the steroid completely, but instead will keep patients on the normal postop LASIK steroid regimen. He says this approach can also help in those CTK cases in which some associated low-grade DLK exists in the periphery. He won't increase or lengthen the steroid course, however. "The mistake many clinicians make in central toxic keratopathy is to increase the steroid to every 30 minutes or put patients on an oral steroid," he says. "That's not the right thing to do."

Dr. Maloney agrees: "For treatment of CTK, the first point is reassurance," he says. "This is because CTK always goes away, though it may take six to nine months. Note that it often leaves the patient hyperopic, but it will resolve. The other aspect is the question of treating CTK with steroids or not. I have taken the position that they should not be used, because CTK is non-inflammatory. We've published articles that show prolonged steroid treatment after LASIK can lead to end-stage glaucoma,[3,4] and it can go undetected because fluid in the flap interface leads to erroneously low IOP readings. So our position is that long-term steroids after LASIK are not a good idea." Surgeons warn against lifting the flap and irrigating in CTK patients, since they say this will actually wind up removing more corneal tissue than is necessary. They say that this is because the condition apparently involves a process of tissue necrosis in the cornea.

Dr. Moshirfar assures surgeons that jumping on DLK early will solve most potential problems. "The most important thing about DLK is, if a patient comes to you suffering slightly from some visual disturbances, and you see him early on, treat his DLK with a topical steroid and see him every 24 hours. You will hardly ever have to lift a flap and irrigate beneath it," he says. "In that patient, the DLK will resolve and not move on to stage 3. I have yet to have a stage-4 DLK walk into my office on the fourth or fifth day. And if I do see one classified as such, most of the time it's probably a CTK that someone deemed a DLK." REVIEW

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Corticosteroids May Benefit DALK Patients

New research from Chicago suggests that the incidence of stromal rejection in deep anterior lamellar keratoplasty is clinically significant and that these patients may benefit from corticosteroid regimens similar to those used in penetrating keratoplasty.

The clinical records of 22 patients undergoing DALK by two surgeons between October 2006 and January 2008 were reviewed to identify patients who experienced stromal rejection. The diagnosis was made after the demonstration of acute stromal edema and/or stromal neovascularization in the absence of confounding preoperative conditions, such as herpetic keratitis. The incidence and clinical features of stromal rejection were compared with other descriptions found in the literature.

Five of 20 eligible patients experienced stromal rejection within 12 months. Two patients were on low-dose corticosteroids when diagnosed. Four of the five patients were treated aggressively with q1 to 3 hourly prednisolone acetate 1% eye drops. The fifth was treated less aggressively with a maximum dose of only q6 hourly prednisolone acetate 1% and subsequently experienced a second rejection episode less than five months later. All episodes resolved completely with treatment.

Cornea 2012;31:969-973
Olson E, Tu E, Basti S.

Retreatment with Anti-VEGF After Stabilization of AMD

European researchers evaluated the three-year therapeutic benefit of intravitreal bevacizumab in neovascular age-related macular degeneration and determined that while the functional and morphological benefits persisted for the first year after treatment, after this time both functional and morphological results were disappointing when visual acuity loss was the main retreatment criterion.

In this interventional clinical study, 181 eyes of 160 consecutive patients with active neovascular AMD meeting recommended inclusion protocol criteria for anti-vascular endothelial growth factor therapy undergoing intravitreal bevacizumab monotherapy were observed. Data of treatment-naive eyes (Group 1, n=114) were analyzed separately from eyes that had undergone previous photodynamic therapy plus intravitreal triamcinolone (Group 2, n=67). Retreatment criteria were based on clinical outcomes following the official European label regimen. After one year of continuous service at an academic referral center, follow-up was performed in private practices in collaboration with the referral center. Main outcome parameters were best-corrected visual acuity and central retinal thickness.

After three years, BCVA decreased in the overall population (0.23 ±0.16 to 0.16 ±0.21, p=0.002) and in both groups compared with baseline (0.24 ±0.21 to 0.17 ±0.21, Group 1, p=0.03; 0.22 ±0.19 to 0.16 ±0.21, Group 2, p>0.05), whereas central retinal thickness increased in the overall population (291 ±92 to 319 ±110 µm, p=0.01) and in both groups (291 ±96 to 325 ±117 µm, Group 1, p>0.05; 290 ±83 to 308 ±96 µm, Group 2, p>0.05) because of chronic cystic degeneration changes of the macula. Mean treatment rate was 5.1 ±3.9 (Group 1) versus 3.7 ±2.7 (Group 2, p=0.01). Five cases of severe intraocular inflammation after intravitreal bevacizumab were documented.

Retina 2012;32:1471-1479
Dunavoelgyi R, Sacu S, Eibenberger K, Palkovits S, et al.

Retinovascular Pathology May Reflect Renal Disease

New findings from the Chronic Renal Failure Insufficiency Cohort (CRIC) study show a strong association between severity of retinopathy and its features and level of kidney function, after adjustment for traditional and non-traditional risk factors for chronic kidney disease, suggesting that retinovascular pathology reflects renal disease.

In this observational cross-sectional study, 2,605 patients of the CRIC study, a multicenter study of chronic kidney disease, were offered participation. Nonmydriatic fundus

Preservative Toxicity Can Complicate Glaucoma Treatment

Preservative toxicity in glaucoma medications may complicate treatment. Eyes may present with subclinical fibroses due to the cumulative effect of years of dosing with multiple preserved glaucoma eyedrops.[1-3] Preservatives can break the tight junctions in the apical epithelial cells in the cornea, with some cytotoxic activity, and impact the barrier function in the cornea. As cells start to be lost from the apical cornea, the ability of the cornea to hold the tear film diminishes.[4] As the tear film becomes more unstable, the eye becomes dry and patients may complain of blurred and fluctuating vision.[5]

While some clinicians will treat OSD in glaucoma patients by adding steroids or other anti-inflammatories, an alternative approach is the "subtractive strategy"—to take the patient off the preserved medications that may further exacerbate OSD symptoms.

Preservative-free glaucoma treatment is an established option in Europe where preservative-free beta blockers have been available for many years. Large epidemiologic surveys in Europe have shown the significant impact (P<0.0001) of switching to a preservative-free medication, or reducing the preservative load by switching out just the preserved beta blocker in patients on multiple IOP-lowering therapies.[6] With the recent availability of new preservative-free glaucoma medications in the U.S., physicians have the opportunity to prescribe completely preservative-free medication regimens.

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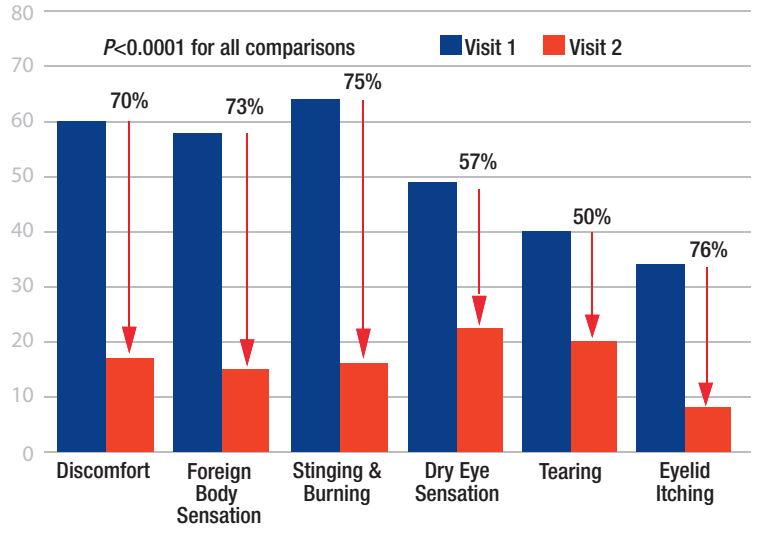

Reports of symptoms of surveyed patients on multiple preserved medications at visit 1, and after having a switch to a preservative-free timolol at visit 2, thereby reducing the number of preserved glaucoma drops (n=981)[6]

Preservative-free TIMOPTIC® in OCUDOSE® may be used when a patient is sensitive to the preservative in Timoptic (timolol maleate ophthalmic solution), benzalkonium chloride, or when use of a preservative-free topical medication is advisable.[7]

IMPORTANT SAFETY INFORMATION
TIMOPTIC® in OCUDOSE® is contraindicated in patients with: bronchial asthma; a history of bronchial asthma; severe chronic obstructive pulmonary disease; sinus bradycardia; second or third degree atrioventricular block; overt cardiac failure; cardiogenic shock; hypersensitivity to any component of this product. This drug is absorbed systemically. The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. Severe respiratory or cardiac reactions, including death, have been reported following systemic or ophthalmic administration of timolol maleate. TIMOPTIC® in OCUDOSE® should be used with caution in patients with cerebrovascular insufficiency. The most frequently reported adverse experiences have been burning and stinging upon instillation.

In patients being considered for add-on therapy after monotherapy with a prostaglandin analog, it makes sense to avoid adding to the preservative load. Preservative-free TIMOPTIC® in OCUDOSE® provides an option for adjunctive therapy when use of a preservative-free topical medication is advisable. When paired with a preservative-free prostaglandin, TIMOPTIC® in OCUDOSE® can be part of a truly preservative-free medication regimen.

Please see reverse side for the Brief Summary of full Prescribing Information for TIMOPTIC® in OCUDOSE® .

REFERENCES 1. Pisella PJ. Pouliquen P. Baudouin C.Prevalence of ocular symptoms and signs with preserved and preservative free glaucoma medication. *Br J Ophthalmol* 2002;a6:418-423 **2.** Manni G. Centofanti M. Oddone F. et al. Interleukin-1_ Tear Concentration in glaucomatous and ocular hypertensive patients treated with preservative-free nonselective beta-blockers. *Am J Ophthalmol* 2005;139:7-77. **3.** Broadway DC, Chang L. Trabeculectomy, risk factors for failure and the preoperative state of the conjunctiva. *J of Glaucoma* 2001; 10: 237–249. **4.** DeJong C. Stolwijk T. Kuppens E. et al. Topical timolol with and without benzalkonium chloride: epithelial permeability and autofluorescence of the cornea in glaucoma. *Graefe's Arch Clin Exp Ophthalmol* (1994) 232:221-224 . **5.** Fechtner et al, Prevalence of Ocular Surface Complaints in Patients With Glaucoma Using Topical Intraocular Pressure–Lowering Medications, Cornea, Volume 29, Number 6, June 2010. **6.** Jaenen N, Baudouin, P. Pouliquen P, et al. Ocular symptoms and signs with preserved and preservative-free glaucoma medications. *European Journal of Ophthalmology* / Vol. 17 no. 3, 2007 / pp. 341-349. **7.** TIMOPTIC IN OCUDOSE [package insert] Aton Pharma, Bridgewater, NJ 2009

Brief Summary of Prescribing Information

ATON PHARMA

PRESERVATIVE-FREE STERILE OPHTHALMIC SOLUTION
in a Sterile Ophthalmic Unit Dose Dispenser

TIMOPTIC®
0.25% AND 0.5%
(TIMOLOL MALEATE OPHTHALMIC SOLUTION)
in OCUDOSE®
(DISPENSER)

CONTRAINDICATIONS

Preservative-free TIMOPTIC in OCUDOSE is contraindicated in patients with (1) bronchial asthma; (2) a history of bronchial asthma; (3) severe chronic obstructive pulmonary disease (see WARNINGS); (4) sinus bradycardia; (5) second or third degree atrioventricular block; (6) overt cardiac failure (see WARNINGS); (7) cardiogenic shock; or (8) hypersensitivity to any component of this product.

WARNINGS

As with many topically applied ophthalmic drugs, this drug is absorbed systemically.

The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported following systemic or ophthalmic administration of timolol maleate (see CONTRAINDICATIONS).

Cardiac Failure

Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, Preservative-free TIMOPTIC in OCUDOSE should be discontinued.

Obstructive Pulmonary Disease

Patients with chronic obstructive pulmonary disease (e.g., chronic bronchitis, emphysema) of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease (other than bronchial asthma or a history of bronchial asthma, in which TIMOPTIC in OCUDOSE is contraindicated [see CONTRAINDICATIONS]) should, in general, not receive beta-blockers, including Preservative-free TIMOPTIC in OCUDOSE.

Major Surgery

The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have experienced protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.

If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of adrenergic agonists.

Diabetes Mellitus

Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

Thyrotoxicosis

Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents that might precipitate a thyroid storm.

PRECAUTIONS

General

Because of potential effects of beta-adrenergic blocking agents on blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with Preservative-free TIMOPTIC in OCUDOSE, alternative therapy should be considered.

Choroidal detachment after filtration procedures has been reported with the administration of aqueous suppressant therapy (e.g. timolol).

Angle-closure glaucoma: In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil. Timolol maleate has little or no effect on the pupil. TIMOPTIC in OCUDOSE should not be used alone in the treatment of angle-closure glaucoma.

Anaphylaxis: While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

Muscle Weakness: Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

Information for Patients

Patients should be instructed about the use of Preservative-free TIMOPTIC in OCUDOSE.

Since sterility cannot be maintained after the individual unit is opened, patients should be instructed to use the product immediately after opening, and to discard the individual unit and any remaining contents immediately after use.

Patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second or third degree atrioventricular block, or cardiac failure should be advised not to take this product. (See CONTRAINDICATIONS.)

Drug Interactions

Although TIMOPTIC (timolol maleate ophthalmic solution) used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with TIMOPTIC (timolol maleate ophthalmic solution) and epinephrine has been reported occasionally.

Beta-adrenergic blocking agents: Patients who are receiving a beta-adrenergic blocking agent orally and Preservative-free TIMOPTIC in OCUDOSE should be observed for potential additive effects of betablockade, both systemic and on intraocular pressure. The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

Calcium antagonists: Caution should be used in the coadministration of beta-adrenergic blocking agents, such as Preservative-free TIMOPTIC in OCUDOSE, and oral or intravenous calcium antagonists, because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, coadministration should be avoided.

Catecholamine-depleting drugs: Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may result in vertigo, syncope, or postural hypotension.

Digitalis and calcium antagonists: The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.

CYP2D6 inhibitors: Potentiated systemic beta-blockade (e.g., decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g., quinidine, SSRIs) and timolol.

Clonidine: Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. There have been no reports of exacerbation of rebound hypertension with ophthalmic timolol maleate.

Injectable epinephrine: (See PRECAUTIONS, General, Anaphylaxis)

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a two-year oral study of timolol maleate administered orally to rats, there was a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats administered 300 mg/kg/day (approximately 42,000 times the systemic exposure following the maximum recommended human ophthalmic dose). Similar differences were not observed in rats administered oral doses equivalent to approximately 14,000 times the maximum recommended human ophthalmic dose.

In a lifetime oral study in mice, there were statistically significant increases in the incidence of benign and malignant pulmonary tumors, benign uterine polyps and mammary adenocarcinomas in female mice at 500 mg/kg/day (approximately 71,000 times the systemic exposure following the maximum recommended human ophthalmic dose), but not at 5 or 50 mg/kg/day (approximately 700 or 7,000 times, respectively, the systemic exposure following the maximum recommended human ophthalmic dose). In a subsequent study in female mice, in which postmortem examinations were limited to the uterus and the lungs, a statistically significant increase in the incidence of pulmonary tumors was again observed at 500 mg/kg/day.

The increased occurrence of mammary adenocarcinomas was associated with elevations in serum prolactin which occurred in female mice administered oral timolol at 500 mg/kg/day, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents that elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in humans. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate (the maximum recommended human oral dosage), there were no clinically meaningful changes in serum prolactin.

Timolol maleate was devoid of mutagenic potential when tested *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 mcg/mL). In Ames tests the highest concentrations of timolol employed, 5,000 or 10,000 mcg/plate, were associated with statistically significant elevations of revertants observed with tester strain TA100 (in seven replicate assays), but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed, and the ratio of test to control revertants did not reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Reproduction and fertility studies in rats demonstrated no adverse effect on male or female fertility at doses up to 21,000 times the systemic exposure following the maximum recommended human ophthalmic dose.

Pregnancy: Teratogenic Effects — Pregnancy Category C.: Teratogenicity studies with timolol in mice, rats and rabbits at oral doses up to 50 mg/kg/day (7,000 times the systemic exposure following the maximum recommended human ophthalmic dose) demonstrated no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (142,000 times the systemic exposure following the maximum recommended human ophthalmic dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 14,000 times the systemic exposure following the maximum recommended human ophthalmic dose, in this case without apparent maternotoxicity.

There are no adequate and well-controlled studies in pregnant women. Preservative-free TIMOPTIC in OCUDOSE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Timolol maleate has been detected in human milk following oral and ophthalmic drug administration. Because of the potential for serious adverse reactions from timolol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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

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

ADVERSE REACTIONS

The most frequently reported adverse experiences have been burning and stinging upon instillation (approximately one in eight patients).

The following additional adverse experiences have been reported less frequently with ocular administration of this or other timolol maleate formulations:

BODY AS A WHOLE: Headache, asthenia/fatigue, and chest pain.

CARDIOVASCULAR: Bradycardia, arrhythmia, hypotension, hypertension, syncope, heart block, cerebral vascular accident, cerebral ischemia, cardiac failure, worsening of angina pectoris, palpitation, cardiac arrest, pulmonary edema, edema, claudication, Raynaud's phenomenon, and cold hands and feet.

DIGESTIVE: Nausea, diarrhea, dyspepsia, anorexia, and dry mouth.

IMMUNOLOGIC: Systemic lupus erythematosus.

NERVOUS SYSTEM/PSYCHIATRIC: Dizziness, increase in signs and symptoms of myasthenia gravis, paresthesia, somnolence, insomnia, nightmares, behavioral changes and psychic disturbances including depression, confusion, hallucinations, anxiety, disorientation, nervousness, and memory loss.

SKIN: Alopecia and psoriasiform rash or exacerbation of psoriasis.

HYPERSENSITIVITY: Signs and symptoms of systemic allergic reactions including anaphylaxis, angioedema, urticaria, and localized and generalized rash.

RESPIRATORY: Bronchospasm (predominantly in patients with preexisting bronchospastic disease), respiratory failure, dyspnea, nasal congestion, cough and upper respiratory infections.

ENDOCRINE: Masked symptoms of hypoglycemia in diabetic patients (see WARNINGS).

SPECIAL SENSES: Signs and symptoms of ocular irritation including conjunctivitis, blepharitis, keratitis, ocular pain, discharge (e.g., crusting), foreign body sensation, itching and tearing, and dry eyes; ptosis; decreased corneal sensitivity; cystoid macular edema; visual disturbances including refractive changes and diplopia; pseudopemphigoid; choroidal detachment following filtration surgery (see PRECAUTIONS, General); and tinnitus.

UROGENITAL: Retroperitoneal fibrosis, decreased libido, impotence, and Peyronie's disease.

The following additional adverse effects have been reported in clinical experience with ORAL timolol maleate or other ORAL beta blocking agents, and may be considered potential effects of ophthalmic timolol maleate: *Allergic:* Erythematous rash, fever combined with aching and sore throat, laryngospasm with respiratory distress; *Body as a Whole:* Extremity pain, decreased exercise tolerance, weight loss; *Cardiovascular:* Worsening of arterial insufficiency, vasodilatation; *Digestive:* Gastrointestinal pain, hepatomegaly, vomiting, mesenteric arterial thrombosis, ischemic colitis; *Hematologic:* Non-thrombocytopenic purpura; thrombocytopenic purpura; agranulocytosis; *Endocrine:* Hyperglycemia, hypoglycemia; *Skin:* Pruritus, skin irritation, increased pigmentation, sweating; *Musculoskeletal:* Arthralgia; *Nervous System/Psychiatric:* Vertigo, local weakness, diminished concentration, reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics; *Respiratory:* Rales, bronchial obstruction; *Urogenital:* Urination difficulties.

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photographs of the disc and macula in both eyes were obtained in 1,936 of these subjects. The photographs were reviewed in a masked fashion at a central photograph reading center using standard protocols. Presence and severity of retinopathy (diabetic, hypertensive or other) and vessel diameter caliber were assessed by trained graders and a retinal specialist using protocols developed for large epidemiologic studies. Kidney function measurements and information on traditional and nontraditional risk factors for decreased kidney function were obtained from the CRIC study.

Greater severity of retinopathy was associated with lower estimated glomerular filtration rate after adjustment for traditional and nontraditional risk factors. The presence of vascular abnormalities usually associated with hypertension was also associated with lower estimated glomerular filtration rate. The authors found no strong direct relationship between estimated glomerular filtration rate and average arteriolar or venular calibers.

Arch Ophthal 2012;130:1136-1144
Grunwald J, Alexander J, Ying G, Maguire M, et al.

SLT an Effective Initial Therapy For OAG or Ocular Hypertension

Results from the Wills Eye Institute support the option of selective laser trabeculoplasty as a safe and effective initial therapy in open-angle glaucoma or ocular hypertension.

In this prospective, randomized clinical trial, 69 patients (127 eyes) with open-angle glaucoma or ocular hypertension were randomized to SLT or medical therapy. Target intraocular pressure was determined using the Collaborative Initial Glaucoma Treatment Study formula. Patients were treated with SLT (100 360-degree applications) or medical therapy (prostaglandin analog). Six visits over one year followed initial treatment. If the target IOP range was not attained with SLT, additional SLT was the next step; in the medical arm, additional medications were added. The primary outcome measured was IOP, with the secondary outcome being the number of steps to achieve target IOP.

Data collection terminated with 54 patients reaching nine- to 12-months follow-up. Twenty-nine patients were in the SLT group and 25 patients in the medical group. Baseline mean IOP for all eyes was 24.5 mmHg in the SLT group and 24.7 mmHg in the medical group. Mean IOP (both eyes) at last follow-up was 18.2 mmHg (6.3 mmHg reduction) in the SLT arm and 17.7 mmHg (7 mmHg reduction) in the medical arm. By the last follow-up, 11 percent of the eyes received additional SLT and 27 percent required additional medication. There was no statistically significant difference between the SLT and medication groups.

J Glaucoma 2012;21:460-468
Katz L, Steinman W, Kabir A, Molineaux J, et al.

Preventing Bleb Failure: Off-label Bevacizumab vs. MMC

In this pilot study, with a small number of subjects, short-term outcomes suggest that subconjunctival bevacizumab (1.25 mg in 0.05 mL) and 0.03% mitomycin-c are equally effective in reducing intraocular pressure, with a better safety profile for bevacizumab in the dosing schedule studied. However, bevacizumab soaked in a sponge appears to have no advantages over MMC.

Thirty-eight consecutive patients with visually significant cataract and coexistent primary open-angle glaucoma or chronic angle-closure glaucoma were randomized into three groups. One group received conventional 0.03% MMC (n=13); the second group received three subconjunctival injections of bevacizumab (1.25 mg in 0.05 mL; n=13); and the third group received bevacizumab soaked in sponges (1.25 mg in 0.05 mL; n=12) intraoperatively on the sclera. Patients were followed up for six months. The primary outcome measure was treatment success and bleb morphology in the study eye at six-month follow-up.

All three groups showed significant reduction in mean IOP at one week after treatment, which was maintained at six months. However, 90 percent of the subconjunctival bevacizumab group had complete success as opposed to 60 percent in each of the other two groups (p=0.04). In both bevacizumab groups, bleb vascularity increased progressively over the six-month follow-up. (One patient in the subconjunctival bevacizumab group showed a local conjunctival necrosis.)

J Glaucoma 2012;21:450-459
Sengupta S, Venkatesh R, Ravindran R.

Two-Year CXL Results in Pediatric Keratoconus Patients

European university researchers report that corneal cross-linking improved uncorrected visual acuity and best spectacle-corrected vision in patients up to age 18 years of age with progressive keratoconus, most likely by significantly reducing corneal asymmetry and corneal, as well as total, wavefront aberrations.

In the prospective, interventional case series, 40 eyes of pediatric patients underwent riboflavin-ultraviolet A-induced CXL. UCVA, BSCVA, sphere and cylinder, topography, aberrometry and endothelial cell counts were evaluated at baseline and at one, three, six, 12 and 24 months.

The improvement in UCVA and BSCVA was significant throughout the postoperative follow-up (p=0.02). Mean logarithm of the minimum angle of resolution baseline UCVA and BSCVA were 0.79 ±0.21 and 0.39 ±0.10. Mean UCVA and BSCVA at two years were 0.58 ±0.18 and 0.20 ±0.09. Mean spherical equivalent refraction showed a significant decrease

(Continued on page 91)

MIGS, Goniotomy with Volk Gonio Lens

For Micro-Invasive Glaucoma Surgery (MIGS) and goniotomy procedures, Volk says its new Surgical Gonio Lens provides clear anterior chamber angle images.

With a 1.2x image magnification, the contact lens' high quality Volk optics deliver crisp, high-resolution views. The Surgical Gonio is particularly well suited for MIGS and all surgical gonio procedures. The lens' small profile is equally useful for pediatric postoperative gonioscopy.

The lens is compatible with both steam and gas sterilization and constructed to withstand repeated sterilization cycles without image degradation over time.

Instead of left hand- or right hand-specific versions of the lens, Volk designed a universal positioning handle that moves to accommodate left hand, right hand and center positions.

For information, call 1 (800) 345-8655, or visit volk.com.

IDS Teams with Corcoran Compliance Connection

Kevin J. Corcoran, founder of Corcoran Compliance Connection LLC, announced the successful completion of final testing of its compliance and coding program for electronic medical records. The first users are customers of Integrity Digital Solutions.

Corcoran Compliance Connection was developed in 2012 to improve coding compliance, reduce risk associated with fraud and abuse and increase practice management efficiency. This proprietary Web-based application interacts with a physician's electronic medical record system to provide fast, accurate coding for eye exams based solely on the EMR entries in a secure, HIPAA-compliant environment, utilizing the available CPT and HCPCS codes integrated with applicable CPT modifiers.

IDS is a leader in EMR software for ophthalmology and optometry. Its management team includes ophthalmologists, optometrists and software engineers who specialize in interface design, workflow optimization and health-care data security.

Corcoran Compliance Connection complements Integrity's web-based software for ophthalmologists and optometrists, known as Integrity EMR for Eyes, designed to expedite EMR implementation with minimal impact on a practice's productivity. For more information on Corcoran Compliance Connection, visit corcoranccg.com/c3.aspx. For information on IDS, visit IntegrityEMR.com or call 1 (877) 353-0373.

ASICO: First Electronic Toric IOL Marker

ASICO (American Surgical Instruments Corp.) has launched two electronic toric markers (AE-2929 and AE-2930). These markers are designed to enhance toric marking accuracy from 5-degree mean error to 0.2-degree error. This will in turn improve the lens effectiveness from 83 percent to 99.4 percent, the company says.

The design of the electronic toric marker allows surgeons to use both the senses of sight and sound to ensure accurate marking by looking at a signal light and listen to a beeping sound when the marker is aligned perfectly horizontal. The ergonomic flat handle helps the surgeon hold the marker stable and move forward toward the eye without unwanted rotation.

This article has no commercial sponsorship.

There is flexibility with five-step sensitivity settings to enable the surgeon to operate from 0.2 degrees to 1 degree based on surgeon preference. For information, visit asico.com.

Gallery-Inspired Frame Displays from Fashion Optical

With the new Prestige line of wall displays, Fashion Optical's designers can create unique gallery-style presentations and merchandising systems for eye-care professionals. The Prestige line offers a variety of molding choices that mix and match with existing furnishings. There are eight new versatile designer moldings available that range from the fashionable, contemporary Tuxedo design to the traditional beauty of the Renaissance style. By choosing a particular Prestige style, Fashion Optical can create a time-honored style, a more innovative look, or an electric boutique that showcases high-end products.

Fashion Optical Displays offer a wide selection of accessories that easily pop on and off the new Prestige wall displays, including graphics, signage and literature holders, tint and lens displays, as well as curved and straight shelves to hold eyewear cases.

For information, visit fashionoptical.com or call 1 (800) 824-4106.

New Accurate, Low-Cost Exophthalmometer

The Double Luedde Exophthalmometer, just released by Richmond Products, is a low-cost and precise alternative to traditional, higher-priced exophthalmometers. The instrument, which retails for $125, requires no special technique and is very easy to use. It has been tested in a university clinic setting and demonstrated results comparable to other devices such as the Hertl Exophthalmometer at half the cost, the company says.

The Double Luedde measures the distance (exophthalmos) between the front-most surface of the cornea and the external orbital notch. In the treatment of diseases affecting exophthalmos, the instrument is used to track the degree of forward (or backward) displacement of the eye.

Construction includes a sturdy metal backbone and two clear side scales that make measurement easy and quick. The head width adjustment includes a scale to permit repeatable setting of the distance from right to left orbital notch. Detailed instructions and storage case are included.

For information visit richmondprodsucts.com.

No More Eye Patching For Kids

XPAND 3D has introduced its Amblyz electronic glasses for the treatment of amblyopia. XPAND's solution focuses on two fundamental issues that neither of the current treatments—eye patches or topical drugs—has addressed. Using an electronic shutter to make one lens intermittently transparent or opaque, Amblyz electronic glasses occlude the healthy, strong eye at regular and intermittent periods to force the amblyopic eye to function and develop its muscles and neural connections. Secondly, the glasses are appealing and eliminate the discomfort and social unease of wearing a patch. These two points are key to increasing the likelihood that the child will receive a full and effective treatment.

Amblyz glasses have been developed by XPAND 3D in conjunction with top ophthalmologists and optometrists, and have been tested in clinical studies that demonstrate comparable effectiveness to current products and superiority in esthetics and comfort. These results were published in *Investigative Ophthalmology & Visual Science*, July 2010.

XPAND Amblyz glasses work by electronically opening and shuttering the lens over the child's good eye. A liquid crystal shutter is built into the lens and is used to block the strong eye periodically. XPAND Amblyz glasses will be available beginning in December 2012. For information visit amblyz.com. REVIEW

Ophthalmic Symposium:

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RESTASIS®
(cyclosporine ophthalmic emulsion) 0.05%
Sterile, Preservative-Free

INDICATIONS AND USAGE

RESTASIS® ophthalmic emulsion is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. Increased tear production was not seen in patients currently taking topical antiinflammatory drugs or using punctal plugs.

CONTRAINDICATIONS

RESTASIS® is contraindicated in patients with active ocular infections and in patients with known or suspected hypersensitivity to any of the ingredients in the formulation.

WARNING

RESTASIS® ophthalmic emulsion has not been studied in patients with a history of herpes keratitis.

PRECAUTIONS

General: For ophthalmic use only.

Information for Patients

The emulsion from one individual single-use vial is to be used immediately after opening for administration to one or both eyes, and the remaining contents should be discarded immediately after administration.

Do not allow the tip of the vial to touch the eye or any surface, as this may contaminate the emulsion.

RESTASIS® should not be administered while wearing contact lenses. Patients with decreased tear production typically should not wear contact lenses. If contact lenses are worn, they should be removed prior to the administration of the emulsion. Lenses may be reinserted 15 minutes following administration of **RESTASIS®** ophthalmic emulsion.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Systemic carcinogenicity studies were carried out in male and female mice and rats. In the 78-week oral (diet) mouse study, at doses of 1, 4, and 16 mg/kg/day, evidence of a statistically significant trend was found for lymphocytic lymphomas in females, and the incidence of hepatocellular carcinomas in mid-dose males significantly exceeded the control value.

In the 24-month oral (diet) rat study, conducted at 0.5, 2, and 8 mg/kg/day, pancreatic islet cell adenomas significantly exceeded the control rate in the low dose level. The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related. The low doses in mice and rats are approximately 1000 and 500 times greater, respectively, than the daily human dose of one drop (28 µL of 0.05% **RESTASIS®** BID into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed.

Cyclosporine has not been found mutagenic/genotoxic in the Ames Test, the V79-HGPRT Test, the micronucleus test in mice and Chinese hamsters, the chromosome-aberration tests in Chinese hamster bone-marrow, the mouse dominant lethal assay, and the DNA-repair test in sperm from treated mice. A study analyzing sister chromatid exchange (SCE) induction by cyclosporine using human lymphocytes in vitro gave indication of a positive effect (i.e., induction of SCE).

No impairment in fertility was demonstrated in studies in male and female rats receiving oral doses of cyclosporine up to 15 mg/kg/day (approximately 15,000 times the human daily dose of 0.001 mg/kg/day) for 9 weeks (male) and 2 weeks (female) prior to mating.

Pregnancy-Teratogenic Effects

Pregnancy category C.

Teratogenic Effects: No evidence of teratogenicity was observed in rats or rabbits receiving oral doses of cyclosporine up to 300 mg/kg/day during organogenesis. These doses in rats and rabbits are approximately 300,000 times greater than the daily human dose of one drop (28 µL) 0.05% **RESTASIS®** BID into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed.

Non-Teratogenic Effects: Adverse effects were seen in reproduction studies in rats and rabbits only at dose levels toxic to dams. At toxic doses (rats at 30 mg/kg/day and rabbits at 100 mg/kg/day), cyclosporine oral solution, USP, was embryo- and fetotoxic as indicated by increased pre- and postnatal mortality and reduced fetal weight together with related skeletal retardations. These doses are 30,000 and 100,000 times greater, respectively than the daily human dose of one drop (28 µL) of 0.05% **RESTASIS®** BID into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed. No evidence of embryofetal toxicity was observed in rats or rabbits receiving cyclosporine at oral doses up to 17 mg/kg/day or 30 mg/kg/day, respectively, during organogenesis. These doses in rats and rabbits are approximately 17,000 and 30,000 times greater, respectively, than the daily human dose.

Offspring of rats receiving a 45 mg/kg/day oral dose of cyclosporine from Day 15 of pregnancy until Day 21 postpartum, a maternally toxic level, exhibited an increase in postnatal mortality; this dose is 45,000 times greater than the daily human topical dose, 0.001 mg/kg/day, assuming that the entire dose is absorbed. No adverse events were observed at oral doses up to 15 mg/kg/day (15,000 times greater than the daily human dose).

There are no adequate and well-controlled studies of **RESTASIS®** in pregnant women. **RESTASIS®** should be administered to a pregnant woman only if clearly needed.

Nursing Mothers

Cyclosporine is known to be excreted in human milk following systemic administration but excretion in human milk after topical treatment has not been investigated. Although blood concentrations are undetectable after topical administration of **RESTASIS®** ophthalmic emulsion, caution should be exercised when **RESTASIS®** is administered to a nursing woman.

Pediatric Use

The safety and efficacy of **RESTASIS®** ophthalmic emulsion have not been established in pediatric patients below the age of 16.

Geriatric Use

No overall difference in safety or effectiveness has been observed between elderly and younger patients.

ADVERSE REACTIONS

The most common adverse event following the use of **RESTASIS®** was ocular burning (17%).

Other events reported in 1% to 5% of patients included conjunctival hyperemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging, and visual disturbance (most often blurring).

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PS Form **3526-R**, September 2007 (Page 2 of 3)

REVIEW Research Review

(Continued from page 83)

of 1.57 D at 24 months (p=0.02). Mean baseline simulated keratometry was 46.33 D in the flattest meridian and 51.48 D in the steepest meridian; at two years, the values were 45.3 D (p=0.04) and 50.21 D (p=0.07). For a 3-mm pupil, there was a significant reduction (p<0.05) in whole eye (total), corneal, higher-order and astigmatic wavefront aberrations at 24 months. A significant difference (p<0.05) in total coma and total spherical aberration two years after CXL was also observed. Mean baseline pupil center pachymetry decreased significantly (p=0.04) at six months, but recovered by 12 months and remained stable thereafter through the two-year follow-up. Endothelial cell count did not change significantly (p=0.32).

Am J Ophthalmol 2012;154:520-526
Vinciguerra P, Albé E, Frueh B, Trazza S, Epstein D.

REVIEW Calendar

NOVEMBER

8
CHICAGO
The Ophthalmology Innovation Summit Unites key players and industry leaders in the development of ophthalmic products, drugs and devices. The mission of OIS is to bring new technologies to market by facilitating information transfer, deal-flow, strategic partnerships and acquisitions. The audience for this show includes clinical and pre-clinical researchers, physicians/clinicians, university technology transfer officers, private and public company executives, corporate business development representatives and investors. For more information, visit ibfconferences.com/ophthalmology-innovation-summit-4th-annual.

8 - 9
CHICAGO
The 43rd Annual Fall Science Symposium of the American Society of Ophthalmic Plastic and Reconstructive Surgery (ASOPRS) will be held at the Swissôtel in Chicago. This meeting will provide a forum for the presentation of new concepts, techniques and clinical experiences in orbital disease and surgery; aesthetic surgery; and oculofacial, orbital and lacrimal surgery. Forum space will also be available to discuss practice management, access to care and physician advocacy. CME credits will be available. For more information, visit asoprs.org.

10 - 13
CHICAGO
The American Academy of Ophthalmology's Annual Meeting will take place in Chicago, at McCormick Place West Convention Center. This will be a joint meeting with the Asia-Pacific Academy of Ophthalmology. APAO is a federation of national societies whose mission is to preserve and protect the vision of the people in the Asia-Pacific region. APAO will have 45 hours of its own programming, focusing on the current challenges facing Asia-Pacific ophthalmologists. The annual meeting will be preceded by Subspecialty Days on the 9th and 10th. CME hours will be available. For more information, visit aao.org.

27 - 29
MANILA, PHILIPPINES
The Asia Cornea Society 3rd Biennial Scientific Meeting, held immediately prior to the Philippine Academy of Ophthalmology annual meeting, will bring together some of the foremost leaders, innovators and visionaries in the field of cornea, external disease, refractive surgery and eye banking from all over the world, as well as hundreds of participants, especially from the dynamic Asia Pacific Region. For more information, visit asiacorneasociety2012manila.com/index.php.

REVIEW Advertising Index

Before reading on, please see p. 94 for presenting complaint, history and examination.

Diagnosis, Workup and Treatment

A workup for systemic and local herpes simplex as well as herpes zoster infection was initiated. Tests included: serum herpes simplex virus antibodies (IgM), varicella zoster virus antibodies (IgG and IgM), human immunodeficiency virus enzyme-linked immunoassay, complete blood count, conjunctival bacterial and herpes simplex viral cultures. HSV conjunctival cultures were positive, but HSV serum IgM was non-reactive. VZV serum IgG was positive and IgM non-reactive, indicating that he had been previously vaccinated and did not have an acute VZV infection. HIV was negative, CBC was within normal limits and conjunctival bacterial cultures were negative. The wound cultures sent by his dermatologist grew *Staphylococcus aureus,* for which he was initiated on a course of amoxicillin clavulanate.

At the Wills Eye emergency room, the diagnosis of bilateral HSV keratoconjunctivitis was made. Oral acyclovir 400 mg five times daily and bacitracin zinc and polymyxin B sulfate ointment to the skin lesions twice daily were started. The following day, the Cornea Service added ganciclovir ophthalmic gel to both eyes five times daily. Within three days the corneal dendrites resolved with no epithelial defects, though he continued to feel systemically ill with subjective fevers, nausea and vomiting. After seven days of treatment, ganciclovir gel was reduced to t.i.d and continued for a total of 10 days, and acyclovir was reduced to b.i.d. Three weeks after he was seen in the emergency room only anterior stromal haze remained and corrected vision returned to 20/25 in the right eye and 20/20 in the left eye. By two months, all stromal haze had resolved and the decision was made to stop acyclovir, though consideration was given to continuing acyclovir at prophylactic dosages for the duration of his isotretinoin treatment for acne.

Discussion

Bilateral herpes simplex virus keratoconjunctivitis is an unusual manifestation of HSV infection and/or reactivation. In a 2003 retrospective observational case series of 544 patients with HSV eye disease by Paula M. Souza, MD, and colleagues, only seven patients (1.3 percent) had bilateral disease.[1] They noted that all of these patients also had atopy (five out of seven), ocular rosacea (two out of seven), or another manifestation of autoimmune disease including ankylosing spondylitis (one out of seven), Crohn's disease (one in seven), or systemic lupus erythematosis (one out of seven). However, the incidence in children and adolescents may be higher, as reported in a 2004 retrospective cohort study of 23 patients under the age of 16 years by Eva-Marie Chong, MBBS, and colleagues.[2] In this study, six patients (26 percent) had bilateral HSV keratitis. Both of these studies reported significant recurrence rates, with recurrent blepharoconjunctivitis in eight eyes (57 percent) and epithelial keratitis in 12 eyes (85.7 percent) over a follow-up period of five years in the first, and 11 patients (48 percent) with at least one herpetic recurrence of either eye at a median of 15 months follow up in the second. Therefore, there is some evidence that prophylactic doses of acyclovir may be indicated in bilateral keratoconjunctivitis among both adult and pediatric populations.

Additional studies—by Fredrick T. Fraunfelder, MD, and colleagues in 2001 and more recently in 2012 by Meira Neudorfer, MD, and colleagues—have found that systemic treatment with isotretinoin may be associated with keratitis.[3,4] The first study found eight cases of reactivation of herpes simplex in the setting of treatment with isotretinoin. The study concluded that although this finding could not be directly linked to treatment with isotretinoin, it certainly warrants further study. Although the mechanism for this is unclear, it may be related to altered meibomian gland secretion and impairment of tear film quality. Given high recurrence rates of HSV keratoconjunctivitis, particularly in pediatric populations, there may be a rationale for either stopping isotretinoin treatment or continuing with an antiviral medication with close ophthalmologic follow-up. It's also important to note that ophthalmologists should be involved in the care of patients considering initiation of isotretinoin, given possible ocular side effects. REVIEW

The author would like to acknowledge Priscilla Fowler, MD, Wills Eye Cornea Service, for her time and assistance in preparing this case report.

1. Souza MF, Holland EJ, Huang AJW. Bilateral herpetic keratoconjunctivitis. Ophthalmology 2003;110:493-6.
2. Chong EM, Wilhelmus KR, Matoba AY, et al. Herpes simplex virus keratitis in children. Am J Ophthalmol 2004;138:474-5.
3. Fraunfelder FT, Fraunfelder FW, Edwards R. Ocular side effects possibly associated with isotretinoin usage. Am J Ophthalmol 2001;132:299-305.
4. Neudorfer M, Goldshtein I, Shamai-Lubovitz O, et al. Ocular adverse effects of systemic treatment with isotretinoin. Arch Dermatol 2012;148:803-8.

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Ocular irritation progresses to redness, crusting and skin lesions, and leads the patient to seek treatment at the Wills ER.

Teri T. Kleinberg, MD, MSc

Presentation

A 16-year-old Caucasian male presented to the Wills Eye Emergency Room with bilateral ocular irritation. Redness, foreign body sensation and crusting started in the right eye six days prior and then spread to the left eye four days later. This was associated with skin lesions over the forehead, cheeks, posterior occipital region, and bilateral upper and lower eyelids. Two days earlier, his primary ophthalmologist suspected vernal conjunctivitis and started prednisolone acetate hourly, moxifloxacin four times daily and olopatadine ophthalmic drops in both eyes. In addition, his dermatologist took cultures of the skin lesions and his pediatrician started him on oral amoxicillin. On review of systems, he noted a sore throat, cough, fever, nausea and general malaise.

Medical History

The patient's past ocular history was significant for soft contact lens use. His past medical history was significant for acne and seasonal allergies. His chronic medications included isotretinoin and occasional oral antihistamines. He was up-to-date on his immunizations, including herpes zoster. He denied sexual activity, alcohol, tobacco or recreational drug use. He did not have pets at home, had no recent travel, but did play multiple sports including wrestling, football, baseball and weightlifting.

Examination

The patient had a corrected visual acuity of 20/40, pinhole to 20/30 in the right eye and 20/30 in the left eye. He had normal pupils. Goldmann applanation tonometry intraocular pressures were 12 mmHg in both eyes. External evaluation revealed posterior occipital, cervical and pre-auricular tender lymphadenopathy. There were honey-crusted lesions over the mid-forehead, upper and lower lids, upper cheeks, and posterior neck *(See Figure 1)*. A survey of his arms, legs and abdomen revealed no additional skin lesions. He had giant papillae of the superior palpebral conjunctiva and follicles on both lower lids *(See Figure 2)*. Corneal sensation was intact. The conjunctiva was injected bilaterally with corneal dendrites seen near the limbus *(See Figure 3)*. He was noted to have patchy subepithelial infiltrates in both eyes without anterior chamber reaction. The dilated funduscopic exam was normal, without retinal necrosis.

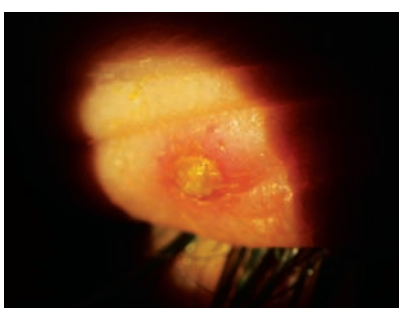


Figure 1. Honey-crusted lesion on the right upper lid.

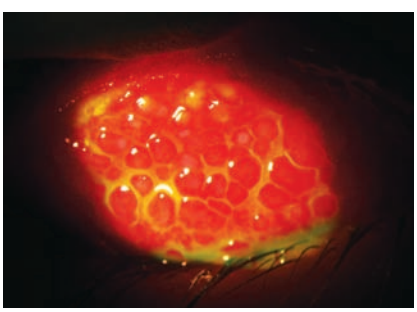


Figure 2. Right upper lid tarsal conjunctiva demonstrates giant papillary conjunctivitis.

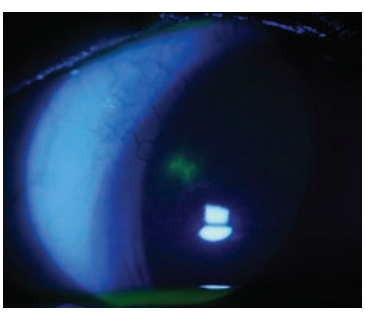
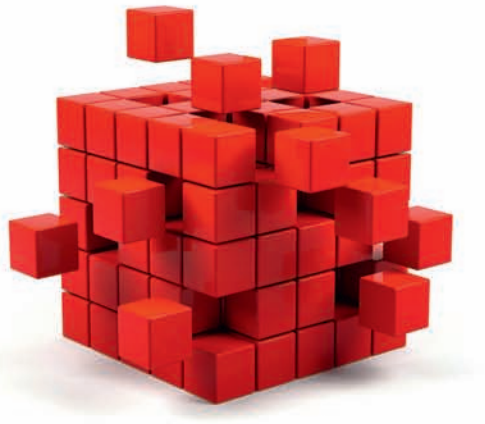


Figure 3. Right cornea with fluorescein staining of dendritic lesion.

What is your differential diagnosis? What further workup would you pursue? Please turn to p. 92

The power of **one**



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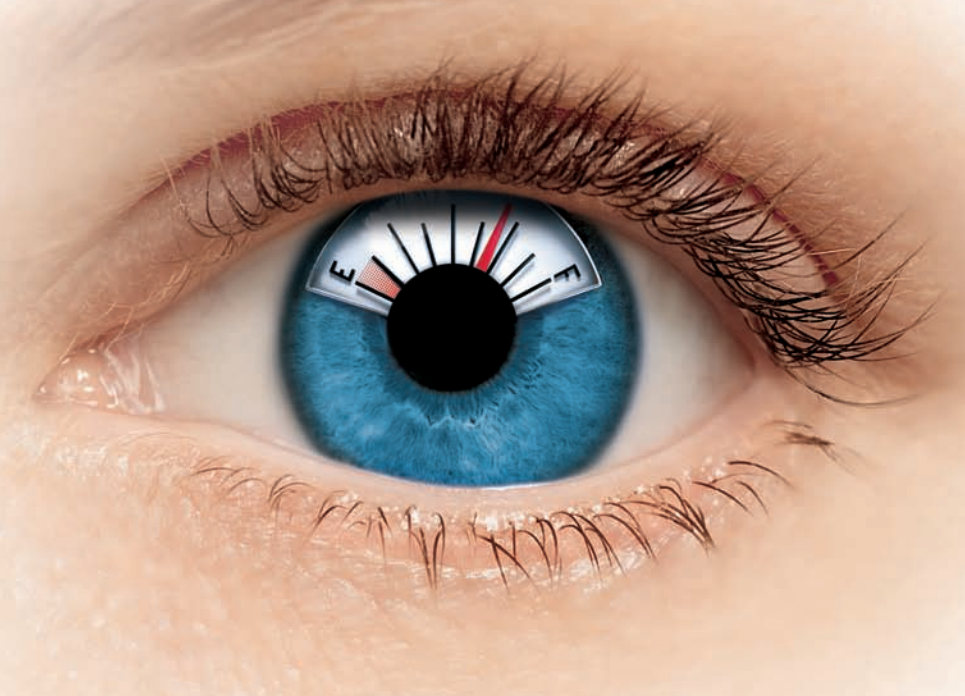

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Important Safety Information

Contraindications: RESTASIS® is contraindicated in patients with active ocular infections and in patients with known or suspected hypersensitivity to any of the ingredients in the formulation.

Warning: RESTASIS® has not been studied in patients with a history of herpes keratitis.

Precautions: The emulsion from one individual single-use vial is to be used immediately after opening for administration to one or both eyes, and the remaining contents should be discarded immediately after administration. Do not allow the tip of the vial to touch the eye or any surface, as this may contaminate the emulsion. RESTASIS® should not be administered while wearing contact lenses. If contact lenses are worn, they should be removed prior to the administration of the emulsion.

Adverse Reactions: The most common adverse event was ocular burning (upon instillation)—17%. Other events reported in 1% to 5% of patients included conjunctival hyperemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging, and visual disturbance (most often blurring).

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