REVIEW® of Ophthalmology

November 2016

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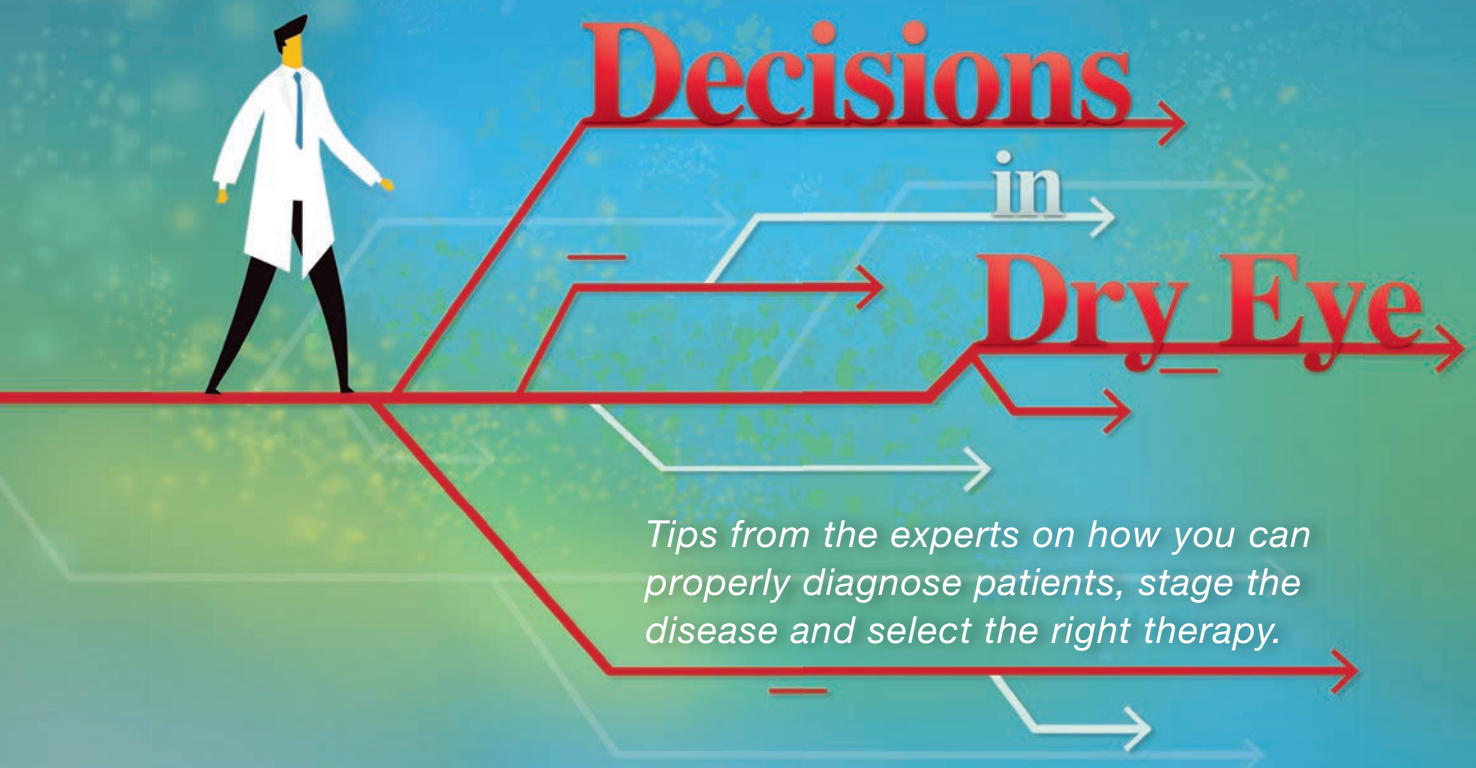

Tips from the experts on how you can properly diagnose patients, stage the disease and select the right therapy.

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- DuraSite increases retention time on the ocular surface and absorption of bromfenac[2-5]
  - Allows for increased aqueous humor concentrations
- Ensures complete coverage throughout the day with BID dosing[1]

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BromSite™
(bromfenac ophthalmic solution) 0.075%
Formulated with DURASITE® DELIVERY SYSTEM

Indications and Usage

BromSite™ (bromfenac ophthalmic solution) 0.075% is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery.

Important Safety Information

- **Slow or Delayed Healing:** All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including BromSite (bromfenac ophthalmic solution) 0.075%, 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.
- **Potential for Cross-Sensitivity:** There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including BromSite (bromfenac ophthalmic solution) 0.075%. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.
- **Increased Bleeding Time of Ocular Tissue:** With some NSAIDs, including BromSite (bromfenac ophthalmic solution) 0.075%, 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 BromSite be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.
- Use of topical NSAIDs may result in keratitis. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including BromSite (bromfenac ophthalmic solution) 0.075%, and should be closely monitored for corneal health. 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 postsurgery may increase patient risk for the occurrence and severity of corneal adverse events.
- BromSite should not be administered while wearing contact lenses. The preservative in BromSite, benzalkonium chloride, may be absorbed by soft contact lenses.
- The most commonly reported adverse reactions in 1% to 8% of patients were anterior chamber inflammation, headache, vitreous floaters, iritis, eye pain, and ocular hypertension.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

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

NSAID=nonsteroidal anti-inflammatory drug.

References: 1. BromSite [package insert]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.; 2016. **2.** Hosseini K, Hutcheson J, Bowman L. Aqueous humor concentration of bromfenac 0.09% (Bromday™) compared with bromfenac in DuraSite® 0.075% (BromSite™) in cataract patients undergoing phacoemulsification after 3 days dosing. Poster presented at: ARVO Annual Meeting; May 5-9, 2013; Seattle, Washington. **3.** Bowman LM, Si E, Pang J, et al. Development of a topical polymeric mucoadhesive ocular delivery system for azithromycin. *J Ocul Pharmacol Ther.* 2009;25(2):133-139. **4.** ClinicalTrials.gov. Aqueous humor concentration of InSite Vision (ISV) 303 (bromfenac in DuraSite) to Bromday once daily (QD) prior to cataract surgery. https://clinicaltrials.gov/ct2/show/results/NCT01387464?sect=X70156&term=insite+vision&rank=1. Accessed July 18, 2016. **5.** Si EC, Bowman LM, Hosseini K. Pharmacokinetic comparisons of bromfenac in DuraSite and Xibrom. *J Ocul Pharmacol Ther.* 2011;27(1):61-66.

SUN-OPH-BRO-014 09/2016

SUN OPHTHALMICS

BromSite™ (bromfenac ophthalmic solution) 0.075% Brief Summary

INDICATIONS AND USAGE
BromSite™ (bromfenac ophthalmic solution) 0.075% is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery.

DOSAGE AND ADMINISTRATION
Recommended Dosing
One drop of BromSite should be applied to the affected eye twice daily (morning and evening) 1 day prior to surgery, the day of surgery, and 14 days postsurgery.

Use with Other Topical Ophthalmic Medications
BromSite should be administered at least 5 minutes after instillation of other topical medications.

Dosage Forms and Strengths
Topical ophthalmic solution: bromfenac 0.075%.

CONTRAINDICATIONS
None

WARNINGS AND PRECAUTIONS
Slow or Delayed Healing
All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including BromSite (bromfenac ophthalmic solution) 0.075%, 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.

Potential for Cross-Sensitivity
There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including BromSite (bromfenac ophthalmic solution) 0.075%. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

Increased Bleeding Time of Ocular Tissue
With some NSAIDs, including BromSite (bromfenac ophthalmic solution) 0.075%, 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 BromSite be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

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, including BromSite (bromfenac ophthalmic solution) 0.075%, 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 postsurgery may increase patient risk for the occurrence and severity of corneal adverse events.

Contact Lens Wear
BromSite should not be administered while wearing contact lenses. The preservative in BromSite, benzalkonium chloride, may be absorbed by soft contact lenses.

ADVERSE REACTIONS
Clinical Trial Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The most commonly reported adverse reactions in 1–8% of patients were: anterior chamber inflammation, headache, vitreous floaters, iritis, eye pain and ocular hypertension.

USE IN SPECIFIC POPULATIONS
Pregnancy

Risk Summary
There are no adequate and well-controlled studies in pregnant women to inform any drug associated risks. Treatment of pregnant rats and rabbits with oral bromfenac did not produce teratogenic effects at clinically relevant doses.

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

Data
Animal Data
Treatment of rats with bromfenac at oral doses up to 0.9 mg/kg/day (195 times a unilateral daily human ophthalmic dose on a mg/m^2 basis, assuming 100% absorbed) and rabbits at oral doses up to 7.5 mg/kg/day (3243 times a unilateral daily dose on a mg/m^2 basis) produced no structural teratogenicity in reproduction studies. However, embryo-fetal lethality, neonatal mortality and reduced postnatal growth were produced in rats at 0.9 mg/kg/day, and embryo-fetal lethality was produced in rabbits at 7.5 mg/kg/day. 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.

Lactation
There are no data on the presence of bromfenac in human milk, the effects on the breastfed infant, or the effects on milk production; however, systemic exposure to bromfenac from ocular administration is low. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for bromfenac and any potential adverse effects on the breast-fed child from bromfenac or from the underlying maternal condition.

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

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

NONCLINICAL TOXICOLOGY
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 (129 times a unilateral daily dose assuming 100% absorbed, on a mg/m^2 basis) and 5 mg/kg/day (540 times a unilateral daily dose on a mg/m^2 basis), respectively revealed no significant increases in tumor incidence.

Bromfenac did not show mutagenic potential in various mutagenicity studies, including the bacterial 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 (195 and 65 times a unilateral daily dose, respectively, on a mg/m^2 basis).

PATIENT COUNSELING INFORMATION
Slow or Delayed Healing
Advise patients of the possibility that slow or delayed healing may occur while using NSAIDs.

Concomitant Topical Ocular Therapy
If more than one topical ophthalmic medication is being used, advise patients to administer BromSite at least 5 minutes after instillation of other topical medications.

Concomitant Use of Contact Lenses
Advise patients not to wear contact lenses during administration of BromSite. The preservative in this product, benzalkonium chloride, may be absorbed by soft contact lenses.

Sterility of Dropper Tip/Product Use
Advise patients to replace the bottle cap after use and do not touch the dropper tip to any surface as this may contaminate the contents.

Advise patients to thoroughly wash hands prior to using BromSite.

Rx Only
Distributed by: Sun Pharmaceutical Industries, Inc. Cranbury, NJ 08512

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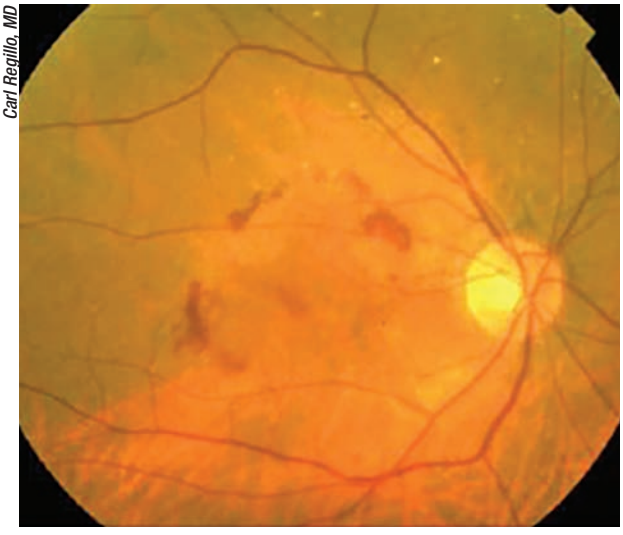
SUN OPHTHALMICS

REVIEW NEWS
Volume XXIII • No. 11 • November 2016

Examining the Link Between Osteoporosis Drugs and AMD

A study published in the August issue of the *American Journal of Ophthalmology* has suggested a link between the use of oral bisphosphonates, often prescribed to help prevent osteoporosis, and wet age-related macular degeneration. The study, conducted by researchers at the University of British Columbia in Vancouver, Canada, used three different designs to evaluate the data: a disproportionality analysis; a case-control study and a self-controlled case series. The first of these used relevant data from the U.S. Food and Drug Administration Adverse Event Reporting System database gathered between 2004 and 2014. The latter two study designs used data from the British Columbia Ministry of Health databases.


Carl Regillo, MD

The disproportionality analysis found reported odds ratios for developing macular degeneration of 3.82 (2.94-4.96) for alendronate, 2.40 (1.49-3.86) for ibandronate and 2.87 (1.58-5.19) for risedronate. The case-control analysis, including 6,367 cases of macular degeneration and 63,670 controls, found that subjects regularly using oral bisphosphonates for three years had an adjusted odds ratio of 1.59 (1.38-1.82) for developing wet AMD. The self-controlled case series analysis included 193 cases of macular degeneration on continuous bisphosphonate therapy; it found the rate ratio was 1.22 (95% CI: 0.76-1.95) after one year of bisphosphonate exposure, which rose to 1.87 (95% CI: 1.32-2.67) after five years of exposure. The ratio didn't differ significantly between men and women.

"Bisphosphonates are pro-inflammatory drugs that have been shown to cause inflammatory eye conditions such as uveitis and scleritis," explains study author Mahyar Etminan, PharmD, MSc, assistant professor of ophthalmology and visual sciences at The University of British Columbia. "We hypothesized that these drugs might increase the risk of wet macular degeneration, another inflammatory eye condition. In terms of our study's limitations, we didn't have information on body mass index or smoking, and our study needs to be validated by other large epidemiologic studies."

"This information is interesting and should be verified by randomized clinical trials," comments David S. Boyer, MD, a retina specialist in Los Angeles and part of the clinical faculty at the Doheny Eye Institute, USC School of Medicine. "Data from excellent long-term studies such as the AREDs studies and population studies such as Blue Mountain, as well as the randomized clinical trials used for approval of the anti-osteoarthritis medications, would also be useful."

"There are significant limitations to this kind of study," notes Jason Hsu, MD, assistant director of retina research at Wills Eye Hospital in Philadelphia. "In particular, the authors did not control for potential confounders such as smoking. It's conceivable that more patients on bisphosphonates may have been smokers, especially given the well-established association between smoking and increased risk of osteoporosis. Smoking also significantly increases the risk of AMD and may have therefore falsely contributed to the appearance that bisphosphonates are to blame. It will be critical that future studies take into account more of these potential confounders before we can draw any conclusions about the association between bisphosphonates and AMD."

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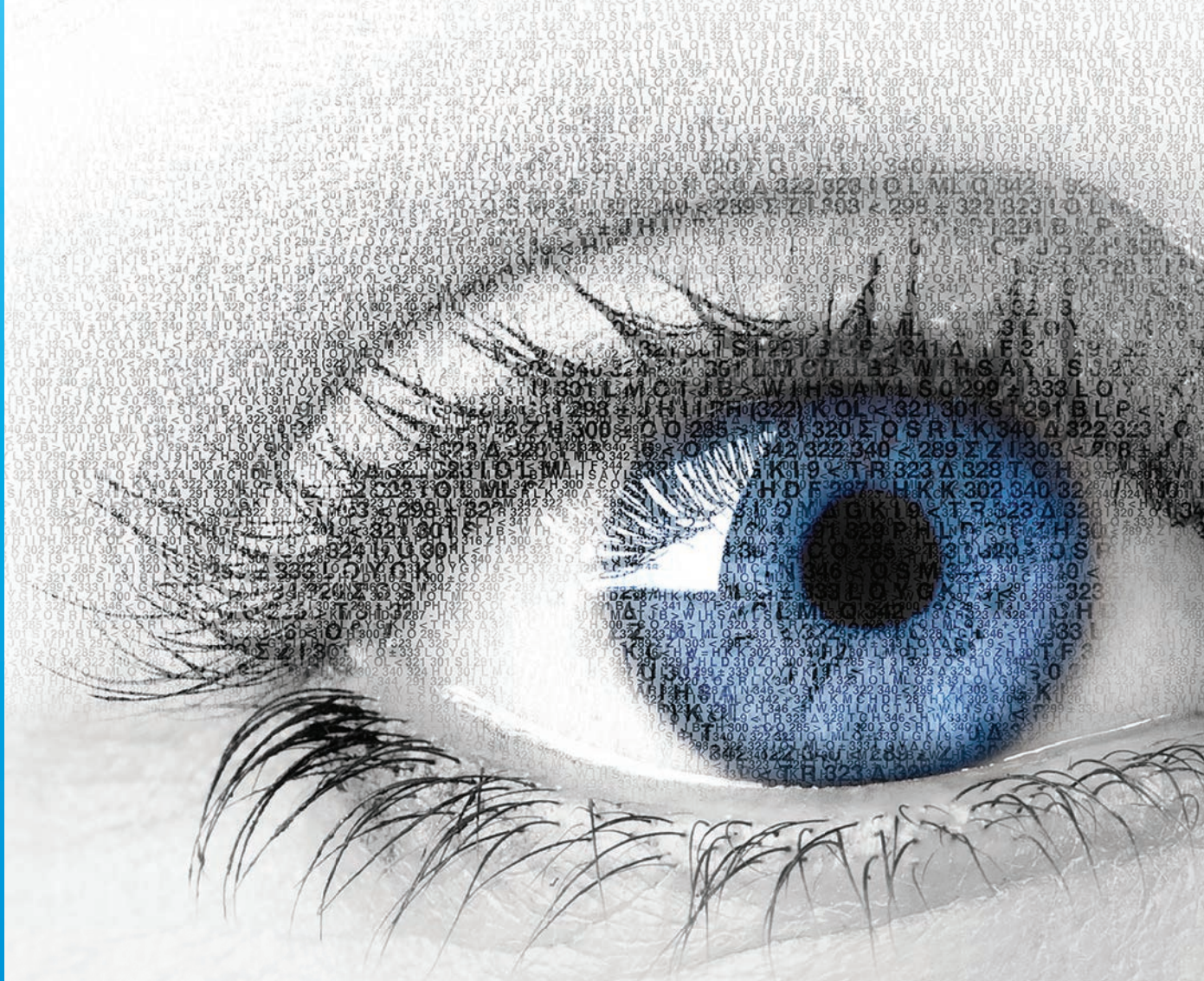

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Ophthalmic Product Development Insights

Matthew Chapin, Andrew Warner, Esq., and Sena Biswas, PhD • Ora Inc., Andover, Mass.

Convertible Financing 101 for the Entrepreneur

In this month's installment of Ophthalmic Product Development Insights, we'll explore convertible notes for seed financing for the early-stage entrepreneur. (As a general rule, neither this article nor any article constitutes legal advice and you should always consult your attorney when getting down to the specifics.)

Before discussing how to approach and use a convertible note, it helps to define some terms. A convertible note is essentially an I.O.U. issued by the entrepreneur's company to the investor in exchange for the investor making a loan to that company. The note can usually be paid back in cash or equity and it is usually set up to automatically convert into equity upon a subsequent financing event (usually referred to as qualified financing). While there are certainly a few more details to keep in mind, the beauty of a note is that it allows the entrepreneur to access much needed financing with simple documentation and without the need to negotiate the terms of a larger equity financing. The note also allows the entrepreneur to avoid the complications and costs that can arise from negotiating a company's valuation without key data points, the impact of that valuation on incentive equity/stock option grants, and the related potential tax implications of equity and/or stock options, giving him the ability to focus more of his time and energy on advancing his vision. On the investor side, the variables, or toggles, referred to as the conversion discount and/or capped price per share (or valuation cap) can allow investors to have the amount of their loan, plus accrued interest, converted into equity at a reduced price relative to the other investors in the subsequent, qualified-financing round. The investors receive these terms to offset some of the early-stage risk they are taking on, as compared to later investors.

Now, on to connecting the dots.

Say you have an idea—maybe even a patent filed—and some early, "reason-to-believe" evidence. The evidence could be preclinical or clinical data and all you need to do is move the project forward to some value inflection point in order to attract investment. Therein lies the proverbial "chicken-or-the-egg" scenario: How do you finance the activities necessary to get to the larger value inflection point when pharma companies, biotech companies, venture capitalists and other institutional investors are often not willing to invest prior to seeing proof of concept? The targeted disease, the *in-vivo* target, the signaling pathways, the clinical development path and the regulatory path are just a few of the considerations at the forefront of the potential investor's mind, any one of which could be a gating item to their investment (a gating item is something that the investor needs to see before proceeding to the next step). Objective manifestations of value such as: a crucial animal model showing efficacy against the standard of care; an *in-vivo* pharmacokinetics study demonstrating sustained release of the delivery platform; or a pre-investigational new drug FDA meeting to firmly establish the development plan and approvable endpoints will help the potential investor get comfortable enough to make that leap. Yet, the achievement of these milestones can't happen without some basic funding. In these types of situations, a convertible note may allow you to access this much needed early-stage capital to fund the efforts necessary to reach these initial proof points and help facilitate a subsequent, much larger pharma, biotech or VC deal. The reader should note that this paradigm is not only applicable to attainment of the first round of substantial external investment, but may also be applied to increase asset value between rounds of investment. Here is an example of how a note might work:

Imagine an investor agrees to loan an entrepreneur $1 million in exchange for a note in the amount of $1 million plus interest that accrues at a rate of 4 percent per year. The note stipulates that the investor can require the entrepreneur to pay the loan back in cash or equity on or after the maturity date of the note. The note further stipulates that when the entrepreneur is able to raise $4 million in financing from other investors (the qualified financing step) the note will automatically convert into equity. Without taking into account the conversion discount and/or capped price per share (valuation cap), the amount of equity (in number of shares) received by the investor will be equal to the principal amount plus interest accrued divided by the share price offered to other investors at the qualified financing. In order to account for the fact that the initial investor (noteholder) put her money in at an earlier stage than the other investors (involving more risk due to less proof of concept/efficacy), the note will generally grant the noteholder a conversion discount and/or capped price per share (or valuation cap). The conversion discount is a multiplier that allows the noteholder to essentially get more equity (shares) for the same dollar amount. By way of example, if the share price is $1 and the conversion discount is 20 percent, then the $1 million note (interest omitted for simplicity) would autoconvert into 1.2 million shares at the qualified financing. The conversion discount is a useful tool when entrepreneur and investor are far apart with regard to their respective views on the value of the asset/company at the time the note is issued.

Additionally, if the investor and entrepreneur are less far apart regarding the asset/company valuation when the note is issued, the toggles referred to as capped price per share (or valuation cap) can be used to account for the same concept of the initial investor putting money in at a more risky stage. The capped price per share and valuation cap toggles create the same net effect because they both put a maximum on the share price that the investor (noteholder) will pay at the qualified financing stage, regardless of what other investors are paying.

Finally, it should be noted that the share price paid by other investors at the qualified financing round may be solely derived from a formal valuation of the asset/company at or around the time of the qualified financing or it may simply be negotiated by the other investors and the entrepreneur (taking into account valuation on some level). The take-home lesson is that the basic structure of the note (simplified here) is adaptive and thus opens the door to attractive scenarios for both entrepreneur and early investor.

Bearing in mind the adaptive nature of convertible notes and further expanding upon their potential application, the entrepreneur should note that the loan/investment can also be made in the form of discounted or

"free" services-in-kind. For example, you may be looking for a loan because: you may require key proof-of-concept preclinical work; external consultants may be needed to hone clinical development plans; or maybe a pre-IND meeting is critical to convincing VC investors to support the budget for further clinical trials, and medical writing and regulatory support is needed. In such scenarios, an entity that provides those services may be willing to provide them at no charge or at a discount in exchange for the issuance of a convertible note. This bartering services for equity is an especially powerful catalyst because it makes it easier for the investor to make the investment (and invest more) since his investment isn't in the form of cash.

The convertible note is a critical financing arrow in the entrepreneur's quiver. As you're likely to also be managing a busy clinical practice, these arrangements can allow quick, easy access to funding so that you can focus on creating value with R&D. The key to ensuring a successful transaction is maintaining an open dialogue so that both entrepreneur and investor understand each other's objectives and sensitivities. Topics such as dilution, granting increased upside in exchange for early investment, protection of downside risk, timing of potential licensing/exit transactions and considerations of whether such an event is expected prior to or after a qualified financing and the mechanics of how such an event is dealt with, etc., will most likely arise. We will be delving into them in subsequent columns. With a spirit of collaboration and the goal of a win-win scenario front and center, the convertible note can be an efficient tool for funding early-stage assets, supporting established program acceleration and/or setting the stage for a mutually fruitful endeavor.

Mr. Chapin is senior vice president of the Corporate Development Group and Mr. Warner is corporate counsel at Ora Inc. Mr. Biswas is managing director at ORA Vision Ventures. Ora provides a comprehensive range of development, clinical-regulatory and product consulting services for developers, investors and buyers; preclinical and turnkey clinical trial services; assistance with regulatory submissions; and the integration of assets, business partnering and financing support in ophthalmology. We welcome your comments or questions. Please send correspondence to mchapin@oraclinical.com or visit www.oraclinical.com.

(continued from page 4)

In the meantime, Dr. Etminan believes that doctors prescribing these drugs should perform a risk-benefit analysis. "If a patient is at high risk of future osteoporosis, the benefits of the drugs may outweigh the risks," he says. "However, the risk of macular degeneration and other adverse events in women who have a low risk of fracture might outweigh its benefits."

U.S. and India to Collaborate on Glaucoma Research

In a joint effort, researchers from the United States and India have begun to look at the genetic risk factors and traits linked to glaucoma in a study funded by the National Eye Institute and India's Department of Biotechnology.

This new study will build upon a report from 2010 that looked at the value of genetic mapping to identify traits that are risk factors for diseases such as glaucoma and macular degeneration—age-related diseases that are the leading cause of blindness in many countries, are costly to treat and threaten patients' ability to live independently. Dr. Ronnie George, senior consultant in the Department of Glaucoma at the Vision Research Foundation, explains the aim of the joint venture: "The goals of the project are to identify genetic markers for glaucoma and factors that influence glaucoma, like intraocular pressure and the optic disc, by targeting families with consanguineous pedigrees," he says. Earlier studies have suggested that consanguineous pedigrees of sufficient size and structure will provide more significant, quantitative trait mapping than a similarly sized collection of nuclear families.

In India, the study will look at 400 people from 30 families of close ancestry in the southern part of the country. "The study will take three years," says Dr. George. "The first two years will consist of patient data collection. All the members of these consanguineous families will have a detailed eye examination measuring more than 15 different parameters in each person, such as intraocular pressure and optic nerve measurements. The researchers will then use the patients' genetic information to try and identify the genetic factors that are responsible for these parameters. The study endpoints will be the identification of the genetic risk factors."

U.S. researchers will focus on genetic analyses to identify the risk factors that might be associated with glaucoma, an effort that will be headed up by Janey Wiggs, MD, PhD, associate director of the Ocular Genomics Institute at Massachusetts Eye and Ear/Harvard Medical School. Both she and Dr. George emphasize the fact that the study is a collaborative effort and that, without both study arms, the study would not be possible. To accomplish her task of tagging the genetic risk factors, Dr. Wiggs will compare the DNA of those with glaucoma to those without, focusing on their genetic differences in the hopes of identifying some genetic precursor to the disease.

In addition to identifying risk factors for glaucoma, one of the study's long-term goals is to use this approach to develop and support a genotype/phenotype database that will enable investigators to discover, assess and validate genes and biomarkers responsible for traits that contribute to other complex ocular diseases.

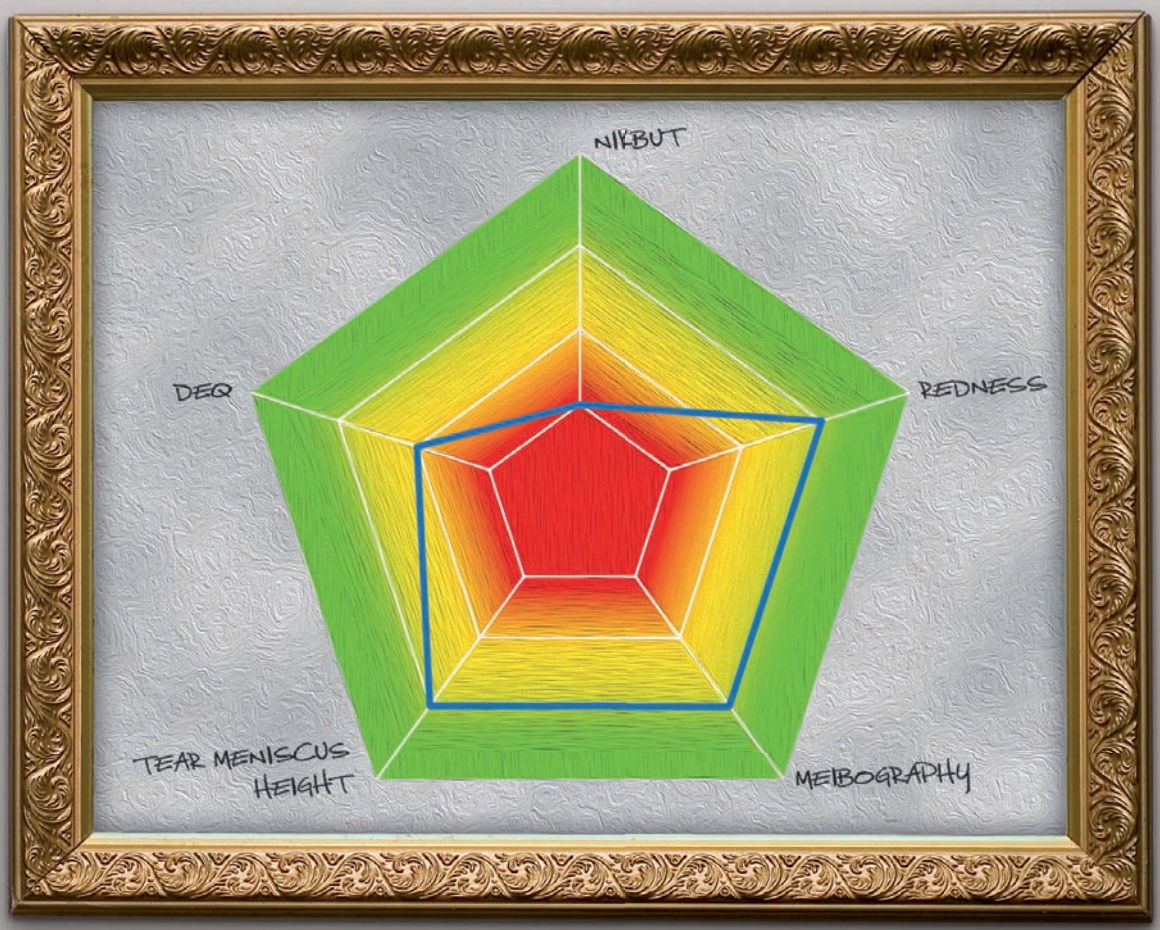
By identifying the genes for disorders such as glaucoma, the investigators hope to get a better idea of these diseases' underlying causes. Ideally, they say, this knowledge will lead to new methods of diagnosis and treatment. "The results will not be directly applicable to the management of glaucoma," says Dr. George. "However, analyzing the genes and pathways for factors that influence the disease could help identify potential drug targets." REVIEW

News Briefs

• *CyPass launches.* Alcon announced the U.S. launch of the CyPass Micro-Stent at the annual meeting of the American Academy of Ophthalmology in Chicago. The device was approved by the U.S. Food and Drug Administration in July for use in conjunction with cataract surgery to lower intraocular pressure in adult patients with mild-to-moderate primary open-angle glaucoma. Implanted during cataract surgery just below the surface of the eye and into the supraciliary space, the device is designed to lower IOP by enhancing aqueous outflow through one of the natural drainage pathways of the eye, with minimal tissue disruption. The CyPass Micro-Stent was developed by Transcend Medical, which Alcon acquired in February 2016. Two-year data from the COMPASS study, published in the online edition of *Ophthalmology*, demonstrated safe and sustained two-year reduction in IOP and glaucoma medication use after CyPass implantation.

• *Lens calculators go live.* Alcon and AMO recently announced the launch of their online toric intraocular lens calculators. The Alcon calculator (acrysoftoriccalculator.com) is equipped with the Barrett Toric Algorithm, which theoretically accounts for posterior corneal astigmatism, calculates patient-specific effective lens position and is designed to improve preop refractive predictability by using a centroid value for surgically induced astigmatism. AMO's calculator (https://www.amoeasy.com) compensates for posterior corneal astigmatism using calculations based on the work of Doug Koch, MD, of Houston, an expert in factoring PCA into lens calculations.

A Masterpiece of Dry Eye Diagnostics



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Down, Boy.

Help Tame Postoperative Ocular Inflammation and Pain With LOTEMAX® GEL

Indication

LOTEMAX® GEL (loteprednol etabonate ophthalmic gel) 0.5% is indicated for the treatment of post-operative inflammation and pain following ocular surgery.

Important Safety Information about LOTEMAX® GEL

- LOTEMAX® GEL is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.
- Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. If this product is used for 10 days or longer, IOP should be monitored.
- Use of corticosteroids may result in posterior subcapsular cataract formation.
- Use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation and occurrence of perforations in those with diseases causing corneal and scleral thinning. The initial prescription and renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification, and where appropriate, fluorescein staining.
- Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infection. In acute purulent conditions, steroids may mask infection or enhance existing infection.
- Use of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and exacerbate the severity of many viral infections of the eye (including herpes simplex).
- Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use.
- Patients should not wear contact lenses when using LOTEMAX® GEL.
- The most common ocular adverse drug reactions reported were anterior chamber inflammation (5%), eye pain (2%) and foreign body sensation (2%).

Please see brief summary of Prescribing Information on adjacent page.

LOTEMAX® GEL
loteprednol etabonate
ophthalmic gel 0.5%

BAUSCH + LOMB

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to prescribe Lotemax Gel safely and effectively. See full prescribing information for Lotemax Gel.

Lotemax (loteprednol etabonate ophthalmic gel) 0.5%

Rx only
Initial Rx Approval: 1998

INDICATIONS AND USAGE

LOTEMAX is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery.

DOSAGE AND ADMINISTRATION

Invert closed bottle and shake once to fill tip before instilling drops.

Apply one to two drops of LOTEMAX into the conjunctival sac of the affected eye four times daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Intraocular Pressure (IOP) Increase

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

Cataracts

Use of corticosteroids may result in posterior subcapsular cataract formation.

Delayed Healing

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

Bacterial Infections

Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection.

Viral Infections

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

Fungal Infections

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

Contact Lens Wear

Patients should not wear contact lenses during their course of therapy with LOTEMAX.

ADVERSE REACTIONS

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

The most common adverse drug reactions reported were anterior chamber inflammation (5%), eye pain (2%), and foreign body sensation (2%).

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: Pregnancy Category C.

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

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

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

Nursing Mothers

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment Of Fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic *in vitro* in the Ames test, the mouse lymphoma tk assay, or in a chromosome aberration test in human lymphocytes, or *in vivo* in the single dose mouse micronucleus assay. Treatment of male and female rats with up to 50 mg/kg/day and 25 mg/kg/day of loteprednol etabonate, respectively, (600 and 300 times the maximum clinical dose, respectively) prior to and during mating did not impair fertility in either gender.

PATIENT COUNSELING INFORMATION

Administration

Invert closed bottle and shake once to fill tip before instilling drops.

Risk of Contamination

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

Contact Lens Wear

Patients should be advised not to wear contact lenses when using LOTEMAX.

Risk of Secondary Infection

If pain develops, redness, itching or inflammation becomes aggravated, the patient should be advised to consult a physician.

Bausch & Lomb Incorporated
Tampa, Florida 33637 USA

US Patent No. 5,800,807

US/LGX/15/0042
Based on 9269100-9269200 Revised: 9/2012

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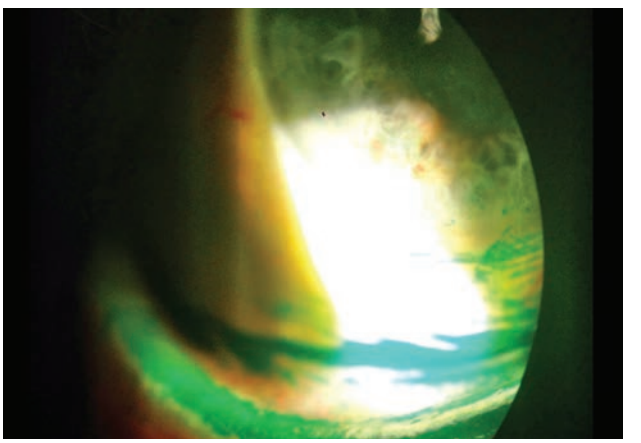

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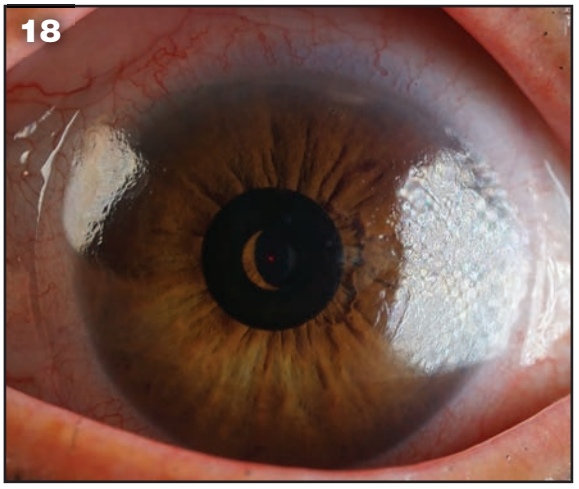

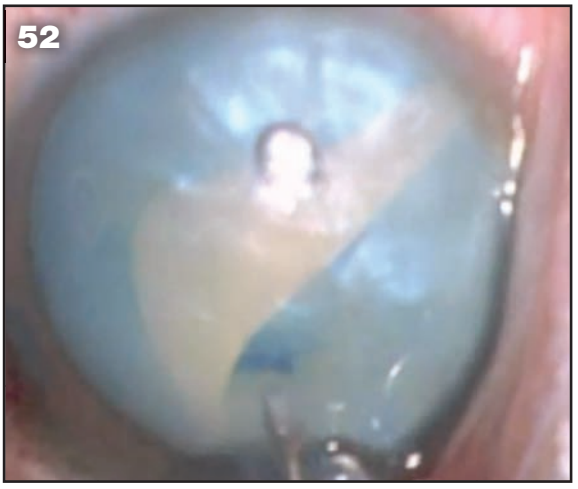

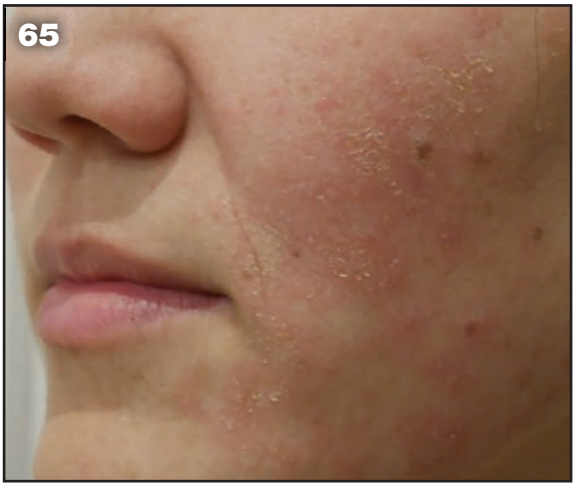

xiidra™
(lifitegrast
ophthalmic solution)5%

Well this CHANGES THIINGS

The first prescription eye drop FDA-approved to treat both the signs and symptoms of Dry Eye Disease

Xiidra is a lymphocyte function-associated antigen-1 (LFA-1) antagonist, the first medication in a new class of drugs.[1]

Check it out at Xiidra-ECP.com

Reference: 1. FDA approves new medication for dry eye disease. FDA News Release. July 2016. *http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm510720.htm*. Accessed July 12, 2016.

Indication Xiidra™ (lifitegrast ophthalmic solution) 5% is indicated for the treatment of signs and symptoms of dry eye disease (DED).

Important Safety Information In clinical trials, the most common adverse reactions reported in 5-25% of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.

To avoid the potential for eye injury or contamination of the solution, patients should not touch the tip of the single-use container to their eye or to any surface.

Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.

Safety and efficacy in pediatric patients below the age of 17 years have not been established.

For additional safety information, see accompanying Brief Summary of Safety Information on the following page and Full Prescribing Information on Xiidra-ECP.com.

Shire

xiidra™ (lifitegrast ophthalmic solution) 5%

Rx Only

BRIEF SUMMARY:
Consult the Full Prescribing Information for complete product information.

INDICATIONS AND USAGE
Xiidra™ (lifitegrast ophthalmic solution) 5% is indicated for the treatment of the signs and symptoms of dry eye disease (DED).

DOSAGE AND ADMINISTRATION
Instill one drop of Xiidra twice daily (approximately 12 hours apart) into each eye using a single use container. Discard the single use container immediately after using in each eye. Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.

ADVERSE REACTIONS
Clinical Trials Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In five clinical studies of dry eye disease conducted with lifitegrast ophthalmic solution, 1401 patients received at least 1 dose of lifitegrast (1287 of which received lifitegrast 5%). The majority of patients (84%) had ≤3 months of treatment exposure. 170 patients were exposed to lifitegrast for approximately 12 months. The majority of the treated patients were female (77%). The most common adverse reactions reported in 5-25 % of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.

USE IN SPECIFIC POPULATIONS
Pregnancy
There are no available data on Xiidra use in pregnant women to inform any drug associated risks. Intravenous (IV) administration of lifitegrast to pregnant rats, from pre-mating through gestation day 17, did not produce teratogenicity at clinically relevant systemic exposures. Intravenous administration of lifitegrast to pregnant rabbits during organogenesis produced an increased incidence of omphalocele at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD], based on the area under the curve [AUC] level). Since human systemic exposure to lifitegrast following ocular administration of Xiidra at the RHOD is low, the applicability of animal findings to the risk of Xiidra use in humans during pregnancy is unclear.

Animal Data
Lifitegrast administered daily by intravenous (IV) injection to rats, from pre-mating through gestation day 17, caused an increase in mean preimplantation loss and an increased incidence of several minor skeletal anomalies at 30 mg /kg /day, representing 5,400-fold the human plasma exposure at the RHOD of Xiidra, based on AUC. No teratogenicity was observed in the rat at 10 mg /kg /day (460-fold the human plasma exposure at the RHOD, based on AUC). In the rabbit, an increased incidence of omphalocele was observed at the lowest dose tested, 3 mg /kg /day (400-fold the human plasma exposure at the RHOD, based on AUC), when administered by IV injection daily from gestation days 7 through 19. A fetal No Observed Adverse Effect Level (NOAEL) was not identified in the rabbit.

Lactation
There are no data on the presence of lifitegrast in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to lifitegrast from ocular administration is low. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for Xiidra and any potential adverse effects on the breastfed child from Xiidra.

Pediatric Use
Safety and efficacy in pediatric patients below the age of 17 years have not been established.

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

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis: Animal studies have not been conducted to determine the carcinogenic potential of lifitegrast.
Mutagenesis: Lifitegrast was not mutagenic in the *in vitro* Ames assay. Lifitegrast was not clastogenic in the *in vivo* mouse micronucleus assay. In an *in vitro* chromosomal aberration assay using mammalian cells (Chinese hamster ovary cells), lifitegrast was positive at the highest concentration tested, without metabolic activation.
Impairment of fertility: Lifitegrast administered at intravenous (IV) doses of up to 30 mg/kg/day (5400-fold the human plasma exposure at the recommended human ophthalmic dose (RHOD) of lifitegrast ophthalmic solution, 5%) had no effect on fertility and reproductive performance in male and female treated rats.

Shire

Manufactured for: Shire US Inc., 300 Shire Way, Lexington, MA 02421.

For more information, go to www.Xiidra.com or call 1-800-828-2088.

US Patents: 8367701; 9353088; 7314938; 7745460; 7790743; 7928122; 9216174; 8168655; 8084047; 8592450; 9085553 and pending patent applications.
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After reviewing the material, it is our hope that you will select and encourage your residents to attend this CSE 2nd Year Resident Program & Wet lab, which is CME accredited to ensure fair balance.

Sincerely,
Jonathan B. Rubenstein, MD
Course Director
Professor and Vice-Chairman of Ophthalmology
Rush University Medical Center

COURSE DIRECTOR:
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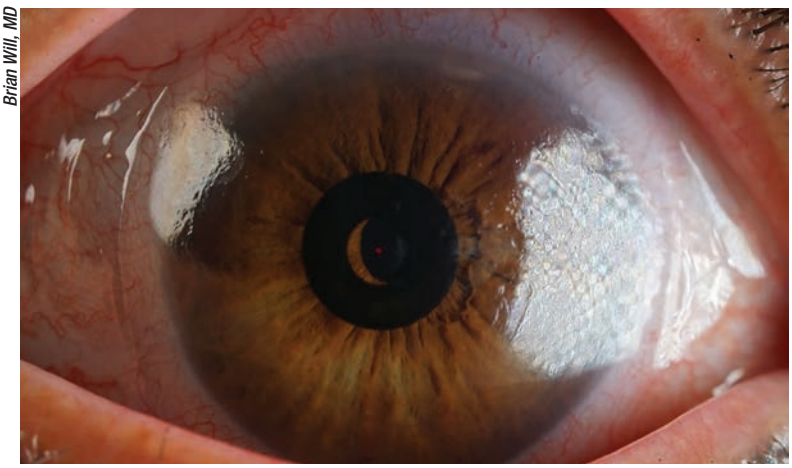
Lights, KAMRA, Action!

A surgeon has developed a novel method for centering the AcuFocus KAMRA corneal inlay using a widely available digital camera.

Kristine Brennan, Senior Associate Editor

Presbyopia remains an inevitable part of aging, but corrective lenses don't have to be, thanks to emerging corneal inlay technologies. Approved by the FDA in 2015, KAMRA (AcuFocus, Irvine, Calif.), is an opaque, permeable, small-aperture inlay that improves near vision in the non-dominant eye by concentrating incoming light through a 1.6-mm opening. The KAMRA inlay is implanted in a stromal pocket made with a femtosecond laser. Optimal centration of the 3.8-mm diameter inlay is key to patient satisfaction. Brian Will, MD, in private practice at Will Vision & Laser Centers, based in Vancouver, Wash., and adjunct clinical professor of ophthalmology at the Loma Linda University School of Medicine, Loma Linda, Calif., has developed a precise way of streamlining the centration process using an ordinary Sony digital camera.


Brian Will, MD

The KAMRA inlay's position is analyzed intraoperatively in the OR by the system's metrology software, which was developed by Brian Will, MD.

In a September presentation to the 34th Congress of the European Society of Cataract and Refractive Surgeons in Copenhagen, Denmark, Dr. Will demonstrated his novel system, which supplements the AcuTarget HD (AcuFocus) diagnostic and surgical planning tool by providing direct intraoperative guidance for KAMRA centration. "We still recommend the AcuTarget HD as the final gold standard," he notes. "The challenge is that to use the AcuTarget HD, the patient must be moved from the OR to the AcuTarget HD, and then back to the OR if inlay position is unacceptable." This back-and-forth, he cautions, might lead surgeons to settle for suboptimal KAMRA placements to maintain efficiency in the operating room.

Dr. Will's repurposed digital camera and its accompanying software helps KAMRA inlay surgery flow smoothly without sacrificing precision, to help spare patients from subsequent repositioning surgery. "In some cases the inlay surgery is performed in a dedicated surgical center that may not have an AcuTarget HD system, where the system is in a different clinic miles away. As a result, the centration can't be checked until another day—a bit too late to make intraoperative adjustments," he says. "The value of this system is speed and the ability to make accurate decisions intraoperatively."

This article has no commercial sponsorship.

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Dr. Will's invention uses a digital camera because, unlike a surgical microscope with a camera attached, it provides a single-lens, coaxial view of the surgical field, elimating offset error. The Sony Alpha a7 RII digital camera has a 44-MP sensor, and a black-and-white setting aids centration in eyes with dark irides. "We need the highest resolution possible to mitigate against image pixelation caused by the digital sensor in the camera," he says.

Clear, error-free visualization is critical to outcomes that will enhance near vision while minimizing impact on distance vision in the implanted eye. Using his system in the OR, Dr. Will can get constant feedback and redirection, positioning the KAMRA in the stromal pocket until he hits his target, which is pre-programmed into his software.

"We have a software program that performs the necessary calculations, then provides the surgeon with a graphic showing target position, achieved position and the metrics describing the centration error. It also provides directions on where to move the inlay, and by how much, in order to bring achieved position versus target to an acceptable margin," he explains. Another plus of the digital camera is immediate transfer of images onto his computer workstation. "We can't be sitting around waiting to pull an SD card or take one photo at a time," Dr. Will notes.

At the ESCRS meeting, he discussed the use of his system in 24 patients. He explains, "Using the feedback from our system, we were able to obtain much better accuracy compared to the method of using just the AcuTarget HD, as we could quickly move the inlay based on the intraoperative feedback from the system, without having to move the patient." He compared 42 consecutive eyes implanted with KAMRA using manual marking and deductive reckoning based on anatomic landmarks in the OR, to 24 consecutive eyes implanted using his camera-based centration system in the OR. Dr. Will's experimental group showed a significantly lower average centration error, at 85 µm (standard deviation: 24 µm; range: 22 to 155 µm), versus 171 µm (standard deviation: 33 µm; range: 57 to 263 µm) for the manual-marking group.

Dr. Will's adaptation of a conventional camera body is garnering the interest of surgeons and vendors alike. "We are considering taking this system to a commercial product," he says. Although its current iteration is meant to assist in KAMRA inlay surgery, he thinks its applications could expand. "We believe that it can be used to check inlay position for the Raindrop (ReVision Optics, Lake Forest, Calif.) and Flexivue inlays (Presbia, Irvine, Calif.), as well," he says. REVIEW

Dr. Will has no financial relationships to any of the companies mentioned in this article.

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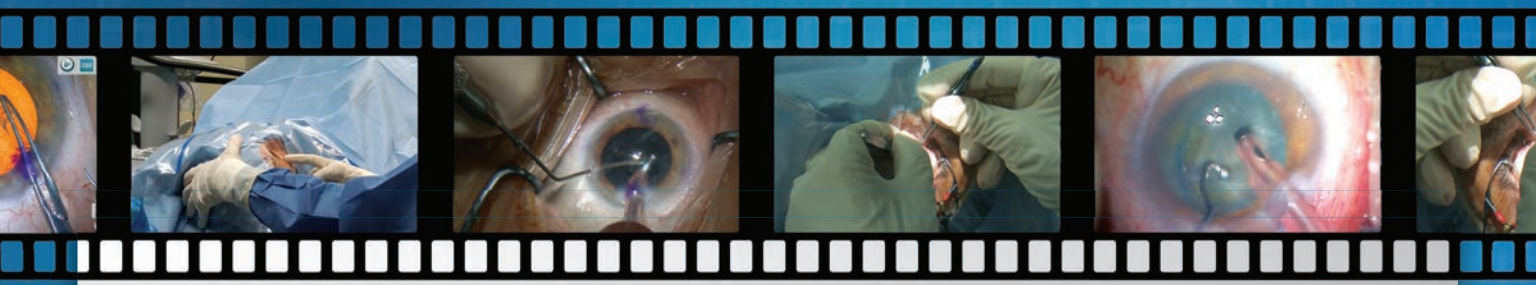

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Episode 11: "Full Thickness (Penetrating) LRIs to Correct Astigmatism During Multifocal IOL Insertion"

Surgical Video by:
Richard J. Mackool, MD

Video Overview:
During this case I demonstrate the differences between phaco aspiration vs phacoemulsification of the nucleus, as well as the use of Penetrating Limbal Relaxing Incisions to control astigmatism in a multifocal IOL patient.

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Richard J. Mackool, MD

I would like to welcome you to a new concept in surgeon education, Mackool Online CME.

Demonstrating ophthalmic surgical techniques has long been part of my everyday practice. Now, thanks to educational grants from several ophthalmic companies, you are able to virtually sit at the microscope with me and see the techniques and instrumentation I use with my own patients. The only editing is to show a different camera view or to remove down time – every step of every procedure will be shown just as if you are with me in the OR. We will release one new surgical video every month, allowing you to earn CME credits or simply watch the video.

CME Accredited Surgical Training Videos Now Available Online: www.MackoolOnlineCME.com

Richard Mackool, MD, a world renowned anterior segment ophthalmic microsurgeon, has assembled a web-based video collection of surgical cases that encompass both routine and challenging cases, demonstrating both familiar and potentially unfamiliar surgical techniques using a variety of instrumentation and settings.

This educational activity aims to present a series of Dr. Mackool's surgical videos, carefully selected to address the specific learning objectives of this activity, with the goal of making surgical training available as needed online for surgeons motivated to improve or expand their surgical repertoire.

Learning Objectives:
After completion of this educational activity, participants should be able to:

1. Describe the use of full-thickness (penetrating) limbal relaxing incisions (PLRIs) to correct astigmatism
2. Discuss methods to safely divide the nucleus with the horizontal chopping technique
3. Determine which techniques minimize the use of ultrasonic energy during nucleus removal
4. Describe a technique to protect the integrity of the posterior capsule during removal of lens cortex
5. Discuss the benefits of epithelium removal from the under-surface of the anterior capsule

Accreditation Statement
This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the Institute for the Advancement of Human Behavior (IAHB) and Postgraduate Healthcare Education, LLC (PHE). IAHB is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation Statement
IAHB designates this live activity for a maximum of .25 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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Review of Ophthalmology®

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New Indication. New Dosing Regimen.

HUMIRA is administered by subcutaneous injection

INITIAL DOSE

80 mg

FOLLOWED BY

40 mg given every other week starting 1 week after the initial dose

The first injection should be given under the supervision of a healthcare professional. A patient may self-inject HUMIRA after appropriate training and monitoring by a healthcare professional.

Visit www.HumiraPro.com to learn more about our education programs for NI uveitis.*

***Intermediate, posterior, and panuveitis.**

Indication[1]

Uveitis: HUMIRA is indicated for the treatment of non-infectious intermediate, posterior, and panuveitis in adult patients.

IMPORTANT SAFETY INFORMATION FOR HUMIRA® (adalimumab)[1]

SERIOUS INFECTIONS

Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Discontinue HUMIRA if a patient develops a serious infection or sepsis.

Reported infections include:

- **Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Test patients for latent TB before HUMIRA use and during therapy. Initiate treatment for latent TB prior to HUMIRA use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider empiric anti-fungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral, and other infections due to opportunistic pathogens, including Legionella and Listeria.**

Carefully consider the risks and benefits of treatment with HUMIRA prior to initiating therapy in patients: 1. with chronic or recurrent infection, 2. who have been exposed to TB, 3. with a history of opportunistic infection, 4. who resided in or traveled in regions where mycoses are endemic, 5. with underlying conditions that may predispose them to infection. Monitor patients closely for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy.

- Do not start HUMIRA during an active infection, including localized infections.
- Patients older than 65 years, patients with co-morbid conditions, and/or patients taking concomitant immunosuppressants may be at greater risk of infection.
- If an infection develops, monitor carefully and initiate appropriate therapy.
- Drug interactions with biologic products: A higher rate of serious infections has been observed in rheumatoid arthritis patients treated with rituximab who received subsequent treatment with a TNF blocker. Concurrent use of HUMIRA with biologic DMARDs (e.g., anakinra or abatacept) or other TNF blockers is not recommended based on the possible increased risk for infections and other potential pharmacological interactions.

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including HUMIRA. Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers, including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all of these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants.

- Consider the risks and benefits of HUMIRA treatment prior to initiating or continuing therapy in a patient with known malignancy.
- In clinical trials, more cases of malignancies were observed among HUMIRA-treated patients compared to control patients.
- Non-melanoma skin cancer (NMSC) was reported during clinical trials for HUMIRA-treated patients. Examine all patients, particularly those with a history of prolonged immunosuppressant or PUVA therapy, for the presence of NMSC prior to and during treatment with HUMIRA.
- In HUMIRA clinical trials, there was an approximate 3-fold higher rate of lymphoma than expected in the general U.S. population. Patients with chronic inflammatory diseases, particularly those with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at higher risk of lymphoma than the general population, even in the absence of TNF blockers.

NOW APPROVED

F1RST AND ONLY FDA-APPROVED ANTI-TNF **FOR TREATING NON-INFECTIOUS (NI) UVEITIS***

HUMIRA® adalimumab *destination you*™

HUMIRA for NI intermediate, posterior, and panuveitis*

A steroid-sparing option proven to prolong time to a combination of disease flare† and decrease of visual acuity.[1]

†Disease flare is defined by an increase in 1 or more inflammatory markers: AC cells, vitreous haze, and/or development of new chorioretinal, and/or retinal vascular lesions.

- Postmarketing cases of acute and chronic leukemia were reported with TNF blocker use. Approximately half of the postmarketing cases of malignancies in children, adolescents, and young adults receiving TNF blockers were lymphomas; other cases included rare malignancies associated with immunosuppression and malignancies not usually observed in children and adolescents.

HYPERSENSITIVITY

- Anaphylaxis and angioneurotic edema have been reported following HUMIRA administration. If a serious allergic reaction occurs, stop HUMIRA and institute appropriate therapy.

HEPATITIS B VIRUS REACTIVATION

- Use of TNF blockers, including HUMIRA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers. Some cases have been fatal.
- Evaluate patients at risk for HBV infection for prior evidence of HBV infection before initiating TNF blocker therapy.
- Exercise caution in patients who are carriers of HBV and monitor them during and after HUMIRA treatment.
- Discontinue HUMIRA and begin antiviral therapy in patients who develop HBV reactivation. Exercise caution when resuming HUMIRA after HBV treatment.

NEUROLOGIC REACTIONS

- TNF blockers, including HUMIRA, have been associated with rare cases of new onset or exacerbation of central nervous system and peripheral demyelinating diseases, including multiple sclerosis, optic neuritis, and Guillain-Barré syndrome.
- Exercise caution when considering HUMIRA for patients with these disorders; discontinuation of HUMIRA should be considered if any of these disorders develop.
- There is a known association between intermediate uveitis and central demyelinating disorders.

HEMATOLOGIC REACTIONS

- Rare reports of pancytopenia, including aplastic anemia, have been reported with TNF blockers. Medically significant cytopenia has been infrequently reported with HUMIRA.
- Consider stopping HUMIRA if significant hematologic abnormalities occur.

CONGESTIVE HEART FAILURE

- Worsening or new onset congestive heart failure (CHF) may occur; exercise caution and monitor carefully.

AUTOIMMUNITY

- Treatment with HUMIRA may result in the formation of autoantibodies and, rarely, in development of a lupus-like syndrome. Discontinue treatment if symptoms of a lupus-like syndrome develop.

IMMUNIZATIONS

- Patients on HUMIRA should not receive live vaccines.
- Pediatric patients, if possible, should be brought up to date with all immunizations before initiating HUMIRA therapy.
- The safety of administering live or live-attenuated vaccines in infants exposed to HUMIRA *in utero* is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants.

ADVERSE REACTIONS

- The most common adverse reactions in HUMIRA clinical trials (>10%) were: infections (e.g., upper respiratory, sinusitis), injection site reactions, headache, and rash.

Reference: 1. HUMIRA Injection [package insert]. North Chicago, IL: AbbVie Inc.

Please see Brief Summary of full Prescribing Information on the following page.

 North Chicago, IL 60064 64C-1859319 June 2016 Printed in U.S.A.

abbvie

HUMIRA® (adalimumab)

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

SERIOUS INFECTIONS

Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions]*. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Discontinue HUMIRA if a patient develops a serious infection or sepsis.

Reported infections include:

- **Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Test patients for latent TB before HUMIRA use and during therapy. Initiate treatment for latent TB prior to HUMIRA use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider empiric anti-fungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral and other infections due to opportunistic pathogens, including Legionella and Listeria.**

Carefully consider the risks and benefits of treatment with HUMIRA prior to initiating therapy in patients with chronic or recurrent infection.

Monitor patients closely for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy *[see Warnings and Precautions and Adverse Reactions]*.

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers including HUMIRA *[see Warnings and Precautions]*. Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all these patients had received treatment with azathioprine or 6-mercaptopurine (6–MP) concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants *[see Warnings and Precautions]*.

INDICATIONS AND USAGE

Rheumatoid Arthritis

HUMIRA is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis. HUMIRA can be used alone or in combination with methotrexate or other non-biologic disease-modifying anti-rheumatic drugs (DMARDs).

Juvenile Idiopathic Arthritis

HUMIRA is indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older. HUMIRA can be used alone or in combination with methotrexate.

Psoriatic Arthritis

HUMIRA is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis. HUMIRA can be used alone or in combination with non-biologic DMARDs.

Ankylosing Spondylitis

HUMIRA is indicated for reducing signs and symptoms in adult patients with active ankylosing spondylitis.

Adult Crohn's Disease

HUMIRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. HUMIRA is indicated for reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

Pediatric Crohn's Disease

HUMIRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate.

Ulcerative Colitis

HUMIRA is indicated for inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of HUMIRA has not been established in patients who have lost response to or were intolerant to TNF blockers.

Plaque Psoriasis

HUMIRA is indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate. HUMIRA should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician *[see Boxed Warning and Warnings and Precautions]*.

Hidradenitis Suppurativa

HUMIRA is indicated for the treatment of moderate to severe hidradenitis suppurativa.

Uveitis

HUMIRA is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Serious Infections

Patients treated with HUMIRA are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death *[see Boxed Warning]*. Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic pathogens including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis and tuberculosis have been reported with TNF blockers. Patients have frequently presented with disseminated rather than localized disease.

The concomitant use of a TNF blocker and abatacept or anakinra was associated with a higher risk of serious infections in patients with rheumatoid arthritis (RA); therefore, the concomitant use of HUMIRA and these biologic products is not recommended in the treatment of patients with RA *[see Warnings and Precautions and Drug Interactions]*.

Treatment with HUMIRA should not be initiated in patients with an active infection, including localized infections. Patients greater than 65 years of age, patients with co-morbid conditions and/or patients taking concomitant immunosuppressants (such as corticosteroids or methotrexate), may be at greater risk of infection. Consider the risks and benefits of treatment prior to initiating therapy in patients:

- with chronic or recurrent infection;
- who have been exposed to tuberculosis;
- with a history of an opportunistic infection;
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or
- with underlying conditions that may predispose them to infection.

Tuberculosis

Cases of reactivation of tuberculosis and new onset tuberculosis infections have been reported in patients receiving HUMIRA, including patients who have previously received treatment for latent or active tuberculosis. Reports included cases of pulmonary and extrapulmonary (i.e., disseminated) tuberculosis. Evaluate patients for tuberculosis risk factors and test for latent infection prior to initiating HUMIRA and periodically during therapy.

Treatment of latent tuberculosis infection prior to therapy with TNF blocking agents has been shown to reduce the risk of tuberculosis reactivation during therapy.

Consider anti-tuberculosis therapy prior to initiation of HUMIRA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Despite prophylactic treatment for tuberculosis, cases of reactivated tuberculosis have occurred in patients treated with HUMIRA. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

Strongly consider tuberculosis in the differential diagnosis in patients who develop a new infection during HUMIRA treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis.

Monitoring

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. Tests for latent tuberculosis infection may also be falsely negative while on therapy with HUMIRA.

Discontinue HUMIRA if a patient develops a serious infection or sepsis. For a patient who develops a new infection during treatment with HUMIRA, closely monitor them, perform a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and initiate appropriate antimicrobial therapy.

Invasive Fungal Infections

If patients develop a serious systemic illness and they reside or travel in regions where mycoses are endemic, consider invasive fungal infection in the differential diagnosis. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider appropriate empiric antifungal therapy, taking into account both the risk for severe fungal infection and the risks of antifungal therapy, while a diagnostic workup is being performed. To aid in the management of such patients, consider consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections.

Malignancies

Consider the risks and benefits of TNF-blocker treatment including HUMIRA prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing a TNF blocker in patients who develop a malignancy.

Malignancies in Adults

In the controlled portions of clinical trials of some TNF-blockers, including HUMIRA, more cases of malignancies have been observed among TNF-blocker-treated adult patients compared to control-treated adult patients. During the controlled portions of 39 global HUMIRA clinical trials in adult patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD), ulcerative colitis (UC) plaque psoriasis (Ps), hidradenitis suppurativa (HS), and uveitis (UV) malignancies, other than non-melanoma (basal cell and squamous cell) skin cancer, were observed at a rate (95% confidence interval) of 0.7 (0.48, 1.03) per 100 patient-years among 7973 HUMIRA-treated patients versus a rate of 0.7 (0.41, 1.17) per 100 patient-years among 4848 control-treated patients (median duration of treatment of 4 months for HUMIRA-treated patients and 4 months for control-treated patients). In 52 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV, the most frequently observed malignancies, other than lymphoma and NMSC, were breast, colon, prostate, lung, and melanoma. The malignancies in HUMIRA-treated patients in the controlled and uncontrolled portions of the studies were similar in type and number to what would be expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race).

In controlled trials of other TNF blockers in adult patients at higher risk for malignancies (i.e., patients with COPD with a significant smoking history and cyclophosphamide-treated patients with Wegener's granulomatosis), a greater portion of malignancies occurred in the TNF blocker group compared to the control group.

Non-Melanoma Skin Cancer

During the controlled portions of 39 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV, the rate (95% confidence interval) of NMSC was 0.8 (0.52, 1.09) per 100 patient-years among HUMIRA-treated patients and 0.2 (0.10, 0.59) per 100 patient-years among control-treated patients. Examine all patients, and in particular patients with a medical history of prior prolonged immunosuppressant therapy or psoriasis patients with a history of PUVA treatment for the presence of NMSC prior to and during treatment with HUMIRA.

Lymphoma and Leukemia

In the controlled portions of clinical trials of all the TNF-blockers in adults, more cases of lymphoma have been observed among TNF-blocker-treated patients compared to control-treated patients. In the controlled portions of 39 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC Ps, HS and UV, 2 lymphomas occurred among 7973 HUMIRA-treated patients versus 1 among 4848 control-treated patients. In 52 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV with a median duration of approximately 0.7 years, including 24,605 patients and over 40,215 patient-years of HUMIRA, the observed rate of lymphomas was approximately 0.11 per 100 patient-years. This is approximately 3-fold higher than expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race). Rates of lymphoma in clinical trials of HUMIRA cannot be compared to rates of lymphoma in clinical trials of other TNF blockers and may not predict the rates observed in a broader patient population. Patients with RA and other chronic inflammatory diseases, particularly those with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF blockers. Post-marketing cases of acute and chronic leukemia have been reported in association with TNF-blocker use in RA and other indications. Even in the absence of TNF-blocker therapy, patients with RA may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia.

Malignancies in Pediatric Patients and Young Adults

Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blockers (initiation of therapy ≤ 18 years of age), of which HUMIRA is a member *[see Boxed Warning]*. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months of therapy (range 1 to 84 months). Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources including registries and spontaneous postmarketing reports.

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HUMIRA *[see Boxed Warning]*. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all of these patients had received treatment with the immunosuppressants azathioprine or 6-mercaptopurine (6–MP) concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants. The potential risk with the combination of azathioprine or 6-mercaptopurine and HUMIRA should be carefully considered.

Hypersensitivity Reactions

Anaphylaxis and angioneurotic edema have been reported following HUMIRA administration. If an anaphylactic or other serious allergic reaction occurs, immediately discontinue administration of HUMIRA and institute appropriate therapy. In clinical trials of HUMIRA in adults, allergic reactions (e.g., allergic rash, anaphylactoid reaction, fixed drug reaction, non-specified drug reaction, urticaria) have been observed.

Hepatitis B Virus Reactivation

Use of TNF blockers, including HUMIRA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Evaluate patients at risk for HBV infection for prior evidence of HBV infection before initiating TNF blocker therapy. Exercise caution in prescribing TNF blockers for patients identified as carriers of HBV. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. In patients who develop HBV reactivation, stop HUMIRA and initiate effective anti-viral therapy with appropriate supportive treatment. The safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known.

Neurologic Reactions

Use of TNF blocking agents, including HUMIRA, has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease, including multiple sclerosis (MS) and optic neuritis, and peripheral demyelinating disease, including Guillain-Barré syndrome. Exercise caution in considering the use of HUMIRA in patients with preexisting or recent-onset central or peripheral nervous system demyelinating disorders; discontinuation of HUMIRA should be considered if any of these disorders develop. There is a known association between intermediate uveitis and central demyelinating disorders.

Hematological Reactions

Rare reports of pancytopenia including aplastic anemia have been reported with TNF blocking agents. Adverse reactions of the hematologic system, including medically significant cytopenia (e.g., thrombocytopenia, leukopenia) have been infrequently reported with HUMIRA. The causal relationship of these reports to HUMIRA remains unclear. Advise all patients to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on HUMIRA. Consider discontinuation of HUMIRA therapy in patients with confirmed significant hematologic abnormalities.

Use with Anakinra

Concurrent use of anakinra (an interleukin-1 antagonist) and another TNF-blocker, was associated with a greater proportion of serious infections and neutropenia and no added benefit compared with the TNF-blocker alone in patients with RA. Therefore, the combination of HUMIRA and anakinra is not recommended *[see Drug Interactions]*.

Heart Failure

Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers. Cases of worsening CHF have also been observed with HUMIRA. Exercise caution when using HUMIRA in patients who have heart failure and monitor them carefully.

Autoimmunity

Treatment with HUMIRA may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with HUMIRA, discontinue treatment *[see Adverse Reactions]*.

Immunizations

In a placebo-controlled clinical trial of patients with RA, no difference was detected in anti-pneumococcal antibody response between HUMIRA and placebo treatment groups when the pneumococcal polysaccharide vaccine and influenza vaccine were administered concurrently with HUMIRA. Patients on HUMIRA may receive concurrent vaccinations, except for live vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving HUMIRA.

It is recommended that pediatric patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating HUMIRA therapy. Patients on HUMIRA may receive concurrent vaccinations, except for live vaccines.

The safety of administering live or live-attenuated vaccines in infants exposed to HUMIRA *in utero* is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants *[see Use in Specific Populations]*.

Use with Abatacept

In controlled trials, the concurrent administration of TNF-blockers and abatacept was associated with a greater proportion of serious infections than the use of a TNF-blocker alone; the combination therapy, compared to the use of a TNF-blocker alone, has not demonstrated improved clinical benefit in the treatment of RA. Therefore, the combination of abatacept with TNF-blockers including HUMIRA is not recommended *[see Drug Interactions]*.

ADVERSE REACTIONS

The most serious adverse reactions described elsewhere in the labeling include the following:

- Serious Infections *[see Warnings and Precautions]*
- Malignancies *[see Warnings and Precautions]*

Clinical Trials Experience

The most common adverse reaction with HUMIRA was injection site reactions. In placebo-controlled trials, 20% of patients treated with HUMIRA developed injection site reactions (erythema and/or itching, hemorrhage, pain or swelling), compared to 14% of patients receiving placebo. Most injection site reactions were described as mild and generally did not necessitate drug discontinuation.

The proportion of patients who discontinued treatment due to adverse reactions during the double-blind, placebo-controlled portion of studies in patients with RA (i.e., Studies RA-I, RA-II, RA-III and RA-IV) was 7% for patients taking HUMIRA and 4% for placebo-treated patients. The most common adverse reactions leading to discontinuation of HUMIRA in these RA studies were clinical flare reaction (0.7%), rash (0.3%) and pneumonia (0.3%).

Infections

In the controlled portions of the 39 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, HS and UV, the rate of serious infections was 4.3 per 100 patient-years in 7973 HUMIRA-treated patients versus a rate of 2.9 per 100 patient-years in 4848 control-treated patients. Serious infections observed included pneumonia, septic arthritis, prosthetic and post-surgical infections, erysipelas, cellulitis, diverticulitis, and pyelonephritis *[see Warnings and Precautions]*.

Tuberculosis and Opportunistic Infections

In 52 global controlled and uncontrolled clinical trials in RA, PsA, AS, CD, UC, Ps, HS and UV that included 24,605 HUMIRA-treated patients, the rate of reported active tuberculosis was 0.20 per 100 patient-years and the rate of positive PPD conversion was 0.09 per 100 patient-years. In a subgroup of 10,113 U.S. and Canadian HUMIRA-treated patients, the rate of reported active TB was 0.05 per 100 patient-years and the rate of positive PPD conversion was 0.07 per 100 patient-years. These trials included reports of miliary, lymphatic, peritoneal, and pulmonary TB. Most of the TB cases occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease. In these global clinical trials, cases of serious opportunistic infections have been reported at an overall rate of 0.05 per 100 patient-years. Some cases of serious opportunistic infections and TB have been fatal *[see Warnings and Precautions]*.

Autoantibodies

In the rheumatoid arthritis controlled trials, 12% of patients treated with HUMIRA and 7% of placebo-treated patients that had negative baseline ANA titers developed positive titers at week 24. Two patients out of 3046 treated with HUMIRA developed clinical signs suggestive of new-onset lupus-like syndrome. The patients improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms. The impact of long-term treatment with HUMIRA on the development of autoimmune diseases is unknown.

Liver Enzyme Elevations

There have been reports of severe hepatic reactions including acute liver failure in patients receiving TNF-blockers. In controlled Phase 3 trials of HUMIRA (40 mg SC every other week) in patients with RA, PsA, and AS with control period duration ranging from 4 to 104 weeks, ALT elevations ≥ 3 x ULN occurred in 3.5% of HUMIRA-treated patients and 1.5% of control-treated patients. Since many of these patients in these trials were also taking medications that cause liver enzyme elevations (e.g., NSAIDS, MTX), the relationship between HUMIRA and the liver enzyme elevations is not clear. In a controlled Phase 3 trial of HUMIRA in patients with polyarticular JIA who were 4 to 17 years, ALT elevations ≥ 3 x ULN occurred in 4.4% of HUMIRA-treated patients and 1.5% of control-treated patients (ALT more common than AST); liver enzyme test elevations were more frequent among those treated with the combination of HUMIRA and MTX than those treated with HUMIRA alone. In general, these elevations did not lead to discontinuation of HUMIRA treatment. No ALT elevations ≥ 3 x ULN occurred in the open-label study of HUMIRA in patients with polyarticular JIA who were 2 to <4 years.

In controlled Phase 3 trials of HUMIRA (initial doses of 160 mg and 80 mg, or 80 mg and 40 mg on Days 1 and 15, respectively, followed by 40 mg every other week) in adult patients with CD with a control period duration ranging from 4 to 52 weeks, ALT elevations ≥ 3 x ULN occurred in 0.9% of HUMIRA-treated patients and 0.9% of control-treated patients. In the Phase 3 trial of HUMIRA in pediatric patients with Crohn's disease which evaluated efficacy and safety of two body weight based maintenance dose regimens following body weight based induction therapy up to 52 weeks of treatment, ALT elevations ≥ 3 x ULN occurred in 2.6% (5/192) of patients, of whom 4 were receiving concomitant immunosuppressants at baseline; none of these patients discontinued due to abnormalities in ALT tests. In controlled Phase 3 trials of HUMIRA (initial doses of 160 mg and 80 mg on Days 1 and 15 respectively, followed by 40 mg every other week) in patients with UC with control period duration ranging from 1 to 52 weeks, ALT elevations ≥3 x ULN occurred in 1.5% of HUMIRA-treated patients and 1.0% of control-treated patients. In controlled Phase 3 trials of HUMIRA (initial dose of 80 mg then 40 mg every other week) in patients with Ps with control period duration ranging from 12 to 24 weeks, ALT elevations ≥ 3 x ULN occurred in 1.8% of HUMIRA-treated patients and 1.8% of control-treated patients. In controlled trials of HUMIRA (initial doses of 160 mg at Week 0 and 80 mg at Week 2, followed by 40 mg every week starting at Week 4), in subjects with HS with a control period duration ranging from 12 to 16 weeks, ALT elevations ≥ 3 x ULN occurred in 0.3% of HUMIRA-treated subjects and 0.6% of control-treated subjects. In controlled trials of HUMIRA (initial doses of 80 mg at Week 0 followed by 40 mg every other week starting at Week 1) in patients with uveitis with an exposure of 165.4 PYs and 119.8 PYs in HUMIRA-treated and control-treated patients, respectively, ALT elevations ≥ 3 x ULN occurred in 2.4% of HUMIRA-treated patients and 2.4% of control-treated patients.

Immunogenicity

Patients in Studies RA-I, RA-II, and RA-III were tested at multiple time points for antibodies to adalimumab during the 6- to 12-month period. Approximately 5% (58 of 1062) of adult RA patients receiving HUMIRA developed low-titer antibodies to adalimumab at least once during treatment, which were neutralizing *in vitro*. Patients treated with concomitant methotrexate (MTX) had a lower rate of antibody development than patients on HUMIRA monotherapy (1% versus 12%). No apparent correlation of antibody development to adverse reactions was observed. With monotherapy, patients receiving every other week dosing may develop antibodies more frequently than those receiving weekly dosing. In patients receiving the recommended dosage of 40 mg every other week as monotherapy, the ACR 20 response was lower among antibody-positive patients than among antibody-negative patients. The long-term immunogenicity of HUMIRA is unknown.

In patients with polyarticular JIA who were 4 to 17 years of age, adalimumab antibodies were identified in 16% of HUMIRA-treated patients. In patients receiving concomitant MTX, the incidence was 6% compared to 26% with HUMIRA monotherapy. In patients with polyarticular JIA who were 2 to <4 years of age or 4 years of age and older weighing <15 kg, adalimumab antibodies were identified in 7% (1 of 15) of HUMIRA-treated patients, and the one patient was receiving concomitant MTX.

In patients with AS, the rate of development of antibodies to adalimumab in HUMIRA-treated patients was comparable to patients with RA.

In patients with PsA, the rate of antibody development in patients receiving HUMIRA monotherapy was comparable to patients with RA; however, in patients receiving concomitant MTX the rate was 7% compared to 1% in RA.

In adult patients with CD, the rate of antibody development was 3%.

In pediatric patients with Crohn's disease, the rate of antibody development in patients receiving HUMIRA was 3%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 32% of total patients studied), the immunogenicity rate was 10%.

In patients with moderately to severely active UC, the rate of antibody development in patients receiving HUMIRA was 5%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 25% of total patients studied), the immunogenicity rate was 20.7%.

In patients with Ps, the rate of antibody development with HUMIRA monotherapy was 8%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 40% of total patients studied), the immunogenicity rate was 20.7%. In Ps patients who were on HUMIRA monotherapy and subsequently withdrawn from the treatment, the rate of antibodies to adalimumab after retreatment was similar to the rate observed prior to withdrawal.

In subjects with moderate to severe HS, the rate of anti-adalimumab antibody development in subjects treated with HUMIRA was 6.5%. However, because of the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among subjects who stopped HUMIRA treatment for up to 24 weeks and in whom adalimumab serum levels subsequently declined to < 2 mcg/mL (approximately 22% of total subjects studied), the immunogenicity rate was 28%.

In patients with non-infectious uveitis, anti-adalimumab antibodies were identified in 4.8% (12/249) of patients treated with adalimumab. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 23% of total patients studied), the immunogenicity rate was 21.1%. Using an assay which could measure an anti-adalimumab antibody titer in all patients, titers were measured in 39.8% (99/249) of non-infectious uveitis patients treated with adalimumab. No correlation of antibody development to safety or efficacy outcomes was observed.

The data reflect the percentage of patients whose test results were considered positive for antibodies to adalimumab or titers, and are highly dependent on the assay. The observed incidence of antibody (including neutralizing antibody) positivity in an assay is highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to adalimumab with the incidence of antibodies to other products may be misleading.

Other Adverse Reactions

Rheumatoid Arthritis Clinical Studies

The data described below reflect exposure to HUMIRA in 2468 patients, including 2073 exposed for 6 months, 1497 exposed for greater than one year and 1380 in adequate and well-controlled studies (Studies RA-I, RA-II, RA-III, and RA-IV). HUMIRA was studied primarily in placebo-controlled trials and in long-term follow up studies for up to 36 months duration. The population had a mean age of 54 years, 77% were female, 91% were Caucasian and had moderately to severely active rheumatoid arthritis. Most patients received 40 mg HUMIRA every other week.

Table 1 summarizes reactions reported at a rate of at least 5% in patients treated with HUMIRA 40 mg every other week compared to placebo and with an incidence higher than placebo. In Study RA-III, the types and frequencies of adverse reactions in the second year open-label extension were similar to those observed in the one-year double-blind portion.

Table 1. Adverse Reactions Reported by ≥5% of Patients Treated with HUMIRA During Placebo-Controlled Period of Pooled RA Studies (Studies RA-I, RA-II, RA-III, and RA-IV)

	HUMIRA 40 mg subcutaneous Every Other Week	Placebo
Adverse Reaction (Preferred Term)	(N=705)	(N=690)
Respiratory		
Upper respiratory infection	17%	13%
Sinusitis	11%	9%
Flu syndrome	7%	6%
Gastrointestinal		
Nausea	9%	8%
Abdominal pain	7%	4%
Laboratory Tests*		
Laboratory test abnormal	8%	7%
Hypercholesterolemia	6%	4%
Hyperlipidemia	7%	5%
Hematuria	5%	4%
Alkaline phosphatase increased	5%	3%
Other		
Headache	12%	8%
Rash	12%	6%
Accidental injury	10%	8%
Injection site reaction **	8%	1%
Back pain	6%	4%
Urinary tract infection	8%	5%
Hypertension	5%	3%

* Laboratory test abnormalities were reported as adverse reactions in European trials

** Does not include injection site erythema, itching, hemorrhage, pain or swelling

Juvenile Idiopathic Arthritis Clinical Studies

In general, the adverse reactions in the HUMIRA-treated patients in the polyarticular juvenile idiopathic arthritis (JIA) trials (Studies JIA-I and JIA-II) were similar in frequency and type to those seen in adult patients *[see Warnings and Precautions and Adverse Reactions]*. Important findings and differences from adults are discussed in the following paragraphs.

In Study JIA-I, HUMIRA was studied in 171 patients who were 4 to 17 years of age, with polyarticular JIA. Severe adverse reactions reported in the study included neutropenia, streptococcal pharyngitis, increased aminotransferases, herpes zoster, myositis, metrorrhagia, and appendicitis. Serious infections were observed in 4% of patients within approximately 2 years of initiation of treatment with HUMIRA and included cases of herpes simplex, pneumonia, urinary tract infection, pharyngitis, and herpes zoster.

In Study JIA-I, 45% of patients experienced an infection while receiving HUMIRA with or without concomitant MTX in the first 16 weeks of treatment. The types of infections reported in HUMIRA-treated patients were generally similar to those commonly seen in polyarticular JIA patients who are not treated with TNF blockers. Upon initiation of treatment, the most common adverse reactions occurring in this patient population treated with HUMIRA were injection site pain and injection site reaction (19% and 16%, respectively). A less commonly reported adverse event in patients receiving HUMIRA was granuloma annulare which did not lead to discontinuation of HUMIRA treatment.

In the first 48 weeks of treatment in Study JIA-I, non-serious hypersensitivity reactions were seen in approximately 6% of patients and included primarily localized allergic hypersensitivity reactions and allergic rash.

In Study JIA-I, 10% of patients treated with HUMIRA who had negative baseline anti-dsDNA antibodies developed positive titers after 48 weeks of treatment. No patient developed clinical signs of autoimmunity during the clinical trial.

Approximately 15% of patients treated with HUMIRA developed mild-to-moderate elevations of creatine phosphokinase (CPK) in Study JIA-I. Elevations exceeding 5 times the upper limit of normal were observed in several patients. CPK levels decreased or returned to normal in all patients. Most patients were able to continue HUMIRA without interruption.

In Study JIA-II, HUMIRA was studied in 32 patients who were 2 to <4 years of age or 4 years of age and older weighing <15 kg with polyarticular JIA. The safety profile for this patient population was similar to the safety profile seen in patients 4 to 17 years of age with polyarticular JIA.

In Study JIA-II, 78% of patients experienced an infection while receiving HUMIRA. These included nasopharyngitis, bronchitis, upper respiratory tract infection, otitis media, and were mostly mild to moderate in severity. Serious infections were observed in 9% of patients receiving HUMIRA in the study and included dental caries, rotavirus gastroenteritis, and varicella.

In Study JIA-II, non-serious allergic reactions were observed in 6% of patients and included intermittent urticaria and rash, which were all mild in severity.

Psoriatic Arthritis and Ankylosing Spondylitis Clinical Studies

HUMIRA has been studied in 395 patients with psoriatic arthritis (PsA) in two placebo-controlled trials and in an open label study and in 393 patients with ankylosing spondylitis (AS) in two placebo-controlled studies. The safety profile for patients with PsA and AS treated with HUMIRA 40 mg every other

week was similar to the safety profile seen in patients with RA, HUMIRA Studies RA-I through IV.

Adult Crohn's Disease Clinical Studies

HUMIRA has been studied in 1478 adult patients with Crohn's disease (CD) in four placebo-controlled and two open-label extension studies. The safety profile for adult patients with CD treated with HUMIRA was similar to the safety profile seen in patients with RA.

Pediatric Crohn's Disease Clinical Studies

HUMIRA has been studied in 192 pediatric patients with Crohn's disease in one double-blind study (Study PCD-I) and one open-label extension study. The safety profile for pediatric patients with Crohn's disease treated with HUMIRA was similar to the safety profile seen in adult patients with Crohn's disease.

During the 4 week open label induction phase of Study PCD-I, the most common adverse reactions occurring in the pediatric population treated with HUMIRA were injection site pain and injection site reaction (6% and 5%, respectively).

A total of 67% of children experienced an infection while receiving HUMIRA in Study PCD-I. These included upper respiratory tract infection and nasopharyngitis.

A total of 5% of children experienced a serious infection while receiving HUMIRA in Study PCD-I. These included viral infection, device related sepsis (catheter), gastroenteritis, H1N1 influenza, and disseminated histoplasmosis.

In Study PCD-I, allergic reactions were observed in 5% of children which were all non-serious and were primarily localized reactions.

Ulcerative Colitis Clinical Studies

HUMIRA has been studied in 1010 patients with ulcerative colitis (UC) in two placebo-controlled studies and one open-label extension study. The safety profile for patients with UC treated with HUMIRA was similar to the safety profile seen in patients with RA.

Plaque Psoriasis Clinical Studies

HUMIRA has been studied in 1696 subjects with plaque psoriasis (Ps) in placebo-controlled and open-label extension studies. The safety profile for subjects with Ps treated with HUMIRA was similar to the safety profile seen in subjects with RA with the following exceptions. In the placebo-controlled portions of the clinical trials in Ps subjects, HUMIRA-treated subjects had a higher incidence of arthralgia when compared to controls (3% *vs.* 1%).

Hidradenitis Suppurativa Clinical Studies

HUMIRA has been studied in 727 subjects with hidradenitis suppurativa (HS) in three placebo-controlled studies and one open-label extension study. The safety profile for subjects with HS treated with HUMIRA weekly was consistent with the known safety profile of HUMIRA.

Flare of HS, defined as ≥25% increase from baseline in abscesses and inflammatory nodule counts and with a minimum of 2 additional lesions, was documented in 22 (22%) of the 100 subjects who were withdrawn from HUMIRA treatment following the primary efficacy timepoint in two studies.

Uveitis Clinical Studies

HUMIRA has been studied in 464 patients with uveitis (UV) in placebo-controlled and open-label extension studies. The safety profile for patients with UV treated with HUMIRA was similar to the safety profile seen in patients with RA.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of HUMIRA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to HUMIRA exposure.

Gastrointestinal disorders: Diverticulitis, large bowel perforations including perforations associated with diverticulitis and appendiceal perforations associated with appendicitis, pancreatitis

General disorders and administration site conditions: Pyrexia

Hepato-biliary disorders: Liver failure, hepatitis

Immune system disorders: Sarcoidosis

Neoplasms benign, malignant and unspecified (including cysts and polyps): Merkel Cell Carcinoma (neuroendocrine carcinoma of the skin)

Nervous system disorders: Demyelinating disorders (e.g., optic neuritis, Guillain-Barré syndrome), cerebrovascular accident

Respiratory disorders: Interstitial lung disease, including pulmonary fibrosis, pulmonary embolism

Skin reactions: Stevens Johnson Syndrome, cutaneous vasculitis, erythema multiforme, new or worsening psoriasis (all sub-types including pustular and palmoplantar), alopecia

Vascular disorders: Systemic vasculitis, deep vein thrombosis

DRUG INTERACTIONS

Methotrexate

HUMIRA has been studied in rheumatoid arthritis (RA) patients taking concomitant methotrexate (MTX). Although MTX reduced the apparent adalimumab clearance, the data do not suggest the need for dose adjustment of either HUMIRA or MTX.

Biological Products

In clinical studies in patients with RA, an increased risk of serious infections has been seen with the combination of TNF blockers with anakinra or abatacept, with no added benefit; therefore, use of HUMIRA with abatacept or anakinra is not recommended in patients with RA *[see Warnings and Precautions]*. A higher rate of serious infections has also been observed in patients with RA treated with rituximab who received subsequent treatment with a TNF blocker. There is insufficient information regarding the concomitant use of HUMIRA and other biologic products for the treatment of RA, PsA, AS, CD, UC, Ps, HS and UV. Concomitant administration of HUMIRA with other biologic DMARDS (e.g., anakinra and abatacept) or other TNF blockers is not recommended based upon the possible increased risk for infections and other potential pharmacological interactions.

Live Vaccines

Avoid the use of live vaccines with HUMIRA *[see Warnings and Precautions]*.

Cytochrome P450 Substrates

The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNFα, IL-6) during chronic inflammation. It is possible for a molecule that antagonizes cytokine activity, such as adalimumab, to influence the formation of CYP450 enzymes. Upon initiation or discontinuation of HUMIRA in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed.

USE IN SPECIFIC POPULATIONS

Pregnancy

Limited clinical data are available from the Humira Pregnancy Registry. Excluding lost-to-follow-up, data from the registry reports a rate of 5.6% for major birth defects with first trimester use of adalimumab in pregnant women with rheumatoid arthritis (RA), and a rate of 7.8% and 5.5% for major birth defects in the disease-matched and non-diseased comparison groups *[see Data]*. Adalimumab is actively transferred across the placenta during the third trimester of pregnancy and may affect immune response in the *in-utero* exposed infant *[see Clinical Considerations]*. In an embryo-fetal perinatal development study conducted in cynomolgus monkeys, no fetal harm or malformations were observed with intravenous administration of adalimumab during organogenesis and later in gestation, at doses that produced exposures up to approximately 373 times the maximum recommended human dose (MRHD) of 40 mg subcutaneous without methotrexate *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and miscarriage is 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal adverse reactions

Monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester [*see Data*]. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to HUMIRA *in utero [see Use in Specific Populations]*.

Data

Human Data

In a prospective cohort pregnancy exposure registry conducted in the U.S. and Canada between 2004 and 2013, 74 women with RA treated with adalimumab at least during the first trimester, 80 women with RA not treated with adalimumab and 218 women without RA (non-diseased) were enrolled. Excluding lost-to-follow-up, the rate of major defects in the adalimumab-exposed pregnancies (N=72), disease-matched (N=77), and non-diseased comparison groups (N=201) was 5.6%, 7.8% and 5.5%, respectively. However, this study cannot definitely establish the absence of any risk because of methodological limitations, including small sample size and non-randomized study design. Data from the Crohn's disease portion of the study is in the follow-up phase and the analysis is ongoing.

In an independent clinical study conducted in ten pregnant women with inflammatory bowel disease treated with HUMIRA, adalimumab concentrations were measured in maternal serum as well as in cord blood (n=10) and infant serum (n=8) on the day of birth. The last dose of HUMIRA was given between 1 and 56 days prior to delivery. Adalimumab concentrations were 0.16-19.7 µg/mL in cord blood, 4.28-17.7 µg/mL in infant serum, and 0-16.1 µg/mL in maternal serum. In all but one case, the cord blood level of adalimumab was higher than the maternal serum level, suggesting adalimumab actively crosses the placenta. In addition, one infant had serum levels at each of the following: 6 weeks (1.94 µg/mL), 7 weeks (1.31 µg/mL), 8 weeks (0.93 µg/mL), and 11 weeks (0.53 µg/mL), suggesting adalimumab can be detected in the serum of infants exposed *in utero* for at least 3 months from birth.

Lactation

Risk Summary

Limited data from case reports in the published literature describe the presence of adalimumab in human milk at infant doses of 0.1% to 1% of the maternal serum level. There are no reports of adverse effects of adalimumab on the breastfed infant and no effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HUMIRA and any potential adverse effects on the breastfed child from HUMIRA or from the underlying maternal condition.

Pediatric Use

Safety and efficacy of HUMIRA in pediatric patients for uses other than polyarticular juvenile idiopathic arthritis (JIA) and pediatric Crohn's disease have not been established. Due to its inhibition of TNFα, HUMIRA administered during pregnancy could affect immune response in the *in utero*-exposed newborn and infant. Data from eight infants exposed to HUMIRA *in utero* suggest adalimumab crosses the placenta *[see Use in Specific Populations]*. The clinical significance of elevated adalimumab levels in infants is unknown. The safety of administering live or live-attenuated vaccines in exposed infants is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants.

Post-marketing cases of lymphoma, including hepatosplenic T-cell lymphoma and other malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blockers including HUMIRA *[see Boxed Warning and Warnings and Precautions]*.

Juvenile Idiopathic Arthritis

In Study JIA-I, HUMIRA was shown to reduce signs and symptoms of active polyarticular JIA in patients 4 to 17 years of age *[see Clinical Studies]*. In Study JIA-II, the safety profile for patients 2 to <4 years of age was similar to the safety profile for patients 4 to 17 years of age with polyarticular JIA *[see Adverse Reactions]*. HUMIRA has not been studied in patients with polyarticular JIA less than 2 years of age or in patients with a weight below 10 kg.

The safety of HUMIRA in patients in the polyarticular JIA trials was generally similar to that observed in adults with certain exceptions *[see Adverse Reactions]*.

Pediatric Crohn's Disease

The safety and effectiveness of HUMIRA for reducing signs and symptoms and inducing and maintaining clinical remission have been established in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate. Use of HUMIRA in this age group is supported by evidence from adequate and well-controlled studies of HUMIRA in adults with additional data from a randomized, double-blind, 52-week clinical study of two dose levels of HUMIRA in 192 pediatric patients (6 to 17 years of age) with moderately to severely active Crohn's disease *[see Clinical Studies]*. The safety and effectiveness of HUMIRA has not been established in pediatric patients with Crohn's disease less than 6 years of age.

Geriatric Use

A total of 519 RA patients 65 years of age and older, including 107 patients 75 years of age and older, received HUMIRA in clinical studies RA-I through IV. No overall difference in effectiveness was observed between these patients and younger patients. The frequency of serious infection and malignancy among HUMIRA treated patients over 65 years of age was higher than for those under 65 years of age. Because there is a higher incidence of infections and malignancies in the elderly population, use caution when treating the elderly.

OVERDOSAGE

Doses up to 10 mg/kg have been administered to patients in clinical trials without evidence of dose-limiting toxicities. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies of HUMIRA have not been conducted to evaluate the carcinogenic potential or its effect on fertility.

PATIENT COUNSELING INFORMATION

Patient Counseling

Provide the HUMIRA "Medication Guide" to patients or their caregivers, and provide them an opportunity to read it and ask questions prior to initiation of therapy and prior to each time the prescription is renewed. If patients develop signs and symptoms of infection, instruct them to seek medical evaluation immediately.

Advise patients of the potential benefits and risks of HUMIRA.

- **Infections**

  Inform patients that HUMIRA may lower the ability of their immune system to fight infections. Instruct patients of the importance of contacting their doctor if they develop any symptoms of infection, including tuberculosis, invasive fungal infections, and reactivation of hepatitis B virus infections.
- **Malignancies**

  Counsel patients about the risk of malignancies while receiving HUMIRA.
- **Allergic Reactions**

  Advise patients to seek immediate medical attention if they experience any symptoms of severe allergic reactions. Advise latex-sensitive patients that the needle cap of the prefilled syringe contains latex.
- **Other Medical Conditions**

  Advise patients to report any signs of new or worsening medical conditions such as congestive heart failure, neurological disease, autoimmune disorders, or cytopenias. Advise patients to report any symptoms suggestive of a cytopenia such as bruising, bleeding, or persistent fever.

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Managing Dry-eye Patients, Step by Step

Christopher Kent, Senior Editor

Surgeons offer advice on making sense of today's diagnostic and treatment options.

With our understanding of the nature and causes of dry eye growing, and options for diagnosis and treatment expanding every year, effectively managing dry-eye patients is becoming increasingly complex. Some doctors still treat all dry-eye patients with the same basic approach, but others are choosing to take the bull by the horns and up their game, helping more of their patients while also improving outcomes in areas such as refractive surgery.

In response to this changing landscape, doctors have attempted to create algorithms to help clinicians navigate the management process. The first algorithms, such as the International Task Force Guidelines for Dry Eye, were created about 10 years ago; however, many clinicians still are not using them. Today, several new algorithms are in the works.

Mark S. Milner, MD, FACS, an associate clinical professor at Yale University School of Medicine and a partner and cornea specialist at the Eye Center of Southern Connecticut, is participating in several dry-eye studies and will soon be publishing his own dry-eye management algorithm. He points out that dry-eye disease can be clinically challenging, for two reasons. "First of all, dry-eye signs and symptoms can be disparate," he says. "You can have a patient with a lot of symptoms but minimal findings, or a patient with a lot of findings but minimal symptoms. Second, there's a misconception among many ophthalmologists that dry-eye disease is simply a quantitative problem—not enough tears. In reality, it may be a tear-quality problem as well. An abnormality in any part of the tear film, including the mucin layer and the oily layer, can lead to dry eye."

Esen Akpek, MD, a professor of ophthalmology and rheumatology at Johns Hopkins University School of Medicine and director of the Ocular Surface Disease and Dry Eye Clinic at the Wilmer Eye Institute, notes that general ophthalmologists often don't appreciate the value of treating dry eye. "Clinicians may assume that because dry eye is not blinding, it has no implications for a patient's vision," she says. "In fact, any irregularity in the tear film or epithelium can decrease quality of life because it blurs vision."

Here, five doctors with extensive experience treating dry eye share their thoughts on diagnosis, treatment and the issues surrounding the creation of a dry-eye management algorithm.

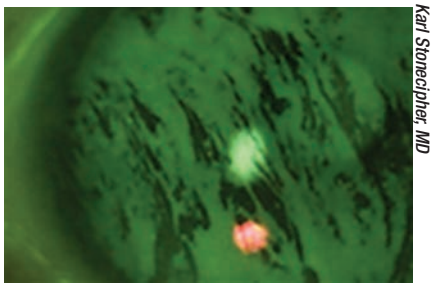
Conducting the Exam

"Dry eye is a complex topic and an

inexact science," notes Christopher J. Rapuano, MD, director of the cornea service at Wills Eye Hospital and professor of ophthalmology at Sidney Kimmel Medical College at Thomas Jefferson University in Philadelphia. "Diagnosis is largely based on the clinical exam, meaning on the symptoms and signs. Tests can be helpful in some cases, but not all."

Francis Mah, MD, who specializes in cornea, external disease and refractive surgery at Scripps Health System in San Diego, is a member of the American Society of Cataract and Refractive Surgery committee that is developing a new algorithm for dry-eye management. Dr. Mah says his basic exam for a dry-eye patient is straightforward. "First, I look at the tear-film meniscus to see what the tear lake looks like," he says. "Then I do conjunctival and corneal stainings, typically with fluorescein. Lissamine green is much more sensitive for identifying conjunctival staining, but it's become difficult to get the compounded 1% lissamine green solution, and the strips are notoriously inconsistent. Next, I do a tear-film breakup test with the fluorescein that's still in the eye. Finally, I press on the lower eyelid to assess the consistency of the meibum."

Stephen C. Pflugfelder, MD, a professor at Baylor College of Medicine in Houston and director of the Ocular Surface Center at Baylor's Cullen Eye Institute, often sees complex cases—patients who have been treated elsewhere without getting relief. "We have a standardized evaluation that helps us identify problems that are less obvious," he says. "Patients fill out two questionnaires: an ocular surface disease index questionnaire and a five-question visual analog scale measuring the frequency and severity of their irritation. Then we perform anterior segment OCT and corneal topography to look at the smoothness of the cornea. Next, we do tear osmolarity, followed by instillation of fluorescein dye to look at tear-film breakup time and corneal staining, and then lissamine green dye to look at the conjunctiva. Finally, we do a Schirmer I test without anesthesia.



Karl Stonecipher, MD

Tear breakup time testing reveals rapid (<7 seconds) tear dissolution.

"In some patients we also measure corneal sensitivity using the Cochet-Bonnet esthesiometer," he adds. "In certain chronic dry-eye conditions such as shingles or herpes zoster, corneal sensation is reduced. The lack of nerve stimulus causes the eye to stop producing tears."

Using the Tools

One factor adding confusion to dry-eye treatment today is the proliferation of point-of-service tests. "I think there are two reasons to do any of these tests," says Dr. Mah. "The first is to make diagnosis and management a little bit easier for the clinician. The second reason is to reassure the patient. It's helpful to be able to show the patient solid evidence that we've pinned down the problem, and that our treatment may help resolve it."

Doctors share their thoughts about the different tools that may come in handy when diagnosing the problem:

• ***Dry-eye questionnaire.*** Dr. Mah says if a patient is not complaining of ocular surface symptoms, his technicians have the patient answer a simple questionnaire. "We use a Standard Patient Evaluation of Eye Dryness, or SPEED questionnaire," he explains. "It's essentially two questions that have been validated to help identify ocular surface disease. If either of the answers is positive, we proceed to perform some basic tests. One survey found that about two-thirds of patients had ocular surface complaints, even though it wasn't the main reason for the visit."

• ***Ocular surface staining.*** Everyone agrees that this is an essential part of any dry-eye exam. "For surface staining I like to use lissamine green and fluorescein separately," says Dr. Akpek. "I test conjunctiva and cornea separately, because Sjögren's-related dry eye tends to be associated with conjunctival staining; other types of dry eye such as blepharitis or evaporative-related dry eye tend to stain the cornea more. I follow the ocular surface staining scoring published in 2010 in the *American Journal of Ophthalmology* by John Whitcher, MD,[1] because my main goal is to differentiate Sjögren's from non-Sjögren's dry eye and identify patients who will need prescription eye drops."

• ***InflammaDry.*** Dr. Mah says he performs the InflammaDry test if the patient is complaining about ocular surface symptoms, or if he gets a positive result from the SPEED questionnaire. "If the InflammaDry is positive, then we follow it with the TearLab osmolarity test," he says. "If the InflammaDry is negative, indicating that there's little or no inflammation, I believe the osmolarity test is still important as a follow-up. In my experience, inflammation will be present whether the problem is blepharitis, meibomian gland dysfunction or an aqueous deficiency, or even if the problem is allergy or infection. So if there's any problem at all, the InflammaDry should turn up positive. However, I would never dismiss a patient's complaint because of a negative test."

Dr. Rapuano points out that this test doesn't tell you what's causing the inflammation. "Nevertheless, it might lead you to use steroids or an anti-inflammatory rather than punctal

plugs, so it can be helpful," he says. Dr. Pflugfelder also notes that because it's a threshold test, it doesn't provide a number to help grade severity.

• ***TearLab osmolarity test.*** "If the InflammaDry test reveals inflammation, the TearLab tests can help identify, at least to a small degree, whether or not it's an evaporative problem," says Dr. Mah. "The osmolarity test also gives us something that we can establish as a baseline, a number the patient can follow."

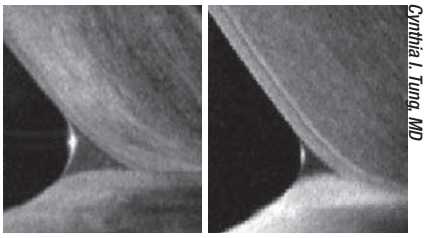
"There are multiple conflicting studies regarding the effectiveness of this test," notes Dr. Akpek. "A normal test result does not guarantee that the eye has no dry-eye disease, but an abnormal result is a good indication that there's a problem."

Dr. Pflugfelder says he uses it on all of his dry-eye patients, but has found it to be highly variable. "I don't find that the test results correlate with disease severity or treatment response," he says. "In my experience this measurement is most useful when it's high; if it's high, something is wrong. But a 'normal' reading doesn't tell me much."

Dr. Rapuano agrees about the variability, but says the test can still be valuable. "We've found that the variability is much higher in dry-eye patients than in normals," he says. "If a patient scores 280 at one visit—which sounds great—but they're 320 at the next visit and then 340 and then 280 again, that indicates abnormality in the tear film. Healthier eyes tend to produce similar readings at every visit. So it's important for clinicians to understand that a one-time measurement is not necessarily the best way to use the test."

• ***The Sjö test.*** Dr. Pflugfelder believes the Sjö test has clear value. "You're identifying people with an autoimmune condition and the test may allow you to identify them earlier," he says.

"It's important to remember that one in 10 patients with clinically significant dry eye has underlying Sjögren's," adds Dr. Akpek. "Only a third of these patients have a diagnosis."



Cynthia J. Tung, MD

Anterior segment OCT can be used to measure tear meniscus height. Left: healthy tear production. Right: Low tear production.

• ***The Oculus keratograph***. "The keratograph does a noninvasive tear breakup measurement and gives you a map of the areas where the tear film is breaking up more rapidly," says Dr. Pflugfelder. "It can also measure the inferior tear meniscus height, which is among the most valuable information you can collect to determine whether patients have an aqueous-deficient or sufficient-tear dysfunction. However, we measure the tear meniscus height with anterior segment OCT." *(See example, above.)*

• ***LipiView.*** "The LipiView instrument helps us assess the quality of the meibomian glands, revealing truncation of the glands and meibomian gland dropout," explains Dr. Milner. "It also measures the lipid layer thickness and can assess how many times the patient blinks, and how many of those were partial blinks."

"Meibomian gland imaging can be useful," says Dr. Akpek. "It's pretty obvious when the glands are permanently and irreversibly damaged. At this point, however, I haven't seen enough evidence to establish a correlation between the imaging and the meibum secretion quality or the ocular surface staining scoring."

• ***Topography.*** Dr. Pflugfelder notes that some topographers provide a measure of the smoothness of the corneal surface, which can be relevant to dry eye. "The topographer we use has validated measurements called the Klyce indices that evaluate the regularity of the rings reflected off the cornea and provide a numerical score," he says. "People with more corneal epithelial disease from dry eye have higher scores. The Klyce Surface Regularity Index, or SRI, is valuable because it correlates with visual acuity and the severity of epithelial disease. So if someone has dry eye and the SRI is high and their vision is reduced, that would tell me that epithelial disease is probably the cause of it."

• ***Schirmer test.*** Although this test is not reimbursable, it's easy to perform, inexpensive and familiar to everyone, so many doctors still perform it. "This test can be helpful, especially if the result is very low or very high," says Dr. Rapuano. "If it's in the middle range, as many results are, it's not that helpful to me."

Dr. Akpek still likes to do the Schirmer test, without anesthesia. "It's a good way to differentiate Sjögren's-related dry eye from non-Sjögren's-related dry eye," she notes. Dr. Pflugfelder also does the test, but says he finds the anterior OCT measurement of the tear meniscus height to be a more valuable measure of tear volume.

Dry-eye Treatment: The Basics

Doctors largely seem to agree about the first treatment steps to take when confronted with a dry-eye patient. "We usually start with over-the-counter drops, mostly preservative-free," says Dr. Akpek. "We'll add a prescription anti-inflammatory eye drop after a few months if the patient isn't getting relief, although we prescribe that right away in patients with a known underlying systemic inflammatory condition."

"If the problem is primarily aqueous deficiency, our stepwise approach is to start with preserved tears, then switch to tears without preservatives, then to tear gels and then tear ointments," says Dr. Rapuano. "Typically I use Restasis as the next step if the

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Can a Dry-eye Algorithm Really Work?

"We don't really have a reliable and agreed-upon algorithm for diagnosing and treating dry eye," says Esen Akpek, MD, a professor of ophthalmology and rheumatology at Johns Hopkins University School of Medicine. "There are two established classification systems that include treatment guidelines: the Delphi panel recommendations, published in 2006, and the Dry Eye Workshop treatment protocol published in 2007. Unfortunately, neither of these systems is widely used in clinic."

Dr. Pflugfelder see a couple of problems with creating a dry-eye management algorithm. "One issue is that clinicians need to have the right tools to obtain the measurements suggested in the algorithm," he says. "For example, the protocol I follow includes measuring the tear volume. To do that, doctors have to have OCT or the keratograph." Dr. Pflugfelder says another issue is that not every useful measurement is currently reimbursable, making their performance potentially too costly.

Nevertheless, several groups and individuals are hard at work developing algorithms that they hope will help clinicians, including the corneal clinical committee at ASCRS, of which Francis Mah, MD, who specializes in cornea, external disease and refractive surgery at Scripps Health System in San Diego, is a member. "The algorithm we're developing should function as a step-by-step decision tree," says Dr. Mah. "If a patient shows up and has certain symptoms, you go in one direction; if not, you go in another direction. If one test is positive or negative, you should do this test next. It's meant to be very comprehensive. We hope that it will develop into something you can hang in the office for reference. It might even be possible to turn it into an app, where you plug in the information that you have and the app makes a recommendation.

"The ASCRS algorithm has to be approved at several levels before it's released," he adds, "but we hope it will become available within the next year."

Christopher J. Rapuano, MD, director of the cornea service at Wills Eye Hospital, sees advantages to creating a more general algorithm. "The DEWS and Delphi Dry Eye algorithms featured treatment suggestions for mild, moderate and severe disease," he notes. "I believe it makes sense to do some things earlier in treatment and some things later, but dry eye can be multifactorial and patients respond differently to the treatments. Also, patients don't always want a given treatment. So trying to spell out steps in a certain order may not be helpful."

Mark S. Milner, MD, FACS, an associate clinical professor at Yale University School of Medicine, however, also sees drawbacks to some of the more general algorithms. "A severity-based approach can be problematic because so many things contribute to dry eye," he notes. "I believe we should be treating these patients based on their diagnosis, not their severity level."

Dr. Akpek is taking part in the Dry Eye Workshop's current attempt to develop new guidelines for dry-eye management. "Unfortunately, I'm not sure that having a classification or treatment algorithm is going to be helpful when it comes to real clinical situations, and I don't know if the results of our efforts will be followed by the majority of clinicians," she says. "Today, half of all dry-eye patients need more treatment than just over-the-counter artificial tears, but only eight percent are currently getting a prescription for dry eye. I think we'll have to better educate clinicians about dry eye if we want them to follow an algorithm."

—CK

problem is chronic and not getting better. Then I use punctal plugs. However, it's important to note that you don't want to use punctal plugs if the patient has a significant meibomian gland problem because you can end up making unhealthy tears sit on the eye, irritating it."

"If a patient who has never used artificial tears comes in with mild dry-eye disease and no keratitis, I recommend artificial tears first," says Dr. Milner. "I prefer nonpreserved tears, but I may start with preserved tears for reasons of cost and convenience. If the problem is more serious, I recommend nonpreserved tears because we know preservatives can exacerbate inflammation and irritation in dry-eye patients. If the patient is using artificial tears more than four or five times a day, I recommend starting Restasis or Xiidra. I don't wait too long to add one of these, because we now believe that dry eye may be chronic and progressive; treating it earlier may help keep it from getting worse."

The approval of Xiidra—which was found to be effective in treating both signs and symptoms of dry eye—raises the question of whether to use it or Restasis. Generally, doctors are saying it's much too early to know when Xiidra or Restasis might be the better option. "Restasis, topical cyclosporine, is indicated to increase tear production in patients whose tear production is presumed to be depressed due to ocular inflammation associated with keratoconjunctivitis sicca," says Dr. Milner. "Both cyclosporine and lifitegrast are anti-inflammatory agents, and they both appear to do an excellent job."

Dr. Milner notes that combining the drugs might also be an option. "Although there are no head-to-head studies or studies combining the two drugs, many of us in the dry-eye world believe that because they affect T-cells in different ways, they will probably be synergistic," he says. "Combined, they may be a better option for patients who require more than one treatment. I've already had a number of patients on both Restasis and Xiidra for a month and a half since Xiidra's approval, and so far, I'm seeing good results."


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Another treatment option is topical steroids. "Many of us are using steroids off-label concurrently with Restasis or Xiidra, early in treatment, to let the steroids eliminate some of the inflammation while the other drug is starting to work," says Dr. Milner. "Of course, the risk of side effects such as glaucoma and cataract make steroids a poor choice for long-term treatment. The other caveat is to be sure to use a 'surface steroid' such as Lotemax or fluorometholone, which have a lower risk of causing side effects."

Dr. Mah says he also advises dry-eye patients to take a supplement containing omega-3 fatty acids. "I'll explain to the patient that omega-3 fatty acids are not only good for the eyes, but also for the heart to prevent stroke, and for the skin and hair," he says. "This basic regimen is kind of a shotgun approach, but it will improve signs and symptoms in the majority of patients."

Dr. Rapuano says he also sometimes prescribes Lacrisert, which acts to stabilize and thicken the precorneal tear film and prolong tear-film breakup time, as well as lubricate and protect the eye. "These are little collagen pellets that sit in the lower cul-de-sac and dissolve over the course of the day," he says. "However, the patient has to have some tears to make them dissolve. If the eye is bone dry, the Lacrisert won't dissolve and will act as an irritant.

"Sometimes a bandage soft contact lens can be used to help relieve symptoms," he adds, "but you have to be careful because dry-eye patients are at a higher risk of infection."

Dr. Mah adds that changes in the patient's environment might also be appropriate. "If a patient spends significant time in front of a computer, for example, it's important to educate the patient on the connection to dry eye," he says. "You can suggest ways to try to help reduce exacerbation such as lowering the monitor, taking short breaks or using drops during long stretches in front of the monitor."

DEWS Treatment Recommendations (by severity level)*

Level 1: Education and environmental/dietary modifications Eliminate offending systemic medications Artificial tear substitutes, gels/ointments Eyelid therapy	**Level 3:** *If Level 2 treatments are inadequate, add:* Serum Contact lenses Permanent punctal occlusion
Level 2: *If Level 1 treatments are inadequate, add:* Anti-inflammatories Tetracyclines (for meibomianitis, rosacea) Punctal plugs Secretogogues Moisture chamber spectacles	**Level 4:** *If Level 3 treatments are inadequate, add:* Systemic anti-inflammatory agents Surgery (lid surgery, tarsorrhaphy; mucus membrane, salivary gland, amniotic membrane transplantation)

*Modified from: International Task Force Guidelines for Dry Eye

Mucin Deficiency & Exposure

In terms of diagnosis, most dry-eye disease can be separated into aqueous deficiency or evaporative-based. "The majority of evaporative dry eye is caused by blepharitis or meibomian gland dysfunction," says Dr. Milner. "However, there are two other causes of evaporative dry eye that are often overlooked, and they require different treatment approaches.

"One is goblet cell deficiency, which leads to mucin deficiency," he explains. "Mucin is critical to keeping the tears on the eye longer. Patients with a goblet cell deficiency could include anyone with cicatricial conjunctivitis, such as Stevens-Johnson Syndrome; toxic epidermal necrolysis; pemphigoid; chemical injuries; or even patients who have chronic irritation from glaucoma drops. In terms of treatment, Allergan's Phase III study showed that cyclosporine caused a 191-percent increase in goblet cell density at six months, compared to a 13-percent increase for the vehicle alone.

"Another subset of evaporative dry eye is that caused by exposure, resulting from lagophthalmos, or partial blink," he continues. "This often gets missed. You can treat for other causes, but if you miss patients who have incomplete blink, they're going to remain dry because their lids aren't completely covering the ocular surface. Once diagnosed, you can try having these patients tape their lids closed at night, or send them to an oculoplastics specialist if the problem is severe. In any case, even if the problem is exposure from an open eye, there may be inflammation that could be helped by cyclosporine or lifitegrast." (Dr. Mah says another option is to have the patient use a gel or ointment at bedtime.)

Meibomian Gland Dysfunction

"If the patient has a meibomian gland problem, we prescribe warm compresses and lid scrubs first," says Dr. Akpek. "If the patient doesn't improve, I add a topical antibiotic, and if that isn't sufficient I also have the patient take an oral antibiotic for several months. Lastly, I resort to tear-conserving strategies such as tear duct plugs or cauterization. Any patient who has used topical over-the-counter tears and anti-inflammatory treatment for several months and still has aqueous tear deficiency might benefit from plugs, although I wouldn't use these as a first-line treatment in a patient with pronounced blepharitis."

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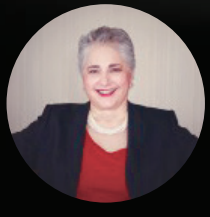

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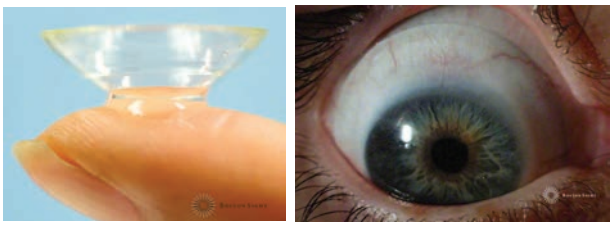
"If the problem looks like meibomian gland dysfunction, I may elect to use prescription minocycline pills instead of Restasis or Xiidra drops," says Dr. Mah. "I usually prescribe one 50-mg pill per day, unless the patient is allergic to it, pregnant or a woman of childbearing age. I like minocycline because I currently practice in San Diego where my patients are exposed to a lot of sunlight. Doxycycline, which I often prescribed when I practiced in Pittsburgh, can cause photosensitivity; minocycline isn't usually associated with that side effect. If the problem still hasn't diminished after several months, I may consider using punctal plugs after Restasis or Xiidra."



Scleral lenses like the PROSE lens from the Boston Foundation for Sight allow the cornea to bathe in fluid all day.

"If the problem is anterior blepharitis, that tends to be mostly infectious, so you'd want to treat that with a topical antibiotic," says Dr. Milner. "I like to use either a topical ointment like erythromycin or bacitracin, or topical azithromycin, which I think works great. In addition to being an effective antibiotic, azithromycin has anti-inflammatory properties because it's a macrolide, which means it can also be helpful for treating posterior blepharitis. A lot of us are also using cyclosporine off-label for posterior blepharitis with great success, and there are studies supporting this use as well."[2]

Dr. Milner uses the LipiFlow instrument to treat some of his meibomian gland dysfunction patients. "LipiFlow is a low-risk, 12-minute procedure that heats the lids to exactly 108 degrees and then massages the glands to express the oils," he explains. "I find it especially useful when patients aren't getting enough benefit from other treatments, or when a patient would rather not add more medications. However, we also need to treat the glands so they start making healthy oils again, so after using LipiFlow we keep the patient on Restasis or Xiidra. We've gotten good results after a single treatment 80 to 85 percent of the time. This is an out-of-pocket cost for the patient, but the cost of the LipiFlow system is about half of what it was a year ago."

Dr. Rapuano says he often prescribes Medibeads, a microwavable pad you put on the eyes. "Commercial lid scrubs often work quite well," he adds. "If the problem doesn't improve, I have the patient use an antibiotic ointment at bedtime, either erythromycin, bacitracin or azithromycin. If that's not enough, then we may go to oral doxycycline or minocycline, or use some mild topical steroids to get people over the hump. Omega-3 pills can also be helpful, and LipiFlow can be beneficial as well."

When the Problem is Severe

Other treatment options can be tried when the dry-eye problem is severe and doesn't respond to these treatments. "Moving up the ladder, you can use autologous serum eye drops, derived from the patient's blood," says Dr. Rapuano. "A laboratory removes the red blood cells, dilutes it and sends the serum back frozen. The patient defrosts little bottles of serum tears to use them, and some patients find them very helpful." *(For an in-depth look at the use of autologous serum, see the feature on p. 44.)*

Another option is scleral lenses. "Scleral lenses sit on the sclera and bathe the cornea with fluid all day," says Dr. Milner. "They can take dry-eye patients who have 20/200 vision and potentially return them to 20/20. This started with the PROSE lens at the Boston Foundation for Sight, but now there are clinics all over the country fitting scleral lenses. Other innovative possibilities for treating severe disease include compounded drops such as albumin, topical hormones like medroxyprogesterone and dehydroepiandrosterone, better known as DHEA. These treatments may work best for aqueous-deficient dry eye."

If a patient has very bad mucus or filaments, Dr. Rapuano suggests trying Mucomyst (acetylcysteine), which can be made up by a compounding pharmacy. "Usually I prescribe a 10% solution four times a day," he says. "That works well for many patients. Also, in a few patients where dry eye is severe, you can perform a small lateral tarsorrhaphy, where the eyelid is sewn closed a little on the lateral side to decrease the amount of evaporation. Patients don't usually like it, but sometimes it really helps."

Strategies for Success

Doctors suggest taking these steps:

• ***Always check your patients for dry eye.*** "Regardless of the reason a patient comes in to see you, you should be checking for dry eye," says Dr. Akpek. "Treating dry eye can do a lot to improve your patient's visual acuity and quality of life, even if the patient isn't complaining about it."

Dr. Rapuano adds that simply downplaying dry-eye problems is a disservice to both your patients and your practice. "As Eric Donnenfeld and others noted years ago," he says, "if you make a dry-eye patient happy, other family members and friends are likely to come to your practice as a result. To see dry-eye treatment as just a drain on your practice is a little shortsighted."

• ***Pay attention to the details of patient complaints.*** Dr. Mah points out that a patient's complaint can often help with the diagnosis. "For example, if the patient is experiencing foreign body sensation in the morning, I'll lean more toward an evaporative problem such as meibomian gland dysfunction or blepharitis," he says. "If the symptoms are appearing late in the day or in the evening, I'm inclined to think the patient has more of an aqueous deficiency problem."

• ***Be sure to gauge the severity of the problem.*** "At the minimum you have to have some sort of marker of severity, both in terms of symptoms and signs," notes Dr. Pflugfelder. "You should always measure tear-film breakup time, because no matter what kind of dry eye or tear dysfunction you have, tear stability will be affected. You should also perform corneal and conjunctival staining, because those are definitely valuable. Some clinicians use osmolarity to gauge severity, but my experience has been that osmolarity isn't trustworthy for that purpose. Others, including myself, rely on tear volume as a marker. If you can't measure the tear meniscus height with OCT or the keratograph, the Schirmer test is an OK fallback.

"It's also important to gauge the severity of the symptoms the patient is complaining about to act as a baseline so you can tell whether your treatment is [subjectively] causing improvement or not," he continues. "You can do this with a dry-eye questionnaire, or by asking basic questions about situational triggers, symptoms, how often it's a problem and how irritated the eyes are."

• ***Get a sense of the impact the symptoms are having on the patient's quality of life.*** "In some cases, the impact is significant to the point at which the patient is depressed and not functional," says Dr. Pflugfelder. "If the impact is that great, you'll probably need to go beyond the simple treatment options, and you may want to refer the patient to a dry-eye specialist."

• ***Remember that the problem is frequently multifactorial.*** "When diagnosing, you have to decide if the problem is primarily aqueous deficiency, or it's more evaporative, which often goes along with meibomian gland and oil problems," says Dr. Rapuano. "The unfortunate reality is, most people have both problems. If it's 90/10 in favor of one cause, you can treat the low-hanging fruit of the primary cause; but if it's 50/50, then you really have to treat both causes or you're not going to make the patient feel better."

• ***Never discount a patient's complaint.*** "Even if the tests are negative, we should never discount the patient's complaint," says Dr. Mah. "The patient knows what he or she is feeling. It's our job to find out why they're having the symptoms and then treat them accordingly."

• ***Read dry-eye studies as they're published.*** "There are multiple publications covering dry eye," notes Dr. Akpek. "Clinicians should read the results and discussion sections, not just the abstract. Often the most important information isn't found in the abstract." REVIEW

Dr. Pflugfelder is a consultant for Allergan, Shire, Santen and Senju. Dr. Rapuano is a consultant for Shire and TearLab. Dr. Mah is a consultant for TearLab, Allergan and Shire. Dr. Milner is a speaker and consultant for Allergan, Shire, TearScience and Sun Pharmaceuticals and owns stock in RPS. Dr. Akpek has received institutional research support from Allergan and is currently a consultant with Shire.

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2. Perry HD, Doshi-Carnevale S, Donnenfeld ED, Solomon R, Biser SA, Bloom AH. Efficacy of commercially available topical cyclosporine A 0.05% in the treatment of meibomian gland dysfunction. Cornea 2006;25:2:171-5.

Treating Dry Eye: Beyond Drops

Michelle Stephenson, Contributing Editor

Ophthalmologists' armamentarium for treating dry eye continues to grow.

Many ophthalmologists are opting not to use only artificial tears as a first-line treatment for dry eye and are adding a variety of other treatments, as well, such as punctal plugs, nutraceuticals and moisture masks. "Some physicians are still hesitant to use medications, much to the chagrin of the pharmaceutical companies," says John Sheppard, MD, professor of ophthalmology, microbiology and molecular biology at Eastern Virginia Medical School and president of Virginia Eye Consultants in Norfolk. "Many doctors favor organic therapies. Tear conservation is right at the top of the list of treatments and so is nutrition. All patients should be treated using both modalities." In this article, dry-eye experts who think similarly to Dr. Sheppard describe the ways in which their treatment options are growing.

Punctal Plugs

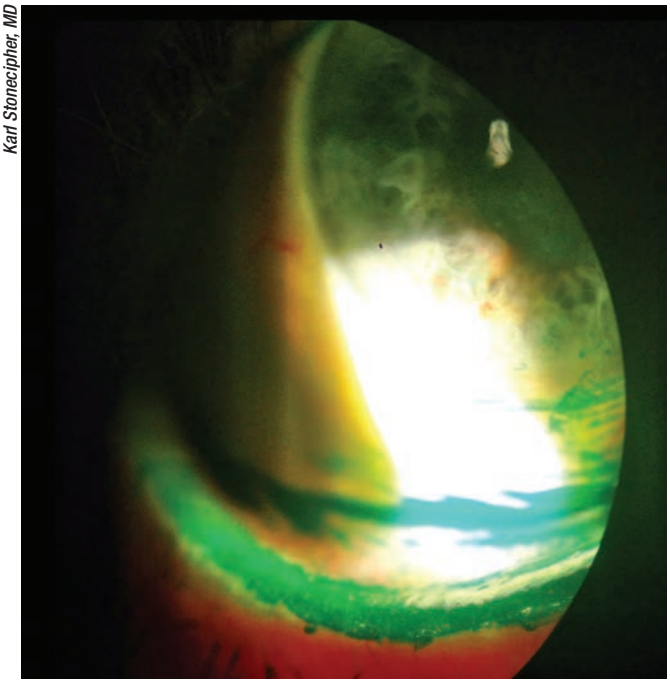
According to Robert Latkany, MD, founder of the New York Eye and Ear Infirmary's Dry Eye Clinic, it can be argued that punctal plugs are a natural treatment because their sole purpose is to keep patients' own tears on their eyes longer. "You can use a temporary plug just to give it a shot and see if it works," he says. "You can always move on to a silicone, non-dissolvable plug afterwards. These are a wonderful option, especially if the patient doesn't have allergies or rosacea."

Karl Stonecipher, MD, who is in private practice in Greensboro, N.C., agrees. "Once the inflammatory process has been stopped, I am a huge fan of plugs," he says. "They are reversible, and they stay in permanently, without any swelling."

Nutritional Supplements

Nutritional supplements are widely used and have also been found to be an effective therapy for dry eye. "Nutritional supplements for dry eye have been around for 10 or 15 years," notes Dr. Latkany. "They are part of my regimen, and I usually start out with 1,000 mg of fish oil a day. Some people are opposed to the fish component, so they use flaxseed oil instead. Patients can titrate upwards based on their response rate."

A number of studies have demonstrated that oral nutritional supplements are an effective treatment for dry-eye symptoms. In one recent report, sponsored by nutraceutical-maker Brudy Technology (Barcelona, Spain), a total of 1,419 patients with dry-eye syndrome who were using artificial tears participated in a 12-



Karl Stonecipher, MD

Classic lissamine green staining two minutes after instillation. These staining patterns show both the patient's lid wiper epitheliopathy and dry-eye disease. Some physicians are turning to organic treatments in addition to traditional tears and prescription medications to treat these patients.

week prospective study.[1] Patients were instructed to take three capsules/day (1.5 g) of the company's nutraceutical formulation Brudysec. The following variables were assessed: dry-eye symptoms (scratchy and stinging sensation, eye redness, grittiness, painful and tired eyes, grating sensation and blurry vision); conjunctival hyperemia; tear breakup time; Schirmer I test; and Oxford grading scheme.

At 12 weeks, all dry-eye symptoms improved significantly, and artificial tear use decreased significantly from 3.77 times per day at baseline to 3.45 times per day. In addition, the Schirmer test scores and the TBUT increased significantly, and there was an increase in patients grading 0 to I on the Oxford scale and a decrease of those grading IV to V. Additionally, significant differences in improvements in dry-eye symptoms were found between compliant and noncompliant patients as well as between those with moderate/severe and those with none/mild conjunctival hyperemia. In another study, oral administration of re-esterified omega-3 fatty acids (Dry Eye Omega, Physician Recommended Nutraceuticals) resulted in a statistically significant improvement in tear osmolarity, as well as improvements in such secondary endpoints as corneal staining and tear breakup time.[2] (Several of the study's physicians received compensation from PRN.)

It's Dr. Sheppard's belief that inflammation is the underlying cause of dry eye. "Essential fatty acids are a non-pharmaceutical way of producing an anti-inflammatory effect," he says, noting that balanced essential fatty acid therapy has been found to significantly improve signs and symptoms of dry eye. "I've also found that gammalinoleic acid is very important for the ocular surface and is universally tolerated. It can be found in some commercial preparations, but it is also readily available in supermarkets and health-food stores as primrose, borage or black currant seed oil."

A recent study sponsored by Taiwanese neutraceutical company Acrobio Healthcare found that oral antioxidant supplements may increase tear production and improve tear-film stability by reducing tear reactive oxygen species.[3] This study employed a

vegetable-based antioxidant supplement that's safe and can be used as an adjuvant therapy to conventional artificial tear therapy for patients with dry-eye syndrome.

This prospective, randomized, double-blind study evaluated the effects of an antioxidant supplement (containing anthocyanosides, astaxanthin, vitamins A, C and E, and several herbal extracts, including *semen Cassiae* and *Ophiopogonis japonicus*) on patients with dry eye. The investigators assessed dry-eye symptoms, visual acuity, Schirmer's test, TBUT, cornea and conjunctiva fluorescein staining, serum anti-SSA/anti-SSB antibodies, and the level of reactive oxygen species in tears. Patients took the supplements for eight weeks, and they were evaluated every four weeks for 16 weeks.

Forty-three patients (20 in the treatment group and 23 in the placebo group) completed the study. Patients' liver and renal functions were normal. Diastolic blood pressure decreased in the treatment group; however, there were no significant differences in systolic blood pressure, dry-eye symptoms, serum anti-SSA and anti-SSB, visual acuity, intraocular pressure or fluorescein corneal staining among the groups. In the treatment group, TBUT scores and Schirmer's tests without topical anesthesia significantly improved. Tear reactive oxygen species level differed between the groups and decreased after treatment. Additionally, patients' overall subjective impression revealed a significant improvement with treatment compared with placebo.

Dr. Stonecipher says that the key to any therapy is making sure that patients are compliant. If patients are going to take a nutritional supplement, he says, it must be easy for them to purchase. He has also found that certain brands work better than others because they are more readily absorbed. "For an over-the-counter omega-3, I recommend PRN, Nordic Naturals or HydroEye," he states. "I give patients a specific brand, and I send them to a specific website to order it online. You've got to make it easy. We used to sell supplements in our office to make it more convenient, but we've found that ordering it online is even easier. Our office has a computer in every lane, and either I or the technician walk through how to order nutraceuticals. When you are recommending an out-of-the-box product, it must be accessible."

"Our patients have welcomed ready access to all of our recommended dry-eye products through our own practice-specific retail website at myeyestore.com," Dr. Sheppard notes.

Masks and Goggles

Dr. Latkany notes that masks and goggles are a great addition to the dry-eye armamentarium. "An enormous number of patients suffer from nocturnal lagophthalmos, which is a major contributor to dry eye, especially upon awakening," he says. "My top recommendation for resolving dry-eye symptoms is a good night's sleep. Many patients with dry eye suffer from anxiety and stress, and it affects the quality of their sleep. Masks and goggles are wonderful additions to improve their sleep pattern. Moisture chamber goggles from Eye Eco form a seal around the eye so no air gets to the eye while the patient is sleeping. They come in different varieties, shapes, and colors, and I commonly recommend them in my practice. Additionally, I have a patent pending on a goggle that closes the eye. It is called Eye Shutters, and it should be out this fall. It will be the first eye mask that actually closes the eye."

Eyeseal 4.0 goggles from Eye Eco help protect patients' eyes while they sleep.

Warm Compresses & Lid Scrubs

According to Dr. Sheppard, meibomian gland awareness and therapy has become a significant area of interest over the past few years. "Now, we are all imaging the meibomian gland and producing more intelligent therapy than traditional baby shampoo," he says. "When we understand that meibomian gland physiology is subject to geriatric and inflammatory degradation like everything else in the body, we can not only document morphologic changes in the meibomian glands, we can incorporate patients enthusiastically into the treatment paradigm, especially when they see that there are anatomical changes."

Several topical scrubs are now available that are not only antiseptic, but also anti-inflammatory. "We have found this to be extremely beneficial, and we now recommend specific scrubs for all of our preoperative patients to sterilize the ocular surface or reduce the floral load and also to improve meibomian gland function and, therefore, provide an alternative therapy for ocular surface disease," Dr. Sheppard adds.

Dr. Stonecipher also recommends the use of anti-dandruff shampoos and lid scrubs. "I use three anti-dandruff shampoos: Head and Shoulders; Selsun Blue; and T/Gel—specifically yellow T/Gel," he avers. "A lot of people have a mixed-mechanism dry eye. Sometimes, this can affect the natural bacteria that are on the face and around the eyes. It is simple to wash your face with an anti-dandruff shampoo while in the shower. Just make sure not to get it in your eyes. I am also a huge fan of lid scrubs like Avenova by NovaBay."

SIMBRINZA®

(brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2%

Aim for Target IOP

Consider Adding SIMBRINZA® Suspension to a PGA

SIMBRINZA® Suspension should be taken at least five (5) minutes apart from other topical ophthalmic drugs

Up to **7.1 mm Hg** additional IOP reduction from baseline when added to a PGA[1]

5.6 mm Hg* additional mean diurnal IOP lowering observed from baseline when added to a PGA[1]

*Treatment difference (mm Hg) and *P* value at Week 6 was -3.7, $P<0.0001$.

IOP Daily Time Points (mm Hg)[1†]

Treatment Arm		8 AM	10 AM	3 PM	5 PM
PGA + SIMBRINZA® Suspension (N=88)	Baseline‡	**24.5**	**22.9**	**21.7**	**21.6**
	Week 6	**19.4**	**15.8**	**17.2**	**15.6**
PGA + Vehicle (N=94)	Baseline‡	24.3	22.6	21.3	21.2
	Week 6	21.5	20.3	20.0	20.1

†Differences (mm Hg) and *P* values at Week 6 time points between treatment groups were -2.14, $P=0.0002$; -4.56, $P<0.0001$; -2.84, $P<0.0001$; -4.42, $P<0.0001$.

‡Baseline (PGA Monotherapy).

Mean Diurnal IOP (mm Hg)[1§]

Treatment Arm		
PGA + SIMBRINZA® Suspension (N=83)	Baseline‖	**22.7**
	Week 6	**17.1**
PGA + Vehicle (N=92)	Baseline‖	22.4
	Week 6	20.5

§Difference (mm Hg) and *P* value at Week 6 between treatment groups were -3.44, $P<0.0001$.

‖Baseline (PGA Monotherapy).

Study Design: A prospective, randomized, multicenter, double-blind, parallel-group study of 189 patients with open-angle glaucoma and/or ocular hypertension receiving treatment with a PGA. PGA treatment consisted of either travoprost, latanoprost, or bimatoprost. Patients in the study were randomized to adjunctive treatment with SIMBRINZA® Suspension (N=88) or vehicle (N=94). The primary efficacy endpoint was mean diurnal IOP (IOP averaged over all daily time points) at Week 6 between treatment groups. Key secondary endpoints included IOP at Week 6 for each daily time point (8 AM, 10 AM, 3 PM, and 5 PM) and mean diurnal IOP change from baseline to Week 6 between treatment groups.[1]

PGA=prostaglandin analog.

24-hour IOP-lowering coverage, including the night — nocturnal efficacy established through an 8 AM time point[2]

INDICATIONS AND USAGE

SIMBRINZA® (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2% is a fixed combination indicated in the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

Dosage and Administration

The recommended dose is one drop of SIMBRINZA® Suspension in the affected eye(s) three times daily. Shake well before use. SIMBRINZA® Suspension may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

IMPORTANT SAFETY INFORMATION

Contraindications

SIMBRINZA® Suspension is contraindicated in patients who are hypersensitive to any component of this product and neonates and infants under the age of 2 years.

Warnings and Precautions

Sulfonamide Hypersensitivity Reactions—Brinzolamide is a sulfonamide, and although administered topically, is absorbed systemically. Sulfonamide attributable adverse reactions may occur. Fatalities have occurred due to severe reactions to sulfonamides. Sensitization may recur when a sulfonamide is readministered irrespective of the route of administration. If signs of serious reactions or hypersensitivity occur, discontinue the use of this preparation.

Corneal Endothelium—There is an increased potential for developing corneal edema in patients with low endothelial cell counts.

Severe Hepatic or Renal Impairment (CrCl <30 mL/min)—SIMBRINZA® Suspension has not been specifically studied in these patients and is not recommended.

Contact Lens Wear—The preservative in SIMBRINZA® Suspension, benzalkonium chloride, may be absorbed by soft contact lenses. Contact lenses should be removed during instillation of SIMBRINZA® Suspension but may be reinserted 15 minutes after instillation.

Severe Cardiovascular Disease—Brimonidine tartrate, a component of SIMBRINZA® Suspension, had a less than 5% mean decrease in blood pressure 2 hours after dosing in clinical studies; caution should be exercised in treating patients with severe cardiovascular disease.

Adverse Reactions

SIMBRINZA® Suspension

In two clinical trials of 3 months' duration with SIMBRINZA® Suspension, the most frequent reactions associated with its use occurring in approximately 3-5% of patients in descending order of incidence included: blurred vision, eye irritation, dysgeusia (bad taste), dry mouth, and eye allergy. Adverse reaction rates with SIMBRINZA® Suspension were comparable to those of the individual components. Treatment discontinuation, mainly due to adverse reactions, was reported in 11% of SIMBRINZA® Suspension patients.

Drug Interactions

Consider the following when prescribing SIMBRINZA® Suspension:

Concomitant administration with oral carbonic anhydrase inhibitors is not recommended due to the potential additive effect. Use with high-dose salicylate may result in acid-base and electrolyte alterations. Use with CNS depressants may result in an additive or potentiating effect. Use with antihypertensives/cardiac glycosides may result in additive or potentiating effect on lowering blood pressure. Use with tricyclic antidepressants may blunt the hypotensive effect of systemic clonidine and it is unknown if use with this class of drugs interferes with IOP lowering. Use with monoamine oxidase inhibitors may result in increased hypotension.

References: 1. Data on file, 2014. **2.** SIMBRINZA® Suspension Package Insert.

Learn more at **myalcon.com/simbrinza**

For additional information about SIMBRINZA® Suspension, please refer to the brief summary of the full Prescribing Information on the following page.

Alcon® a Novartis company

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

SIMBRINZA® (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2% is a fixed combination of a carbonic anhydrase inhibitor and an alpha 2 adrenergic receptor agonist indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

DOSAGE AND ADMINISTRATION

The recommended dose is one drop of SIMBRINZA® Suspension in the affected eye(s) three times daily. Shake well before use. SIMBRINZA® Suspension may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

DOSAGE FORMS AND STRENGTHS

Suspension containing 10 mg/mL brinzolamide and 2 mg/mL brimonidine tartrate.

CONTRAINDICATIONS

Hypersensitivity - SIMBRINZA® Suspension is contraindicated in patients who are hypersensitive to any component of this product.

Neonates and Infants (under the age of 2 years) - SIMBRINZA® Suspension is contraindicated in neonates and infants (under the age of 2 years) *[see Use in Specific Populations]*.

WARNINGS AND PRECAUTIONS

Sulfonamide Hypersensitivity Reactions - SIMBRINZA® Suspension contains brinzolamide, a sulfonamide, and although administered topically is absorbed systemically. Therefore, the same types of adverse reactions that are attributable to sulfonamides may occur with topical administration of SIMBRINZA® Suspension. Fatalities have occurred due to severe reactions to sulfonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias. Sensitization may recur when a sulfonamide is re-administered irrespective of the route of administration. If signs of serious reactions or hypersensitivity occur, discontinue the use of this preparation *[see Patient Counseling Information]*.

Corneal Endothelium - Carbonic anhydrase activity has been observed in both the cytoplasm and around the plasma membranes of the corneal endothelium. There is an increased potential for developing corneal edema in patients with low endothelial cell counts. Caution should be used when prescribing SIMBRINZA® Suspension to this group of patients.

Severe Renal Impairment - SIMBRINZA® Suspension has not been specifically studied in patients with severe renal impairment (CrCl < 30 mL/min). Since brinzolamide and its metabolite are excreted predominantly by the kidney, SIMBRINZA® Suspension is not recommended in such patients.

Acute Angle-Closure Glaucoma - The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive agents. SIMBRINZA® Suspension has not been studied in patients with acute angle-closure glaucoma.

Contact Lens Wear - The preservative in SIMBRINZA® Suspension, benzalkonium chloride, may be absorbed by soft contact lenses. Contact lenses should be removed during instillation of SIMBRINZA® Suspension but may be reinserted 15 minutes after instillation *[see Patient Counseling Information]*.

Severe Cardiovascular Disease - Brimonidine tartrate, a component of SIMBRINZA® Suspension, has a less than 5% mean decrease in blood pressure 2 hours after dosing in clinical studies; caution should be exercised in treating patients with severe cardiovascular disease.

Severe Hepatic Impairment - Because brimonidine tartrate, a component of SIMBRINZA® Suspension, has not been studied in patients with hepatic impairment, caution should be exercised in such patients.

Potentiation of Vascular Insufficiency - Brimonidine tartrate, a component of SIMBRINZA® Suspension, may potentiate syndromes associated with vascular insufficiency. SIMBRINZA® Suspension should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangiitis obliterans.

Contamination of Topical Ophthalmic Products After Use - There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers have been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface *[see Patient Counseling Information]*.

ADVERSE REACTIONS

Clinical Studies Experience - Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to the rates in the clinical studies of another drug and may not reflect the rates observed in practice.

SIMBRINZA® Suspension - In two clinical trials of 3 months duration 435 patients were treated with SIMBRINZA® Suspension, and 915 were treated with the two individual components. The most frequently reported adverse reactions in patients treated with SIMBRINZA® Suspension occurring in approximately 3 to 5% of patients in descending order of incidence were blurred vision, eye irritation, dysgeusia (bad taste), dry mouth, and eye allergy. Rates of adverse reactions reported with the individual components were comparable. Treatment discontinuation, mainly due to adverse reactions, was reported in 11% of SIMBRINZA® Suspension patients.

Other adverse reactions that have been reported with the individual components during clinical trials are listed below.

Brinzolamide 1% - In clinical studies of brinzolamide ophthalmic suspension 1%, the most frequently reported adverse reactions reported in 5 to 10% of patients were blurred vision and bitter, sour or unusual taste. Adverse reactions occurring in 1 to 5% of patients were blepharitis, dermatitis, dry eye, foreign body sensation, headache, hyperemia, ocular discharge, ocular discomfort, ocular keratitis, ocular pain, ocular pruritus and rhinitis.

The following adverse reactions were reported at an incidence below 1%: allergic reactions, alopecia, chest pain, conjunctivitis, diarrhea, diplopia, dizziness, dry mouth, dyspnea, dyspepsia, eye fatigue, hypertonia, keratoconjunctivitis, keratopathy, kidney pain, lid margin crusting or sticky sensation, nausea, pharyngitis, tearing and urticaria.

Brimonidine Tartrate 0.2% - In clinical studies of brimonidine tartrate 0.2%, adverse reactions occurring in approximately 10 to 30% of the subjects, in descending order of incidence, included oral dryness, ocular hyperemia, burning and stinging, headache, blurring, foreign body sensation, fatigue/drowsiness, conjunctival follicles, ocular allergic reactions, and ocular pruritus.

Reactions occurring in approximately 3 to 9% of the subjects, in descending order included corneal staining/erosion, photophobia, eyelid erythema, ocular ache/pain, ocular dryness, tearing, upper respiratory symptoms, eyelid edema, conjunctival edema, dizziness, blepharitis, ocular irritation, gastrointestinal symptoms, asthenia, conjunctival blanching, abnormal vision and muscular pain.

The following adverse reactions were reported in less than 3% of the patients: lid crusting, conjunctival hemorrhage, abnormal taste, insomnia, conjunctival discharge, depression, hypertension, anxiety, palpitations/arrhythmias, nasal dryness and syncope.

Postmarketing Experience - The following reactions have been identified during postmarketing use of brimonidine tartrate ophthalmic solutions in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to brimonidine tartrate ophthalmic solutions, or a combination of these factors, include: bradycardia, hypersensitivity, iritis, keratoconjunctivitis sicca, miosis, nausea, skin reactions (including erythema, eyelid pruritus, rash, and vasodilation), and tachycardia.

Apnea, bradycardia, coma, hypotension, hypothermia, hypotonia, lethargy, pallor, respiratory depression, and somnolence have been reported in infants receiving brimonidine tartrate ophthalmic solutions *[see Contraindications]*.

DRUG INTERACTIONS

Oral Carbonic Anhydrase Inhibitors - There is a potential for an additive effect on the known systemic effects of carbonic anhydrase inhibition in patients receiving an oral carbonic anhydrase inhibitor and brinzolamide ophthalmic suspension 1%, a component of SIMBRINZA® Suspension. The concomitant administration of SIMBRINZA® Suspension and oral carbonic anhydrase inhibitors is not recommended.

High-Dose Salicylate Therapy - Carbonic anhydrase inhibitors may produce acid-base and electrolyte alterations. These alterations were not reported in the clinical trials with brinzolamide ophthalmic suspension 1%. However, in patients treated with oral carbonic anhydrase inhibitors, rare instances of acid-base alterations have occurred with high-dose salicylate therapy. Therefore, the potential for such drug interactions should be considered in patients receiving SIMBRINZA® Suspension.

CNS Depressants - Although specific drug interaction studies have not been conducted with SIMBRINZA® Suspension, the possibility of an additive or potentiating effect with CNS depressants (alcohol, opiates, barbiturates, sedatives, or anesthetics) should be considered.

Antihypertensives/Cardiac Glycosides - Because brimonidine tartrate, a component of SIMBRINZA® Suspension, may reduce blood pressure, caution in using drugs such as antihypertensives and/or cardiac glycosides with SIMBRINZA® Suspension is advised.

Tricyclic Antidepressants - Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with SIMBRINZA® Suspension in humans can lead to resulting interference with the IOP lowering effect. Caution is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

Monoamine Oxidase Inhibitors - Monoamine oxidase (MAO) inhibitors may theoretically interfere with the metabolism of brimonidine tartrate and potentially result in an increased systemic side-effect such as hypotension. Caution is advised in patients taking MAO inhibitors which can affect the metabolism and uptake of circulating amines.

USE IN SPECIFIC POPULATIONS

Pregnancy - *Pregnancy Category C*: Developmental toxicity studies with brinzolamide in rabbits at oral doses of 1, 3, and 6 mg/kg/day (20, 60, and 120 times the recommended human ophthalmic dose) produced maternal toxicity at 6 mg/kg/day and a significant increase in the number of fetal variations, such as accessory skull bones, which was only slightly higher than the historic value at 1 and 6 mg/kg. In rats, statistically decreased body weights of fetuses from dams receiving oral doses of 18 mg/kg/day (180 times the recommended human ophthalmic dose) during gestation were proportional to the reduced maternal weight gain, with no statistically significant effects on organ or tissue development. Increases in unossified sternebrae, reduced ossification of the skull, and unossified hyoid that occurred at 6 and 18 mg/kg were not statistically significant. No treatment-related malformations were seen. Following oral administration of ^{14}C-brinzolamide to pregnant rats, radioactivity was found to cross the placenta and was present in the fetal tissues and blood.

Developmental toxicity studies performed in rats with oral doses of 0.66 mg brimonidine base/kg revealed no evidence of harm to the fetus. Dosing at this level resulted in a plasma drug concentration approximately 100 times higher than that seen in humans at the recommended human ophthalmic dose. In animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent.

There are no adequate and well-controlled studies in pregnant women. SIMBRINZA® Suspension should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers - In a study of brinzolamide in lactating rats, decreases in body weight gain in offspring at an oral dose of 15 mg/kg/day (150 times the recommended human ophthalmic dose) were observed during lactation. No other effects were observed. However, following oral administration of ^{14}C-brinzolamide to lactating rats, radioactivity was found in milk at concentrations below those in the blood and plasma. In animal studies, brimonidine was excreted in breast milk.

It is not known whether brinzolamide and brimonidine tartrate are excreted in human milk following topical ocular administration. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from SIMBRINZA® (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2%, 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 - The individual component, brinzolamide, has been studied in pediatric glaucoma patients 4 weeks to 5 years of age. The individual component, brimonidine tartrate, has been studied in pediatric patients 2 to 7 years old. Somnolence (50-83%) and decreased alertness was seen in patients 2 to 6 years old. SIMBRINZA® Suspension is contraindicated in children under the age of 2 years *[see Contraindications]*.

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

OVERDOSAGE

Although no human data are available, electrolyte imbalance, development of an acidotic state, and possible nervous system effects may occur following an oral overdose of brinzolamide. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored.

Very limited information exists on accidental ingestion of brimonidine in adults; the only adverse event reported to date has been hypotension. Symptoms of brimonidine overdose have been reported in neonates, infants, and children receiving brimonidine as part of medical treatment of congenital glaucoma or by accidental oral ingestion. Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility - Brinzolamide caused urinary bladder tumors in female mice at oral doses of 10 mg/kg/day and in male rats at oral doses of 8 mg/kg/day in 2 year studies. Brinzolamide was not carcinogenic in male mice or female rats dosed orally for up to 2 years. The carcinogenicity appears secondary to kidney and urinary bladder toxicity. These levels of exposure cannot be achieved with topical ophthalmic dosing in humans.

The following tests for mutagenic potential of brinzolamide were negative: (1) *in vivo* mouse micronucleus assay; (2) *in vivo* sister chromatid exchange assay; and (3) Ames *E. coli* test. The *in vitro* mouse lymphoma forward mutation assay was negative in the absence of activation, but positive in the presence of microsomal activation. In this assay, there was no consistent dose-response relationship to the increased mutation frequency and cytotoxicity likely contributed to the high mutation frequency. Carbonic anhydrase inhibitors, as a class, are not mutagenic and the weight of evidence supports that brinzolamide is consistent with the class. In reproduction studies of brinzolamide in rats, there were no adverse effects on the fertility or reproductive capacity of males or females at doses up to 18 mg/kg/day (180 times the recommended human ophthalmic dose).

Brimonidine tartrate was not carcinogenic in either a 21-month mouse or 24-month rat study. In these studies, dietary administration of brimonidine tartrate at doses up to 2.5 mg/kg/day in mice and 1 mg/kg/day in rats resulted in plasma drug concentrations 80 and 120 times higher than the human plasma drug level at the recommended clinical dose, respectively. Brimonidine tartrate was not mutagenic or cytogenic in a series of *in vitro* and *in vivo* studies including the Ames test, chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells, a host-mediated assay and cytogenic studies in mice, and a dominant lethal assay. In reproductive studies performed in rats with oral doses of 0.66 mg brimonidine base/kg (approximately 100 times the plasma drug concentration level seen in humans following multiple ophthalmic doses), fertility was not impaired.

PATIENT COUNSELING INFORMATION

Sulfonamide Reactions - Advise patients that if serious or unusual ocular or systemic reactions or signs of hypersensitivity occur, they should discontinue the use of the product and consult their physician.

Temporary Blurred Vision - Vision may be temporarily blurred following dosing with SIMBRINZA® Suspension. Care should be exercised in operating machinery or driving a motor vehicle.

Effect on Ability to Drive and Use Machinery - As with other drugs in this class, SIMBRINZA® Suspension may cause fatigue and/or drowsiness in some patients. Caution patients who engage in hazardous activities of the potential for a decrease in mental alertness.

Avoiding Contamination of the Product - Instruct patients that ocular solutions, if handled improperly or if the tip of the dispensing container contacts the eye or surrounding structures, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions *[see Warnings and Precautions]*. Always replace the cap after using. If solution changes color or becomes cloudy, do not use. Do not use the product after the expiration date marked on the bottle.

Intercurrent Ocular Conditions - Advise patients that if they have ocular surgery or develop an intercurrent ocular condition (e.g., trauma or infection), they should immediately seek their physician's advice concerning the continued use of the present multidose container.

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Alternative therapies in this area, such as LipiFlow, are becoming popular. "They are becoming a centerpiece for practice growth and patient awareness," says Dr. Sheppard. "Additionally, in many cases, it is more readily adopted by patients [than prescription therapy]. All of the alternative methods that we have discussed and the many others that are out there are synergistic and complementary to prescription therapy, as well."

Also, a recent study found that the therapy known as transcutaneous electrical stimulation can improve patients' dry eye, both subjectively and objectively, without any adverse effects, so it may be a potential addition to the ophthalmologist's dry-eye armamentarium.[4]

In this study, 27 patients with dry eye underwent transcutaneous electrostimulation. Electrodes were placed on the periorbital region of both eyes along with manual stimulation with a hand-piece conductor moved by the operator. Each patient underwent 12 sessions that lasted 22 minutes each. Sessions were spread over two months, with two sessions per week in the first month and one session per week in the second month. Ocular Surface Disease Index questionnaire, TBUT, fluorescein staining of the cornea, Schirmer I test and adverse events were assessed at baseline, at the end of treatment, and at six and 12 months after treatment.

Patients' OSDI improved from 43 ±19.2 at baseline to 25.3 ±22.1 at the end of treatment, and this improvement was maintained at both six-month and 12-month follow-up evaluations. There was TBUT improvement in the right eye at the end of treatment and after 12 months in the left eye. The Oxford scores changed in both eyes at the end of treatment and at the six-month visit. Additionally, Schirmer I scores improved significantly at the end of treatment in the left eye and in both eyes at the 12-month evaluation. At the end of treatment and during the follow-up period, there was a significant reduction of the use of tear substitutes. No complications were reported.

A novel intranasal neurostimulation therapy for dry eye may be approved as early as the first quarter of 2017.

"There is also excitement in the dry-eye community regarding neurostimulation therapy to stimulate natural tear production, which may be approved as early as the first quarter of 2017," Dr. Sheppard notes, referring to the Allergan/Oculeve intranasal tear neurostimulator device.

One study of intranasal neurostimulation included 40 patients with mild to severe dry eye disease who were provided with a nasal stimulation device and instructed to use it at home four times daily.[5] The study was sponsored by the device's maker, Oculeve. The nasal stimulation device is noninvasive with probes that are placed in the nose to stimulate the lacrimal glands to produce tears. Patients were followed for up to 180 days. Schirmer scores were used to determine the difference between unstimulated and stimulated tear production. The study found that the mean stimulated Schirmer scores were significantly higher than the unstimulated scores at all visits. Additionally, corneal and conjunctival staining and symptom scores from baseline to day 180 were significantly reduced.

Also, a study has found that intense pulsed light therapy effectively treats evaporative dry eye disease. IPL has been used by dermatologists as a rosacea treatment for years, and now it is being used to treat meibomian gland disease and evaporative dry eye. The treatment consists of delivering 10 to 15 treatment spots to the upper cheek and lateral canthal area with an intense pulsed-light handpiece. The physician usually makes two passes. In a study of IPL, researchers reviewed clinical data from 100 patients who were diagnosed with evaporative dry eye.[6] On average, patients underwent four IPL sessions during the two-year study period, and there was a significant decrease in scoring of lid margin edema, facial telangiectasia, lid margin vascularity, meibum viscosity and OSDI score. Additionally, there was a significant increase in oil flow score and TBUT.

As far as the future of alternative dry-eye therapies, Dr. Sheppard says: "The fact that the marketplace is expanding tells us that these therapies are working." REVIEW

Dr. Sheppard is a consultant for Allergan, Alcon, Novartis, Abbvie, Science Based Health, TearLab, Tear Science, Shire and Bausch + Lomb. Dr. Latkany has a licensing agreement with Eye Eco for his eye mask. Dr. Stonecipher is a consultant for AMO, Alcon, Allergan, Bausch + Lomb, Ellex, Nidek, Presbia, Refocus and Shire.

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Thicker than Water: Autologous Serum

Kristine Brennan, Senior Associate Editor

The benefits and limitations of this unique corneal therapy.

Autologous serum was one of the fluids used in a 1975 study testing the ability of a perfusion pump to keep chemically burned eyes moist.[1] The first study describing the benefits of serum eye drops in Sjögren's syndrome patients with keratoconjunctivitis sicca was published in 1984.[2] Eye drops derived from a patient's own blood have gained therapeutic standing over the intervening decades, helping many dry-eye patients live better lives. Autologous serum eye drops (ASED) are many things: effective, well tolerated and full of substances that artificial tears can't replicate. They are also costly and not readily available to every patient who might benefit from them. Here, three practitioners discuss the benefits and challenges of using ASED to treat dry-eye patients.

How They're Made

Preparation protocols for ASED vary, but they all share these fundamental steps: The patient donates blood; the blood coagulates and is centrifuged to extract the serum; and a quantity of serum is placed into a dropper bottle, usually with diluent—often a sterile saline solution. Most drops are 20% serum, although some patients use 25%, 50%, or even 100% serum drops.

Darren G. Gregory, MD, associate professor of ophthalmology at the University of Colorado School of Medicine, spearheaded an ASED program at the University of Colorado Eye Center in Aurora, Colo., now in its second decade. "The patient gets blood drawn at the hospital's outpatient blood-draw center, and then the inpatient pharmacy centrifuges and prepares the drops. Then the patient can pick up the drops from the hospital pharmacy," he explains. The pharmacy's standard dilution is 25%, but the strength can be titrated up to 100% serum.

Anat Galor, MD, MSPH, a staff physician at the Miami Veterans Affairs Medical Center and associate professor of clinical ophthalmology at Bascom Palmer Eye Institute University of Miami Miller School of Medicine, credits her colleague, Victor L. Perez, MD, with setting up a serum tears laboratory in the Bascom Palmer Ocular Surface Center that makes procuring ASED easy for patients. "I just write a prescription and I send it to the lab, where it's all done for them," she says. Dr. Galor says that their standard dilution is 20%, "but we can escalate the dosage up to 50% in our lab, based on effect."

Christopher J. Rapuano, MD,

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Reference: 1. Srinivasan S, Ngo W, Jones L. The relief of dry eye signs and symptoms using a combination of lubricants, lid hygiene, and ocular nutraceuticals. Poster presented at: ARVO annual meeting; April 2015; Denver, CO.

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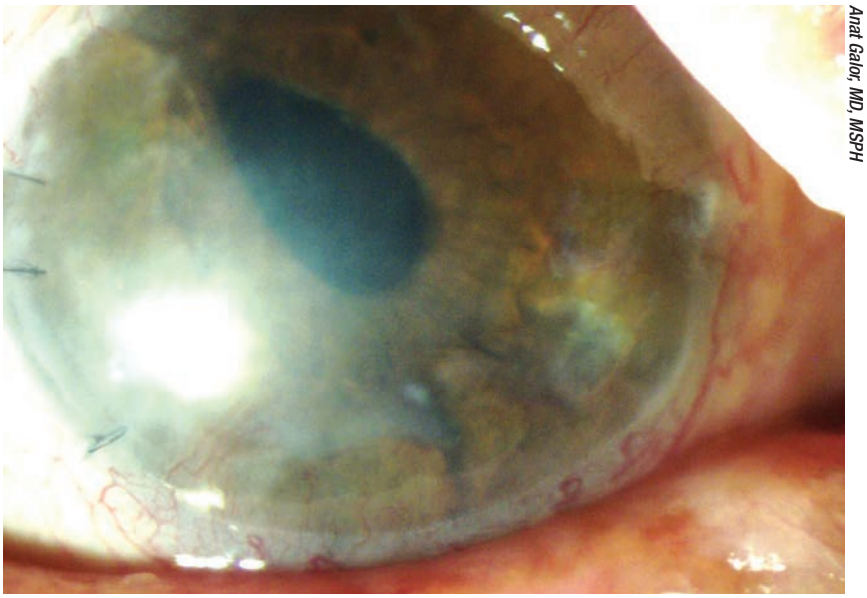
chief of the cornea service at Wills Eye Hospital in Philadelphia, also typically starts his patients at 20% dilution. "We can go up to about 50%, but there's no right or wrong on that," he says. His patients currently get their drops made outside of Wills Eye. Dr. Rapuano calls a designated blood-draw facility to advise that a patient is coming to donate. The blood then goes to a specialized compounding pharmacy in Maryland, which in turn ships the finished ASED to his patients.



Anat Galor, MD, MSPH

Patients with limbal stem-cell deficiency undergoing PK are at risk of developing dry eye. Autologous serum eye drops started preoperatively can help prevent this.

The Benefits

To launch an ASED protocol at his hospital, Dr. Gregory had to pitch its potential benefits. "I had to convince a lot of committees that such a program was a viable option," he recalls. "We think that the various growth factors and nutrients that are contained in the serum provide a lot of things for the surface of the eye that may be missing when the eye is very dry, or if there is scarring or other abnormality on the surface of the eye. It can often alleviate dry-eye symptoms in patients who have not had good relief from other available treatments. It can also help non-healing corneal epithelial defects," he explains.

"Dry eye is a huge category," adds Dr. Rapuano, "including patients with severe ocular surface disease, chemical burns, Stevens-Johnson syndrome and ocular cicatricial pemphigoid." He tells his patients that ASED contain "goodies" found in the body but unavailable in artificial tears, such as antibodies and growth factor. "It often helps them feel better, see better, and it helps the health of the ocular surface."

"Whatever the underlying biology is, clinically, they work," says Dr. Galor. "I'm a total believer in autologous serum tears." She uses them in patients with neuropathic eye pain, neurotrophic keratitis and for "patients who have a lot of signs of dry eye, such as diffuse staining" that is refractory to traditional therapies. "In those cases, it may be that the density of the serum tears—the fact that they have a lot of albumin—could be coating the eye and driving the beneficial effect," she says. "Then again, it could be that helping the nerves secondarily helps the epithelium, so that it all comes down to nerve health." In addition to using ASED before and after certain high-risk corneal transplants and SLET procedures, Dr. Galor prescribes them for post-vitrectomy diabetics. "I also use them in patients when I'm worried about their limbal stem-cell environment," she explains. "That's a very specific subtype of dry eye that is not very common, but it's very difficult to keep the epithelium healthy in those patients."

Serum contains bioactive agents that may promote healthy cell growth and healing of the ocular surface, including albumin, vitamin A, and nerve and epidermal growth factors. Evaluating evidence regarding the efficacy of ASED is not helped by the fact that sample sizes tend to be small with little follow-up; there is also no universal protocol for preparing and storing the eye drops. Studies have, however, demonstrated instances of ASED surpassing artificial drops in promoting comfort and improving the quality of the tear film.[3,4]

Sjögren's syndrome can cause severe dry eye stemming from diminished basal and reflexive tear production.[5] Dr. Galor says that patients with Sjögren's and other autoimmune diseases can benefit from ASED. "There's always a question regarding patients with autoimmune disease, because they have circulating autoantibodies: Is their blood going to be helpful for serum tears? But we have a very large group of patients with Sjögren's syndrome and graft-versus-host disease, and these patients seem to do well."

A multifactorial condition with numerous treatment options, dry eye sometimes proves recalcitrant to measures such as artificial tears, ointments, eyelid hygiene, moisture masks, glasses, goggles and punctal plugs. When other therapies fail, ASED can improve quality of life for patients, either alone or with other modalities. Why, then, have they

failed to become a standard part of the dry-eye armamentarium?

While Dr. Gregory counts himself fortunate to offer his patients ASED, he has had to advocate for it. "We've squabbled with the hospital committee," he acknowledges. "The pharmacy was looking at all of their overhead costs—factoring in the cost of lighting in the lab, for example. They did an analysis from start to finish: The blood-draw center had its charge; they figured in a charge for the in-hospital courier who walks the blood from the blood-draw center up to the pharmacy lab where they mix it." Dr. Gregory estimates that a three-month supply of drops starts at $180 for his patients. "There were times when they tried to raise the price to nearly $300 for a batch, but the patients just aren't going to be able to pay that," he continues. "We gave patient testimonials to the various leadership folks in the hospital. We presented them with a number of articles from the medical literature supporting the use of this type of drop. Because we are a big academic center, we try to provide care that is not readily available elsewhere, so they recognized the importance of that. Thankfully, we've been able to maintain the program for over 10 years now."

The Right Patients

While ASED can and do help many patients, they aren't for everyone. "About half of the patients we try it on seem to benefit and we continue; but half don't benefit enough to want to continue," says Dr. Rapuano. "It's a hassle to get your blood drawn every three, four, or six months, depending on how much they draw, which depends on the percentage of the drops you use."

Some settings follow blood-donor guidelines that disqualify certain patients from supplying their own blood for the drops. Positive serology testing is not an exclusion criterion at Bascom Palmer Eye Institute. "We practice universal precautions, and we do not test the blood prior," Dr. Galor says. "We've had good success with patients who have infectious serological markers. Our patients with HIV, for example, seem to do well. We haven't found specific blood types that are a contraindication to the clinical effect of serum tears; and again, there are very strict universal precautions, no matter who the patient is."

Prior to the protocol that Dr. Rapuano currently uses for his patients, the lab that did blood draws required testing. "I'm told that's not required anymore," he says. "It was always a little bit funny to me as to why that was required, because universal precautions are taken by the people who draw the blood and the people who treat the blood; so whether or not there are infectious components in there, the people handling it shouldn't ever be exposed."

Dr. Gregory's ASED program does not require testing, either. "We haven't run into trouble. I guess that's part of the benefit of the rigorous system that we have in our hospital for preparing the drops," he says. "We have a careful process. There are certainly practices that will prepare them in their own offices for patients, but I think that's a little riskier."

While safe handling of blood products during ASED formulation is critical, so is the safe handling of finished eye drops. Patients must be counseled to store their unopened droppers in the freezer. A dropper in use should be refrigerated to preserve beneficial agents and retard the growth of harmful microorganisms. Although adverse events are rare in the literature, dropper bottles can culture bacterial and fungal contamination.[6,7,8] "Theoretically, bacteria could start to grow and patients could be giving themselves bacteria in the eye," notes Dr. Rapuano. "That's why they have to take care of the drops and keep them in the freezer before use. We always tell patients there's a little bit of risk to this, but that we think there's a bigger risk to the current eye problem we're trying to treat."

Logistics and Costs

Not only must patients comply with safe storage and use guidelines to benefit from ASED; they must also follow the steps it takes to obtain drops—several times per year, possibly for years to come. Even though Dr. Gregory's patients can get their drops made on one campus, that location is the only large academic eye facility in a 500-mile radius, so many travel great distances. "The process is a bit cumbersome," he says. "The patient has to get the blood drawn, and then there's usually only one day per week that we have a technician who's assigned to prepare the drops." Dr. Gregory adds that shipping is available to patients in Colorado, but patients from Wyoming, Kansas, and Nebraska may need to come back a few days after blood donation to pick

Table 1. Possible Infections

Although infections are rare in the literature surrounding the use of ASED, studies of dropper bottles have shown positive microbiological cultures for fungi and bacteria, including:

- *Aspergillis spp*[7]
- *Bacillus sp*[6]
- *Candida sp*[6]
- *Fonsecaea spp*[7]
- *Klebsiella pnueumoniae*[6]
- *Micrococcus sp*[6,8]
- *Psuedomonas aeruginosa*[6]
- *Staphylococcus aureus*[6,8]
- *Staphylococcus epidermidis*[8]
- *Streptococcus viridans*[6,8]

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up their eye drops.

Last—but certainly not least—on the list of challenges to widespread use of autologous serum is the cost, which is almost always borne by the patient. "It's cash: Insurance generally won't cover it," says Dr. Gregory. "It's a couple of dollars a day when you add it all up, but when patients pay it up front, it seems like an awful lot of money for some drops." Dr. Galor estimates that a two-month supply costs about $220. "It's not cheap," she acknowledges, but her VA patients are spared out-of-pocket costs. "One nice thing is that the veterans get it paid for," she notes.

Researchers have attempted to develop uniform preparation protocols that would be accessible, affordable, and replicable in most health-care settings. A paper published in 2011 estimated that ASED cost U.S. patients anywhere from $25 to more than $600 out of pocket for a two- to three-month supply.[9] Researchers from Hamilton Eye Institute in Memphis, Tenn., proposed a protocol wherein blood-draw centers would take the lead in serum preparation as well as blood collection. Factoring in the costs of materials and technician time to produce one three-month supply of ASED, they posited an estimated cost of $80, which didn't include packaging or shipping. Another estimated cost was $82 for annual serological tests: The protocol excluded patients with markers for HIV, hepatitis or syphilis.

Are Alternatives Coming?

Given the inherent challenges of ASED use, are any other modalities in the pipeline that would confer their benefits without the hassles? Dr. Galor sees two emerging technologies, neither of which replaces autologous serum tears: a preparation kit to make them more accessible to patients; and the potential addition of other autologous blood components to increase their clinical effects. She cites a proprietary kit being developed by a company in Spain that would simplify the production of serum tears. "I don't have access to it, but I know that it's being looked at as a way to get the technology out," she says. "Another area of interest is adding other blood products, such as making platelet-rich serum tears, to make the serum tears more effective. There is still a lot that's unknown about the best percentages, formulations, and other blood products you may want in there to enhance the effect. Those are some of the things that people are talking about."

Dr. Gregory notes that RegenerEyes, a Florida-based company, has made amniotic-fluid eye drops commercially available, and cites plasma rich in growth factors as another potential avenue of dry-eye therapy. His hospital was involved in human trials of an eye drop derived from recombinant bovine albumin. "I'm not sure what became of it," he says. "We had just a handful of patients using it. We didn't know if they were getting placebo or the actual medication, so I didn't have a great sense of whether or not it was helpful. But I think it always comes down to the same problem: None of these treatments, to my knowledge, are currently covered under people's insurance, so it's all out-of-pocket and expensive. Unfortunately, nothing has really grabbed hold or become logistically simple or affordable."

Reflecting on his ASED program, Dr. Gregory remains convinced of its importance to his severe dry-eye patients. "The serum drops, with our preparation protocol, have shown themselves to be a reliable, safe treatment, that, despite the cost and some of the hurdles, has proven very helpful for those who haven't gotten great benefits from the more readily available treatment options. We've been glad to have them for our patients," he affirms.

Doctors who want this option for their patients need to screen those patients carefully, candidly discussing the financial and logistical burdens that ASED treatment may impose. They can refer patients to appropriate phlebotomy and compounding facilities to have the drops made, or face the formidable task of developing a safe in-house protocol. Educating patients about the safe storage and handling of ASED is also important. Despite this lengthy to-do list, autologous serum eye drops can offer patients with recalcitrant dry eyes—and the suffering that accompanies them—a good measure of bang for the buck, provided they have the money to spend.

"They help a lot of people," says Dr. Rapuano. "We tell patients that this is an unusual use, and we're doing it to address an unusual problem." REVIEW

Dr. Gregory, Dr. Galor, and Dr. Rapuano report no financial interest in any of the products mentioned in this article.

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[1] **Epitropoulos**, **Alice T.**, **Donnenfeld**, **Eric D.**, et al., Effect of Oral Re-esterified Omega-3 Nutritional Supplementation on Dry Eyes. Cornea 2016;0:1-7

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Ten Things NOT To Do As a Surgeon

Bennie H. Jeng, MD
Baltimore

Sometimes, you can do what's right just by knowing what's wrong.

Ophthalmology is the greatest specialty in medicine, and studies have shown that we ophthalmologists are, in general, among the most satisfied and content physicians when compared to our colleagues in other specialties. Before I knew these statistics about satisfaction, though, I sensed it, even as a medical student: The cliché of ophthalmology being a nice blend of medicine and surgery was true, and I found it especially appealing that I could be a transplant surgeon without dealing with blood (for the most part). As such, I was sure that if I made it into ophthalmology, cornea would be my specialty, since it's the only part of the eye that can be transplanted (for now). This notion, coupled with the fact that I was unable to see the retina in residency, made cornea the field for me.

Words to Live By

When I finished my fellowship training, I felt that I was well-trained and had been armed with excellent advice about how to build a practice: Go out and meet other practitioners in the area; communicate with referring doctors and return patients to them; be available to see their patients any time; be nice to patients; and invest some time in making your practice efficient. Looking back, this was all true, and it's advice that I continue to pass along to all of the trainees with whom I have the privilege of working.

While these are words to live by, however, they're rather general suggestions, and I would like to provide more-specific ideas. Many times, when asked for advice, experts will give you their top 10 reasons to do something. Since my status as an expert is questionable, I thought I would change things up and give you my top 10 things NOT to do when you are starting out as an ophthalmic surgeon. These may seem obvious, but having them in writing can be a useful reminder:

1) DON'T show off. Picture this: It's your first week at your practice's ASC and you want everyone to know that you're a great surgeon. Even though you probably are great, if your average phaco time is 10 minutes, don't try to push it and do a five-minute phaco just to show everyone how awesome you are. If you push it, bad things will happen—and then you won't look so awesome.

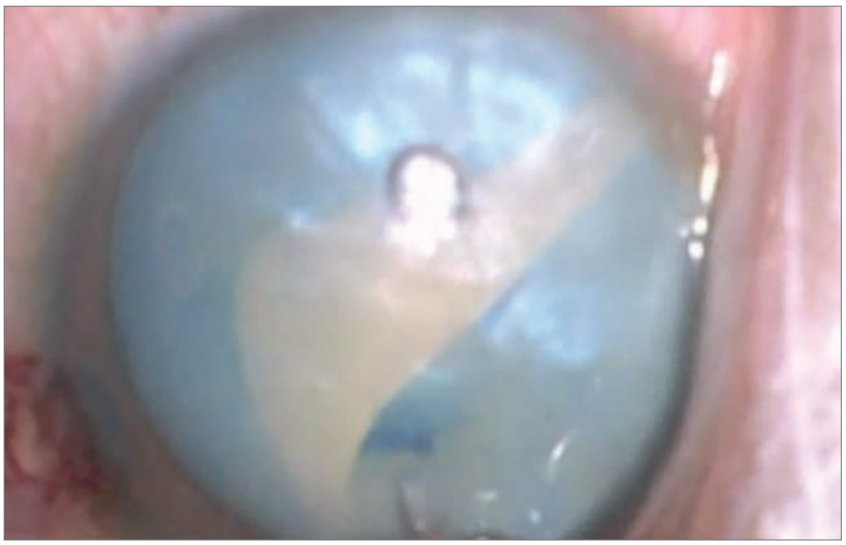
Whether you feel it or not, when performing surgery, there's a big jump

from being a supervised trainee to being the one who is fully responsible. Let that sink in as you get back into the groove before turning it up a notch to achieve that five-minute case.

2) DON'T cut corners. During training, many residents and fellows have the luxury of not having to see every patient in a faculty practice. Trainees can spend their time with "interesting" patients who provide educational value, along with more mundane tasks such as suture removal and retinal injections. Then you hit the real world—and every patient that is scheduled to see you is yours. However, we each see patients at a different pace. If 20 patients in a half day leads you to cut corners on patient care, then cut back the schedule until you can increase your or your practice's efficiency, but don't cut corners on taking care of your patients. The extra time you spend with them in the beginning will generate the word of mouth that'll help build your practice in the end.

The same idea goes for surgery. We just talked about not showing off in the OR, but we also inherently don't want to look like we're too slow, so we often feel the pull to cut corners here and there. You might instinctively feel that that the wound is most likely watertight, and so you don't want to have to ask for a 10-0 nylon suture to close it and subsequently take an extra two minutes in the OR. Just remember that those extra two minutes can save hours the next day if you have to take the patient back to put a suture in—or worse, have to deal with an endophthalmitis. If you think you might want to do something in the OR so you'll sleep better, just do it, and don't cut that corner.

3) DON'T forget to be nice to everyone and let them know how much you appreciate them. Yes, you are inherently nice, but when you realize that everything in your practice and ASC is now your responsibility, sometimes the stress can build up until you're short with—or lose it on—a staff member. If that happens, apologize, because saying you're sorry can have a very positive effect on people. Yes, you're now the boss, but always remember that you can't do anything without your staff: It would take more than twice as long to do surgery if you had to be both the scrub technician and the surgeon. A little appreciation goes a long way and can encourage your staff to go the extra mile for you and the practice.

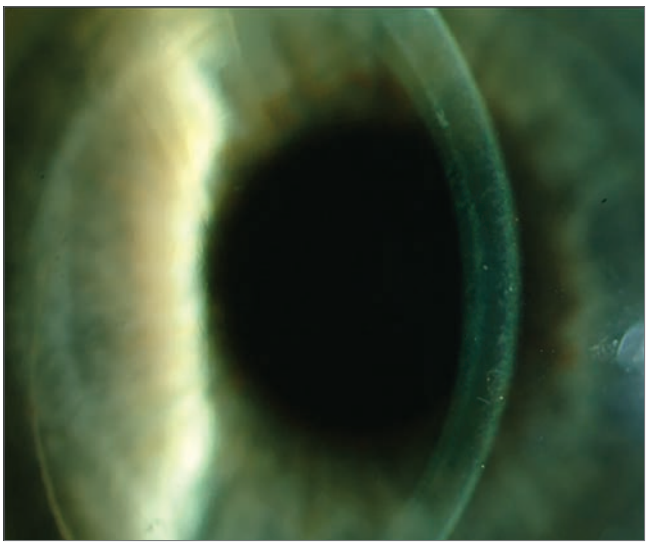


The Argentinian Flag sign—it happens. Remember that you're human *(See tip #9)*, but just be prepared ahead of time and know what you will do when this occurs.

4) DON'T stop learning. When you complete your residency and fellowship, it's easy to think that you've learned everything you need to know. However, chances are there are things you didn't have the opportunity to learn in training, and there are definitely things you haven't seen in your office or done in the OR. As such, you should still seek out opportunities to learn. This is especially true for surgical procedures: as newer techniques evolve, the techniques that you learned in training can become obsolete, and you need to keep up with the times to be able to provide the best care for your patients. I can personally attest to this: The field of cornea has changed greatly in the past decade. For instance, during my fellowship, which was less than 15 years ago, I only did full-thickness grafts, as lamellar keratoplasty was not yet popularized or refined. Now, in most cases for certain indications, lamellar keratoplasty is considered the standard of care. If I didn't go out and learn endothelial keratoplasty on my own, I'd be in trouble, and I wouldn't be providing the best care possible to my patients.

5) DON'T lose touch with your mentors. You chose your residency and fellowship for a number of reasons, including the clinical experience you'd get, the faculty you'd interact with and the research opportunities

that would be available to you. But it doesn't end there: Just because you're done with official training doesn't mean that they can't continue to help you clinically or surgically. Though you may worry that you are "bothering" them, or maybe you're uncomfortable asking them a question that might make them think you weren't paying attention in training, your mentors should be flattered that you're still willing to ask them for advice. I still love it when my previous fellows (sometimes from years ago) send me an email asking for tips on how to handle an upcoming surgical case. You can ask many different people, but your mentors are the ones who most likely know you the best and know what you're capable of doing.



If I only relied on what I learned in fellowship, I wouldn't have been able to give this patient a great outcome with a short recovery period with endothelial keratoplasty. Don't stop learning *(See tip #5)*.

6) DON'T be too proud to ask for help. As in #4 above, you will not have encountered every clinical/surgical scenario during your training, and sometimes, you just don't know the answer. Being able to admit that you need help can actually earn the respect of patients and colleagues. There are still occasions when I'll tell patients that I have absolutely no idea what they have, and I'll even do this in front of the residents and fellows. The patients have all appreciated my honesty and my plan to ask my mentors for advice *(See #5)*, and will eagerly come back during follow-up to ask what I've learned to help them. In addition, it's also a good idea to freely offer patients the opportunity to see another provider for a second opinion; they always appreciate that, and they respect you more for offering. And they'll be more comfortable with you should they come back to have surgery with you.

7) DON'T forget that you were an amateur at one point. If you're working in a training program, remember that you, too, were once a resident or fellow, and if you are reading this, you were likely one not too long ago. There was a time when you also made mistakes, so please remember to be patient with the trainees. Use your own mistakes to help teach your trainees.

8) DON'T forget that you are human. Though you are no longer the "amateur," you are still human, and we humans all make mistakes. I was told in residency that if you have never had a complication during surgery, then you haven't done enough surgery. This is totally true, as even the best cataract surgeons find vitreous every now and again. The important part of this is to recognize your mistakes, then acknowledge them and learn from them. I still encounter tough situations that I think in retrospect about how I might have handled differently, or how I might have done something differently to avoid them. Thinking about and replaying your mistakes will help you be come a better surgeon. Just remember that we all make mistakes.

9) DON'T forget that under the drapes there's a real, live patient. You may be a super-slick surgeon who can perform 30 phacos per day from the get-go (remembering #1 above), but don't forget that you originally entered medicine to help people. The people you help have names, and aren't just disembodied eyes, patient record numbers or "3+ PSC cataracts." Though it may only be a five-minute procedure to you, remember that the patient may be terrified, and even just a few words of comfort will go a long way toward reassuring him or her.

10) DON'T forget rules 1 through 9. Lest you think that I just ran out of ideas, I actually planned for this particular suggestion. Surgery, ophthalmology and medicine all require a lifetime of learning, and learning requires repetition. So, continuously reminding yourself of rules 1 through 9 will help you be the best ophthalmologist, and person, that you can be. REVIEW

Dr. Jeng is a professor and chair of the Department of Ophthalmology and Visual Sciences at the University of Maryland School of Medicine. He can be reached at (667) 214-1232 and bjeng@som.umaryland.edu.

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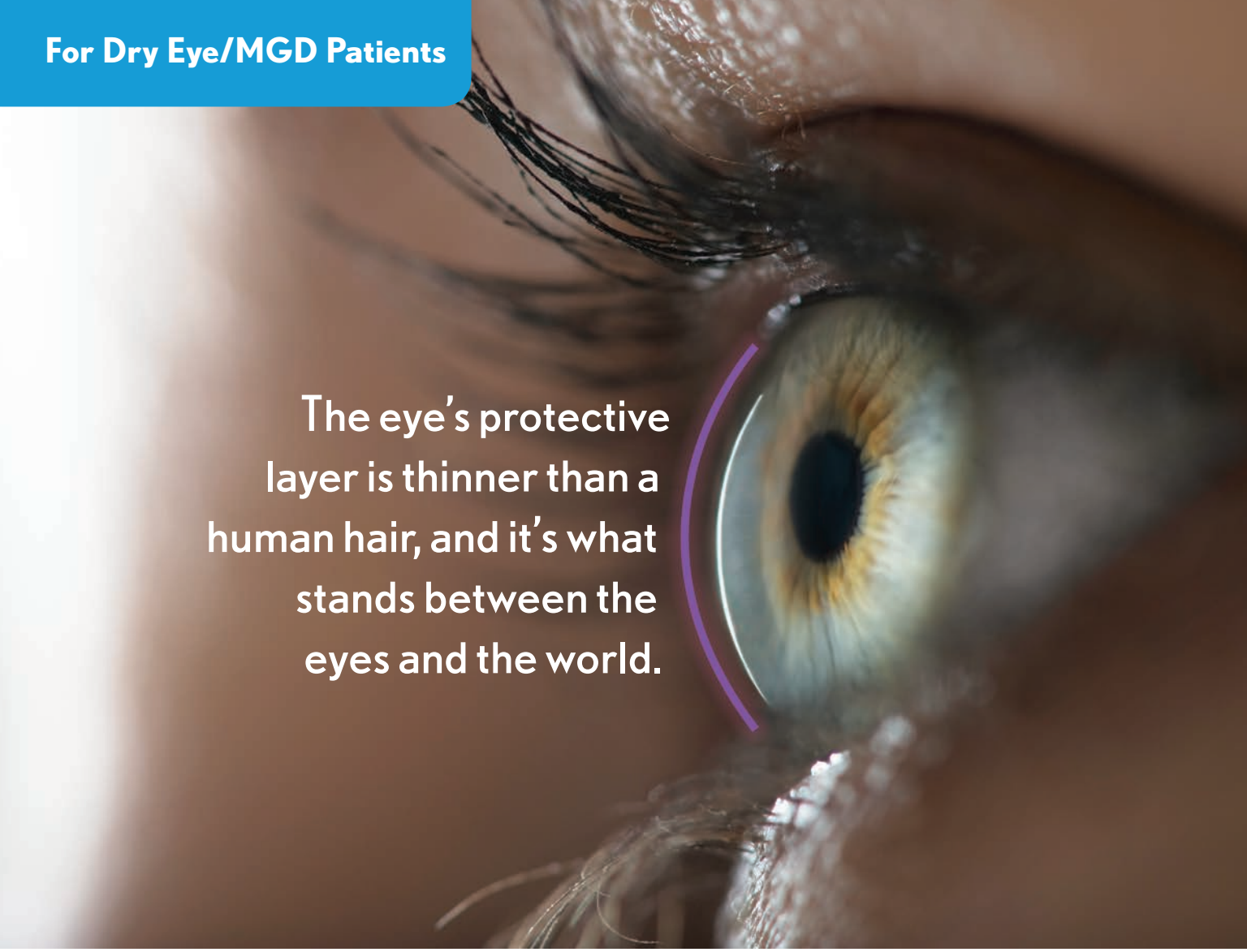

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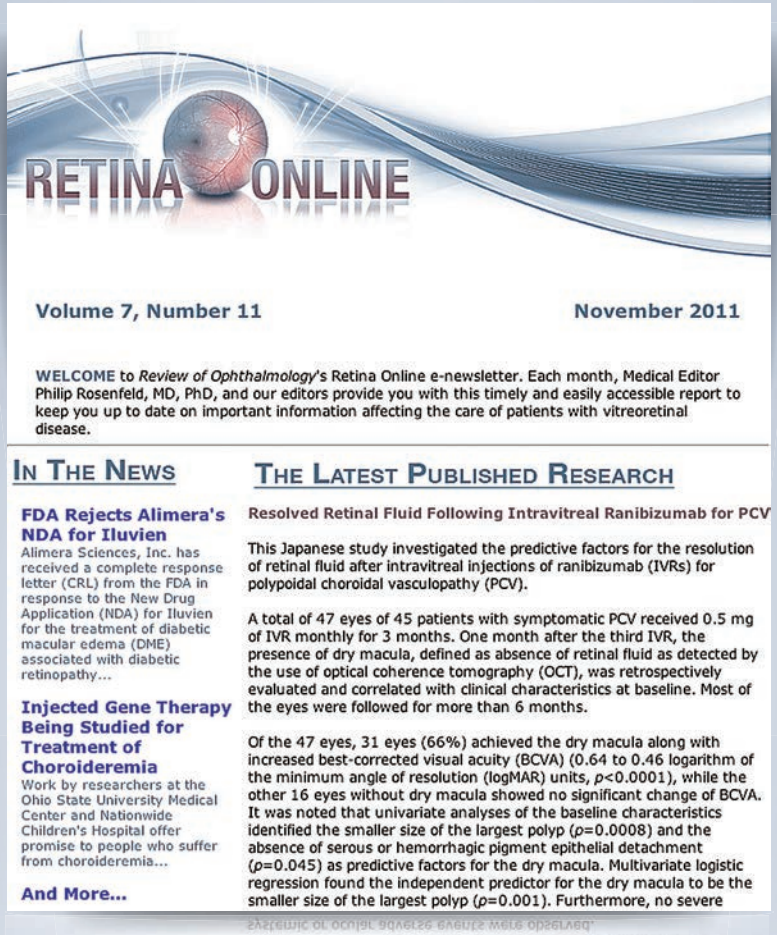

RETINA ONLINE

Volume 7, Number 11 November 2011

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Resolved Retinal Fluid Following Intravitreal Ranibizumab for PCV

This Japanese study investigated the predictive factors for the resolution of retinal fluid after intravitreal injections of ranibizumab (IVRs) for polypoidal choroidal vasculopathy (PCV).

A total of 47 eyes of 45 patients with symptomatic PCV received 0.5 mg of IVR monthly for 3 months. One month after the third IVR, the presence of dry macula, defined as absence of retinal fluid as detected by the use of optical coherence tomography (OCT), was retrospectively evaluated and correlated with clinical characteristics at baseline. Most of the eyes were followed for more than 6 months.

Of the 47 eyes, 31 eyes (66%) achieved the dry macula along with increased best-corrected visual acuity (BCVA) (0.64 to 0.46 logarithm of the minimum angle of resolution (logMAR) units, $p<0.0001$), while the other 16 eyes without dry macula showed no significant change of BCVA. It was noted that univariate analyses of the baseline characteristics identified the smaller size of the largest polyp ($p=0.0008$) and the absence of serous or hemorrhagic pigment epithelial detachment ($p=0.045$) as predictive factors for the dry macula. Multivariate logistic regression found the independent predictor for the dry macula to be the smaller size of the largest polyp ($p=0.001$). Furthermore, no severe

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REVIEW® of Ophthalmology


Avoiding the Traps of Hydroxychloroquine Use

Proper communication between specialties and using the correct formula for dosing can curb toxicity.

David J. Browning, MD, PhD, Charlotte, N.C.

Patients who have a malady requiring the cooperation of physicians from different specialties face risks due to miscommunication, different perceived goals and variable knowledge bases across subspecialties. One example concerns the prescription of hydroxychloroquine by internists for autoimmune diseases and the screening for toxic dosing and retinopathy by ophthalmologists. In this overview, I'll identify the gaps in understanding and communication between specialties that lead to avoidable cases of retinopathy, and discuss how you can bridge them.

A Persistent Problem

Why do cases of hydroxychloroquine retinopathy continue to develop, when its pathogenesis has been known since the 1980s? Among several contributing causes, the main one is that too many patients are prescribed toxic daily doses.[1] Hydroxychloroquine is stored in lean tissues, and is largely excluded from fat.[2] Therefore, dosing of HC should be based on the lean body mass.[3] In most people this can be determined from tables of ideal body weight (IBW) based on height. However, in thin, asthenic patients in whom actual body weight is less than ideal, dosing should be based on the actual body weight (ABW), not IBW.[4] Although a few cases exist, it's extremely rare to develop HR if daily dose does not exceed 6.5 mg/kg based on using the lesser of ABW and IBW for the denominator.[5]

Ophthalmic publications are partially responsible for the confusion that exists regarding the importance of daily dosing in preventing HR. Consider what three consecutive sets of guidelines from the American Academy of Ophthalmology have to say *(Table 1)*: The 2002 guidelines state that daily dose is of "paramount importance," and advise the use of ABW except in obese patients, in which case IBW is recommended. In 2011, the guidelines flipped, discounting the importance of daily dose unless a patient is obese, in which case dosing by IBW is advised. In 2016, the guidelines flopped, reaffirming the importance of daily dose, but discounting dosing by IBW while stressing dosing by ABW and introducing a different conversion factor.

With such inconsistency, it's easy to understand how rheumatologists and ophthalmologists might be confused about the importance of the daily dose and how it should be calculated. The 2002 guidelines were potentially dangerous because of their lack of specificity regarding how to use ABW or IBW in the calculation of the daily dose. The 2011 guidelines were potentially dangerous for the person whose ABW is less than IBW *(See case 1)*. The 2016 guidelines are dangerous for the obese person in whom IBW is less than ABW *(See case 2)*.

Safe prescribing of hydroxychloroquine isn't difficult. One takes the lesser of the ABW and IBW based on height.[4] The daily dose shouldn't exceed 6.5 mg/kg/d based on the lesser of ABW and IBW. Which algorithm to use for IBW is controversial, but as a practical concern, probably doesn't matter. I prefer the National Heart, Lung, and Blood Institute algorithm *(Table 2)*.[3]

In the following sections, I'll describe case reports involving HC and explain the dosing issues involved.

Case Report #1

A 74-year-old woman with rheumatoid arthritis was started on hydroxy-

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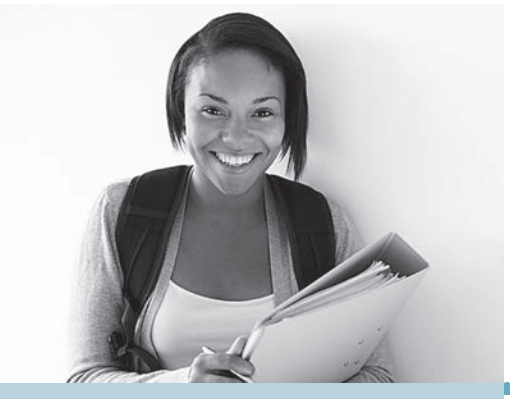

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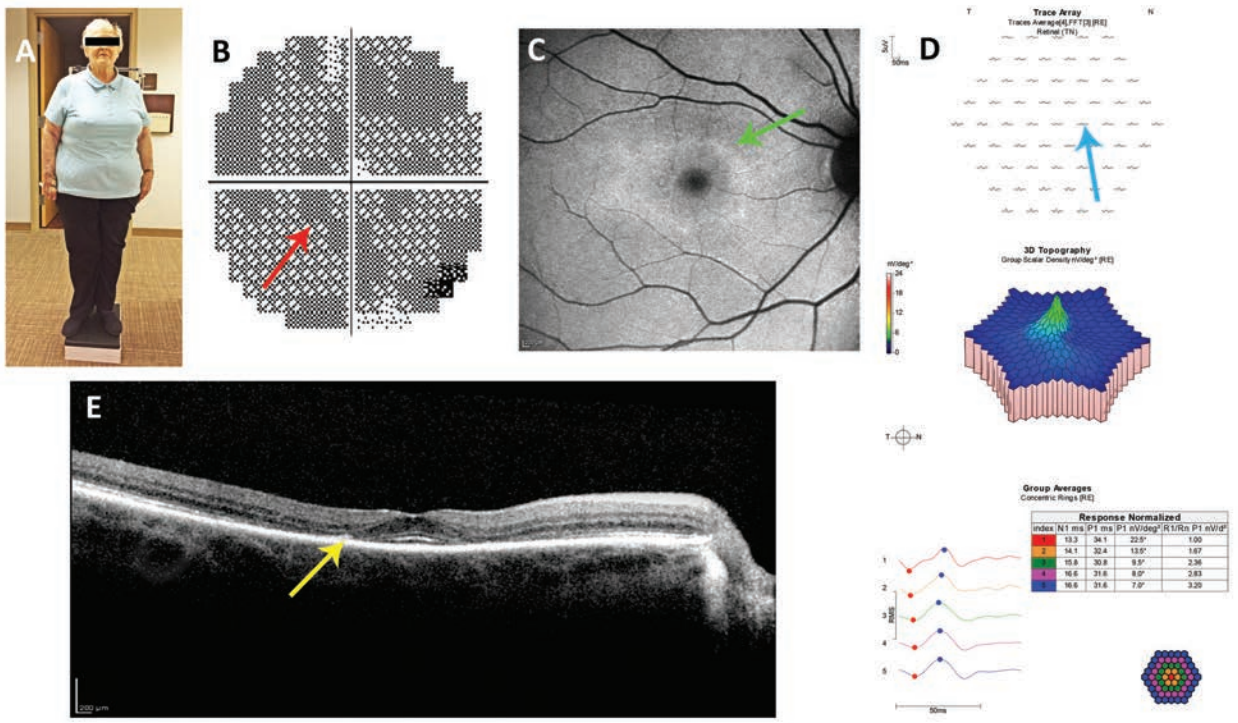

Figure 1. Case report #1. A: Note the somatotype. In the short, obese patient, dosing based on ideal body weight, not actual body weight, is appropriate. B: Paracentral scotomata (red arrow) in her 10-2 visual field test of 2012, missed by her ophthalmologist. C: Annulus of hyperautofluorescence (green arrow) on blue fundus autofluorescence imaging from 2014. D: Reduced paracentral wavelet amplitudes (blue arrow) on multifocal electroretinography. E: Paracentral loss of the ellipsoid line and thinning of the outer nuclear layer (yellow arrow) on spectral domain optical coherence tomography.

chloroquine 400 mg/d in 2004. She was 5 ft. tall, weighed 198 pounds, and had no renal or liver insufficiency *(Figure 1)*. She was first referred by her rheumatologist for screening for retinopathy in 2012, and had lost the left eye to trauma as a child.

The ophthalmologist who screened her in 2012 found her to have a corrected visual acuity of 20/20 in her right eye and interpreted her 10-2 visual field and multifocal electroretinogram as normal, although they were not. He didn't recognize her toxic dosing and made no recommendation to change it. She was asked to return in six months but never did.

A different ophthalmologist examined her in 2014. Her corrected visual acuity was 20/20 in the right eye and her fundus examination was normal. A 10-2 VF using a red test object showed progression of an annular scotoma that was present in 2012. A spectral domain optical coherence tomography imaging study of the macula showed loss of the parafoveal ellipsoid zone and thinning of the outer nuclear layer.

This case illustrates the following avoidable, commonly seen traps in the multidisciplinary management of the patient taking HC:

Table 2. An Algorithm for Ideal Body Weight

Height (inches)	Weight (pounds)
60	123
61	127
62	131
63	135
64	140
65	144
66	148

Source: Nat'l Heart, Lung, and Blood Institute

• ***The rheumatologist prescribed a toxic dose of HC based on the patient's height and weight.*** The patient was 5 ft. tall, with an ideal body weight of 123 pounds (55.9 kg, see Table 2) and a maximal daily safe dose of 55.9 x 6.5=363 mg/d of HC. To achieve this using the available pill size of 200 mg, one considers the fact that HC has a long half-life (approximately 40 days[1]). Thus, one can omit a day of dosing in a week and arrive at a suitable average daily dose. Over a week's duration, this patient can take up to 7 x 363=2,543 mg of HC safely. If she takes two tablets per day Monday through Saturday and skips HC on Sunday, her weekly total dose will be 2,400 mg which averages out to 2,400/7=343 mg/d, which is less than a toxic dose.

• ***The patient had no baseline ophthalmic screening examina-***

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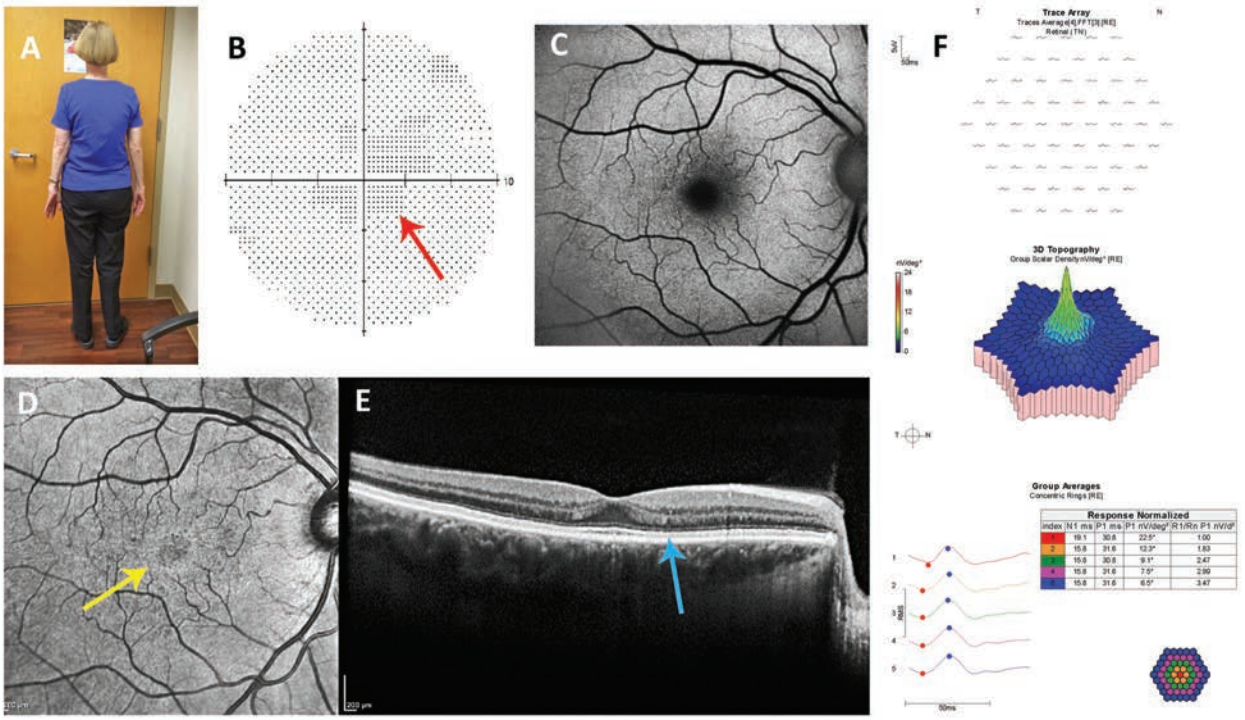

Figure 2. Case report #2: A: Note the somatotype. In the asthenic patient, dosing based on actual body weight, not ideal body weight, is appropriate. B: Nonreproducible central scotoma (red arrow) in her 10-2 visual field test isn't typical of hydroxychloroquine retinopathy. C: Blue fundus autofluorescence imaging is normal. D: Near infrared reflectance imaging shows a hyperreflective annulus (yellow arrow) which has low sensitivity and specificity for hydroxychloroquine retinopathy. E: The reflectivity of the ellipsoid line in the parafovea is slightly less than in the fovea, a potentially early sign of retinopathy. F: Multifocal electroretinography is normal.

tion and wasn't sent for screening by an ophthalmologist until eight years into therapy. This occurred despite the patient having a high risk for toxicity based on her daily dosing. AAO guidelines state that a baseline exam should be obtained and then, for low-risk patients, yearly examinations should begin five years later. Ophthalmologists have regularly rejected these recommendations.[4,7] Rather than continuing to recommend a gap in screening that's rejected by those tasked with screening for retinopathy, it would be better if the guidelines embraced the practical reality that annual screening is the norm, which in the first years is mainly aimed at detecting and correcting toxic daily dosing.

• ***The doctor failed to recognize and correct the toxic dosing of HC.*** Toxic dosing is consistently found in 12.8 to 74.7 percent of patients taking HC.[4,8-10] Correcting toxic daily dosing is the most common action taken by the screening ophthalmologist, and is the main reason to screen patients taking HC. Where safe dosing is assumed, as in Great Britain, screening isn't recommended because the rarity of HR in these circumstances makes it a wasteful use of scarce resources.[11]

• ***The first ophthalmologist failed to recognize the evidence of toxicity on the initial 10-2 VF.*** The diagnosis of HR is based on ancillary testing: 10-2 VF; SD-OCT; mfERG; and fundus autofluorescence imaging. Ophthalmologists who screen for HR have an obligation to understand what constitutes a positive test, what the potential artifacts are, and how to use multiple modalities to raise clinical confidence in a diagnosis. The topic has been thoroughly explored in multiple publications.[1,12,13] Failure to properly interpret patient testing has formed the basis of large malpractice settlements in missed cases of HR.

Case Report #2

In 2015, an ophthalmologist examined a 63-year-old woman with rheumatoid arthritis who had been taking HC 400 mg/d since 1990 (25 years, 3,650 g cumulative dose). She was 5 ft. 3 in. tall and weighed 112 pounds. She had no renal or liver disease. Her corrected visual acuity was 20/20 and her fundus examination was normal bilaterally. Her 10-2 visual field performed with a red test object showed a nonreproducible relative central scotoma *(Figure 2)*. Her fundus autofluores-

Table 1. AAO Recommendations for Daily Dosing: Three Iterations Over 14 Years

2002: "The great majority of reports of hydroxychloroquine toxicity have occurred in individuals taking more than 6.5 mg/kg/d, which suggests that daily dosage is of paramount importance … Obesity is a risk factor because antimalarials are not retained in fatty tissues. Ingested amounts of the drug accumulate only in lean weight, and the "safe" dose for individuals with a high percentage of weight is less than 6.5 mg/kg …"
2011: "… recent surveys of patients taking hydroxychloroquine found that the risk of toxicity depended on cumulative exposure and was independent of daily dose or dose/kg … We suggest that daily doses be limited to 400 mg hydroxychloroquine and that lower doses (in the range of 6.5 mg/kg hydroxychloroquine … calculated on the basis of ideal body weight) be used for individuals who are of short stature. ...Obese individuals should be dosed on the basis of height, which allows estimation of an asthenic or 'ideal' body weight."
2016: "… we recommend that all patients using hydroxychloroquine keep daily dosage < 5 mg/kg real weight. …Ideal weight formulas result in overdose in thin individuals…The most cited risk factor for the development of hydroxychloroquine toxicity is excessive daily dose by weight."

cence imaging was normal. Her near infrared reflectance imaging showed a faint hyperreflective ring, which has inconsistently been associated with early HR.[14] The SD-OCT showed a slightly less hyperreflective ellipsoid line and a suggestion of outer nuclear layer thinning. Multifocal electroretinography was normal.

Because there was no definite retinopathy, she was cleared for continued use of HC, but her toxic dosing was corrected. The lesser of her ABW and IBW was her ABW, which was 112 pounds. Therefore, the upper limit of her safe daily dose was 330 mg. It was recommended that she take no more than 200 mg/d for the next six months at which time repeat ancillary testing was recommended to determine if there was a signal for early retinopathy given her large cumulative dose.

Rheumatologic publications also contribute to confusion on dosing. In an April online article from the rheumatology website RheumNow.com, the author writes, "The known risk factors for the development of ocular deposition include duration of therapy, cumulative dose and renal function."[15] She doesn't mention the most important, and only modifiable, risk factor—daily dosing. She goes on to write, "The American Academy of Ophthalmology (AAO) [citing the 2011 guidelines] advises weight-based dosing of 6.5 mg/kg, with an upper limit of 400 mg/day. Exceptions are individuals of short stature and obese patients, for whom the AAO advises calculating dosage based on ideal body weight for height." This is not what the quoted reference states, however. Instead, it states, "The prior recommendation [the 2002 guidelines] emphasized dosing by weight. However, most patients are routinely given 400 mg of HCQ daily. ...This dose is now considered acceptable, except for individuals of short stature, for whom the dose should be determined on the basis of ideal body weight to avoid overdosage."[16]

The author continues, "The sensitivity and specificity of these tests are not yet known for hydroxychloroquine-related retinal toxicity. There is a high rate of baseline abnormalities, in particular in those who are elderly or have comorbid disease, which make the changes challenging to interpret. Another issue is that systemic lupus erythematosus itself associates with the presence of retinal abnormalities, adding further to the complexity of deciphering these tests." These are incorrect statements. The relative sensitivity and specificity of the tests are known (mfERG is most sensitive, 10-2 VF next, and SD-OCT least; SD-OCT is most specific, 10-2 VF is next, and mfERG is least).[17] The rate of baseline abnormalities is high for 10-2 VF testing, but not for SD-OCT or mfERG. SLE rarely affects any of the tests.

Finally, the author advocates dosing based on 6.5 mg/kg/actual body weight. This is a dangerous recommendation for the short, obese patient as exemplified in Case Report 1.

In a rheumatologic review of HR the authors wrote, "A French study showed that whole-blood HC concentration >1,000 ng/ml reduced risk of lupus flares. Measurement of HC blood levels may suggest that some patients require >6.5 mg/kg/day to achieve the recommended level. These patients should not be at increased risk of toxicity, providing levels are monitored, but it may be important to monitor cumulative dose as well when assessing risk of ocular toxicity."[18] The statement erroneously suggests that there is a known relationship between HC blood levels and HR, but this is not the case.

If prescribing internists and screening ophthalmologists put a clearer understanding of correct daily dosing into practice, the prevalence of HR would fall. In most cases, the condition is iatrogenic and can be avoided. Daily dosing is the only modifiable risk factor and deserves the greatest attention in screening visits, especially in the first five years of use of the drug, before the irreversible, cumulative load has built up and raises the retinopathy risk. The recommendation that low-risk cases have screening omitted for five years after a baseline examination has been widely rejected by those who do the screening, and is probably misguided given the high prevalence of toxic dosing. Detection and correction of

toxic dosing is of greatest value for the prevention of retinopathy in the early years of taking HC. The extremely rare cases that develop retinopathy despite safe dosing are more likely to be detected when a more sensitive and more specific ancillary test, for example, 10-2 VF and SD-OCT, are used together and when interpretation is competently done. REVIEW

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Review of Ophthalmology®

Periocular Peels And Potions

A look at the chemical agents patients can use topically in an effort to fight the effects of aging.

Teri Kleinberg, MD, Worcester, Mass.

A search for "crow's feet cream" on Amazon.com revealed more than 3,000 products, one of which costs nearly $1,000 for less than 1 oz. of cream and claims to be an "effective anti-wrinkle serum which acts on all types of facial lines, thanks to an exclusive combination of four targeted active ingredients ... expression lines are immediately smoothed and relaxed, dehydration lines are erased and plumped, and deep wrinkles are plumped from the inside with spectacular results after four weeks of use." When facing this avalanche of marketing lingo, unless you've had cosmetics plastics training or have spent time sifting through the literature, it's hard to know which claims are based on good data and which are just hype. The following article, the second in a two-part series, reveals chemical agents that have strong evidence to support their use in periocular anti-aging.

Alpha Hydroxy Acids

Chemicals that can be used for peels can be used at much lower concentration with daily application. As discussed in the first part of this series, "Chemical Peels Demystified," in the October issue of *Review*, alpha hydroxy acids *(See Table 1)*, including glycolic acid derived from sugarcane, cause superficial exfoliation by keratinocyte discohesion at the level of the stratum granulosum in the epidermis with resulting improvement in skin texture.[1] AHAs can be combined with retinoids to accelerate skin turnover from 28 days to 10 to 12 days in preparation for subsequent chemical peels.[1] Glycolic acid products can be used as daily skin-care products at concentrations as low as 5 to 15%.

Table 1. Common Alpha Hydroxy Acid Products

Brand Name	Product (concentration)
Obagi	Nu-Derm Exfoderm Forte (6% glycolic acid, 4% lactic acid)
NeoStrata	Foaming Glycolic Wash (18% glycolic acid) Daily Antioxidant Peel (10% citric acid)
SkinCeuticals	Retexturing Activator (20% glycolic acid)
SkinMedica	Glypro products (proprietary % glycolic acid)

Vitamin C

Vitamin C, or ascorbic acid, is a well-studied antioxidant for the treatment of photodamaged skin. The effects are thought to occur via transcriptional up-regulation of collagen synthesis, scavenging of reactive oxygen species, and inhibition of elastin biosynthesis and tyrosinase to reduce elastin accumulation and pigment synthesis, respectively.[2,3] Unlike most plants and animals, humans cannot synthesize ascorbic acid; it must be obtained via diet or topical application.[3] However, oral ingestion of ascorbic acid doesn't provide adequate replenishment of skin ascorbic acid stores. Due to difficulty in stabilization, a topically absorbed version of L-ascorbic acid has only recently been available.[4] Topical L-ascorbic acid can be used to alleviate skin inflammation from ultraviolet light exposure, as well as erythema from laser resurfacing procedures.[4] A porcine study demonstrated that best skin absorption of L-ascorbic acid occurs at a pH less than 3.5 and a con-

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Table 2. Commercially Available L-Ascorbic Acid Preparations

Brand	Product Name	% L-Ascorbic Acid	pH
SkinCeuticals	C+AHA	15	Unknown
SkinCeuticals	AOX+ Eye Gel	5	Unknown
SkinCeuticals	C E Ferulic	15	Unknown
SkinCeuticals	AOX+	10, 15 or 20	Unknown
Cellex-C	High Potency Serum	10	2.2
Cellex-C	Sensitive Skin Serum	Unknown	3.3
Cellex-C	Eye Contour Gel	Unknown	Unknown
Cellex-C	Advanced C Serum	17.5	Unknown
Obagi	Professional-C	10, 15 or 20	Unknown

Table 3. Forms of Retinoids Available Topically

Form	Brand Names (concentration)
Retinol	Multiple brands including: Jan Marini Skin Research Age Intervention Enlighten, Luminate, Luminate Eye, Retinol Plus (all proprietary percentages) Obagi (0.5%, 1%) SkinMedical Lytera (proprietary percentage), Retinol Complex (0.25%, 0.5%, 1%) SkinCeuticals (0.5%, 1%)
Retinaldehyde (Retinal)	Multiple brands including: Avene RetrinAL Eyes (proprietary percentage), Retrinal Plus (0.05%, 0.1%) Glytone Enhance (0.05%)
Tretinoin	Atralin (0.05%), Avita (0.025%), Retin-A (0.025%, 0.05%, 0.1%), Retin-A Micro (0.04%, 0.1%), Renova (0.02%)
Isotretinoin	Isotrexin (0.05%)
Tazarotene	Avage (0.1%), Tazorac (0.05%, 0.1%)
Adapalene	Differin (0.1%)

centration of 20%, with minimal absorption of L-ascorbic acid derivatives such as magnesium ascorbyl phosphate, ascorbyl-6-palmitate and dehydroascorbic acid. Higher percentages of L-ascorbic acid failed to increase absorption.[5] The mean time to clinical improvement of skin texture is one month of daily application, and the mean time to improvement of coarse rhytids, telangiectasias, pigmentation, keratoses, sallowness and histological collagen deposition is three months.[4,6]

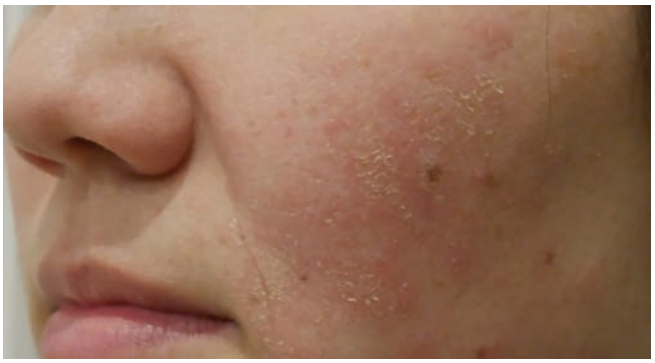
Retinoids

Retinoids are a family of vitamin A-related compounds that have been used topically and orally since the 1940s for a multitude of skin conditions, primarily acne.[7] Their ability to rejuvenate photoaged skin was popularized in the 1980s.[7] They are thought to reduce wrinkles by increasing type I procollagen expression and inhibiting dermal collagen degradation in the upper papillary dermis.[7,8] Skin texture is improved by increasing epidermal proliferation and differentiation, compacting stratum corneum, thickening of the granular layer, and increasing epidermal and dermal glycosaminoglycan deposition.[7,8] There is evidence that pretreatment with a retinoid for at least two weeks prior to chemical peels can reduce post-peel inflammation, improve peel uniformity and accelerate re-epithelialization.[7] Topically applied retinol (vitamin A, all-trans-retinol) is converted into retinaldehyde and subsequently into the active metabolite retinoic acid (tretinoin) by dehydrogenases in human keratinocytes.[9] Active stereoisomers 9-cis-retinoic acid (alitretinoin) and 13-cis-retinoic acid (isotretinoin) as well as adapalene, tazarotene and seletinoid G are applied in their active form.[7]

Tretinoin and tazarotene are approved for photodamage treatment. The typical protocol is 0.05% tretinoin cream applied nightly, with improvement in epidermal thickness and fine wrinkles at three months (based on Level II Evidence, and well-designed case-controlled, cohort or non-randomized trials) and improvements in fine and coarse wrinkling, sallowness, dyschromias, roughness and laxity at six months (based on Level I Evidence and evidence from at least one randomized, controlled trial).[7]

Optimized dosing consists of balancing efficacy and side effects. The dose-dependent retinoid reaction that usually occurs early in the treatment course consists of erythema, scaling, xerosis and pruritis.[7] The most important predictive feature of those likely to suffer the retinoid reaction is sensitive skin, such as Fitzpatrick type 1; historical intolerance of other topical agents; those with a tendency for skin flushing, exposure to large amounts of cosmetics; or skin with other conditions such as eczema, rosacea or seborrheic dermatitis.[7] Although the retinoid reaction subsides, it's seen in the majority of patients using 0.05% tretinoin and in approximately 90 percent of patients using 0.1% tretinoin.[7] Long-term use of tretinoin (over 11 months) has shown no difference in outcomes between higher (0.05%) and lower (0.01% or 0.02%) concentrations.[7,10]

Given the topical instability of reti-



Classic retinoid reaction with erythema, scaling and xerosis from use of topical retinol daily for a week. This was treated by stopping the cream and starting 1% hydrocortisone until symptoms resolved.

nol and the side-effect profile of tretinoin, there are a slew of retinol esters and derivatives. Of these, retinaldehyde (0.05% to 0.1%) may have comparable performance to tretinoin (0.5%) with more limited side effects.[7,8] There is no evidence at this point to support the use of other retinoids, including retinyl-palmitate, retinyl-propionate and retinyl-acetate.[7]

Photosensitivity is a known side effect of topical retinoid therapy, so avoidance of excessive sun exposure and daily sunscreen use are mandatory when using retinoids. Make sure to accompany these measures with good moisturizers such as hyaluronic acid or ceramides to limit the scaling and flaking seen with the retinoid reaction. Although there have been no systemic side effects or reported teratogenicity in over three decades of topical use, pregnant and lactating females should be advised to avoid use due to lack of safety data.[7,8] REVIEW

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Accommodation For the Aging Eye

Mark B. Abelson, MD, CM, FRCSC, FARVO, David A. Hollander, MD, MBA, and Connie Slocum, PhD
Andover, Mass.

Like death and taxes, presbyopia is one of life's certainties, an inevitable companion to the aging process: Sometime between your 35th and 45th birthday, you wake up to the reality that your arms are no longer long enough to hold the medicine bottle at a proper reading distance. While not pathological, this condition requires some form of treatment to correct the failing near vision. The change in visual function patients experience at midlife is particularly impactful in today's age of electronic devices used both at home and in the workplace. And while the process of accommodation may be the single most studied physiological process in the visual system, we still do not fully understand its intricacies. This month, we survey some of the latest research and consider the growing interest in the development of alternative therapies for this harbinger of advancing age.

Presbyopia by the Numbers

Presbyopia's incidence and impact are rising in conjunction with the aging of the population, both in the United States and around the world. Now, as the baby boomers transition into their 60s, our aging population continues to expand: By 2030, about one in five Americans will be older than 65. Globally, data collected from 228 countries in 2005 estimated that presbyopia affected more than 1 billion people. By 2050, this number is projected to increase to almost 1.8 billion.[1]

Although the incidence rates of presbyopia are very high, public awareness of this condition, its origins and what can be done to correct it are surprisingly low. A 1996 study reported that more than half of patients queried did not know the meaning of the word,[2] while a more recent survey found that more than eight in 10 American consumers couldn't provide a definition for presbyopia; of those that could, more than six in 10 mistakenly believed that it could lead to blindness.[3]

Typically, a patient learns of presbyopia at an age when more frequent ocular health examinations are recommended because of the increased risk of age-related ocular diseases such as glaucoma, cataracts and macular degeneration.[4] This timing can have the effect of downplaying the significance and impact of the condition. Once diagnosed, many patients resist seeking treatment due to the stigma associated with aging. Most grudgingly accept the inevitability of reading glasses, but a growing contingent want more information and are interested in exploring treatment options for presbyopia that include contact lenses, LASIK and other approaches.[5] A number of surgical options are also available, but results can be variable, and some procedures are contraindicated in certain patient populations. The limitations of current treatment options, together with the growing numbers of affected individuals, have driven increased scientific and clinical interest in presbyopia in recent years.

The Physiology of Presbyopia

The process of accommodation, or focusing on near objects, occurs by a concerted action of the ciliary muscle on the zonule fibers which hold the lens in place. The ciliary muscle is a ring of smooth muscle that, upon contraction, relaxes the tension on the zonular fibers and allows the lens to become more spherical. This increase in axial thickness results in an increase in the dioptric power, facilitating accommodation for improved near vision. With ciliary muscle relaxation, the tension on the zonules increases, resulting in lens flattening and a reduction in dioptric power. All of these structures are modified by the aging process, but it is the reduction in lens flexibility that's most associated with loss of

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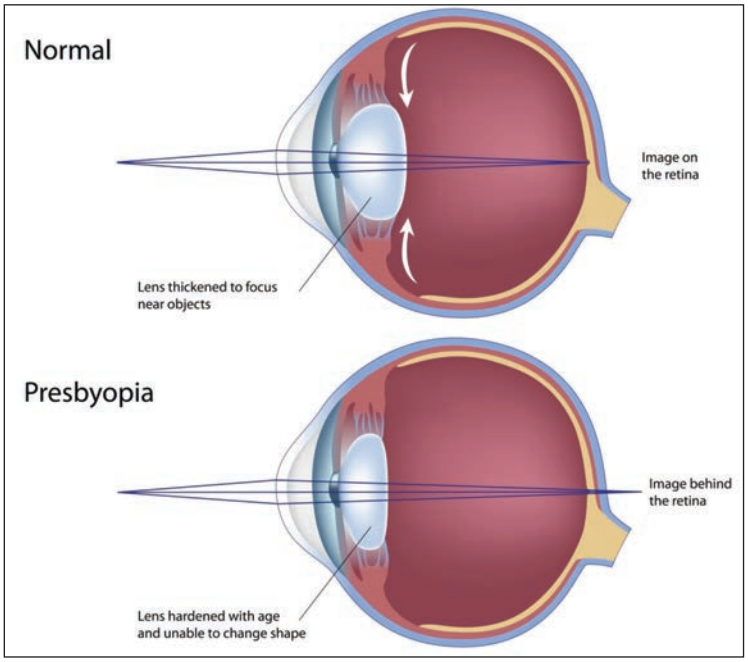
accommodation.[6-8] Decreased lens flexibility limits the lens rounding and thickening needed for near focus. Models of the process suggest that as the lens becomes less flexible with age, ciliary muscles apply greater tension to zonules, causing ligament fatigue. Muscular atrophy is also a contributing factor.[9] These paired changes in the physical properties of the focal apparatus collectively result in the presbyopic condition. The end effect is loss of near focus, accompanied by blurred vision, eye strain and headaches in many individuals. For some, these secondary effects are exacerbated after reading or computer use.[6]



A look at our current understanding of presbyopia's physiology.

Much of what we know about accommodation comes from research on non-human primates. Studies in the rhesus monkey have shown that ciliary body displacement plays a key role in the accommodation process. The force of contraction moves the muscle in an anterior direction, and this displacement is attenuated in aging animals. One study confirmed the roles of both muscle atrophy and decline in ligament elasticity in the development of presbyopia,[9] and another recently showed that similar movement occurs in the human eye.[10] Hopefully, these findings can provide clues to pharmacological strategies to reverse or reduce accommodative loss.

The use of contact lenses to address visual changes associated with presbyopia has been an area of great promise but only modest success. The limitation to this approach may be that the great diversity of visual tasking and visual activity among patients has led to limited success for individual approaches including bifocal or progressive lenses, monovision lenses (one eye for distance, one eye for near vision), and reduced-aperture (pinhole) lenses. Development of predictive algorithms may be the key to making progress with this treatment modality.[11]

Inlays and Surgeries

In recent years, surgery has been the new frontier for presbyopia therapy, by either direct intraocular replacement of the lens or by modification of extraocular structures such as the cornea or sclera.[12] Modification involves the use of corneal inlays, devices that are surgically placed within the corneal stroma of the non-dominant eye to change the optical properties of the cornea.[12] Inlays serve as an attractive option for correction of presbyopia, since they are an additive, removable technology. Unlike laser refractive surgery, which ablates corneal tissue, the inlay can easily be removed if the patient is unable to adapt to this type of vision correction. The development of corneal inlays has become possible through major advancements made in biomaterials as well as surgical devices such as the femtosecond laser.[5]

Femtosecond laser technology has numerous advantages over traditional surgical techniques and can be applied to a variety of different ophthalmic procedures. Still, this is a relatively new technology and is limited by training and cost issues.[13] Examples of corneal inlays employing femtosecond laser technology include the KAMRA inlay (AcuFocus), which is an opaque polymer ring that employs the pinhole concept to expand the depth of focus and allow for improvement in near visual acuity.[5] In one study of 223 presbyopes who first underwent LASIK to correct their pre-existing refractive error, subsequent KAMRA implantation increased their average uncorrected near vision from J8 to J2.[14] Another recently approved inlay, the Raindrop Near Vision Inlay (ReVision Optics), is a clear hydrogel implant that increases the anterior corneal curvature to add optical power, with a refractive index approximating that of the cornea.[12] Other devices are in development, such as the Presbia Flexivue Microlens (PresbiBio).[15]

Although the safety of corneal inlays is well-established, the use of some, such as the KAMRA inlay, has been associated with the development of corneal changes.[5] The improvement of uncorrected near vision may be accompanied by decreased distance vision, increased glare or halos, reduced contrast sensitivity, and the development of dry-eye symptoms secondary to the creation of the corneal flap/

channel for inlay insertion.[12] Despite these issues the frequency of explants has been reasonably low.

Another approach to presbyopia is excimer laser surgery, which remodels the corneal curvature to improve uncorrected vision and reduce dependence on glasses or contacts. Approved in 2001, one of the most popular techniques, LASIK, has seen tremendous improvements in technology, which now includes correction of presbyopia, or "presbyLASIK." While conventional monovision LASIK corrects the dominant eye for distance and the non-dominant eye for near, presbyLASIK involves a number of different approaches.[12] Nevertheless, there is no "one size fits all" for presbyopia; each surgical strategy presents its own unique benefits and limitations that involve some degree of compromise between distant and near visual acuities.[16] For example, crystalline lens removal and replacement with an IOL may not be preferable in a young patient with presbyopia without refractive error.[16] Similarly, treatment of the crystalline lens may not be a suitable choice for a patient with early cataract. Thus, there are a number of considerations that have limited the widespread acceptance of surgical correction, keeping the correction of presbyopia a significant challenge for refractive surgeons.

Pharmacotherapy

Pharmacotherapy for presbyopia is on the rise, as many patients seek freedom from spectacle use without the risk and cost of surgical approaches. For some time, there has been interest in a topical drop that can provide a safe, albeit transient, improvement in accommodation, even if it reduces distance vision. In a recent study, use of miotic parasympathomimetic drugs such as carbachol, alone or in combination with alpha-adrenergic agonists such as brimonidine, was shown to provide acceptable reading vision for presbyopes.[17] Many of these drugs have the benefit of a well-established safety profile due to a long history of usage in diagnostics. Another study, evaluating a cocktail of topical agents that included pilocarpine and phenylephrine, showed an improvement in near vision without a significant effect on distance vision.[18]

Other research efforts have reached the clinic for study: The California-based startup Presbyopia Therapies is evaluating the efficacy and safety of their proprietary drop PRX-100 in presbyopes.[19] PRX-100 has been formulated to induce miosis without stimulation of accommodation, and has been shown to be safe and effective in increasing near vision for up to eight hours. Presbyopia Therapies hopes that PRX-100 will supplement current presbyopia treatments by providing short-term, self-administered correction for daytime near vision.

An interesting alternative to pharmacological modulation of the ciliary apparatus is being pursued by another emerging biotech firm, Encore Vision. Their approach is aimed at directly increasing flexibility of the aging lens. A key aspect of lens rigidity involves formation of disulfide crosslinks between lens protein fibers, and studies have shown a strong positive correlation between lens age and the number of disulfide bonds in lenses.[20] In preclinical studies, researchers have shown that treatment of isolated lenses with a lipoic-acid reducing agent can reduce disulfide bonds and increase elasticity.[21] This approach holds real promise, especially if the prevailing wisdom that lens inflexibility is the most significant contributing factor in the development of presbyopia proves to be true.

The aging population represents a impending explosion of unmet medical need. Though sight-threatening conditions such as AMD often dominate the conversation of age-related diseases, it's important to remember that conditions such as presbyopia impact the quality of life of many more individuals. While surgical and device-based treatments for this condition hold promise, it's also exciting to see the innovations provided by pharmaceutical approaches. REVIEW

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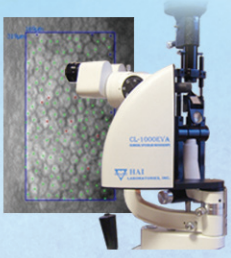

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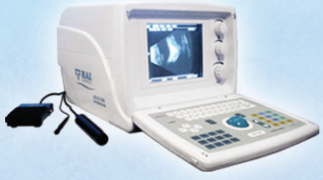

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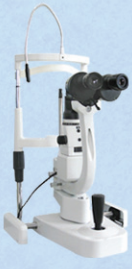

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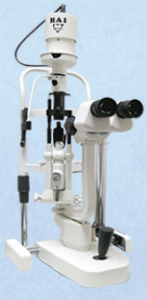

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Chronic Prostaglandins Associated with MGD

In early July, researchers from the department of ophthalmology at Hacettepe University Faculty of Medicine, Ankara, Turkey, published findings from a study looking at the association of long-term prostaglandin analog use with meibomian gland dysfunction in medically treated glaucoma patients. Researchers determined that long-term administration of PGA is associated with an obstructive type of MGD.

In their prospective, cross-sectional study (conducted in an academic setting), researchers looked at 70 eyes of 70 patients with a medical diagnosis of glaucoma that were on long-term (>12 months) topical hypotensive medications. Patients were classified based on whether they were on PGA or non-PGA classes of medications. Forty-five age-matched, healthy control subjects who were not on any topical medications were also included.

In total, 25 patients (35.7 percent) were on PGA monotherapy, 21 (30 percent) were treated with fixed or unfixed PGA combination regimens and 24 (34.3 percent) were on non-PGA medications. MGD prevalence was higher in patients treated with PGA monotherapy (92 percent) compared with those receiving non-PGA therapy (58.6 percent, $p<0.02$). The obstructive type of MGD was detected in the majority of patients treated with PGAs (95.7 percent). Grade two and three MGD was noted in 80.5 percent of patients using PGAs. Patients on PGAs had worse ocular surface disease index scores and ocular surface test results than those of control subjects ($p<0.001$).

J Glaucoma 2016;25:770-774

Mehmet M, Enes, U, Sibel K, Jale K, Murat I.

Long-term Outcomes of DMEK

In this retrospective, consecutive case series, researchers sought to evaluate the long-term clinical outcomes (up to five years) after Descemet's membrane endothelial keratoplasty. They found that DMEK not only provides fast visual rehabilitation but maintains its clinical outcome over a five-year follow-up period.

The researchers reviewed 310 DMEK operations for endothelial decompensation. Ninety-seven eyes of 84 patients met the inclusion criterion of a minimum three-year follow-up. Retrospective evaluation of clinical examinations occurred at one and three months and annually up to five years after DMEK.

Mean follow-up was 53 ±13 months. Corrected distance visual acuity improved from 0.62 ±0.42 logMAR before DMEK to 0.13 ±0.12 logMAR ($p<0.001$) postop. Fifty-seven percent of eyes without ocular comorbidities reached ≥20/25 at five years after DMEK. Endothelial cell density was stable after the initial post-surgical decrease, from 2,602 ±243 cells/mm^2 before DMEK to 1,460 ±179 cells/mm^2 at five years. Central corneal thickness decreased from 644 ±67 µm before DMEK to 557 ±49 µm at five years, with a minimum of 530 ±54 µm at three months. Cumulative probability of five-year graft survival was 95 percent.

Visual acuity and endothelial cell loss remained stable between three months and five years after DMEK.

Notwithstanding the limitations of the study's retrospective nature and the relatively high proportion of patients lost to long-term follow-up, the investigators say these data support the implication that for patients meeting the characteristics of those in this study, the three- to five-year clinical results of DMEK are at least comparable to those previously reported for DSEK/DSAEK. The researchers add that these findings further strengthen DMEK as a first choice in the treatment of corneal endothelial dysfunction, and that further studies may demonstrate better long-term results.

J Ophthalmol 2016;69:218-226

Andreas S, Theofilos T, Friedrich K, Julia W.

Anterior Uveitis' Effect on the Endothelium

In a cross-sectional, observational study, researchers investigated a possible effect of intraocular inflammation on corneal endothelium by measuring corneal endothelial cell density and morphologic variables in eyes with anterior uveitis. They also looked at factors that may influence these findings. They found that the observed relationships suggest that anterior segment inflammation adversely affects the corneal endothelium, but note that longitudinal studies are warranted to determine whether longstanding anterior uveitis increases the risk of endothelial dysfunction, especially in the setting of intraocular surgery.

Researchers looked at 52 patients (84 eyes) with histories of unilateral or bilateral anterior segment inflammation (anterior, intermediate or panuveitis).

They found that central ECD was lower among eyes that had undergone cataract or glaucoma surgery or both (n=28, p=0.0004). After exclusion of eyes with surgery, variables for eyes with uveitis (n=56) were compared with two historical populations of normal, age-matched controls and with contralateral eyes in individuals with unilateral uveitis. Central ECD was lower in eyes with uveitis than in control eyes for all age groups ($p \leq 0.01$ for four of six 10-year age intervals, compared with the primary control group).

Among patients with unilateral uveitis who had not undergone surgery in either eye (n=12), central ECD was lower in eyes with uveitis (2,324 cells/mm^2) than in contralateral eyes (2,812.5 cells/mm^2), and percentage of hexagonality was lower in eyes with uveitis (54 percent) than in contralateral eyes (58.8 percent). There was no significant difference in central corneal thickness between eyes with and without uveitis (p=0.27). No eyes had clinically apparent central corneal edema.

Relationships remained unchanged after exclusion of eyes with herpetic anterior uveitis, the researchers say. Host and disease-related characteristics were evaluated as risk factors for variations in outcome measures, and central ECD was correlated with the duration of active uveitis (r=–0.41; p<0.0001), maximum intraocular pressure during the course of disease (r=–0.40, p=0.0002), and maximum laser flare photometry value (r=–0.26, p=0.020).

Ophthalmology 2016;123:1637-1645

Abdullah A, Gary H, Fei Y, Mathew M, JoAnn G, Anthony A.

Keeler's Z Series Slit Lamp

With a focus on doctor preferences and practice needs, Keeler recently introduced its new Z Series slit lamp, which the company says is highly customizable to user preference. The new slit lamp is equipped with either converging or parallel oculars and is available with either a three-step rotating drum (10x to 25x magnification) or a five-step rotating drum (6x to 40x magnification). It also includes two mounting options: a refraction arm table mount or a rolling table mount configuration.

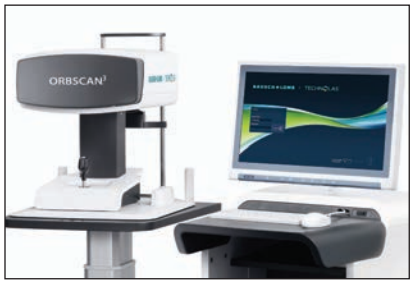
The slit lamp is the first available with a 1 mm square aperture and 14-mm variable slit width. Keeler says that the customization available for the Z Series may appeal to doctors with specific or specialized clinical interests, such as intraocular inflammation. For instance, the preset apertures include 0.2, 2, 3, 5 and 9 mm, a 14-mm circle, and a 1-mm square specifically designed for assessing uveitis. It also includes space for additional preset apertures. The slit angle can be adjusted a full 360 degrees. The Z Series includes a shutter trigger on the joystick and camera exposure controls on its base.

For more information, call 1-800-523-5620 or visit keelerusa.com.

Alcon's NGENUITY 3D Visualization

In an effort to enhance the visualization of the posterior segment for vitreoretinal surgeons, Alcon recently launched its NGENUITY 3-D visualization system (a platform for digitally assisted vitreoretinal surgery).

The new visualization system allows surgeons to operate while looking at a high-definition, 3-D screen, instead of through an operating microscope. Because of the duration of vitrectomy surgeries (ranging anywhere from 30 minutes to three hours), Alcon says the microscope-free viewing design may improve the surgeon's experience and comfort during the procedure, adding that the system's high dynamic range camera creates an image with excellent resolution, depth, clarity and contrast. With this new view, the surgeon may now have access to depth perception not previously available on standard monitors.



Surgeons can also magnify the 3-D image while maintaining a wide field of view. The new system provides digital filters that allow surgeons to highlight ocular structures and tissue layers crucial in visualizing the back of the eye. This visualization also minimizes light exposure to the patient's eye, while still allowing surgeons to operate.

Alcon claims that the NGENUITY system is an excellent teaching and collaborative tool, since the system uses a wide-screen monitor that allows the operating team to see what the surgeon is seeing, in real time.

For more information on Alcon's NGENUITY 3D system, visit novartis.com.

Bausch + Lomb ORBSCAN³

For surgeons performing the latest refractive procedures, Bausch + Lomb has introduced a new anterior segment analyzer, the ORBSCAN³. The new device provides data regarding corneal biomechanics and stability by examining anterior and posterior astigmatism and optical pachymetry. Using these results, surgeons can make informed choices and identify appropriate candidates for their procedures. The ORBSCAN³ also allows surgeons to provide high-quality refractive care through its ability to assess the size, shape and extent of surface abnormalities.

The ORBSCAN³ features a touchscreen that's user-friendly, with new software which allows for the analysis of the elevation and curvature on both the anterior and posterior surfaces of the cornea. It is also able to mea-

This article has no commercial sponsorship.

sure full corneal pachymetry, white-to-white distance, anterior chamber depth and angle kappa. It accomplishes all of this through a contact-free analysis of the eye's anterior segment using slit scanning.

For more information on Bausch + Lomb's ORBSCAN[3], visit bausch.com.

Eschenbach's Visolux HD Magnifier

In September, with a focus on providing reading comfort to patients with vision loss, Eschenbach released Visolux Digital HD, a 7-in. hand-held video magnifier. The Visolux has magnification capabilities of 2x to 22x, including an HD camera and HDMI/USB connectivity, allowing it to connect to both computers and televisions.

At the higher magnification levels, its dynamic line-scrolling capability allows the user to scroll through the image selection without moving the device. The Visolux also includes 14 color contrast modes, three brightness settings and optional underlineline and blinds function, allowing users to underline or highlight text. Eschenbach says the device's fold-out stand creates a comfortable and effective reading level, and that the Visolux's orientation marks, found on the outside of the device, provide guidance for the HD camera's positioning.

For more information on the Visolux, visit eschenbach.com.

M&S Tech Clinical Trial Suite

In early October, M&S Technologies introduced its clinical trial suite, a customizable set of protocols designed for use in research and clinical trials. In conjunction with the M&S DataRight module, the CTS allows doctors and researchers to retrieve raw data and test results immediately. DataRight's encrypted data transfer also ensures the security of any clinical trial data, M&S says.

Coming equipped with a full range of hardware options, M&S says that the CTS can be fully customized to fit the specific trial's needs. Through visual acuity and contrast sensitivity protocols, CTS guides the user through eye charts step by stem and responds to user input.

The module exports the data and test results via an XML or CSV file. These files can then be reviewed for immediate analysis on-site or securely transferred to a reading center.

For more information, visit mstech-eyes.com.

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OPHTHALMOLOGY

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REVIEW of Ophthalmology

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OPHTHALMIC
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REVIEW® of Ophthalmology

A middle-aged woman presents with painless double vision and lid swelling that results in a referral to Wills' Ocular Oncology Service.

Lucas Bonafede, MD

Presentation

A 53-year-old Caucasian female presented to her retina specialist, with whom she had been following for a left choroidal nevus, with new complaints of painless diplopia. She had been having progressive symptoms for the past four months, and noted associated swelling of the left upper lid. *(Figure 1)*. The retina specialist pursued magnetic resonance imaging of the orbit, which revealed a large, well-circumscribed mass in the left superonasal orbit, compressing the globe and measuring 30 mm anteroposteriorly. The mass was low signal on T1 and demonstrated heterogenous signal on the T1 series with fat-suppresion and gadolinium enhancement. *(Figure 1)*. The T2 series revealed a slightly heterogeneous mass with crisp margins. The patient was referred to the Ocular Oncology Service at Wills Eye Hospital for further evaluation and management.

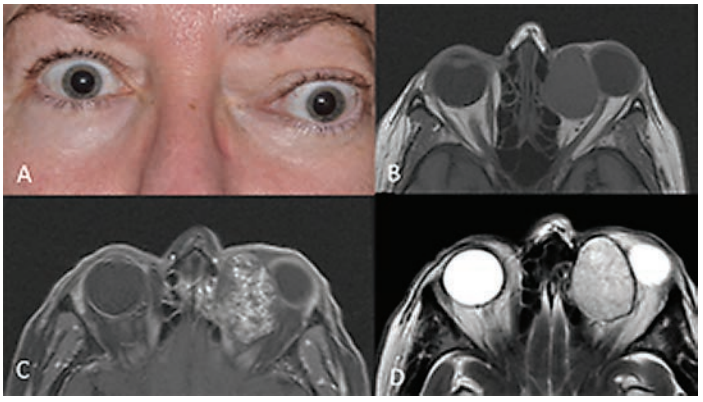

Figure 1. A 53-year-old woman was noted to have (A) left hypoglobus, exotropia and proptosis from an orbital mass superomedially. Magnetic resonance imaging revealed a well-circumscribed orbital mass compressing the globe with (B) low signal on axial T1 imaging, (C) heterogeneous signal on T1 with gadolinium enhancement and (D) slightly heterogeneous signal with crisp margins on T2 imaging.

Medical History

The patient had a past medical history of seasonal allergies for which she took loratadine as needed. She did not have any additional ocular history or chronic medications. There was no personal or family history of cancer. She had no history of tobacco smoking or excessive alcohol intake. The review of systems was unremarkable.

Examination

On ocular examination, her best corrected visual acuity was 20/20 in the right eye and 20/40 in the left. Intraocular pressure was 14 mmHg in both eyes. There was no afferent pupillary defect, and Ishihara color plates were full (8/8) OU. Hertel exophthalmometry demonstrated 5 mm of relative proptosis on the left.

An external exam revealed a downwardly displaced globe OS with a 3-cm, firm, palpable orbital mass underlying the medial portion of the left upper eyelid. Extraocular motility was full OD and reduced by 50 percent in elevation, adduction and depression OS.

Anterior segment slit lamp examination was normal OU. Funduscopic examination OD was only remarkable for a slightly tilted disc *(Figure 2)*. Funduscopic examination OS revealed prominent chorioretinal folds, a tilted disc, tortuous retinal vessels and a blunted foveal

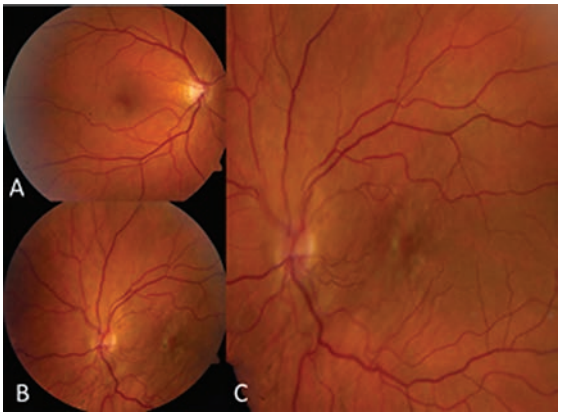

Figure 2. Fundus photography of the right eye (A) showing a tilted disc and otherwise normal findings. The left eye (B) revealed a tilted disc with prominent chorioretinal folds, tortuous retinal vessels, blunted foveal reflex and retinal pigment epithelial mottling.

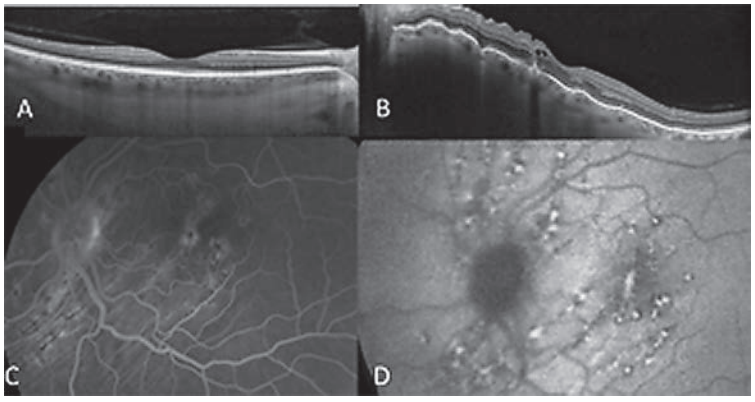

Figure 3. In this patient's case, optical coherence tomography of the right eye (A) showed a normal macula. The left eye (B) showed prominent chorioretinal folds concentrated in the papillomacular region, intraretinal cystoid edema and disruption of the outer retinal layers. Angiography of the left eye (C) at 7 minutes 23 seconds showed alternating bands of hyper- and hypofluorescence, and focal areas of deep staining. Fundus autofluorescence of the left eye (D) showed linear hyper- and hypo-autofluorescence corresponding to the choroidal folds.

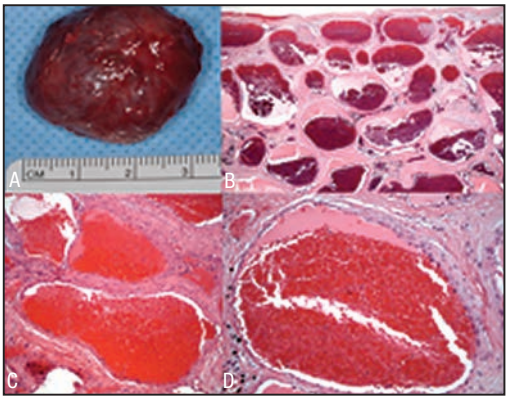

Figure 4. Image of gross specimen (A) showed a large purple tumor measuring 30 mm x 26 mm x 19 mm. Low-magnification microscopic image (B) showed large vascular channels lined with endothelial cells and containing thick septae and smooth muscle. High-magnification microscopic images (C and D) demonstrate the large vascular channels in the mass.

reflex *(Figure 2)*. The cup-to-disc ratio was 0.2 OU.

Optical coherence tomography OD was normal *(Figure 3)*. OCT OS revealed prominent chorioretinal folds concentrated in the papillomacular region. There was additional intraretinal cystoid edema and disruption of the outer retinal layers *(Figure 3)*.

Fluorescein angiography was normal OD, and displayed the clinically evident chorioretinal folds OS. Unfortunately, the early phase was not captured, but FA at 23 seconds showed alternating bands of hyper- and hypofluorescence corresponding to the obliquely oriented chorioretinal folds OS. FA at seven minutes showed a similar pattern for the folds with no obvious leakage *(Figure 3)*.

Fundus autofluorescence OS clearly demonstrated a similar configuration of alternating hyper- and hypo-autofluorescence representing shifting of the RPE along the folds, with liopofuscin showing a bright signal *(Figure 3)*.

What is your differential diagnosis? What further workup would you pursue?

Diagnosis, Workup and Treatment

The patient's presentation of proptosis and diplopia was in line with an orbital process, as confirmed with MRI. It is not uncommon for an intraconal mass to cause secondary globe compression resulting in the notable chorioretinal folds seen on fundoscopic assessment.

Therefore, the next step was to obtain tissue for a definitive diagnosis. Fortunately, the MRI was very helpful in making a presumptive diagnosis of cavernous hemangioma, given its rather characteristic radiological findings.

The patient underwent left orbitotomy with complete removal of a 30 mm x 26 mm x 19 mm circumscribed vascular mass *(Figure 4)*. Microscopic pathology demonstrated an encapsulated tumor composed of endothelium-lined vascular channels separated by septae, with areas of smooth muscle as well as chronic inflammation *(Figure 4)*. There was no evidence of malignancy. The features were consistent with a diagnosis of orbital cavernous hemangioma.

At three years' follow-up, the patient has done well with visual acuity of 20/20 OD and 20/25 OS. Extraocular muscle surgery allowed for resolution of myogenic diplopia. Funduscopically, the left eye revealed persistent RPE changes with resolution of the chorioretinal folds.

Discussion

Orbital cavernous hemangioma is a benign, slowly progressive tumor that typically manifests as a unilateral mass, most often located within the muscle cone.[1-4] In 2004, Jerry Shields, MD and co-workers conducted a survey of 1,264 patients who were referred to their clinic for evaluation of space-occupying lesions, and found that orbital cavernous hemangioma was the third most commonly diagnosed orbital mass.[1] Orbital cavernous hemangioma accounted for 6 percent of the total cases and 36 percent of vasculogenic lesions.[1]

Patients with orbital cavernous hemangiomas typically present with painless proptosis.[2-5] Other signs include globe compression with choroidal/chorioretinal folds, optic nerve compression with decreased vision, visual field changes, acquired hyperopia and diplopia.[1-5] The characteristic MRI findings of orbital cavernous hemangiomas include a well-defined mass that is hypointense on T1-weighted imaging and hyperintense on T2-weighted imaging.[3,6-7] Contrast enhancement shows initial heterogeneous enhancement, which progresses to homogeneous enhancement.[3,6-7] One study of 214 cases of orbital cavernous hemangiomas found that imaging using echography and computed tomography or MRI could correctly diagnose 93 percent of cases prior to surgery.[8]

The differential diagnosis for a round, well-circumscribed, solid mass includes cavernous hemangioma, hemangiopericytoma, schwannoma, solitary fibrous tumor, neurofibroma and melanoma.[2] Other conditions to consider in the differential diagnosis include lymphoma, fibrous histiocytoma, lymphangioma, metastasis and inflammatory lesions.[1-6]

Management of orbital cavernous hemangioma varies depending on the clinical presentation. Small, asymptomatic orbital cavernous hemangiomas can be monitored for progression.[2] Dr. Shields noted that only 52 percent of orbital cavernous hemangiomas necessitated surgical removal.[1] If surgical removal is indicated due to tumor size or symptoms, various techniques can be used depending on tumor location and size. The two main surgical approaches include the transconjunctival technique for tumors located anteriorly and the lateral orbitotomy for tumors in the mid and posterior orbit.[2] A transcranial approach and an endoscopic approach have been described for posterior tumors located near the orbital apex.[2]

Chorioretinal folds are relatively common in patients with orbital tumors. The patient in this case had unilateral oblique chorioretinal folds. These folds are seen as linear alterations at the level of the retina, retinal pigment epithelium and choroid, which represent undulations of the tissue, often causing shifting of the RPE.[9-12] Such folds generate a broad differential diagnosis, including hyperopia, hypotony, AMD, thyroid eye disease, scleritis, uveitis, orbital or choroidal tumor, postop changes, uveal effusion syndrome and optic nerve head swelling.[9-13] One study noted that the rate of diagnosis of idiopathic chorioretinal folds has been decreasing, likely due to more accurate diagnostic tests.[10]

The laterality of the chorioretinal folds can provide a diagnostic clue to help narrow the diagnosis. Two recent studies found that 42 to 44 percent of chorioretinal folds were bilateral and that the rest were unilateral.[11,13] In one study, researchers compared 54 cases of bilateral and unilateral chorioretinal folds and found that, in addition to idiopathic, the most common causes of bilateral chorioretinal folds were AMD and hypotony, while unilateral cases were most commonly due to scleritis, ocular tumors, retinal vascular occlusion and hypotony.[13] The characteristics and orientation of the chorioretinal folds can also provide useful information about the underlying cause. In this study, researchers described five unique orientations for chorioretinal folds: horizontal; oblique; vertical; radiating; and concentric.[13] The horizontal orientation was noted in 70 to 77 percent of folds.[13]

Another report described the biomechanical forces that lead to chorioretinal folds in different etiologies, including orbital tumors.[11] The author explained that intraconal orbital tumors lead to optic nerve displacement and cause the choroidal folds to originate from the nerve and radiate outwards.[13] On the other hand, he found that extraconal tumors will lead to compression of the sclera and choroid, causing the folds.[13] One notable finding was that an investigation of the pattern of the folds can help determine the tumor location.[13]

In conclusion, orbital cavernous hemangioma is a benign, slowly progressive vascular tumor that generally manifests in middle-aged patients. This mass can cause painless proptosis as well as compressive features such as chorioretinal folds accompanied by vision loss. Surgical removal of the tumor can resolve vision loss in some cases. REVIEW

The author would like to thank Carol Shields, MD, and Sara Lally, MD, of the Wills Eye Ocular Oncology Service, and Ralph Eagle, MD, of Wills' Ophthalmic Pathology Department for their assistance with this report.

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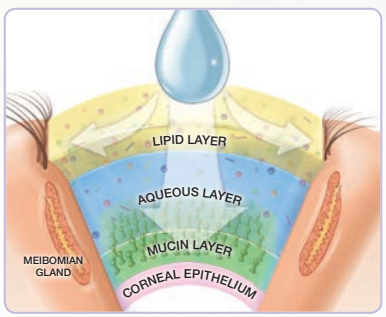

SYSTANE® BALANCE Lubricant Eye Drops forms a protective matrix that is designed to replenish the lipid layer for long-lasting relief from the symptoms associated with evaporative dry eye (MGD). This unique formulation is designed to work on all 3 layers of the tear film, specifically increasing LLT. This helps create a protective environment for the ocular surface.[2]

SYSTANE® Brand products are formulated for the temporary relief of burning and irritation due to dryness of the eye.

References: 1. Akpek EK, Smith RA. Overview of age-related ocular conditions. *Am J Manag Care.* 2013;19 (5 suppl):S67-S75. **2.** Korb DR, Blackie CA, Meadows DL, Christensen M, Tudor M. Evaluation of extended tear stability by two emulsion based artificial tears. Poster presented at: 6th International Conference on the Tear Film and Ocular Surface: Basic Science and Clinical Relevance; September 22-25, 2010; Florence, Italy.

Your recommendation counts.

Make sure your patients get the lasting symptom relief they need by offering them SYSTANE® BALANCE Lubricant Eye Drops.[2]

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