A RETROSPECTIVE, POPULATION-BASED, controlled study analyzing data from an unselected patient population undergoing cataract surgery found that neither the need for unplanned postoperative visits for complications nor the incidence of visually disturbing cystoid macular edema (CME) was significantly reduced by adding a topical NSAID to postoperative topical steroid treatment. The research, however, did highlight increased susceptibility to postoperative CME in eyes with pre-existing vitreoretinal conditions.

"Results of randomized controlled trials indicate that the occurrence of CME is reduced in eyes treated with an NSAID, either in combination with a steroid or alone," said Jan Gärdin, MD, resident, Department of Ophthalmology, Linköping University, Linköping, Sweden. Dr. Gärdin noted that it is sometimes difficult to relate study results to what is perceived as clinical reality. "In our investigator-initiated study including a large number of eyes from an unselected patient population, we were not able to demonstrate a clear benefit for the cohort that received combination therapy," he added.

A LARGE RETROSPECTIVE STUDY is supporting the efficacy and safety of dropless cataract surgery with transzonular injection of a corticosteroid and fluoroquinolone for preventing postoperative infection and inflammation. One surgeon notes that the efficacy with topical medications used to prevent infection and inflammation after cataract surgery is challenged by dependence on patient compliance and the need for the active ingredient to penetrate to the target sites.

INDICATIONS AND USAGE
XELPROS™ (latanoprost ophthalmic emulsion) 0.005% is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS
XELPROS is contraindicated in patients with a known hypersensitivity to latanoprost, or any other ingredients in this product.

Please see Important Safety Information on the back cover and brief summary of Full Prescribing Information inside.

Visit XelprosDelivered.com to learn more
Brief Summary of Prescribing Information for XELPROSTM
(latanoprost ophthalmic emulsion) 0.005%,
for topical ophthalmic use

XELPROSTM (latanoprost ophthalmic emulsion) 0.005%
See package insert for Full Prescribing Information.

INDICATIONS AND USAGE
XELPROS is indicated for the reduction of elevated
intraocular pressure (IOP) in patients with open-angle
glaucoma or ocular hypertension.

CONTRAINDICATIONS
Known hypersensitivity to latanoprost, or any other
ingredients in this product.

WARNINGS AND PRECAUTIONS
Pigmentation
XELPROS may cause changes to pigmented
tissues. The most frequently reported changes are
increased pigmentation of the iris, periorbital tissue
(eyelid), and eyelashes. Pigmentation is expected to
increase as long as XELPROS is administered. After
discontinuation of XELPROS, iris pigmentation is
likely to be permanent. Patients who receive treatment
should be informed of the possibility of increased
pigmentation. The long-term effects of increased
pigmentation are not known.

Eyelash Changes
XELPROS may gradually change eyelashes and vellus
hair in the treated eye, including increased length,
thickness, pigmentation, and number of lashes. The
changes are usually reversible upon discontinuation
of treatment.

Intraocular Inflammation
XELPROS should be used with caution in patients with
a history of intraocular inflammation (iritis/uveitis) and
should generally not be used in patients with active
intraocular inflammation.

Macular Edema
XELPROS should be used with caution in aphakic
patients, in pseudophakic patients with a torn
posterior lens capsule, or in patients with known risk
factors for macular edema.

Herpetic Keratitis
XELPROS should be used with caution in patients
with a history of herpetic keratitis. XELPROS should
be avoided in cases of active herpes simplex keratitis
because inflammation may be exacerbated.

Bacterial Keratitis
There have been reports of bacterial keratitis
associated with the use of multiple-dose containers
of topical ophthalmic products.

Use with Contact Lenses
Contact lenses should be removed prior to
administration of XELPROS and may be reinserted
15 minutes following administration.

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

Across multiple clinical trials conducted with
XELPROS, the most frequently reported ocular adverse
reactions were eye pain/stinging upon instillation and
ocular hyperemia, reported in 55% and 41% of patients
-treated with XELPROS, respectively. Other adverse
reactions reported (incidence ≥5%) were conjunctival
hyperemia, eye discharge, growth of eyelashes,
and eyelash thickening. Less than 1% of patients
discontinued therapy because of intolerance to the
eye pain/stinging or to the ocular hyperemia.
DRUG INTERACTIONS
Precipitation may occur if drugs containing thimerosal are used concomitantly with XELPROS. If such drugs are used, they should be administered at least 5 minutes apart.

USE IN SPECIFIC POPULATIONS
Pregnancy
Pregnancy Category C
Reproduction studies have been performed in rats and rabbits. In rabbits, an incidence of 4 of 16 dams had no viable fetuses at a dose that was approximately 80 times the maximum human dose, and the highest nonembryocidal dose in rabbits was approximately 15 times the maximum human dose. There are no adequate and well-controlled studies in pregnant women. XELPROS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether latanoprost or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when XELPROS 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 or effectiveness have been observed between elderly and younger patients.

PATIENT COUNSELING INFORMATION
Potential for Pigmentation
Advise patients about the potential for increased brown pigmentation of the iris, which may be permanent. Patients should also be informed about the possibility of eyelid skin darkening, which may be reversible after discontinuation of XELPROS.

Potential for Eyelash Changes
Inform patients of the possibility of eyelash and vellus hair changes in the treated eye during treatment with XELPROS. These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

Handling the Container
Instruct patients to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to 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 emulsions.

When to Seek Physician Advice
Advise patients that if they develop an intercurrent ocular condition (eg, trauma or infection) or have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician’s advice concerning the continued use of the multiple-dose container.

Use with Contact Lenses
Advise patients that contact lenses should be removed prior to administration of the emulsion. Lenses may be reinserted 15 minutes following administration of XELPROS.

Use with Other Ophthalmic Drugs
Advise patients that if more than one topical ophthalmic drug is being used, the drugs should be administered at least 5 minutes apart.

Rx Only
Distributed by: Sun Pharmaceutical Industries, Inc. Cranbury, NJ 08512
INDICATIONS AND USAGE
XELPROS™ (latanoprost ophthalmic emulsion) 0.005% is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS
XELPROS is contraindicated in patients with a known hypersensitivity to latanoprost, or any other ingredients in this product.

WARNINGS AND PRECAUTIONS

Pigmentation: XELPROS may cause changes to pigmented tissues. The most frequently reported changes are increased pigmentation of the iris, periorbital tissue (eyelid), and eyelashes. Pigmentation is expected to increase as long as XELPROS is administered. After discontinuation of XELPROS, iris pigmentation is likely to be permanent. Patients who receive treatment should be informed of the possibility of increased pigmentation. The long-term effects of increased pigmentation are not known.

Eyelash Changes: XELPROS may gradually change eyelashes and vellus hair in the treated eye, including increased length, thickness, pigmentation, and number of lashes. The changes are usually reversible upon discontinuation of treatment.

Intraocular Inflammation: XELPROS should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation.

Macular Edema: XELPROS should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Herpetic Keratitis: XELPROS should be used with caution in patients with a history of herpetic keratitis. XELPROS should be avoided in cases of active herpes simplex keratitis because inflammation may be exacerbated.

Bacterial Keratitis: There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products.

Use with Contact Lenses: Contact lenses should be removed prior to administration of XELPROS and may be reinserted 15 minutes following administration.

ADVERSE REACTIONS
The most common ocular adverse reactions in clinical trials (incidence ≥5%) for XELPROS were eye pain/stinging, ocular hyperemia, conjunctival hyperemia, eye discharge, growth of eyelashes, and eyelash thickening.

DRUG INTERACTIONS
Precipitation may occur if drugs containing thimerosal are used concomitantly with XELPROS. If such drugs are used, they should be administered at least 5 minutes apart.

Please see brief summary of Full Prescribing Information on the reverse side.

BAK=benzalkonium chloride.

A RETROSPECTIVE, POPULATION-BASED, controlled study analyzing data from an unselected patient population undergoing cataract surgery found that neither the need for unplanned postoperative visits for complications nor the incidence of visually disturbing cystoid macular edema (CME) was significantly reduced by adding a topical NSAID to postoperative topical steroid treatment. The research, however, did highlight increased susceptibility to postoperative CME in eyes with pre-existing vitreoretinal conditions.

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Dr. Gärdin noted that it is sometimes difficult to relate study results to what is perceived as clinical reality. “In our investigator-initiated study including a large number of eyes from an unselected patient population, we were not able to demonstrate a clear benefit for the cohort that received combination therapy,” he added.

Continues on page 51 : NSAID
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Lens cracking

Broken zonules

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SEPTEMBER 15, 2019 :: Ophthalmology Times

Chuck Hess, vice president and general manager of the U.S. Surgical Division at Bausch + Lomb, shares what’s in the company’s surgical pipeline at the 2019 meeting of the American Society of Retina Specialists in Chicago.

OphthalmologyTimes.com/ASRS2019ChuckHess

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Treat dry eye with recombinant human nerve growth factor is the focus of a phase IIb study, with about 300 patients at 11 U.S. sites expected to participate.

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There is plenty of “crossover” among ophthalmology and other medical specialties, giving physicians today more tools to ensure the best outcome for patients.

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3 New treatment reduces corneal oedema after cataract surgery
ophthalmologytimes.com/cornealoedema

4 Quieting the neuropathic components of ocular pain
ophthalmologytimes.com/neuropathicocularpain

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**Video**

Chuck Hess, vice president and general manager of the U.S. Surgical Division at Bausch + Lomb, shares what’s in the company’s surgical pipeline at the 2019 meeting of the American Society of Retina Specialists in Chicago.

OphthalmologyTimes.com/ASRS2019ChuckHess

**eNewsletter**

**INDICATION**

DEXTENZA is a corticosteroid indicated for the treatment of ocular inflammation and pain following ophthalmic surgery.

**IMPORTANT SAFETY INFORMATION**

**CONTRAINDICATIONS**

DEXTENZA is contraindicated in patients with active corneal, conjunctival or canalicular infections, including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella; mycobacterial infections; fungal diseases of the eye, and dacryocystitis.

**WARNINGS AND PRECAUTIONS**

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. Intraocular pressure should be monitored during treatment.

Corticosteroids may suppress the host response and thus increase the hazard for secondary ocular infections. In acute purulent conditions, steroids may mask infection and enhance existing infection.

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

Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal culture should be taken when appropriate.

Use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation.

**ADVERSE REACTIONS**

The most common ocular adverse reactions that occurred in patients treated with DEXTENZA were: anterior chamber inflammation including iritis and iridocyclitis (10%); intraocular pressure increased (6%); visual acuity reduced (2%); cystoid macular edema (1%); corneal edema (1%); eye pain (1%) and conjunctival hyperemia (1%).

The most common non-ocular adverse reaction that occurred in patients treated with DEXTENZA was headache (1%).

Please see brief summary of full Prescribing Information on adjacent page.
Money trail: The economics of drug development

Demand, potential for growth factors into decision-making process

By Conni Bergmann Koury

Drug development can be compared to a Las Vegas table game, with key players betting on whether a new pharmaceutical drug will come to the market after a lead compound has been identified through the research and discovery process. For Joseph Lawler, MD, PhD, founder and managing member of Austin, Texas-based JFL Capital Management LLC, it really is much of a gamble.

“My position gives me a blissfully unencumbered perspective when it comes to drug development, because if a drug works, I am happy to bet with it, and if it does not work, then I will bet against it,” he said. “As such, I have a definite perspective and perhaps even bias on how drugs should be developed.”

UNMET NEEDS

The first question for a drug developer is, where are the unmet needs? For example, a glaucoma drop that needed to be instilled only once per day would probably find a place in the market, Dr. Lawler said.

Similarly, an orifice for macular degeneration would be welcome. These are unmet needs. These less-prevalent diseases with less-efﬁcacious (or no) treatments are known as orphans, and they are not very common, Dr. Lawler explained. One might reasonably think drug-making entrepreneurs would steer clear of orphans because what exists is pretty good. On the other hand, there are non-orphans for things like glaucoma and cataracts. Although prevalent, manufacturers cannot charge very much for new treatments, because what exists is pretty good, he said. On the other hand, orphan drugs target diseases that are considered “rare” or “less prevalent.”

If a manufacturer is going to develop a drug to treat a prevalent disease like glaucoma, it also needs a big sales force and a uniquely large marketing budget in order to succeed. For orphan drugs, the patients are diagnosed at some point before the orphan drug is on the market.

‘There is extensive patient pressure on the FDA to approve these drugs.’

— Joseph Lawler, MD, PhD

DEXTENZA was studied in four randomized, vehicle-controlled studies (n = 567). The mean age of the population was 68 years (range 35 to 87 years), 59% were female, and 83% were white. Forty-seven percent had brown iris color and 30% had blue iris color. The most common ocular adverse reactions that occurred in patients treated with DEXTENZA were: anterior chamber inflammation including iritis and iridocyclitis (10%); intraocular pressure increased (6%); visual acuity reduced (2%); cystoid macular edema (1%); corneal edema (1%); eye pain (1%); and conjunctival hyperemia (1%).

The most common non-ocular adverse reaction that occurred in patients treated with DEXTENZA was headache (1%).

Topical ocular administration of 0.15% dexamethasone (0.75 mg/kg/day) on gestational days 10 to 13 produced embryofetal lethality and a high incidence of cleft palate in a mouse study. A daily dose of 0.75 mg/kg/day in the mouse is approximately 5 times the entire dose of dexamethasone in the DEXTENZA product, on a mg/m² basis. In a rabbit study, topical ocular administration of 0.1% dexamethasone through organogenesis produced embryofetal lethality, cleft palate and multiple visceral malformations (see Animal Data).

Animal Data

Topical ocular administration of 0.15% dexamethasone (0.75 mg/kg/day) on gestational days 10 to 13 produced embryofetal lethality and a high incidence of cleft palate in a mouse study. A daily dose of 0.75 mg/kg/day in the mouse is approximately 5 times the entire dose of dexamethasone in the DEXTENZA product, on a mg/m² basis. In a rabbit study, topical ocular administration of 0.1% dexamethasone through organogenesis (0.36 mg/day, on gestational day 6 followed by 0.24 mg/day on gestational days 7–18) produced intestinal anomalies, intestinal aplasia, gastrorrhaphis and hypoplastic kidneys. A daily dose of 0.24 mg/day is approximately 6 times the entire dose of dexamethasone in the DEXTENZA product, on a mg/m² basis.

2.6 Lactation

Systemically administered corticosteroids appear in human milk and could suppress growth and interfere with endogenous corticosteroid production; however the systemic concentration of dexamethasone following administration of DEXTENZA is low (see Clinical Pharmacology (12.2)). There is no information regarding the presence of DEXTENZA in human milk, the effects of the drug on the breastfed infant or the effects of the drug on milk production to inform risk of DEXTENZA to an infant during lactation. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for DEXTENZA and any potential adverse effects on the breastfed child from DEXTENZA.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

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

17 PATIENT COUNSELING INFORMATION

Advise patients to consult their surgeon if pain, redness, or itching develops.
and then they know they have the disease. It does not require marketing and a large sales force is not needed, Dr. Lawler explained.

**BENEFITS OF ORPHAN DEVELOPMENT**

The likelihood of FDA approval is far greater for orphan drugs than for non-orphan drugs. The technical definition of an orphan disease, for which an orphan drug would be developed, is a disease that affects fewer than 200,000 Americans, and the biological basis of the disease is pretty well understood. There are no fees for developing an orphan drug, once granted orphan drug status.

Often, drug manufacturers can use a surrogate endpoint to secure approval, making the regulatory standard less rigorous.

“There is extensive patient pressure on the FDA to approve these drugs,” Dr. Lawler said. “Consider the fact that Sarepta Therapeutics received approval for a drug called Eteplirsen, to treat Duchenne muscular dystrophy. It was a contentious approval. In fact, two senior FDA reviewers resigned because they did not think the drug worked.”

A non-orphan drug can be marketed exclusively as long as the patents last. With an orphan drug, there is guaranteed ironclad exclusivity for seven years, because the FDA is precluded from approving a generic competitor for that period of time. It is also difficult for payers to limit price. High-priced patient numbers can generate significant revenue. These are very profitable businesses once their drugs get approved. Of course, the medications still have to work.

**IMPORT?**

How do we solve the drug pricing crunch in America? Republicans and Democrats do not agree on much, but they generally agree that drug pricing is a mess.

Dr. Lawler noted that three things must happen to ignite change. The first two require congressional action.

First, is permit drug importation.

In many cases, these drugs are getting made in the very same factory—the only difference is the ZIP Code they are shipped to and the price—which can vary by 50 times. The industry will respond predictably, curtailing shipments to countries that import back to the United States, to limit their supply, effectively blocking importation, he explained.

Second, insist upon most favored nation status for drug because it is the best of the PD-1 antibodies,” he concluded. “If it turns out that these agents behave more like commodities, well then let the competitive bidding begin.”

“In a couple of years, sales of these are likely to top $20 billion per year,” he said. “We do not know if any one of the antibodies is better than any of the others.”

The option, according to Dr. Lawler, is to do a big study in a big indication, like non-small cell lung cancer. “With this approach, American citizens cannot lose, because if it works and it shows that one antibody is best, then we will all know to put our patients on that drug because it is the best of the PD-1 antibodies,” he concluded. “If it turns out that these agents behave more like commodities, well then let the competitive bidding begin.”
Cultural equality
Informed consent a differentiator among countries

“ALL CULTURES ARE not equal” says a New York Times headline,¹ and certainly this is true when it comes to medicine.

A while ago, I was visiting another ophthalmologist in a country outside the United States. The topic of informed consent came up, and my colleague asked me what we American doctors do when a patient needs surgery.

I responded with the usual spiel: We explain the diagnosis, recommend the treatment, discuss the risks and alternatives (including the option of doing nothing), answer the patient’s questions, and then we do what they consent to in writing.

“Well, that is ridiculous,” said my host, shaking his head in disbelief. “Patients do not know enough to make good decisions or choose alternatives better than what a doctor recommends!”

A DIFFERENT VIEW
In his country, I learned, the doctor tells the patient what surgery he or she needs and the patient (knowing that the doctor is highly trained) will automatically agree.

“We do not waste time discussing alternatives,” he said.

In yet another country I visited, the doctor merely tells the patient when to come to have their operation performed. There is no requirement for anything resembling what we in the United States would recognize as informed consent, and nothing need be documented in writing.

“Patients know that we doctors will do the right thing for them” a friend in this country told me. “There is no need to spend time discussing details.”

In a third country, I observed yet another twist on the consent process. In this case, when a female patient needs surgery the doctor turns to her male husband/family member and a brief discussion occurs while the patient listens. The male companion gives consent.

“Probably, there is going to be an interesting discussion in the car on the way home,” I thought.

Finally (and I have not observed this directly but colleagues have told me about it) there is a culture in which healthcare decisions are made by a presumably highly respected and wise village elder. If the elder says it is appropriate, the inhabitants of his village go with that decision.

Because the actual patient might not even be present to hear this discussion between the doctor and the elder, and the elder might not even be a member of the patient’s family, I consider this twist to be the most unlike what I have considered to represent best practice when it comes to informed consent.

CONSTANT STRUGGLE
There is no doubt in my mind that considerable effort is expended on informed consent in my country in anticipation that an unhappy patient might hire a lawyer and assert that the consent was inadequate. I have seen where a lawyer tells the jury that the informed consent document, signed and initialed by the patient, was too short, and did not list a particular rare complication that may have occurred. I have also seen lawyers argue just the opposite, claiming that a consent form was purposely made too long and detailed and therefore was overwhelming to a patient.

For these plaintiffs attorneys, the consent forms are either too long or too short—never are they “just right.”

I actually liked the country where the public feels confident that doctors will always do the right thing for their patients.

All the doctor has to say is “your vision problems are caused by a cataract. It needs to come out. The surgery will be on Tuesday.”

And all the patient has to say is “Thank you, doctor. See you Tuesday.”

But I realize that in today’s American culture and legal system, this is not realistic.

REFERENCE
• https://www.nytimes.com/2005/08/11/opinion/all-cultures-are-not-equal.html

By Peter J. McDonnell, MD
director of the Wilmer Eye Institute,
Johns Hopkins University School of Medicine, Baltimore, and chief medical editor of Ophthalmology Times.

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600 N. Wolfe St. Baltimore, MD 21287-9278
Phone: 443/287-1511 Fax: 443/287-1514
E-mail: pmcdn1@jhmi.edu
XIIDRA MAY INTERRUPT THE CYCLE OF INFLAMMATION CENTRAL TO DRY EYE DISEASE¹,²

The exact mechanism of action of Xiidra in Dry Eye Disease is not known.¹

Xiidra blocks the interaction of ICAM-1 and LFA-1, which is a key mediator of the inflammation central to Dry Eye Disease. In vitro studies have shown that Xiidra may inhibit the recruitment of previously activated T cells, the activation of newly recruited T cells, and the release of pro-inflammatory cytokines.¹

Check out Xiidra-ECP.com

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

Important Safety Information
Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients.

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 adjacent page and Full Prescribing Information on Xiidra-ECP.com.

References:

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Postmarketing Experience

sine

tic, lacrimation, eye discharge, eye discomfort, eye pruritus and conjunctival hyperemia, eye irritation, headache, increased

administration

contraindicated in patients with known hypersensitivity to lifitraget or to any of the other ingredients in the formulation.

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 lifitraget ophthalmic solution, 1,401 patients received at least 1 dose of lifitraget (1287 of which received lifitraget 5%). The majority of patients (84%) had ≤3 months of treatment exposure. 170 patients were exposed to lifitraget 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.

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Xiidra. 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 drug exposure.

Rare cases of hypersensitivity, including anaphylactic reaction, bronchospasm, respiratory distress, pharyngeal edema, swollen tongue, and urticaria have been reported. Eye swelling and rash have been reported.

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 lifitraget to pregnant rats, from pre-mating through gestation day 17, did not produce teratogenicity at clinically relevant systemic exposures. Intravenous administration of lifitraget 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 lifitraget 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

Lifitraget 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 lifitraget in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to lifitraget 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 lifitraget. Mutagenesis: Lifitraget was not mutagenic in the in vitro Ames assay. Lifitraget was not clastogenic in the in vivo mouse micronucleus assay. In an in vitro chromosomal aberration assay using mammalian cells (Chinese hamster ovary cells), lifitraget was positive at the highest concentration tested, without metabolic activation. Impairment of fertility: Lifitraget 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 lifitraget ophthalmic solution, 5%) had no effect on fertility and reproductive performance in male and female treated rats.
Inspiration in the Golden State
Annual meeting returns to San Francisco with focus on instruction, symposia, practice management, continuing education

By Lynda Charters

San Francisco is the city of new beginnings and a leader in education and culture-changing movements that ultimately affect the country and the world. This year’s theme, *Inspire!,* beautifully reflects the challenge to ophthalmologists to continue to innovate envelope-pushing ideas and technologies with the goal of providing patients with the best vision possible.

The American Academy of Ophthalmology (AAO) will hold its annual meeting, Oct. 12 to 15, in the City by the Bay.

“The theme for this year’s meeting, *Inspire!,* serves as an invitation to all members and participants to rediscover what inspires them, network with other industry experts, and continue educating each other on the newest research, technology, clinical developments, etc. moving eye care forward,” said Maria M. Aaron, MD, secretary for the AAO’s annual meeting.

“Premium IOLs are used basically to provide spectacle independence and restore accommodation, and they are appealing for use in older children.”

Maria M. Aaron, MD

In line with that theme, *Inspire!* also anticipates the launch of the AAO’s Truhlsen-Marmor Museum of the Eye, set to open in San Francisco in early 2020. The free-to-the-public museum will celebrate...
the history of ophthalmology, educate the public on the importance of eye health, and inspire the next generation of eye physicians and surgeons.

To search the program, go to www.aao.org/programsearch

WHAT IS NEW
The AAO has announced several new additions to its lineup this year. They include:

1. COMPLIMENTARY MEETINGS ON DEMAND PRODUCTS AVAILABLE.
   To take advantage of all the annual meeting has to offer, “Meetings on Demand” is a collection of recorded programming and sessions. This makes it easy for participants to catch up on things they missed or refresh their knowledge after AAO 2019. Starting this year, members who are subscribed for any of the Subspecialty Day meetings will receive complimentary access to the All-Subspecialty Meetings on Demand package. For members who purchase the AAO 2019 Academy Plus course pass, the AAO 2019 Highlights Meetings on Demand package will be included for free. For more information, visit www.aao.org/annual-meeting/aao-on-demand

2. AMERICAN SOCIETY OF OPHTHALMIC REGISTERED NURSES (ASORN) MEETING INTEGRATION
   Starting this year, the ASORN annual meeting, which will run on Friday, Oct. 11 and Saturday Oct. 12, is fully integrated with the AAO’s annual meeting. In an effort to support professional collaboration, ASORN meeting participants will now have access to AAO educational assets, including access to the symposia and spotlight sessions, papers, e-posters, and videos.

AAO GOES DIGITAL.
For the first time in AAO history, all posters this year will be in digital form. Members will be able to participate in lively, interactive discussions on the latest e-posters being presented this year.

SUBSPECIALTY DAYS
The Subspecialty Day program, beginning one day before the main meeting, covers Friday, Oct. 11 and Saturday, Oct. 12, and is comprised of seven Subspecialty Day meetings during the two-day period. Ophthalmologists in each subspecialty will have a plethora of exceptional presentations from which to choose during the Subspecialty Day presentations. The programs for all subspecialties can be viewed online through Program Search at www.aao.org/annual-meeting/subspecialty-day. Readers can click the red “Filter” button at the top of the page then choose the “Topics” menu to refine the search results by subspecialty.

FRIDAY, OCTOBER 11
- Refractive Surgery Subspecialty Day 2019: As Far as the Eye Can See
- Retina Subspecialty Day 2019: I2-Inspire Innovation

SATURDAY, OCTOBER 12
- Cornea Subspecialty Day 2019: Keeping Disease at Bay
- Glaucoma Subspecialty Day 2019: Crossing the Golden Gate to Exceptional Glaucoma Care
- Neuro-Ophthalmology Subspecialty Day 2019: Diagnostic Errors and Challenges—Avoid the Traps!
- Oculofacial Plastic Surgery Subspecialty Day 2019: A Decade to Remember 2010–2019
- Pediatric Ophthalmology Subspecialty Day 2019: San Francisco Sound Meets Science
- Retina Subspecialty Day 2019: I2-Inspire Innovation

OPENING SESSION
The opening session and annual business meeting is held from 8:30 a.m. to 10 a.m. on Sunday, Oct. 13. A highlight of this session is the Jackson Memorial Lecture that this year will be presented by Emily Chew, MD, director, Division of Epidemiology and Clinical Applications and deputy clinical director, National Eye Institute, National Institutes of Health. The lecture, titled “Age-related Macular Degeneration: Nutrition, Genes and Deep Learning” will focus on her clinical and research interests in diabetic eye disease and age-related eye diseases.

Marilyn Miller, MD, will receive the Laureate Award during the opening session for her special interest in international ophthalmology and her dedication to preventing blindness and visual impairment in underserved regions in Africa, Asia, and Central and South America. She is professor of ophthalmology, Illinois Eye and Ear Infirmary, University of Illinois, Chicago.

Another highlight of the opening session is the 2019 Academy Awards that will recognize guests of honor and recipients of the Distinguished Service Award.
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INDICATION FOR USE. The iStent inject® Trabecular Micro-Bypass System Model G2-M-IS is indicated for use in conjunction with cataract surgery for the reduction of intraocular pressure (IOP) in adult patients with mild to moderate primary open-angle glaucoma. CONTRAINDICATIONS. The iStent inject is contraindicated in eyes with angle-closure glaucoma, traumatic, malignant, uveitic, or neovascular glaucoma, discernible congenital anomalies of the anterior chamber (AC) angle, retrobulbar tumor, thyroid eye disease, or Sturge-Weber Syndrome or any other type of condition that may cause elevated episcleral venous pressure. WARNINGS. Gonioscopy should be performed prior to surgery to exclude congenital anomalies of the angle, PAS, rubeosis, or conditions that would prohibit adequate visualization of the angle that could lead to improper placement of the stent and pose a hazard. MRI INFORMATION. The iStent inject is MR-Conditioned, i.e., the device is safe for use in a specified MR environment under specified conditions; please see Directions for Use (DFU) label for details. PRECAUTIONS. The surgeon should monitor the patient postoperatively for proper maintenance of IOP. The safety and effectiveness of the iStent inject have not been established as an alternative to the primary treatment of glaucoma with medications, in children, in eyes with significant prior trauma, abnormal anterior segment, chronic inflammation, prior glaucoma surgery (except SLT performed > 90 days preoperatively), glaucoma associated with vascular disorders, pseudoxenophic, pigmented or other secondary open-angle glaucomas, pseudophakic eyes, phakic eyes without contraindicated cataract surgery or with complicated cataract surgery, eyes with medicated IOP > 24 mmHg or unmedicated IOP < 21 mmHg or > 36 mmHg, or for implantation of more or less than two stents. ADVERSE EVENTS. Common postoperative adverse events reported in the randomized pivotal trial included stent obstruction (6.2%), intraocular inflammation (0.7% for iStent inject vs. 4.2% for cataract surgery only), secondary surgical intervention (0.4% vs. 1.0%) and BCVA loss ≥ 2 lines ≤ 3 months ≥ 36 months (2.8% vs. 4.2%). CAUTION. Federal law restricts this device to sale by or on the order of a physician. Please see DFU for a complete list of contraindications, warnings, precautions, and adverse events.


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NAMED LECTURES

In addition to the keynote address during the opening session, numerous distinguished lectures will be delivered during various symposia throughout the annual meeting.

“In addition to artificial intelligence and other leading technologies changing the field of ophthalmology to a look at how millennial physicians are disrupting the industry, this year’s meeting offers myriad timely and fascinating topics,” Dr. Aaron commented.

**SUNDAY, OCTOBER 13**

- 10:30 a.m.-12 p.m. Marshall M. Parks Lecture, “How Artificial Intelligence Will Affect the Future of ROP Care,” Michael F. Chiang, MD
- 12:45 p.m.-1:45 p.m. Michael F. Marmor Lecture in Ophthalmology and the Arts, “Blind Organists and the King of Instruments,” Bruce Lamott, PhD
- 2 p.m.-4 p.m. Arnall Patz Lecture, “The Evolving Pathophysiology and Treatment of Retinopathy of Prematurity,” Mary Elizabeth Hartnett, MD, FACS
- 3:45 p.m.-5:15 p.m. Ruedemann Lecture, “An I for an Eye Removal: Innovations in Enucleation,” Jeremiah Tao, MD

**MONDAY, OCTOBER 14**

- 8:15 a.m.-12:15 p.m. Charles D. Kelman Lecture, “Artificial Iris Implantation,” Kevin M. Miller, MD

**TUESDAY, OCTOBER 15**

- 8:30 a.m.-10 a.m. Parker Heath Lecture, “Precision Medicine, Health Economics and Practice Patterns,” Barbara McAneny, MD
- 10:15 a.m.-11:45 a.m. Wendell L. Hughes Lecture, “Ocular Melanoma: Marching Forward with Imaging, Nanoparticles, and Immunorevolution,” Carol L. Shields, MD
- 12:45 p.m.-1:45 p.m. C. Stephen and Lecture on Uveitis and Immunology, “Ebola, Emerging Infectious Diseases, and the Eye: Patient and Public Health Implications,” Steven Yeh, MD
- 3:15 p.m-4:15 p.m. Dr. Allan Jensen & Claire Jensen Lecture in Professionalism and Ethics, “Ethical Aspects of Global Ophthalmic Practice,” Anthony J. Aldave, MD

**Attractions**

If you are attending this year’s American Academy of Ophthalmology Annual Meeting in San Francisco, the agenda for the event offers plenty of great educational and business opportunities. If you have any extra time during your visit to the City by the Bay, here are some interesting sights worth checking out.

**THE GOLDEN GATE BRIDGE**

A San Francisco landmark, it is a must-see during any visit to the city. Sightseeing is free, and the bridge is accessible all day every day by bus, car, bicycle or on foot. Some other landmarks worth seeing include Coit Tower, Angel Island State Park, Lombard Street, Land’s End, Mission District, and Baker Beach.

**ALCATRAZ ISLAND**

While the former federal prison is long closed, it is open for tours. Entrance to Alcatraz is free; however, you will need to purchase a ferry ticket to get to the island. Tickets start at $39.90 for adults, but most travelers say the price offers great value. Tickets include a scenic boat trip to the island and the audio guide.

**FISHERMAN’S WHARF**

A popular tourist attraction that is another must-see. This waterfront neighborhood features a laundry list of things to do, as well as a few popular San Francisco sites. One of these is Pier 39. The Pier features plenty of shopping and restaurant options for tourists. The Wharf also houses plenty of family friendly attractions and activities, including a Madame Tussauds wax museum, Ripley’s Believe It or Not!, the San Francisco Dungeon and the Aquarium of the Bay, the last three of which can be found on Pier 39.
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While most ophthalmologists focus their energies on their patients, it is also important to remind them to take care of themselves. The AAO is working to improve ophthalmologists’ well-being through multiple resources at the annual meeting.

One course that is a must is entitled “Extinguishing Burnout and Reigniting Joy in Medicine,” which is presented by Susan E. Connolly, MD. Ophthalmologists also are advised to investigate a variety of activities at the Wellness Lounge, West, Booth 7561 and EyePlay Experience, South, Booth 2545. Both of these promote well-being and relaxation and include the use of therapy animals, art therapy, and complimentary seated massages.

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**SYMPOSIA AND SPOTLIGHTS**

The conference is planning to offer more than 50 symposia. The AAO highlights a small sampling of these sessions:

- **SATURDAY-TUESDAY, OCTOBER 12-15**
  - Vascular Disease in Neuro-Ophthalmology
  - A Critical Evaluation of Top-Line Data-Cornea Ophthalmic Technology Assessments That Will Change Your Practice
  - In This Corner…The Retina Debates, 2019

The Spotlight sessions focus on hot topics in ophthalmology and target the comprehensive ophthalmologist. The following are of special interest:

- Spotlight on Cataract: Complicated Phaco Cases—My Top 5 Pearls
- Spotlight on New Technology in Ophthalmology
- Spotlight on Physician Extenders

According to the AAO, other sessions include:

- The Evolution and Effect of Genomic Medicine, Blockchain, and Robot-assisted Surgery on the Practice of Ophthalmology (SYM30), Chair: Kevin Thomas Flaherty, MD
- The Impact of AI on Ophthalmology (SYM20)
- Project Human Genome: Genetic Testing for Inherited Eye Diseases (LAB142)
- The Millennial Movement: How Gender Equality, Big Data and Technology Will Be Embraced by the Young Ophthalmologist (SYM52)

**AAO EXECUTIVES PRACTICE MANAGEMENT PROGRAM**

This program gives ophthalmologists the opportunity to learn from the experts, converse with colleagues, and obtain takeaways that you can share and immediately put into clinical. The program includes over 80 instruction courses, seven master classes and two coding sessions, three Saturday specials, a general session, hot topics roundtables, and conversations with the experts.

- **FRIDAY-TUESDAY, OCTOBER 11-15**

**ADDITIONAL LEARNING EXPERIENCES**

**STOP THE BLEED** Session 1 of this innovative session will run from 1-10 to 11 a.m., session 2 from 11:30 a.m. to 12:30 p.m., and session 3 from 1:30-2:30 p.m.

This session is a new event outside-the-box experience for ophthalmologists to learn to save a life in 30 minutes or less. The AAO points out that ophthalmologists can easily learn to STOP THE BLEED and assist other bystanders while awaiting the arrival of professional emergency responders. Attendees can participate in a hands-on training for tourniquet application, wound dressing, and packing to save a life in an emergency situation. The course is free and available on a first-come first-served basis.

- **SATURDAY, OCTOBER 12**

**WELLNESS**

The Exhibit Hall is located in the North building, Exhibition Level, South building, Exhibition Level; and West building, Level 1.

Attendees can learn about the latest technologic innovations in the Learning Lounge, the Technology Pavilion, and the Product Theater. Visit Ophthalmology Times at Booth 7511.

- **SATURDAY-TUESDAY, OCTOBER 12-15**

**OTHER LEARNING OPPORTUNITIES**

Ophthalmologists should not overlook the instruction courses, original paper presentations, posters, and the Scientific ePoster Theater that too numerous to mention and can be sampled throughout the conference.

- **SUNDAY-TUESDAY, OCTOBER 13-15**

The Academy offers over 350 courses in topics from cataract to vision rehabilitation. This includes over 100 courses in practice management topics such as practice quality and coding & reimbursement. All instruction courses and Skills Transfer didactic lectures are part of the Academy Plus course pass.

The Scientific ePoster Theater on the South Exhibition level, offers free 90-minute, small-group, peer-moderated discussions of selected posters in the Poster Theater. Each session will focus on a specific subject.

**THE ACADEMY CAFÉ**

This free venue encourages ophthalmologists to sip free coffee and listen to expert panels debate the issues. Participation in the discussions is possible using a laptop or smartphone to send an email or text message with questions to the speakers. The following topics will be discussed uveitis, private equity, cataract, glaucoma, retina, oculoplastics, pediatric ophthalmology and strabismus, and cornea/external disease.

- **SATURDAY-TUESDAY, OCTOBER 12-15**

The Moscone Center complex consists of three main halls spread out across three blocks and 87 acres in the South of Market neighborhood. There are a number of hotels and restaurants within walking distance of the center.
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Nutraceutical offers hope as cytoprotective AMD option

Studies show procedure improves mitochondrial health, decreases VEGF gene

By Cheryl Guttman Krader; Reviewed by Sonali Nashine, PhD

Findings from a series of laboratory evaluations support further research to investigate *emblica officinalis* (EO) as a potential nutraceutical treatment for age-related macular degeneration (AMD).

The studies were done using retinal pigment epithelial (RPE) cell lines containing damaged mitochondria from patients with AMD and showed that treatment with EO had cytoprotective effects, improved mitochondrial health, and decreased VEGF gene expression.

**HEALTH BENEFITS**

*Emblica officinalis,* which is commonly known as Indian gooseberry, is an edible fruit found in tropical southeast Asia and has been described as having numerous properties associated with health benefits, including antioxidant, anti-inflammatory, and anti-aging activity,” said Sonali Nashine, PhD, Arnold and Mabel Beckman postdoctoral fellow, Gavin Herbert Eye Institute, University of California Irvine, Irvine, CA. She studied the role of apoptotic proteins in retinal degeneration disease models of glaucoma and retinitis pigmentosa. Her focus is to identify counter as a nutraceutical,” she said. “Going forward, we hope to conduct clinical studies using EO in combination with other nutraceuticals that might protect against mitochondria-induced cellular toxicity to develop an effective, noninvasive and inexpensive therapeutic intervention for AMD.”

**SCREENING CELLS**

Dr. Nashine is a recipient of the 2017 ARVO Genentech AMD Translational Research Fellowship and works in Dr. M. Cristina Kenney’s laboratory, where she screens various drugs, peptides and other compounds for protective activity to rescue damaged mitochondria and cells.

The AMD RPE cells used for the research are created by fusing mitochondrial DNA-deficient APRE-19 cells with platelets isolated from patients with AMD.

“These AMD RPE cells containing diseased AMD mitochondria have been shown to undergo apoptotic cell death,” she explained.

**ABOUT THE STUDIES**

The studies evaluating the activity of EO were done using purified EO extract and powder taken from capsules available over-the-counter, and the research found protective effects with both forms of EO. Tests of cell survival showed that EO rescued the AMD RPE cells at 24, 48 and 72 hours and reduced apoptosis at 24 and 48 hours as evaluated by staining for Caspase-3/7 and reduced Caspase-3 gene expression.

Additional assays that included evaluations of reactive oxygen species levels and SOD2 gene expression showed that EO protected against oxidative stress.

**CONCLUSIONS**

EO improved cellular and mitochondrial health, thereby playing a key cytoprotective role in AMD in vitro. Further studies are required to examine the mechanisms that mediate the cytoprotective effects of EO.

“The MT-RNR2 gene is coded from the 16S rRNA region of human mitochondrial DNA, and previous studies have shown that it codes for peptides that are cytoprotective.’” – Sonali Nashine, PhD

Therapeutic drugs for retinal degenerative diseases.

Dr. Nashine noted it is high in vitamin C and has been shown to improve eyesight and boost immunity in several studies.

“*Emblica officinalis* is currently sold over-the-counter as a nutraceutical,” she said. “Going forward, we hope to conduct clinical studies using EO in combination with other nutraceuticals that might protect against mitochondria-induced cellular toxicity to develop an effective, noninvasive and inexpensive therapeutic intervention for AMD.”

**TAKE-HOME**

Laboratory testing to screen *emblica officinalis* as a possible treatment for age-related macular degeneration is producing encouraging results.

**SIGNS OF UPREGULATION**

Assays to measure expression of the PGC-1α gene, which is a regulator of mitochondrial biogenesis, showed up-regulation of PGC-1α in cells treated with EO.

Other tests showed that treatment with EO downregulated VEGF gene expression and protected against cellular stress induced by exogenously added amyloid-β (Aβ) peptides.

Expression of the MT-RNR2 gene was evaluated to explore the mechanisms underlying the cytoprotective effects of EO, and the MT-RNR2 gene was found to be upregulated by severalfold in the treated AMD RPE cells compared to the untreated controls.

**REFERENCES**

‘The MT-RNR2 gene is coded from the 16S rRNA region of human mitochondrial DNA, and previous studies have shown that it codes for peptides that are cytoprotective.’ – Sonali Nashine, PhD

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The research has been published. [Nashine S, et al. *Aging*. 2019;11(4):1177-1188].

Sonali Nashine, PhD

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This article is adapted from a presentation at the 2019 meeting of the Association for Research in Vision and Ophthalmology. Dr. Nashine has no relevant financial interests.
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TREASURING DRY EYE WITH RECOMBINANT HUMAN NERVE GROWTH FACTOR

New therapies under review to address the root causes of ocular surface disease

By Lynda Charters; Reviewed by Melissa Toyos, MD

Moderate-to-severe dry eye disease is coming under attack from a new direction. Oxervate (Dompé), a first-in-class recombinant human nerve growth factor (rhNGF) that successfully treats neurotrophic keratitis, is being investigated in a phase IIb trial to see how patients with moderate-to-severe dry eye disease fare with this therapy.

WHY RHNGF?

A neurotrophin, rhNGF is a key element in the proper functioning of the central and peripheral nervous systems, endocrine, immune, and visual systems. NGF also is essential for the corneal and conjunctival trophism, sensitivity and healing.

The therapeutic potential of human NGF was realized when Dompé created a recombinant version of this protein and its safety and effectiveness were seen for treating neurotrophic keratitis. NGF has been shown in previous studies to act through specific high-affinity and low-affinity receptors on the lacrimal gland, epithelium, conjunctiva, endothelial cells and corneal nerves and is thought to work by supporting epithelial survival and maintenance, tear production, and corneal innervation, the investigators explained.

Dompé recently announced that the study enrollment began on June 10 to investigate the novel mechanism of action of the drug. This trial, Study NGF0118 (NCT03982368), is a multicenter, randomized, double-masked, vehicle-controlled, parallel group study to be performed in select sub-populations of patients with dry eye disease. The estimated primary completion data was in September, and the estimated study completion date is mid-2020, according to Melissa Toyos, MD, who is in private practice in Nashville and an investigator in the trial.

About 300 patients at 11 U.S. sites are expected to participate in this study of the safety and efficacy of rhNGF eye solution [20 μg/ml] compared with vehicle.

Dry eye disease will be diagnosed through a variety of measures of dryness, and patient-reported ocular comfort.

The patients, who will be randomly placed in three groups, will initially have four weeks of active treatment followed by a 12-week period of observation, Dr. Toyos explained.

The ClinicalTrials.gov website described the study design. The test and reference will be instilled in both eyes of each patients according to the following scheme that includes three groups of patients: group 1, one drop of rhNGF 20 μg/ml will be instilled in both eyes three times daily (every six to eight hours, e.g. 7 a.m., 2 p.m.; 9 p.m.); group 2, one drop of rhNGF 20 μg/ml will be instilled in both eyes twice daily plus one drop (40 μL) of vehicle will be instilled in both eyes once daily (every six to eight hours, e.g. 7:00 am, 2:00 pm; 9 p.m.). NB: rhNGF will be instilled in the morning and in the evening while the vehicle will be instilled in the afternoon; and group 3, vehicle eye one drop will be instilled in both eyes three times daily (every 6-8 hours, e.g. 7 a.m., 2 p.m.; 9 p.m.).

TAILORED TREATMENTS

She also reported that the company will conduct another separate clinical study with the goal of collecting a variety of biomarker information from patients with dry eye disease in order to develop tailored treatments.

This tailored approach is important because of the wide diversity of symptoms. Flavio Mantelli, MD, PhD, explained the benefits of this approach.

“The effects of currently available treatments for chronic dry eye disease mostly address only inflammatory and neuro-sensory abnormalities, which could result in a disease modifying therapy. The primary study endpoint is the change from baseline in ocular surface tear wetting measured using the Schirmer I test. The secondary endpoints are the signs and symptoms of dry eye disease, including ocular surface staining, which is an objective measure of ocular surface integrity and health.

PREVIOUS PROMISING DATA

A phase IIa study, a prospective open-label, multiple-dose, efficacy and safety study of rhNGF eye drops in a cohort of patients with dry eye disease preceded the current study.

The phase IIa study, which was supported by Dompé, was conducted in Austria. The results were published in the British Journal of Ophthalmology (Sacchetti M, et al. Published Online first: 03 April 2019. doi: 10.1136/bjophthalmol-2018-312470). In this study, the authors reported, “The data of this study indicate that rhNGF eye drops in both doses [20 μg/mL or 4 μg/mL] is safe and effective in improving symptoms and signs of [dry eye disease].”

“Dry eye is a complex disease that is often treated incompletely with currently available therapies. We are excited to explore how NGF uniquely addresses the root causes of ocular surface disease and, most importantly, we are intrigued by the extended therapeutic effect seen in earlier studies,” Dr. Toyos concluded.

TAKE-HOME

Oxervate is being investigated in a phase IIb trial to test its safety and effectiveness in patients with moderate-to-severe dry eye disease.

‘Dry eye is a complex disease that often is treated incompletely with currently available therapies.’ — Melissa Toyos, MD

Dr. Toyos went on to explain that because of the challenge of both diagnosing and managing dry eye, she is excited to investigate the potential of a treatment that may address the underlying tear production deficiency and the neuro-sensory abnormalities, which could result in a disease modifying therapy.

MELISSA TOYOS, MD
E: mtoyos@toyosclinic.com
Dr. Toyos is an investigator in the trial that has no other financial relationships to report.
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Findings from a large retrospective study support the efficacy and safety of dropless cataract surgery with transzonular injection of a corticosteroid and fluoroquinolone (Tri-Moxi, Imprimis Pharmaceuticals) for preventing postoperative infection and inflammation, according to Barry Emara, MD.

Aiming to characterize outcomes from his first 1,000 patients, Dr. Emara reviewed outcomes in 1,166 eyes that received a 0.2 mL transzonular injection of triamcinolone acetonide and moxifloxacin hydrochloride at conclusion of cataract surgery. The series included all patients who underwent dropless cataract surgery between February 2016, when he first began using the technique, through September 2018.

Dr. Emara noted that postoperative treatment with a topical corticosteroid was needed by 106 eyes (9.1%), and there were no cases of endophthalmitis. The need for a topical corticosteroid was similar in an updated series that included an additional 221 eyes. In the expanded population, 118 (8.6%) of 1387 eyes required topical corticosteroid treatment, and there were no cases of endophthalmitis.

“Efficacy with topical medications used to prevent infection and inflammation after cataract surgery is challenged by dependence on patient compliance and the need for the active ingredient to penetrate to the target sites,” said Dr. Emara, adjunct professor of ophthalmology, Schulich School of Medicine and Dentistry, Western University, Windsor, Canada. He also operates his private surgical practice out of the Windsor Surgical Centre.

“Challenges often lead to innovation, and the compounded injectable triamcinolone-moxifloxacin formulation address

**TAKE-HOME**

- The transzonular injection of a corticosteroid and fluoroquinolone can prevent postoperative infection and inflammation.
The study population included 884 eyes of 501 patients who underwent bilateral (383 patients) or unilateral (118 patients) conventional cataract surgery and 282 eyes of 165 patients who had bilateral (117 patients) or unilateral (48 patients) femtosecond laser-assisted cataract surgery (FLACS). A topical steroid was added after surgery when patients presented with symptomatic inflammation.

Dr. Emara noted that additional steroid drops were needed for 72 eyes (8.1%) that had conventional cataract surgery and 34 eyes (11.9%) that had FLACS. In his updated series, additional steroid drops were needed for 82 (7.7%) of 1058 eyes that had conventional cataract surgery and 36 (12.6%) of 329 FLACS cases.

“From the data it appears that eyes undergoing FLACS are more prone to inflammation than those having conventional cataract surgery,” Dr. Emara said. “Based on this information, surgeons might consider pretreating FLACS patients with a topical NSAID or steroid and possibly using a topical NSAID postoperatively to reduce the susceptibility to inflammation.”

Dr. Emara noted that more than 1 million eyes have undergone dropless cataract surgery in the United States during the past six years, and he cited data reported by other surgeons supporting its efficacy and safety.

Dr. Emara said that placement of the anti-inflammatory and antibiotic medications in the vitreous is preferred over intracameral administration because residence time will be longer in the vitreous and because the vitreous is the site where endophthalmitis establishes itself.

Intravitreal delivery during cataract surgery can be accomplished by either transzonular injection using a cannula or pars plana delivery with a needle. Dr. Emara said he prefers the transzonal route in which the injection is done after IOL implantation because of its convenience and because it maximizes workflow efficiency.

‘Efficacy with topical medications used to prevent infection and inflammation after cataract surgery is challenged by the dependence on patient compliance and the need for the active ingredient to penetrate target sites.’

— Barry Emara, MD

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This article is based on a paper presented by Dr. Emara at the 2019 ASCRS Symposium in San Diego, CA. Dr. Emara has no relevant financial interests to disclose.
Targeted subretinal surgery for delivery of a novel bio-synthetic retinal pigment epithelial (RPE) monolayer in eyes with advanced dry age-related macular degeneration (AMD) has been shown to be feasible using new intraoperative surgical methods, according to Amir H. Kashani, MD, PhD.

Dr. Kashani described exploratory findings from the intraoperative experience and surgical data of patients enrolled in a phase I/IIA study evaluating the efficacy and safety of the investigational implant.

Dr. Kashani is assistant professor of clinical ophthalmology, Keck School of Medicine of USC, Los Angeles.

Known as the California Project to Cure Blindness RPE 1 (CPCB-RPE1), the 3.5 mm x 6.25 mm implant is comprised of a human embryonic stem cell-derived RPE monolayer on an ultrathin synthetic parylene substrate.

"With the emergence of cell-based therapies, targeted delivery to specific regions of the retina is increasingly important," Dr. Kashani said. "We have demonstrated the feasibility of a surgical method that specifically targets the area of geographic atrophy (GA) for RPE replacement."

SAFETY FIRST

Dr. Kashani noted that whereas safety is the primary objective of the phase I/IIA study, the researchers are also assessing the potential efficacy of their implant, and they look forward to analyzing the functional outcomes data.

"More broadly, however, by showing that our surgical technique can specifically target the subretinal space that was previously thought to be inaccessible, our experience allows us to think farther ahead about which patients we can successfully treat through subretinal implantation and what other types of therapies we can deliver," he added.

PATIENTS ENROLLED

A total of 16 patients with advanced dry AMD were enrolled in the phase I/IIA study. The first seven cases were done using a standard vitrectomy-enabled operating microscope with 3D binocular viewing system, and the last nine procedures were performed with an intraoperative optical coherence tomography (iOCT) enabled microscope.

All of the surgeries in connection with the study were done at the Outpatient Surgery Center of the University of Southern California, Keck School of Medicine.

Intraoperative OCT-based measurements per-
formed before and after implant placement showed that a significant area of the geographic atrophy could be targeted and covered with the implant. In at least three subjects, the implant covered 100% of the area of GA, and in the last 14 patients, the area of GA coverage was >50%.

Dr. Kashani noted that previous efforts at delivering stem cell-derived RPE cells or other types of stem cells have involved injection of cell suspensions into the vitreous space or into the subretinal space surrounding the GA region with the aim of providing trophic support to the surrounding viable RPE.

Unlike the technique used for implanting CPCB-RPE1, the earlier methods did not target creation of a space that specifically involved the area of GA and did not reliably result in cell delivery to the disease-affected area.

"With the other approaches, the delivered cells usually do not reach the area of GA because the retina there is very adherent to the underlying Bruch’s membrane and does not detach easily," said Dr. Kashani.

In order to separate the area of GA from the underlying Bruch’s membrane to create a space that would match the implant’s dimensions and keep it in place, the USC team of ophthalmologists developed a method where they used a 41-gauge subretinal infusion cannula to elevate a bleb immediately outside the region of the GA and then hydrodissected the retina overlying the area of GA using a curved subretinal infusion cannula.

“This required fairly delicate maneuvers, but it was very doable,” Dr. Kashani said. “We found that with our technique, the area of detachment reproducibly included only the GA region and about one-disc-diameter around its periphery, which was our goal.”

“Other methods that have been used for subretinal injections with only a 41-gauge tip result in a bleb that tends to migrate unpredictably.”

To prepare the retinotomy site for implant delivery, the subretinal injection site was enlarged to about 1 mm using a vertical scissor. Then, the implant was loaded into and delivered with a custom-designed and manufactured surgical insertion forceps.

Perfluorocarbon (PFC) heavy liquid was injected to flatten the retina overlying the implant, air-fluid exchange was performed, the PFC was completely removed, and expansile gas or silicone oil was instilled for tamponade.

**ADDING VALUE**

Dr. Kashani reported that iOCT guidance facilitated the procedure and helped improve efficiency of the surgical steps.

“We were able to do the first several cases without iOCT, but the subsequent cases were enhanced by iOCT because it provided high-resolution visualization of the subretinal space and implant,” he explained. “For example, iOCT was helpful for allowing us to see where the retina was detaching, localizing subretinal adhesions and for guiding accurate implant placement.”

As a result, its use improved our surgical efficiency, Dr. Kashani noted.

“As we gained experience and refined our techniques, we were able to complete the surgery in about two hours, indicating that it should be feasible to do the implantation as an outpatient procedure,” he said.
Examining comparable surgical methods for IOL dislocation

Displacement issue can arise in patients years after seemingly routine cataract surgery

By Lynda Charters

A COMPLICATION OF implantation of an IOL in the capsular bag is dislocation of the IOL, which can happen years after an uncomplicated cataract surgery. While the 10-year cumulative incidence of dislocation is low, an estimated 0.5% to 1.0%, the frequency with which this occurs is sizable because of the high rate at which cataract surgeries are performed and the increased life expectancies of patients. The average time between IOL implantation and dislocation is 7 to 10 years, Marius Dalby, MD, and colleagues pointed out. The notable culprits that are involved in IOL dislocation are pseudoxfoliation, high myopia, and previous vitrectomy.

To date, investigators have not reached a consensus on how to address the problem of a dislocated IOL. IOL repositioning was evaluated in one prospective study that included in-the-bag and out-of-the-bag cases of dislocations with the findings of satisfactory improvement in vision and low complication rates, but the study considered a mean follow-up period of only 17 months.

The investigators published their findings in the American Journal of Ophthalmology (doi: https://doi.org/10.1016/j.ajo.2019.05.030).

There were no significant differences in visual acuity between IOL repositioning and IOL exchange two years after surgery.

— Marius Dalby, MD

undertook a clinical trial to evaluate the long-term follow-up of patients with late in-the-bag IOL dislocations. The investigators compared scleral repositioning of the IOL with IOL exchange with a new iris-claw IOL being substituted for the original lens. The main study outcomes were the distance-corrected visual acuity (DCVA) and long-term complications at the 2-year time point.

Over a three-year period, 104 patients with dislocations of their in-the-bag IOLs were randomized to undergo either scleral suturing of the original IOL (n=54) or to IOL exchange with a new retro-pupillary fixated iris-claw IOL (n=50) in this prospective, randomized, parallel-group clinical trial.

The exchange procedure involved looping of a 1-0 prolene suture around each IOL haptic and fixation to the scleral wall. The exchange procedure involved explantation of the IOL capsule complex through a 5.5-millimeter scleral pocket front incision. An aphakic iris-claw IOL (Verisyse, VRSA54, Abbott Laboratories) was then introduced and retro-pupillary fixated to the iris, according to Dr. Dalby, who is a PhD candidate from the Department of Ophthalmology, Oslo University Hospital, Oslo, Norway.

Eighteen patients could not participate after two years because of severe illness, another 18 died, one declined to participate, and one moved out of the country. The average age of the 66 patients who remained in the study was 79.6 years versus 85.2 years for those who left the study.

Examinations were conducted preoperatively and then at six months and one and two years postoperatively. During these examinations, two ophthalmologists and optometrists measured the CDVA and intraocular pressure and conducted slit-lamp examination of the anterior and posterior segments and slit-lamp photography of the anterior segment.

The examiners sought any degree of IOL decentration with a gap between the pupillary edge and the IOL with the optic still covering the visual axis and four indicating complete IOL dislocation.

The investigators defined CDVA worsening as a decrease of 0.10 or more in the logarithm of the minimum angle of resolution (logMAR) VA. The investigators also recorded any complications that developed during the first two postoperative years.

Dr. Dalby reported that two years postoperatively, the mean CDVAs were 0.20 ± 0.29 logMAR and 0.22 ± 0.30 logMAR, respectively, in the IOL repositioning group and the exchange group, a difference that did not reach significance (p = 0.69). Compared with baseline, 88% of the patients in both groups achieved a CDVA that was equal to or better. A CDVA of 20/40 or better was achieved by 76% of patients.

Cystoid macular edema developed in four (12%) eyes in the repositioning group and in five (15%) eyes in the exchange group (p = 0.72). The IOL dislocated again in one eye in each group. Five (15%) patients and one (3%) in the repositioning group and exchange group, respectively, had grade 1 IOL decentration. Retinal detachment or endophthalmitis did not develop in either group.

Dr. Dalby and associates also pointed out that an important implication in this study was that these patients had an overall good visual prognosis after they underwent surgery and the degree of the IOL dislocation at baseline, which ranged from grades 1 to 3, did not affect the long-term visual outcome.

CONCLUSION

“The there were no significant differences in visual acuity between IOL repositioning and IOL exchange two years after surgery,” Dr. Malby and the team concluded. “The two methods were equally efficient and safe from a long-term perspective and are both considered acceptable treatments.”

The investigators published their findings in the American Journal of Ophthalmology (doi: https://doi.org/10.1016/j.ajo.2019.05.030).
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ETM eases diagnosis for screening refractive surgery

Technology detects mild keratoconus, subtle epithelial basement membrane dystrophy

By Lynda Charters; Reviewed by Ella G. Faktorovich, MD

Widefield epithelial thickness mapping (ETM) with Optovue Avanti optical coherence tomography (OCT) has been recognized as an important addition to topography and tomography for screening candidates for refractive surgery.

Investigators recently concluded that the corneal ETM patterns in eyes with one mild topographic or tomographic abnormality were similar to the patterns observed in normal eyes in patients with myopia. This is an important observation when considering the number of candidate patients seeking LASIK or PRK.

According to Ella Faktorovich, MD, topography and tomography are the mainstays of screening patients for corneal refractive surgery.

“Diagnostic decisions are easy to make in patients with clearly discernible abnormalities, such as significant inferior or central steepening, skewed astigmatism axes, very thin corneas, and significant posterior float,” she said. “The presence of these problems typically prevents patients from undergoing LASIK and possibly even PRK depending on the severity of the abnormality.”

However, the decision is not always so simple in other patients with more subtle findings. Surgeons must grapple with some key issues, including whether inferior corneal steepening of 1.5 D would rule out LASIK or a 490-μm-thick cornea and a mild prescription would require PRK.

“When faced with such dilemmas, I often have wished for another reasonably sensitive and specific diagnostic method to assess the cornea to ensure that I am safely recommending a procedure to a patient,” said Dr. Faktorovich, who is in private practice in San Francisco.

Her evaluation of published studies on ETM has revealed a discernible pattern of epithelial thickness distributions in normal corneas compared with corneas with severe to mild keratoconus. These two types of ETM patterns (normal corneas versus corneas with keratoconus) were highly reproducible when different staff conducted the measurements and also reproducible between different studies, she pointed out.

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TAKE-HOME

The results of widefield epithelial thickness mapping with the Optovue Avanti OCT in eyes with a single mild topographic or tomographic abnormality were similar to normal eyes in myopes, which eases decision making surrounding refractive surgery.

A RETROSPECTIVE EVALUATION

In light of this, she and her colleagues retrospectively analyzed the ETMs, topographies (Atlas 9000, Zeiss), and tomographies (OCULUS Pentacam) in normal eyes compared with eyes with mild topographic and tomographic abnormalities. Two hundred ninety-eight eyes of 149 consecutive patients were included who were myopic and stopped wearing soft contacts a week before the scans, which were part of their preoperative workup.

Only patients with normal-appearing corneas and normal tear film on slit-lamp examinations were included in the evaluation. Patients with corneal scars, epithelial basement membrane dystrophy, superficial punctate keratitis, and decreased tear break-up time were excluded.

The analysis showed that 190 eyes (95 patients) (group 1) had normal topography and tomography scans; 89 eyes (49 patients) (group 2) had one of the following: pachymetry 475 to 510 μm (10 eyes/five patients), 1.50 D or less of inferior steepening;
ing (35 eyes/22 patients), 1.50 D or less of superior steepening (16 eyes/eight patients), central steepening (eight eyes/four patients), claw shape (14 eyes/seven patients), and posterior float (six eyes/three patients). The minimal pachymetry thickness, central epithelial thickness, ratio of inferior epithelial thickness to the superior epithelial thickness, minimal epithelial thickness, the difference between the maximal and minimal epithelial thickness were compared between the two groups.

When the investigators compared the ETM patterns in the two groups, they found no differences in any parameters between the normal eyes and those with one mild topographic or tomographic abnormality.

The retrospective chart review also identified 10 eyes (five patients) with a thin cornea (475 to 500 μm) and an additional mild abnormality, i.e., central steepening, a corneal thickness less than 475 μm, or a slightly skewed astigmatic axis. Dr. Faktorovich recounted that the 10 eyes had epithelial thinning over the thinnest corneal spot, consistent with one of the possible ETM findings in patients with forme fruste keratoconus.

**RECOMMENDATIONS**

Dr. Faktorovich provided the following pearls:

1. If the ETM is normal in patients with one mild topographic or tomographic abnormality, they may be good LASIK candidates. Therefore, the ETM is a useful additional screening tool for patients with topographic or tomographic abnormalities that pose a diagnostic dilemma regarding whether to recommend LASIK, PRK, or any corneal surgery. “I often find this technology helpful as a tie breaker when patients present to me for a third or fourth opinion after receiving different recommendations from different surgeons based on their topographies and tomographies. If the ETM is normal, I recommend LASIK if the residual stromal bed is sufficiently thick. If the ETM is abnormal, I recommend PRK or even no surgery, depending on the severity of the abnormality,” she stated.

2. Patients with several abnormalities on topography and/or tomography, even if very mild, should be approached cautiously. “We found that ETMs are consistent with forme fruste keratoconus in these patients. PRK or no corneal surgery, rather than LASIK, may be best for them,” she advised. She recounted the case of a 39-year-old trauma surgeon with corneal pachymetry of 498 μm and very slight skewing of the astigmatic axis. If the ETM had been normal, LASIK may have been recommended. Instead, the ETM pattern of epithelial thinning overlying the thinnest corneal spot that was displaced slightly inferotemporally led to a recommendation for PRK.

3. Mild inferior corneal steepening and areas of epithelial thickening on ETMs could be signs of epithelial basement membrane dystrophy even when patient’s cornea appears normal on slit lamp exam. PRK is recommended over LASIK to avoid epithelial loosening and sloughing during flap lift often seen in patients with epithelial basement membrane dystrophy.

The technology has proven so valuable that Dr. Faktorovich has incorporated it into the screening protocol of all refractive surgery candidates.

**FIGURE 1:** Topography and ETM of the eye, showing a normal-appearing cornea on slit-lamp examination without clinical evidence of epithelial basement membrane dystrophy. Topography shows mild inferior steepening. **FIGURE 2:** In the opposite eye, epithelial basement membrane dystrophy and negative corneal staining are seen. (Photos courtesy of Ella Faktorovich, MD)

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Dr. Faktorovich has no financial interest in any aspect of this report.
Ophthalmology can ‘adopt’ technologies from other specialties

Patients can benefit as physicians take advantage of new treatment options

By Laura M. Periman, MD; Special to Ophthalmology Times

There is plenty of "crossover" between ophthalmology and other medical specialties, giving physicians more tools to ensure the best outcome for patients.

References:

Retinoblastoma screening rules set foundation for care

AAOOP offers ground rules for physicians, sparking ongoing discussion among experts

By Vanessa Caceres; Reviewed by Alison H. Skalet, MD, PhD

When a group of members of the American Association of Ophthalmic Oncologists and Pathologists (AAOOP) was selected in 2015 to develop guidelines for screening children with retinoblastoma, their goal was to develop national guidelines and outline a simple, rational approach that emphasized the importance of genetic testing, according to Alison H. Skalet MD, PhD, ocular oncologist, and director, Retinoblastoma Service at Casey Eye Institute, Oregon Health and Science University, Portland, OR.

Those selected for the consensus panel were from leading centers across North America. An initial survey of the expert panelists’ screening strategies demonstrated differences in approach, including a lack of agreement about exam frequency and the length of necessary screenings related to retinoblastoma, Dr. Skalet said.

The results were presented to the AAOOP membership at the annual meeting in 2015 and were followed by an open discussion. Members who were present agreed that the creation of guidelines was a worthwhile endeavor, that screening based upon pretest risk stratification was reasonable, and that genetic testing was important for clarifying risk.

That legwork helped to lead the team publication of nine recommendations in Ophthalmology last year.

Among the recommendations are the following, according to Dr. Skalet:

1. Serial dilated eye exams by an ophthalmologist are recommended for children with higher than population risk for retinoblastoma risk due to family history.
2. All children with a family history of retinoblastoma benefit from genetic counseling and testing to clarify their risk.
3. Children are stratified into high, intermediate, and low-risk categories. Frequency of recommended examinations varies based upon a child’s age and level of risk, decreasing in frequency for all children as they grow older.

The recommendations went through rigorous peer-review and received endorsement from the American Academy of Ophthalmology (AAO), American Academy of Pediatrics, American Association for Pediatric Ophthalmology and Strabismus, and the American Society of Pediatric Hematology/Oncology.

Yet since publication of the guidelines, there’s been what Dr. Skalet called an “ongoing spirited discussion” about them. “In particular, it’s been questioned if it’s advisable to differentiate how we are screening children and what method we are using. It has also been questioned whether it is necessary to screen children beyond four or five years,” she said.

Dr. Skalet acknowledged the importance of continued review of the guidelines and pointed out that there was very little level 1 and 2 evidence from which to create the guidelines. Most often, those developing the guidelines had to use expert opinions and noncontrolled studies. She emphasized that the development of higher-quality data would be beneficial.

Dr. Skalet commented that a survey of AAOOP members is planned to gauge awareness of the retinoblastoma screening guidelines and to help define areas of agreement and disagreement.

The group also is investigating the use of the AAO’s IRIS Registry for “real-world” data regarding retinoblastoma screening and outcomes in the United States. “Publication of the U.S. guidelines has been a helpful step in improving care for children at risk for familial retinoblastoma in part because it has stimulated discussion of this important issue among experts not only in the U.S. but around the world,” Dr. Skalet said. “We agree on more than we disagree, and the attention is stimulating research efforts that will allow us to improve upon our current recommendations in the future.”

‘Publication of the U.S. guidelines has been a helpful step in improving care for children at risk for familial retinoblastoma in part because it has stimulated discussion of this important issue not only in the U.S. but around the world.’ — Alison H. Skalet, MD, PhD

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This article was adapted from Dr. Skalet’s presentation at the Ocular Oncology and Pathology Subspecialty Day at the annual meeting of the American Academy of Ophthalmology. Dr. Skalet is a consultant for Castle Biosciences and Immunocore.
Weight connection to diabetic retinopathy target of study

Research finds inverse association between DR, body fat found on Korean patients

By Lynda Charters

OVER THE YEARS, studies have reached conflicting results regarding the relationship between obesity and diabetic retinopathy (DR). However, a recent study found that obese Korean patients with diabetes might be less likely to develop vision-threatening DR.

In addition, the authors uncovered a gender difference in women where total body fat was associated with a lower presence of DR.

Establishing an association between DR and diabetes is important because vision-threatening complications have been known to develop in up to 10% of the patient population, the investigators noted.

“Although previous epidemiologic studies have demonstrated that poor glycemic control, hypertension, dyslipidemia, and a longer duration of diabetes increase the risk of DR, the known effects of controlling glucose and blood pressure are limited in reducing the risk of DR,” the authors commented. “Thus, other pathogenic or risk factors are important in understanding the development and progression of DR.”

CURRENT STUDY

In the current study, the authors, led by In Cheol Hwang, MD, MPH, PhD, conducted a nationwide survey to evaluate the association between body mass index (BMI), waist circumference, and body fat with diabetes.

A total of 1,130 patients with diabetes were identified who had undergone opthalmic examination. A total of 887 patients (men, 48.6%) ultimately were included; the rest were excluded because of ungradable fundus images.

SURVEY FINDINGS

The median patient age was 64 years (range, 22-93 years). DR developed in 185 (20.9%) of these patients; 130 (24.7%) had mild to moderate DR, and 55 (6.2%) had vision-threatening DR; 702 (79.1%) patients had no DR. The authors reported their findings in Eye (2019; https://www.nature.com/articles/s41433-019-0352-z).

Multivariate-adjusted analyses indicated that a higher BMI (P = 0.001), larger waist circumference (P = 0.047), and higher total body fat (P < 0.001) were associated significantly with a lower risk of vision-threatening DR, the investigators reported.

Interestingly, those factors did not confer any protective effects in patients with mild/moderate DR in either continuous or categorical analyses.

This finding about the effect of a higher BMI agrees with other recent studies conducted in Asian populations. For example, the Singapore Epidemiology of Eye Diseases cohort studies reported an inverse association of BMI with both the presence and severity of DR, and the Shanghai Diabetes Registry Database study also showed that overweight patients with type 2 diabetes had a lower risk of DR than subjects whose weight was normal. However, this effect was not found in studies of Western patients and may indicate the effect of different ethnic groups or study methods.

When stratified by sex, the current multivariate analyses showed no significant associations between DR and BMI or waist circumference in patients with type 2 diabetes. However, the research team reported that in female patients, the total body fat was associated significantly with the presence of DR (P = 0.009). After they adjusted for BMI and waist circumference, a significance inverse relationship was observed between total body fat and the severity of the DR in women (P for trend = 0.004) but not in men (P for trend = 0.126).

“Sex-stratified analyses revealed that total body fat was significantly associated with lower prevalence of DR in women with type 2 diabetes.”

The authors speculated about a possible reason for this finding. “The sex-specific effect of body fat on DR might be related to intrinsic hormonal responses or body fat distribution,” they noted. “Some studies have suggested that estrogen might play an important role in body fat distribution in women, who have more peripheral and lower body fat distribution, than in men, who typically have more truncal and upper body fat deposition.”

The investigators also speculated that because men have a “narrow range of total body fat,” this may explain the lack of association between body fat and DR.

CONCLUSION

“In Korean patients with type 2 diabetes, obese patients might be less likely to have vision-threatening DR,” the investigators concluded. “Total body fat in women appears to be inversely and independently associated with DR prevalence and progression.”

The authors, who were from Gil Medical Center, Gachon University College of Medicine, Incheon, Republic of Korea, and Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, reported no financial interests in any aspect of this report.

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A total of 1,130 patients with diabetes were identified who had undergone opthalmic examination. A total of 887 patients (men, 48.6%) ultimately were included; the rest were excluded because of ungradable fundus images.

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‘Sex-stratified analyses revealed that total body fat was significantly associated with lower prevalence of DR in women with type 2 diabetes.’

— research team led by In Cheol Hwang, MD, MPH, PhD

By Lynda Charters
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Pigmentation: XELPROS may cause changes to pigmented tissues. The most frequently reported changes are increased pigmentation of the iris, periorbital tissue (eyelid), and eyelashes. Pigmentation is expected to increase as long as XELPROS is administered. After discontinuation of XELPROS, iris pigmentation is likely to be permanent. Patients who receive treatment should be informed of the possibility of increased pigmentation. The long-term effects of increased pigmentation are not known.

Eyelash Changes: XELPROS may gradually change eyelashes and vellus hair in the treated eye, including increased length, thickness, pigmentation, and number of lashes. The changes are usually reversible upon discontinuation of treatment.

Intraocular Inflammation: XELPROS should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation.

Macular Edema: XELPROS should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Herpetic Keratitis: XELPROS should be used with caution in patients with a history of herpetic keratitis. XELPROS should be avoided in cases of active herpes simplex keratitis because inflammation may be exacerbated.

Bacterial Keratitis: There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products.

Use with Contact Lenses: Contact lenses should be removed prior to administration of XELPROS and may be reinserted 15 minutes following administration.

ADVERSE REACTIONS
The most common ocular adverse reactions in clinical trials (incidence ≥5%) for XELPROS were eye pain/stinging, ocular hyperemia, conjunctival hyperemia, eye discharge, growth of eyelashes, and eyelash thickening.

Drug Interactions
Precipitation may occur if drugs containing thimerosal are used concomitantly with XELPROS. If such drugs are used, they should be administered at least 5 minutes apart.

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

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INDICATIONS AND USAGE
XELPROS™ (latanoprost ophthalmic emulsion) 0.005% is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

CONTRAINdications
Known hypersensitivity to latanoprost, or any other ingredients in this product.

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

Across multiple clinical trials conducted with XELPROS, the most frequently reported ocular adverse reactions were eye pain/stinging upon instillation and ocular hyperemia, reported in 55% and 41% of patients treated with XELPROS, respectively. Other adverse reactions reported (incidence ≥5%) were conjunctival hyperemia, eye discharge, growth of eyelashes, and eyelash thickening. Less than 1% of patients discontinued therapy because of intolerance to the eye pain/stinging or to the ocular hyperemia.

DRUG INTERACTIONS
Precipitation may occur if drugs containing thimerosal are used concomitantly with XELPROS. If such drugs are used, they should be administered at least 5 minutes apart.

USE IN SPECIFIC POPULATIONS
Pregnancy
Pregnancy Category C
Reproduction studies have been performed in rats and rabbits. In rabbits, an incidence of 4 of 16 dams had no viable fetuses at a dose that was approximately 80 times the maximum human dose, and the highest nonembryocidal dose in rabbits was approximately 15 times the maximum human dose. There are no adequate and well-controlled studies in pregnant women. XELPROS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether latanoprost or its metabolites is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when XELPROS 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 or effectiveness have been observed between elderly and younger patients.

PATIENT COUNSELING INFORMATION
Potential for Pigmentation
Advise patients about the potential for increased brown pigmentation of the iris, which may be permanent. Patients should also be informed about the possibility of eyelid skin darkening, which may be reversible after discontinuation of XELPROS.

Potential for Eyelash Changes
Inform patients of the possibility of eyelash and vellus hair changes in the treated eye during treatment with XELPROS. These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

Handling the Container
Instruct patients to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to 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 emulsions.

When to Seek Physician Advice
Advise patients that if they develop an intercurrent ocular condition (eg, trauma or infection) or have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician’s advice concerning the continued use of the multiple-dose container.

Use with Contact Lenses
Advise patients that contact lenses should be removed prior to administration of the emulsion. Lenses may be reinserted 15 minutes following administration of XELPROS.

Use with Other Ophthalmic Drugs
Advise patients that if more than one topical ophthalmic drug is being used, the drugs should be administered at least 5 minutes apart.

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IPL therapy gains traction as latest chalazion treatment option

Approach requires no incisions, injections, medications; offers quick result for patients

By Laura M. Periman, MD; Special to Ophthalmology Times

CHALAZION, THAT TELLTALE “red bump” on the eyelid indicating an inflammatory lesion on a meibomain gland, is a fairly common sight in our practices.

Traditionally, we’ve sent patients home with warm compresses and a topical steroid/antibiotic drop or ointment. When these conservative measures fail, the lesions may require incision and drainage or an injection of triamcinolone acetonide (Kenalog, Bristol-Myers Squibb). In my clinic, we’re always looking for new things to offer our patients, so we’ve explored another treatment option with marked success: intense pulsed light (IPL) therapy.

IPL is indicated for benign inflammatory skin lesions. It is quite logical within that indication to treat inflammatory lesions on the skin of the eyelid with IPL technology and appropriate ocular protection in place.

There is a natural marriage between IPL’s mechanisms of action and the underlying causes of chalazia. IPL has demodicidal, anti-inflammatory, and anti-microbial, anti-telangiectatic properties, all of which address the inflammatory nature of chalazia. In addition, IPL features photobiomodulation, a process that stimulates cell mitochondria, promoting healthy cell function.

Using sixth-generation IPL technologies (Optima IPL with the OPT technology, Lumenis), coupled with a laser-grade corneal shield, my clinic has seen excellent success with IPL therapy for both acute and chronic chalazia.

With IPL, we’ve also had success in resolving chronic chalazia (typically resolves in 2 weeks) that persisted despite previous incision and drainage procedures, home care, and medications.

Our patients really like that we offer a treatment option without drugs, drops, injection, or incision. They appreciate the reduced home-care burden as well. (Warm compresses and BID are marginally effective and represent a significant compliance challenge for patients.)

We often see people who have an upcoming job interview or vacation, and they want help fast. For vacationers, clinicians want to avoid wound exposure during swimming and other activities. IPL is fast, effective, and incision-free, so there is no conjunctival scar or disruption in the normal meibomian gland and tarsal plate architecture.

One IPL treatment is usually enough for acute chalazia, and our patients tell us that acute chalazia are gone in 3 to 5 days. It’s hard to make the problem disappear that quickly with other modalities.

Patients appreciate several aspects to IPL for chalazia: the incision-free, injection-free, and medication-free approach for physicians to offer patients.

TAKE-HOME

› For the treatment of chalazia, IPL offers an incision-free, injection-free, and medication-free approach for physicians to offer patients.

We often see people who have an upcoming job interview or vacation, and they want help fast. For vacationers, clinicians want to avoid wound exposure during swimming and other activities. IPL is fast, effective, and incision-free, so there is no conjunctival scar or disruption in the normal meibomian gland and tarsal plate architecture.

One IPL treatment is usually enough for acute chalazia, and our patients tell us that acute chalazia are gone in 3 to 5 days. It’s hard to make the problem disappear that quickly with other modalities.

Patients appreciate several aspects to IPL for chalazia: the incision-free, injection-free, and medication-free approach; the speed, comfort, and completeness of IPL therapy; the effectiveness in addressing underlying comorbidities that contributed to the chalazion in the first place; and the potential to reduce the incidence of future chalazia.

My patients with a history of frequent chalazia report back that the frequency is greatly diminished.
PIONEERING RESEARCH IN

OCULAR ONCOLOGY

ADVANCES CONTINUE TO PROGRESS FOR DIAGNOSIS, THERAPEUTICS AND TREATMENT

A FUNDOSCOPIC IMAGE OF A UVEAL MELANOMA IN A PATIENT. (PHOTO COURTESY OF JOHN O. MASON III)

UVEAL MELANOMA STUDY SHOWS GENETIC FACTORS MAY BE IN PLAY

Data from study population show that cluster of cases not tied to environment

By Lynda Charters; Reviewed by John O. Mason III, MD

A study population of uveal melanoma in two different locations may shed light on genetic causes of the disease.

cases of uveal melanoma in Huntersville, NC, and at Auburn University in Auburn, AL, are considered to comprise a “unique study population,” which differs from a cluster that is defined by the National Institutes of Health as “a greater than expected number of cancer cases among a group of people in a defined geographic area over a specific time period.”

Clusters that meet this definition are simply random occurrences, according to John O. Mason III, MD.

“We term the Huntersville and Auburn University patients a ‘unique study population,’” said Dr. Mason, associate professor of ophthalmology, University of Alabama at Birmingham, director of the Retina Service and Ocular Oncology, and in private practice at Retina Consultants of Alabama, Birmingham.

HUNTERSVILLE CASES

Located hundreds of miles east of Auburn University is Huntersville, NC, a suburb of Charlotte, with a population of about 150,000 individuals. Ocular melanoma was diagnosed in three young women, all of whom had been students at the same high school, and whom initially were the focus of attention.

Between 2009 and 2014, a total of eight cases of ocular melanoma had been diagnosed in the town, and in 2014, the North Carolina Department of Public Health, along with the CDC, started an investigation as a response to the diagnoses. A study identified 22 cases that developed between 2000 and 2017, 15 (11 women, 4 men) of which met the inclusion criteria; tissue samples were available for eight of the 15 patients, Dr. Mason recounted.

The study parameters included geospatial and environmental analyses, as well as genetic analyses of serum and tissue samples. The geospatial analysis, i.e., the science of looking at both space and time that facilitates an environmental focus, did not identify a hot spot. The analysis included the patients’ homes, workplaces, and places they frequented. A large number of environmental culprits were possible causes, but without a hot spot, an environmental investigation was impossible.

The genetic analysis showed that the serum samples of all patients were BAP1 germline negative. The tissue samples obtained from biopsies, enucleation, and liver specimens underwent genomic analysis and interim findings suggest there were DNA extraction difficulties, with final analysis pending, Dr. Mason stated.

Whole serum genome sequencing was not performed.

AUBURN UNIVERSITY CASES

Dr. Mason described the findings at this location as “even more dramatic.”

Takami Sato, MD, and Marlana Orloff, MD, both from Thomas Jefferson University, Philadelphia, noticed that four women who had attended Auburn University between 1986 and 1993 developed ocular metastatic melanoma. The patients started a campaign on social media to possibly identify other such patients who were former students of the university; the search identified 13 subjects.

The Alabama Department of Public Health and Dr. Mason identified another 17 subjects, all of whom had attended the university or were employed there, for a total of 30 subjects who were

Continues on page 37: Melanoma study
Pearls for managing care of high-risk uveal melanoma patients

Physicians turning to sunitinib as part of increasing efforts in adjuvant treatment

By Vanessa Caceres; Reviewed by Carol L. Shields, MD

WHEN IT COMES to adjuvant treatment for high-risk uveal melanoma, physicians are turning to sunitinib malate (Sutent, Pfizer) as a viable option, according to Carol L. Shields, MD, chief, ocular oncology service, Wills Eye Hospital, Philadelphia.

Sunitinib malate is an oral multi-targeted tyrosine kinase inhibitor with anti-tumor and immune modulating effects, Dr. Shields said. It is used to treat gastrointestinal stromal tumors that fail on imatinib mesylate (Gleevec, Novartis), and it is used to prevent renal cell carcinoma metastasis in high-risk patients.

Dr. Shields and colleagues found improved survival rates with sunitinib in their high-risk uveal melanoma patients.

Physicians can help identify high-risk uveal melanoma by using genetics alone, genetics and American Joint Committee on Cancer (AJCC) classification, or gene expression profiling. In a study of more than 1,000 patients with uveal melanoma that looked at cytogenetic profiles, Dr. Shields and fellow researchers found chromosome 3 monosomy and eight abnormalities as the strongest predictors of prognosis.

“So, if you have chromosome 3 loss and 8q gain, you have an 11 to 123 times greater risk of metastatic disease,” she said.

Other research has found that by using the AJCC classification, physicians can further refine prognosis, Dr. Shields added.

At Wills Eye, there is a 96% yield for cytogenetics via use of a fine-needle aspiration biopsy, Dr. Shields said. There are ways through gene expression profiling to neatly separate melanoma into two groups, Dr. Shields said.

To help treat these patients, sunitinib malate, valproic acid, and some of the newer immune therapy options are available, Dr. Shields said. The now-available immune therapy options include vaccines, immune-modulated T-cells against cancer, and checkpoint inhibitors. Sunitinib malate is what Dr. Shields uses most frequently.

A pilot study conducted among researchers at Wills Eye and Thomas Jefferson University included 20 patients and focused on those with uveal melanoma metastasis who failed other treatment. In 30% of cases, there was progression-free survival at six months, which Dr. Shields described as a modest effect. However, when using low-dose sunitinib malate in high-risk uveal melanoma patients with no metastasis but high-risk cytogenetics, there was improved survival of 85% at 6 years compared with only 40% in those not using additional medications. This benefit appeared in patients under age 60 years. Side effects of sunitinib malate include fatigue, diarrhea, nausea and vomiting, and heartburn, Dr. Shields concluded.

REFERENCES

CONCLUSION
“Genetic evaluations are crucial and could potentially be the cause of uveal melanoma, although environmental factors may play a role,” he concluded. “The National Ocular Melanoma Registry is currently being developed. Raising public awareness for eye examinations is important.”

MELANOMA STUDY

(Continued from page 36)

Investigators noted that most of the cases in Huntersville involved women. However, at Auburn University, the patients were evenly split between men and women. The mean age at diagnosis was 44 years, and the median time having attended the university was 1988.

Unlike the Huntersville population, the investigation of the Auburn patients will include whole serum genome sequencing and duplex sequencing to identify molecular signatures from carcinogens. Dr. Mason explained that specific carcinogens can produce distinct genetic and molecular signatures in associated cancers that can then be compared to the Cancer Genome Atlas Project.

“This can reveal unique genetic features in these patients,” he said.

Tissue samples from liver and enucleation specimens will be evaluated using different DNA extraction techniques than the ones done for the Huntersville group. IRB approval for the above genetic evaluation is pending.

Dr. Mason recommended continuing investigations to identify commonalities in patients in Huntsville, AL, and Auburn with potential genetic and/or environmental causes.
Research eyes risk of second cancers occurring in retinoblastoma patients

Chance of getting, dying from non-ocular malignancies differs between men, women

By Cheryl Guttman Krader; Reviewed by Ruth Kleinerman, PhD

THE 10-YEAR SURVIVAL rate for patients with hereditary retinoblastoma is excellent, but these individuals are at increased risk for developing secondary cancers and have elevated mortality compared to age-matched individuals in the general population.

According to analyses of data for retinoblastoma patients in the United States, there are gender-related differences in both the incidence of the different types of second non-ocular malignancies and cause-specific mortality, said Ruth Kleinerman, PhD.

“Based on this information, evidence-based guidelines for long-term surveillance and follow-up of retinoblastoma survivors should take gender into account,” said Dr. Kleinerman, deputy branch chief, Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD. “International pooling of second cancer data for retinoblastoma survivors will increase the number of cases of second cancers and provide statistical power to further investigate gender disparity in risk with greater precision.”

Information on the incidence of second cancers in retinoblastoma survivors and rates of mortality related to the subsequent cancers is available from the National Cancer Institute Long-term Follow-up Study of Retinoblastoma Survivors. It includes data on 1,129 patients with hereditary retinoblastoma diagnosed between 1914 through 2006, of whom approximately 50% were still alive in 2016.

Dr. Kleinerman said that the most common second cancers in the hereditary retinoblastoma survivors are bone cancer, soft tissue sarcoma, and melanoma.

Analyses of cause-specific mortality compare the rates of death among retinoblastoma survivors with those reported for the U.S. population. The data show that female retinoblastoma survivors have a higher risk of dying of bone cancer, melanoma, and brain tumors and a slightly higher risk of dying of nasal cavity cancers compared with females in the general population.

Rates of death due to lung, bladder, and colon cancer among female retinoblastoma survivors also appear to be higher than females in the general population. Male retinoblastoma survivors are at higher risk of dying of pancreatic cancer than males in the general population.

The RB1 gene is the spark for the creation of a protein called pRB, which acts as a tumor suppressor, meaning that it regulates cell growth and keeps cells from dividing to fast or in an uncontrolled way.

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For example, RB1 is in the same cell cycle control pathway as CDKN2A, which is a susceptibility gene for familial melanoma and pancreatic cancer,” Dr. Kleinerman said.

Host characteristics, such as age and sex, as well as lifestyle and environmental factors, such as smoking history and sun exposure, may also play a role.

TREATMENT
- Past treatments for RB were similar
- Different sensitivity to radiation or chemotherapy?

LIFESTYLE/ENVIRONMENT
- Baseline cancer rates differ
- Smoking M>F
- Sun exposure M>F

GENETIC SUSCEPTIBILITY
- RB1 mutation location, type, variants
- Other pathways

WHY THE INCREASED RISK?

Genetic susceptibility, treatment, and other factors might contribute to the increased risk of second cancers in patients with hereditary retinoblastoma. Hereditary retinoblastoma is caused by germline mutations in RB1, and the location of the mutation or the type of the mutation may be involved in the risk of some secondary cancers, including lung, bladder, and brain tumors.

In addition, the patients may be carrying mutations in other related pathways.

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RUTH KLEINERMAN, PHD
E: kleinerr@exchange.nih.gov
This article is based on a presentation given by Dr. Kleinerman at the Ocular Oncology/Pathology Subspecialty Day meeting. The mortality data were subsequently published in the Journal of the National Cancer Institute (Kleinerman RA, et al. Patterns of cause-specific mortality among 2053 survivors of retinoblastoma, 1914-2016. J Natl Cancer Inst. 2019 Jun 30. Doi: 10.1093/jnci/djy227 [Epub ahead of print]). Dr. Kleinerman has no relevant financial interests to disclose.
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Survival can improve uveal melanoma

Dr. Sapna Patel, MD, associate professor, Department of Melanoma Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston.

Dr. Patel shared results from a variety of trials and research to show how the efforts under way could help to improve survival rates.

Dr. Patel then focused on the natural history of uveal melanoma.

**TAKE-HOME**

- Survival can improve for uveal melanoma, although more work remains in the area of adjuvant therapy.

---

**COUNTERPOINT**

No change in survival from uveal melanoma

**TAKE-HOME**

- Uveal melanoma survival rates have not improved in recent decades.

---

**REFERENCES**


I didn’t realize
STARS
were little dots that twinkled

—Misty L, RPE65 gene therapy recipient

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FightBlindness.org
Efficacy signals positive for dry AMD phase I study

Mitochondrial-targeted drug proves to be safe, well tolerated by participants

By Cheryl Guttman Krader

Results of ReCLAIM, a phase I study investigating elamipretide (Stealth BioTherapeutics) in patients with intermediate dry age-related macular degeneration (AMD) manifest as high-risk drusen, demonstrated that the novel mitochondrial protective drug was safe and well-tolerated. In addition, analyses of exploratory efficacy endpoints yielded encouraging indications that elamipretide may improve visual function in eyes with high-risk drusen, said Michael J. Allingham, MD, PhD, assistant professor of ophthalmology, Duke Eye Center, Durham, NC.

“Mitochondrial dysfunction plays a role in the pathophysiology of dry AMD, and we showed in the laboratory that one month of treatment with elamipretide reversed vision dysfunction in the ApoE4 mouse model of AMD and was associated with a corresponding improvement in ERG B-wave amplitudes and subretinal pigment epithelial deposits,” he explained.

Dr. Allingham added that the findings in the patients with drusen and non-central geographic atrophy, “he said.

To be included in ReCLAIM patients had to have dry AMD with high-risk drusen, ETDRS BCVA ≥55 letters, and a low luminance VA (LLVA) deficit ≥5 letters. High-risk drusen was defined as at least one large (≥125 μm) druse or multiple medium-size (63-124 μm) drusen. Patients with non-central geographic atrophy who met the inclusion criteria were studied as a separate subgroup.

A total of 21 patients were enrolled in the cohort with only high-risk drusen. The baseline demographic characteristics of the enrolled patients were typical for a dry AMD study population, Dr. Allingham said.

All of the patients were white, they were predominantly female (62%) and had a mean age of 71 years, almost two-thirds of the patients had never smoked, and none were current smokers.

Patients were treated with subcutaneous elamipretide 40 mg daily for 24 weeks and returned for monthly follow-up visits. Visual function data through week 24 were evaluated for 19 patients. Mean BCVA was 79.4 ± 7.4 letters at baseline, and at six months it had increased by a mean of 3.6 ± 6.4 letters (p = .025). Improvement in BCVA was observed early, with the change being statistically significant at week eight for the standard condition testing and by week four for the dim light testing, and the improvements were maintained during the six-month study.

“The magnitude of improvement in our study group was likely limited by the excellent starting visual acuity, but it was statistically significant,” Dr. Allingham said.

Mean LLVA was 63.7 ± 10.0 letters at baseline and increased by a mean of 5.6 ± 7.8 letters (p = .006) at six months. Again, the improvement was seen early, and it gradually increased between the one-month and six-month visits.

“Most subjects had an improvement in LLVA, and there was a subset that was highly responsive in terms of gaining LLVA,” said Dr. Allingham.

Reading acuity under standard and simulated low luminance conditions was also tested using MNRAD acuity charts. Under standard lighting conditions, mean logMAR best-corrected reading acuity was 0.01 ± 0.18 at baseline and improved by a mean of -0.11 ± 0.15 (p = .005); the change is equivalent to a gain of approximately 1 line. Mean logMAR low luminance reading acuity tested through a log 2 neutral density filter (LLRA) was 0.39 ± 0.23 at baseline and improved by a mean of -0.28 ± 0.17 (p < .001), representing approximately a three-line improvement.

The improvements in reading acuity also occurred early, with the change being statistically significant at week eight for the standard condition testing and by week four for the dim light testing, and the improvements were maintained during the six-month study.

According to Dr. Allingham, safety was excellent. There were no serious adverse events, and local reactions at the injection site were the most common type of adverse event recorded. One patient withdrew from the study because of an injection site reaction.

The preclinical study led to ReCLAIM, which is the first clinical trial investigating elamipretide in elderly patients.

“Currently, a phase II, placebo-controlled clinical trial is ongoing investigating elamipretide in preclinical study led to ReCLAIM, which is the first clinical trial investigating elamipretide in elderly patients.

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“The magnitude of improvement in our study group was likely limited by the excellent starting visual acuity, but it was statistically significant,” Dr. Allingham said. “A scatter plot analysis of BCVA change showed that it improved in the majority of patients.”

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Can lipid-lowering drugs reduce risk of diabetic retinopathy?

Patients less likely to be treated with intravitreal injections of VEGF, laser, vitrectomy

By Lynda Charters

A LARGE RETROSPECTIVE cohort study of patients with type 2 diabetes found that these patients benefited from lipid-lowering medications, in that those drugs seem to be associated with lower incidences rates of nonproliferative diabetic retinopathy (NPDR), PDR, and diabetic macular edema (DME).

The study also reported “modest evidence” that the patients were less likely to undergo treatment with intravitreal injections of anti-vascular endothelial growth factor (VEGF) drugs, laser, or vitrectomy.

The negative effects of diabetes cannot be overemphasized, and the disease has been observed to be increasing steadily among adults in the United States, with more than 40% of the population being diabetic or pre-diabetic.

However, children and adolescents also are being adversely affected, with the disease having increased by an estimated 7% annually in younger individuals from 2002 to 2012, according to the authors of a recent report.1

The authors of the study are from the Byers Eye Institute, Department of Ophthalmology, Stanford University School of Medicine, Palo Alto, CA and All Eyes Consulting, LLC, which is based in New York.

**RISK FACTORS**

In addition to diabetes, other identified risk factors for DR are hypertension, smoking, high blood glucose values, and dyslipidemia. Initially, in 2007, there was not enough evidence in a systematic review to advocate lipid-lowering drugs to prevent DR, but since then interest has been mounting in the association between dyslipidemia, lipid-lowering drugs, and ocular diseases associated with diabetes.

The data that have been emerging worldwide on the relationship between lipid-lowering medications and DR led Daniel Vail and colleagues to perform a retrospective cohort analysis of a database of commercial insurance claims in the United States that encompassed a diverse population of patients, with the goal of evaluating the effect of lipid-lowering medications on DR and diabetic complications that required intervention in that population.

The main study outcomes were any signs of DR, as measured by diagnostic codes for NPDR, PDR, DME, and procedural codes for treatments for retinopathy in the patient records, such as anti-VEGF injections, laser, and vitrectomy, the investigators explained and noted that the exposure of interest in this study was use of lipid-lowering drugs before and after the patients were diagnosed with diabetes.

**STUDY FINDINGS**

The study included 269,753 patients with type 2 diabetes who were covered by commercial insurance from 2008 to 2015.

The investigators found that there were 99,233 (37%) of these who were taking lipid-lowering drugs, and about 6% of them had a diagnostic code for NPDR, PDR, or DME or they had a procedural code for intravitreal injections, pars plana vitrectomy, or laser after they had been diagnosed with diabetes compared with 6.5% of patients who were not taking lipid-lowering medications (p < 0.01).

The research team reported further that adjusted time-to-event analyses showed that patients who took lipid-lowering medications before being diagnosed with type 2 diabetes were both less likely to progress to any retinopathy diagnosis (hazard ratio [HR], 0.60, 95% confidence interval [CI], 0.55-0.65) and less likely to receive any treatment for retinopathy (HR, 0.81, 95% CI, 0.78-0.84).

They pointed out that these findings were significant both at the aggregate level and at the individual diagnostic level (NPDR: HR, 0.63, 95% CI 0.57-0.69; PDR: HR, 0.45, 95% CI 0.37-0.54; and DME: HR, 0.39, 95% CI, 0.33-0.45) and at each treatment category level (anti-VEGF injection: HR, 0.81, 95% CI, 0.78-0.84; laser: HR, 0.62, 95% CI, 0.47-0.81; and vitrectomy: HR, 0.71, 95% CI, 0.59-0.85).

The authors commented that they found consistent evidence that patients who were taking lipid-lowering medications were less likely to develop NPDR, PDR, or DME, and modest evidence that these patients were less likely to receive intravitreal injections of anti-VEGF medication, laser treatments, or vitrectomy.

The current findings agree with the analyses of two large Japanese and Taiwanese claims databases, which have relatively homogeneous populations.

“As patients in the U.S. may have different risk profiles for ophthalmic disease in the setting of diabetes, and commercially insured patients in the U.S. who are diagnosed with [DR] may face different treatment pathways than patients in Taiwan or Japan, countries with very different health systems,” the investigators noted.

**CONCLUSION**

The research team noted that their findings have implications for the management of a common condition with significant ophthalmic morbidities and health systems costs.

“At the level of the individual provider, our findings support the use of lipid-lowering medications in diabetic patients with hyperlipidemia, as these medications may have visual benefits beyond their systemic indications,” the research team concluded. “Further research is needed to conclusively confirm the role of lipid-lowering medications in the prevention of [DR] and to estimate the consequences that these medications may have for ophthalmic use.”

The study was supported by the Heed Ophthalmic Foundation.

**REFERENCE**

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**Green light given in early trial for agent targeting neovascular AMD**

Clinical study finds safety, positive efficacy signal for novel oral option

By Cheryl Guttman Krader; Reviewed by Michael Stewart, MD

A SECOND PHASE Ila trial has found that AKST4290 (Alkahest), an investigational oral C-C chemokine receptor type (CCR3) antagonist, is safe and well tolerated in patients with neovascular age-related macular degeneration (nAMD).

AKST4290 also offered gains in visual acuity for both treatment naïve and treatment refractory patient groups. Monotherapy with AKST4290 was also associated with a functional benefit in the study, which enrolled patients with active nAMD refractory to intravitreal anti-VEGF injections, although morphological improvements were not observed during the treatment period, according to Michael W. Stewart, MD, chairman, Department of Ophthalmology, Mayo Clinic, Jacksonville, FL.

Dr. Stewart said the early data proved to be promising, with increases in visual acuity occurring over a six-week period.

**THE STUDY**

The single arm, open-label, phase Ila study enrolled 26 patients, of whom 24 completed the six week treatment period and four weeks of additional follow-up. AKST4290 was administered at a dose of 400 mg twice daily.

At the primary endpoint analysis at six weeks, BCVA improved by a mean of 2.0 ETDRS letters from baseline, was stable or improved in 72% of eyes, and improved by a mean of 7.7 letters among responders, defined as eyes with a gain of ≥5 letters. In a parallel study that enrolled treatment-naïve patients with nAMD, six weeks of oral AKST4290 treatment was associated with a mean BCVA improvement of seven ETDRS letters, stable or improved vision in 83% of patients, and an improvement of at least three lines in 21%.

The majority of patients across both studies experienced improvement in best-corrected visual acuity (BCVA), and there were no severe or serious adverse events reported.

Dr. Stewart explained that intravitreal anti-VEGF therapy is standard of care for nAMD. “Although effective, the treatment is burdensome, expensive, and may be associated with serious adverse events,” he pointed out. “In addition, not all patients achieve adequate morphological or visual acuity improvement. Hence, an alternative therapy or incremental therapy for eyes that are incomplete responders would be a therapeutic advance.”

**EFFICACY, SAFETY**

Dr. Stewart also explained that the data from the phase Ila trials of AKST4290 represent early but intriguing data on its efficacy and safety as an oral treatment for nAMD. “Randomized, placebo-controlled and mechanistic studies are planned to further explore the early visual acuity and morphologic trends in nAMD patients,” he explained. AKST4290, formerly known as ALK4290, is an orally administered CCR3 inhibitor that blocks the action of eotaxin, an immunomodulatory protein that increases as humans age.

By targeting eotaxin and its downstream effects, AKST4290 may slow the hallmark inflammation and neovascularization of wet AMD as well as other age-related diseases. CCR3 and its ligand CCL11 are highly expressed in subretinal neovascular lesions, and CCL11 levels are increased in choroidal endothelial cells and in the systemic circulation of patients with AMD,” Dr. Stewart said.

Dr. Stewart also pointed out that inhibition of CCR3 “interrupts endothelial cell migration and thereby reduces the morphological changes associated with pathological choroidal neovascularization.”

The study of anti-VEGF refractory patients required that participants have persistent subretinal and/or intraretinal fluid and absence of improvement of BCVA after receiving at least three consecutive anti-VEGF injections, the last of which was slated to have been administered within 30 to 90 days prior to the screening visit for the AKST4290 trial. BCVA marks at screening had to be between 70 and 24 ETDRS letters and central subfield thickness (CST) had to be ≥250 μm.

The baseline and demographic characteristics of the enrolled patients were typical of patient cohorts with nAMD. The patients had a mean age of 76 years and were predominantly female (61.5%). They had a mean disease duration of 1.9 years, and mean BCVA of 52.7 ETDRS letters at study entry.

**CONCLUSION**

Dr. Stewart reported that although there was little change in CST during the treatment period, a significant worsening was observed at the end of the four-week follow-up after AKST4290 was stopped.

Retinal pigment epithelium (RPE) detachment maximum height, CNV size and CNV leakage size were also measured in the study, and none of those morphological endpoints changed significantly from baseline.

“In the study evaluating AKST4290 in patients who were treatment-naive, however, RPE detachment height improved significantly while the patients were on therapy,” Dr. Stewart explained, adding that the potential for gaining meaningful visual improvement with an oral agent in neovascular AMD represents a major step forward for patients, and results warrant further study.

**SAFETY PROFILE**

AKST4290 had a favorable safety profile. In the study of treatment refractory patients, there were few systemic or ocular adverse events. No patients experienced a serious adverse event, and no patient discontinued therapy because of an adverse event.
Brolucizumab gaining traction as nAMD treatment option

Investigational anti-VEGF agent offers sustained results compared to alternatives in analyses

By Cheryl Guttman Krader

POST-HOC ANALYSES OF data from the two phase II registration studies investigating brolucizumab (Novartis) for the treatment of neovascular age-related macular degeneration (nAMD) show that sustained dryness of the retina is achieved earlier and by more patients treated with the investigational anti-VEGF agent compared with aflibercept (Eylea, Regeneron), according to Carl D. Regillo, MD.

“The results of these post-hoc analyses are consistent with the superior retina fluid outcomes previously reported for brolucizumab from preplanned analyses of change in central subfield thickness (CST), and the benefits of brolucizumab occurred with fewer injections,” said Dr. Regillo, professor of ophthalmology, Sidney Kimmel Medical College, Thomas Jefferson University, and chief, Retina Service, Wills Eye Hospital, Philadelphia.

HAWK and HARRIER, the two phase III studies investigating the efficacy and safety of brolucizumab for the treatment of nAMD, randomized patients to intravitreal treatment with brolucizumab 3 mg (HAWK only), brolucizumab 6 mg, or aflibercept 2 mg.

In a loading phase, patients received three injections of assigned study medication at weeks zero, four, and eight. After that, aflibercept was administered on a fixed schedule every eight weeks (Q8W). Brolucizumab was administered Q12W. That schedule could be reduced to Q8W and maintained with the frequency based on evaluations at predefined disease activity assessment visits. In both studies, more than 50% of patients receiving brolucizumab 6 mg were maintained on a Q12W regimen after completing the set of loading injections out through week 48.

HAWK and HARRIER demonstrated that BCVA improvement from baseline to week 16 and week 48. The differences favoring brolucizumab were maintained at week 96.

Dr. Regillo explained that the rationale for the time to dry analyses considered that sustained drying of the retina is an indicator of better disease control and may be associated with improved long term outcomes.

The post-hoc analyses compared brolucizumab and aflibercept for time to achieve sustained dryness and the cumulative incidence rate of sustained dryness up to week 96. Time to first sustained dryness was evaluated by Kaplan-Meier analysis and a proportional hazard analysis. Cumulative incidence of sustained dryness to week 96 was derived from that analysis.

“In both studies and for both definitions of sustained dryness, the incidence of patients achieving sustained dryness remained higher through week 96 in patients receiving brolucizumab,” Dr. Regillo said.

Pairwise comparisons of groups from both studies showed that the cumulative incidence of ≥2 or ≥3 consecutive fluid free visits was significantly higher for all brolucizumab groups versus aflibercept at both weeks 48 and 96.

TAKE-HOME

The results of post-hoc analyses are consistent with the superior retina fluid outcomes previously reported for brolucizumab from preplanned analyses of change in central subfield thickness.

CARL D. REGILLO, MD
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This article is based on Dr. Regillo’s presentation at the recent American Society of Retina Specialists meeting. Dr. Regillo is a consultant to Novartis and to other companies that market or are developing treatments for AMD.
Ranibizumab injections offer hope for radiation retinopathy patients

During study, visual acuity maintained or improved in all three groups

By Lynda Charters; Reviewed by Amy C. Schefler, MD

A NUMBER OF retrospective studies have reported the effects of anti-vascular endothelial growth factor (VEGF) for radiation retinopathy.

In those studies, bevacizumab (Avastin, Genentech Inc.) was administered at varying intervals. Only one prospective study has reported on administration of ranibizumab (Lucentis, Genentech Inc.) to 40 patients every two months from the time of proton beam therapy for 24 months. The investigators reported a significant visual improvement compared with historical controls with 90% of patients achieving 20/200 or better vision, Amy Schefler, MD, said.

Considering those results, Dr. Schefler and her colleagues conducted a phase II, multicenter, prospective, randomly selected trial of 40 patients divided among three groups. Cohort A included patients treated with ranibizumab monthly for one year, while cohort B included on ly ranibizumab and panretinal photocoagulation targeted to areas of ischemic retina (tPRP) as seen on wide-field angiography. Cohort C, a loading dose (three injections) of ranibizumab then-as-needed ranibizumab and tPRP to areas of ischemic retina.

The second year of the study was a treat-and-extend regimen for each cohort with prespecified optical coherence tomography (OCT) criteria, noted Dr. Schefler, clinical associate professor, Weill Cornell Medicine and University of Texas Health Science Center at Houston. The inclusion criteria included clinically evident cystoid macular edema that was associated with radiation retinopathy seen on OCT and fundus examinations, a history of plaque radiotherapy, external beam radiation, or proton-beam therapy, and a baseline visual acuity (VA) in the range of 20/25 to 20/400. The exclusion criteria included recent anti-VEGF therapy or steroid therapy.

**TAKE-HOME**

» In the study, investigators reported a significant visual improvement compared with historical controls with 90% of patients achieving 20/200 or better vision.

**FIRST-YEAR RESULTS**

Dr. Schefler noted the patients who had good baseline VA were equally stratified among the three cohorts. “Over the course of the study, the VA was maintained or improved in all three groups,” she said. The greatest mean change in the best-corrected VA (BCVA) was in cohort A that was treated with monthly ranibizumab.

“The patients in this group finished the year with a gain of four letters compared with baseline,” Dr. Schefler pointed out. Cohort B, which was treated with monthly ranibizumab and tPRP gained one letter at one year, and cohort C treated with a loading dose of ranibizumab and as-needed ranibizumab and tPRP lost 1.5 letters of vision. The central macular thickness decreased in all groups. In cohort C, the retinas thickened and then became thinner with the ranibizumab injection, a finding that has been reported in other disease states such as neovascular AMD. The monthly ranibizumab groups fared better, with mean decreases in the central retinal thickness of 97 and 105 microns in cohorts A and B.

Dr. Schefler commented that 86% of patients during the first year of the study who had 20/40 or better maintained that vision. Overall, 32% of patients had 20/40 or better vision, and 87% of patients had 20/200 or better vision at one year. A 10-letter improvement in VA was seen in 22% of study patients.

Patients who were treated monthly had the most significant visual gains of an average of four letters at one year compared with baseline and with patients who received as-needed treatment. The reporting of the two-year results of the study indicated that the visual gains achieved in year one were not fully sustained over the second year of the study. Further details will be published soon.
Trio of phase III studies focus on efficacy of dexamethasone insert

Replacement for corticosteroid drops to control postoperative pain, inflammation eyed

By Lynda Charters; Reviewed by Sydney L. Tyson, MD, MPH

THE COMBINED RESULTS of three phase III studies of a dexamethasone ophthalmic insert (Dextenza, Ocular Therapeutics), a preservative-free, 0.4-mg dexamethasone insert that is FDA-approved for intracanicular use, found that the device is efficacious for up to 30 days after one administration, according to Sydney L. Tyson, MD, MPH.

While corticosteroid drops are currently the mainstay of cataract treatment to manage postoperative pain and inflammation, the regimens are complex and the results depend on patient compliance, explained Dr. Tyson, who is in private practice in Vineland, NJ.

In contrast, the dexamethasone ophthalmic insert is resorbable and delivers a 0.4-mg dose of dexamethasone for up to 30 days, and, therefore, negates the need for patients to place corticosteroid drops. The insert can be placed in the inferior canaliculus as early as one day after cataract surgery postoperatively to treat postop pain and inflammation.

Dr. Tyson recounted that the three studies were comprised of patients undergoing cataract surgery. All studies were prospective, multicenter, double-masked, parallel-arm studies in which one arm was treated using the dexamethasone insert and the other arm using a placebo-hydrogel insert that did not contain a drug.

The first two studies featured randomly selected patients given dexamethasone or placebo in a 2:1 ratio, and in the third study, in a 1:1 ratio. The patients underwent follow-up examinations on days two, four, eight, 14, 30, and 45/60. At each visit, the investigators evaluated the patients to determine the absence of both pain (scores of 0) on day eight and anterior chamber cells on day 14. The primary endpoints were pain and inflammation at those two time points. The secondary endpoints were the absence of pain and anterior chamber cells and their mean scores at all other time points.

The safety of the device was based on the extent of exposure, adverse events, visual acuity, intraocular pressure, slit-lamp, punctal examination, and funduscopy findings. The duration of exposure of the insert also was measured through visualization via fluorescein at every visit, Dr. Tyson explained.

The studies included a total of 926 subjects (541 randomly selected to dexamethasone and 385 to placebo) at 58 sites in the United States.

Dr. Tyson reported that the dexamethasone implant was effective for treating ocular pain, with significantly more patients who received the active treatment reporting no ocular pain as early as day two postoperatively. On day eight, 79.2% of patients randomly selected for the dexamethasone implant reported no pain compared with 56.9% randomly selected to placebo. The respective percentages for the absence of anterior chamber cells were 42.7% and 27.5%. Both results reached significance (p ≤ 0.0001).

Significance differences also were seen in the absence of anterior chamber flare, trace cells or less, mean anterior chamber cells, and anterior chamber flare as early as day 4 in two of the three trials.

Regarding safety, 263 (48.9%) patients randomly selected for the dexamethasone implant reported at least one adverse event compared with 215 (55.8%) patients randomly selected for placebo. Four and two adverse events, respectively, were treatment related in the dexamethasone and placebo groups. The most frequently occurring ocular adverse events were eye and anterior chamber inflammation, increased intraocular pressure, and corneal edema. The dexamethasone insert could be visualized in over 99% of subjects on day 14 and in less than 89% of subjects on day 30.

Dr. Tyson noted complete absence of pain on day eight was demonstrated across trials. “Patients who received the dexamethasone implant did better than patients who received placebo on day 14 across trials in the absence of anterior chamber cells,” he concluded. “In one trial, the difference was not significant. The integrated analysis showed that early onset of action with efficacy was seen as rapidly as day two postoperatively for pain relief and day four for inflammatory clearance.”

There have been two recent development regarding Dextenza. The first is that the FDA approved a supplemental new drug application (NDA) for Dextenza that includes the treatment of ocular inflammation after ophthalmic surgery as an additional indication. According to the supplemental new drug application announcement Dextenza is now approved to treat both ocular inflammation and pain after ophthalmic surgery.

The second is that the Centers for Medicare and Medicaid Services has assigned a specific and permanent reimbursement J-code through the Healthcare Common Procedure Coding System for Dextenza (dexamethasone ophthalmic implant) 0.4 mg, which according to the supplemental NDA is approved to treat ocular inflammation and pain following ophthalmic surgery. The code for Dextenza, J1096, becomes effective Oct. 1.
Seeking the goal line for patients’ glaucoma medication compliance

More than a third of patients do not receive anti-glaucoma drugs, study shows

By Lynda Charters

ABOUT 2.2 MILLION adults in the United States have glaucoma, and by as early as next year that number is expected to increase to 3.36 million, estimate researchers.

Ironically, while IOP drugs are effective at decreasing the development and progression of open-angle glaucoma, compliance is poor among aging patients for a few reasons, including reliance on staff in nursing homes and subacute rehabilitation centers as well as transfer of care from inpatient hospitals, according to a study by Tavish Nanda, MD, and colleagues from the Harkness Eye Center of Columbia University Irving Medical Center and Northwell Health of Lenox Hill Hospital, both in New York.

“Medication reconciliation is the process by which a patient’s outpatient medication regimen is documented and converted to synonymous medications in the hospital formulary,” the study’s authors explained. “The intention of this process is to continue all outpatient medications during a patient’s hospital stay, unless otherwise contraindicated.”

However, while this process is primarily an electronic one, “medication reconciliation on hospital admission and discharge is fraught with discrepancies, with errors occurring as often as 70% to 85% of the time,” they noted and explained that the frequency of these error rates associated with anti-glaucoma medications is unknown.

In addition, glaucoma is not considered to be as important as other chronic conditions such as diabetes and hypertension. The authors theorized that reconciliation of glaucoma drugs is suboptimal in inpatient hospitals, resulting in noncompliance.

THE STUDY

In light of this, they conducted a retrospective, cross-sectional, hospital-based study that included 475 patients (46.3% women; average age, 80.2 years) who had been admitted to a general medicine regional hospital service (average stay, 4.61 ± 3.7 days). The investigators reviewed the administrative database and cross-referenced patient charts and the following information was collected: demographic data, past medical problems, inpatient orders, intake history and physical, length of stay, and admitting diagnosis. The main outcome measures were twofold:

- the effect of outpatient glaucoma drop reconciliation and recognition of glaucoma as a pertinent past medical problem in a patient’s intake history and physical on inpatient eye-drop administration, resulting in noncompliance.

In the study, 386 (81.3%) patients who had successful reconciliation of their anti-glaucoma medications, these patients achieved significantly different rates of eye-drop administration, i.e., 283 (73.3%) of the 386 patients received anti-glaucoma medications on the floor compared with 19 (21.0%) of 89 patients without successful reconciliation who received their medications, a difference that reached significance ($p < 0.001$).

Another important finding was that the presence of glaucoma was recognized in the history and physical in less than half of patients, 42.5%.

“Recognition of glaucoma as a pertinent medical problem was poor, with only 202 of 475 (42.5%) patients having glaucoma listed in their intake history and physical,” the authors noted. Among those with glaucoma listed, 153 of 202 patients (75.7%) received glaucoma medications. In comparison, in those without glaucoma listed (150/273), 55.0% received glaucoma medications ($p < 0.001$).

TAKE-HOME

- Glaucoma medication compliance in an inpatient setting is poor, with more than a third of patients not receiving their anti-glaucoma drugs.

‘Glaucoma treatment incurs a high rate of medication noncompliance, especially in the elderly.’

—study led by Tavish Nanda, MD

CONSIDERATIONS

The study also emphasized the importance of accurate recording of the patients’ medication regimen before admission to a hospital in order to improve eye-drop administration during their stay. This could be improved, they suggested, by using teaching rounds or morning case presentations as opportunities for residents and staff to become familiar with the various types of anti-glaucoma drops and administration regimens that are frequently prescribed.

“This ideally would include a table or chart providing the generic medications that are available in the hospital formulary and their synonyms in the outpatient setting,” according to the study. “It is imperative that these teachings also emphasize the chronic nature of this disease and the vision-threatening consequences of prolonged noncompliance.”

MEDICATION NONCOMPLIANCE

They suggested that small cards listing basic medication information, such as the name, dose, side effects, and regimen, be provided with the goal of improving quality as well as serving as a reminder to inquire about glaucoma as a patient’s chronic medical problem.

“Glaucoma treatment incurs a high rate of medication noncompliance, especially in the elderly,” the study stated. “The present study demonstrates that more than one third of patients admitted to an academic medical center do not receive their glaucoma medications.

The study indicated that patients discharged to nursing homes, subacute rehabilitation, and assisted living facilities rely on appropriate discharge medication reconciliations, resulting in forced abstinence during transition of care.

“An emphasis on appropriate medical reconciliation and recognition of glaucoma as a pertinent past medical problem will improve rates of eye-drop administration on inpatient admission significantly,” it concluded.

This article is adapted from a poster presented at the American Glaucoma Society annual meeting. The authors reported no financial interest in any aspect of this report. These results also were reported in Ophthalmology Glaucoma (2019;2:188-191).
NATIONAL EYE INSTITUTE

Continued from page 1

“The incidence of clinically significant CME among patients in our study who had an ERM was 10-fold higher than in our patients without diabetes and no ERM, indicating patients with an ERM had a drastically increased risk.” —Jan Gärdin, MD

Björn Johansson, MD, PhD, co-investigator in the study and associate professor of ophthalmology, Linköping University, said the study has highlighted some interesting treatment options.

“Although randomized controlled studies remain the gold standard for evaluating the efficacy of new treatments, adequately designed and conducted clinical studies such as our retrospective population-based trial are an important complement to clarify how medical and surgical treatments are used in an optimal fashion in unselected clinical populations.” —Björn Johansson, MD, PhD

“...adequately designed and conducted clinical studies such as our retrospective population-based trial are an important complement to clarify how medical and surgical treatments are used in an optimal fashion in unselected clinical populations.” —Björn Johansson, MD, PhD

Unplanned visits within six months after phacoemulsification: Two different protocols for anti-inflammatory treatment

Unplanned visit due to any reason

Unplanned visit due to CME

FIGURE 1 A cataract is removed from the eye of a patient. FIGURE 2 An IOL is shown inserted into the eye of a patient. Topical steroids and topical NSAID are given three times daily. (Images courtesy of Jan Gärdin, MD)

A review of preoperative ocular comorbidities showed the percentage of eyes with pseudoeofoliation was higher in the group that received the steroid alone compared with those treated with combination therapy. The group receiving combination therapy had higher percentages of eyes with an epiretinal membrane (ERM) and with diabetic maculopathy or retinopathy. The number of patients with diabetes and with age-related macular degeneration was similar in the two groups.

Though a higher rate of unplanned postoperative visits was found for the group receiving combination treatment than among eyes treated only with a steroid, the difference was not statistically significant (16.6% versus 12.6%; p = 0.073). CME occurred in eight eyes (1.6%) in the combination treatment group and in six eyes (1.4%) treated with steroid alone.

“The overall incidence of CME in our total cohort was 1.2%, but when patients with diabetes or an ERM were removed, the overall incidence of CME decreased to 0.8%,” Dr. Gärdin pointed out.

Clinically significant CME occurred in 2.9% of eyes in patients with diabetes mellitus and in 8.2% of eyes with an ERM.

“The incidence of clinically significant CME among patients in our study who had an ERM was 10-fold higher than in our patients without diabetes and no ERM, indicating patients with an ERM had a drastically increased risk,” Dr. Gärdin concluded.

TAKE-HOME

Researchers highlight an increased susceptibility to postoperative CME in eyes with pre-existing vitreoretinal conditions.

Unplanned visits within six months after phacoemulsification: Two different protocols for anti-inflammatory treatment

NSAID

Unplanned visit due to any reason

Unplanned visit due to CME

(Chart courtesy of Jan Gärdin, MD)
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Ophthalmology Times
Dealing with upset patients is a tough job. Your job is to resolve the complaint and grow as a problem solver. Build a culture that rewards employees for the service industry tracking of complaints reveals that most complaints are caused by the consumer. Your job is to resolve the complaint that allows the patient to keep his or her dignity intact without making financial concessions on behalf of the practice. Do the best you can and jot down word patterns that worked and which ones didn’t.

A patient complaint is one of the most direct and effective ways for them to tell the practice that there is room for improvement. If a large percentage of your patients appear to struggle with mental confusion or forgetting details, protect your employees from verbal assaults by adding structure, routine and predictability to the selection process.

It could be as simple as 1-2-3:

1. Take a picture of the patient in the new frame with his or her phone. By having the patient look slightly to the side the frame temple details are visible.

2. Write down the brand and model number on the back of the Lensguide. Circle the lens technology that the patient purchased in the guide and give it to the patient. Example: “I know you are excited about today’s purchase. Feel free to show this to your friends and family.”

Continues on page 56: Pearls
Macular Degeneration Association unveils AMD Centers of Excellence

New program shares best-practice methods in disease evaluations, treatments

By Joshua Mali, MD; Special to Ophthalmology Times

THE MACULAR DEGENERATION Association (MDA) recently unveiled its AMD Centers of Excellence, a program that shares best-practice methods in disease evaluations and treatments.

This age-related macular degeneration (AMD) COE will help patients locate treatment facilities in their area. Founded in 2007, the MDA is a nonprofit health organization dedicated to educating and empowering patients with AMD. It funds research, publishes scientific findings, and provides funding for AMD awareness programs. The association advocates for scientific research and the rights of people with AMD.

As a speaker for the organization, I have participated in patient education programs that allow AMD patients to take control of their disease through education. Here are some of the highlighted criteria for an AMD COE with the MDA accreditation:

- Completion and submit enrollment application.
- Facility must contain space for equipment appropriate to the services designated on the enrollment application, facilities for hand washing, adequate patient privacy accommodations, and the storage of both business records and current medical records.
- The facility should have all applicable diagnostic testing equipment available at the physical site.
- Testing equipment must be calibrated and maintained per instructions and in compliance with applicable manufacturer’s suggested maintenance and calibration standards. Each physician/facility should meet at least one of the following:
  - At least 30% of the practice should be AMD patients
  - Participate in a multicenter study investigating a new treatment for AMD
  - Lecture on AMD
  - Author a paper or publication on AMD
- Additional conditions include:
  - Keep a catalog of diagnostic equipment.
  - Stay current on new technology.
- All physicians agree to have available the following medications: bevacizumab (Avastin, Genentech); ranibizumab (Lucentis, Genentech); aflibercept (Eylea, Regeneron), and any new anti-vascular endothelial growth factor (VEGF)/similar medication approved by the FDA and Medicare.
- Have technical staff on duty with the appropriate credentials to perform diagnostic tests. The facility must be able to show federal or state licenses or certifications of staff performing these services.
- Applications and documents will be reviewed by the MDA’s medical director for approval as an AMD Center of Excellence.

In anticipation of retina specialists receiving a formal invitation to participate in this patient resource, visit, www.macularhope.org, for updates.

PEARLS

(Continued from page 55)

3. In addition to the credit card receipt give the patient a dated receipt from your practice software that shows product details.


Your pain is real, and I don’t want to trivialize the patience it takes to deal with a confused patient. I cannot imagine how you must feel sometimes. I suspect it feels like the patient is taking advantage of you and the practice. It is not pretty when the patient screams. Not only does it leave you shaken but the patient may be embarrassed and cover the embarrassment by becoming even angrier and more self-righteous.

P R A C T I C E Y O U R C O M M U N I C A T I O N T E C H N I Q U E S

It is essential that your entire team be trained to handle the volatile patient. Angry people do not typically get any angrier than they initially present if handled well. Also, while certain people are conditioned to ask for a full refund, it is possible to defuse the situation before those words are spoken.

An explosion must be acknowledged before a problem can be resolved. This is why listening is so important.

They obviously feel they have something to say and listening without interrupting moves the patient toward resolution. In order to become an expert at listening (and asking questions) to angry customers, you need to memorize a technique and practice it in role-play situations. Develop alternative questions and demonstrate how something positive can happen.

Remember, you are trying to take the angry energy and turn it into such a positive feeling that this person becomes a thriving fan of the practice. Please don’t expect to win them all. No matter how patient, helpful and understanding you are, there will be a small percentage of irate patients impossible to satisfy.

Unfortunately, some patients really do get their satisfaction from giving others a hard time. If a patient shows definite signs of becoming hostile or violent, don’t try to handle it alone. There should be a procedure in your policy manual about how to handle these folks.

Dealing with upset patients takes a wealth of self-control and is a tough job. Reduce internal stress by practicing self-care, taking conflict resolution classes regularly, and don’t expect to be perfect in dealing with every patient every time. You are human, too.
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“...And I buy all my glasses off the internet...”

Confession Booth

in case you missed it

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10 effective habits of a cataract surgeon

Highlights: 2019 European Society of Cataract and Refractive Surgeons

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TECNIS PERSONALIZED VISION

TECNIS® Symfomy® + TECNIS® Multifocal IOLs

TECNIS SYMFONY® EXTENDED RANGE OF VISION IOL

INDICATIONS: The TECNIS Symfomy® Extended Range of Vision IOL, Model ZXR00, is indicated for primary implantation for the visual correction of aphakia, in adult patients with less than 1 diopter of pre-existing corneal astigmatism, in whom a cataractous lens has been removed. The lens mitigates the effects of presbyopia by providing an extended depth of focus. Compared to an aspheric monofocal IOL, the lens provides improved intermediate and near visual acuity, while maintaining comparable distance visual acuity. The Model ZXR00 IOL is intended for capsular bag placement only. WARNINGS: Patients with any of the conditions described in the Directions for Use may not be suitable candidates for an intraocular lens because the lens may exacerbate an existing condition, may interfere with diagnosis or treatment of a condition, or may pose an unreasonable risk to the patient’s eyesight. Lenses should not be placed in the ciliary sulcus. May cause a reduction in contrast sensitivity under certain conditions, compared to an aspheric monofocal IOL; fully inform the patient of this risk before implanting the lens. Special consideration should be made in patients with macular disease, amblyopia, corneal irregularities, or other ocular disease. Inform patients to exercise special caution when driving at night or in poor visibility conditions. Some visual effects may be expected due to the lens design, including: a perception of halos, glare, or starbursts around lights under nighttime conditions. These will be bothersome or very bothersome in some people, particularly in low-illumination conditions, and on rare occasions, may be significant enough that the patient may request removal of the IOL. SERIOUS ADVERSE EVENTS: The most frequently reported serious adverse events that occurred during the clinical trial of the TECNIS Symfomy lens were cystoid macular edema (2 eyes, 0.7%) and surgical reintervention (treatment injections for cystoid macular edema and endophthalmitis, 2 eyes, 0.7%). No lens-related adverse events occurred during the trial.

TECNIS® MULTIFOCAL FAMILY OF 1-PIECE IOLs

INDICATIONS: The TECNIS Multifocal 1-Piece intraocular lenses are indicated for primary implantation for the visual correction of aphakia in adult patients with and without presbyopia in whom a cataractous lens has been removed by phacoemulsification and who desire near, intermediate, and distance vision with increased spectacle independence. The intraocular lenses are intended to be placed in the capsular bag. WARNINGS: Physicians considering lens implantation should weigh the potential risk/benefit ratio for any conditions described in the Directions for Use that could increase complications or impact patient outcomes. Multifocal IOL implants may be inadvisable in patients where central visual field reduction may not be tolerated, such as macular degeneration, retinal pigment epithelium changes, and glaucoma. The lens should not be placed in the ciliary sulcus. Inform patients about the possibility that a decrease in contrast sensitivity and an increase in visual disturbances may affect their ability to drive a car under certain environmental conditions, such as driving at night or in poor visibility conditions. PRECAUTIONS: Prior to surgery, inform prospective patients of the possible risks and benefits associated with the use of this device and provide a copy of the patient information brochure to the patient. Secondary glaucoma has been reported occasionally in patients with controlled glaucoma who received lens implants. ADVERSE EVENTS: The rates of surgical re-interventions, most of which were non-lens related, were statistically higher than the FDA grid rate for the ZLB00 (+3.25 D) lens model. The re-intervention rate was 3.3% for both the first and second eyes in the ZLB00 group.