Study: Therapy reduces proptosis, diplopia in TED

By Lynda Charters; Reviewed by Raymond S. Douglas, MD, PhD, and Sara T. Wester, MD, FACS

AN INVESTIGATIONAL NOVEL antigen-specific therapy that blocks insulin-like growth factor-1 receptor (IGF-1R)—teprotumumab (Horizon Therapeutics)—significantly reduced both diplopia by one grade and proptosis in patients with active thyroid eye disease (TED) in a phase III placebo-controlled trial.

These findings confirmed those of the phase III study in which more patients had a significant (p < 0.001) improvement in proptosis, the primary study endpoint, compared with placebo, i.e., 82.9% of treated patients compared with 9.5% of placebo patients (Smith et al. New Engl J Med 2017;376:1748-1761).

TED is a debilitating, progressive ocular disease with many facets, according to Raymond Douglas, MD, PhD, a principal investigator of the Treatment of Graves’ Orbitopathy (Thyroid Eye Disease) to reduce proptosis with teprotumumab infusions in a randomly selected, placebo-controlled, clinical study (OPTIC) Study.

The disease causes an array of visual impairments, with diplopia developing in about 50% of patients with active thyroid eye disease (TED).

IN VIEW

TOP
A patient with active thyroid eye disease.

BOTTOM
The same patient after treatment with teprotumumab. (Images courtesy of Horizon Therapeutics)

AAO 2019 | SURGERY

Traversing the CXL pathway: WHERE DO WE GO FROM HERE?

Supplemental oxygen a simple way to increase efficiency

By Lynda Charters; Reviewed by Theo Seiler, MD, PhD

A NEW understanding of the effect of oxygen on corneal collagen crosslinking (CXL) may allow clinicians to compensate for the lack of oxygen, said Theo Seiler, MD, PhD.

“The oxygen level was not a consideration in the early evolution of the technique,” explained Dr. Seiler, professor of ophthalmology, Institute for Refractive and Ophthalmic Surgery, Zurich, Switzerland.

In the beginning, the standard for the procedure initially was a riboflavin concentration of 0.1%, irradiance of 3 mW/cm² for 30 minutes with application of 5.4 joules/cm², and use of 20% oxygen.

The results showed, according to Dr. Seiler, that the normal corneal architecture was disrupted to about 250 µm deep and the keratocytes were killed. At the depth of 293 µm, the keratocytes appeared normal.

Irradiance levels exceeding 9 mW/cm² resulted in significantly reduced efficacy of the procedure.

By Lynda Charters; Reviewed by Theo Seiler, MD, PhD

CLINICAL DIAGNOSIS
Small changes can help beat endophthalmitis bug

IMAGING
Macular OCT: Why it’s a must for glaucoma treatment

DEVICE TECHNOLOGY
Novel vitreoretinal tools advancing surgical outcomes

GENE THERAPY
Light-activated agent unique option for uveal melanoma

OphthalmologyTimes.com
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.

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ADVERSE EVENTS. Common postoperative adverse events reported in the randomized pivotal trial included stent obstruction (6.2%), intraocular inflammation (5.7% for iStent inject vs. 4.2% for cataract surgery only), secondary surgical intervention (5.4% vs. 5.0%) and BCVA loss ≥ 2 lines ≥ 3 months (2.6% 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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Researchers are finding that endophthalmitis rates after intravitreal injections can decrease with the implementation of a few relatively easy changes.
Perils of Project Nightingale

Google-Ascension deal ignites private data debate

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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“It is a capital mistake to theorize before you have all the evidence.” – Sherlock Holmes, A Study in Scarlet

I WAS invited to participate in a recent panel about emerging trends in the future of healthcare. Artificial intelligence, telemedicine, gene therapy, and immuno- oncology are all fascinating scientific advances that people like to think about.

As we enter another election cycle, some politicians are calling for dramatic overhauls of the U.S. healthcare system. This includes price controls and European-style, mandatory single-payer governmental insurance (“Medicare for All”), which suggest the possibility of enormous change in how this huge industry works.

The panel discussion was moving along in a reasonable way and the audience of a few hundred seemed to be listening closely. Each panelist would address the question asked of him or her and the room was otherwise fairly quiet. If the moderator or a panelist inserted a little humor into the discussion, the audience would laugh politely, but that was about it.

Then a question was asked of one of my fellow panelists: “There is tremendous interest in many sectors (insurance companies, pharmaceutical companies, researchers, etc.) in obtaining and analyzing the healthcare data of large numbers of patients. My question to you is: Who owns that data?”

The panelist, an executive of a medical device manufacturer, responded quickly. “Patients own their data.” After a one-second pause, the audience, previously quiet, burst into loud applause.

“People clearly care a great deal about this issue,” was my immediate thought.

The recent revelation about the existence of “Project Nightingale” and the ensuing uproar were both interesting and predictable. The Wall Street Journal reported that Google began the project in secret last year with St. Louis-based Ascension, a Catholic chain of 2,600 hospitals, doctors’ offices and other facilities and the second largest health system in the United States.

“The data involved in the initiative encompasses lab results, doctor diagnoses and hospitalization records, among other categories, and amounts to a complete health history, including patient names and dates of birth. Neither patients nor doctors have been notified. At least 150 Google employees already have access to much of the data on tens of millions of patients.”

As I understand it, based on news reports I have read, Ascension’s position maintains that analyzing the data using artificial intelligence and machine learning will result in strategies to ultimately improve care of patients. The assertion is that the use of the data for this purpose is legal and ethical, and the companies did not need to secure permission from patients to start mining the data and did not need to inform its doctors that this huge data mining project was under way.

Not everyone else is so sure. According to Ellen Clayton, professor biomedical ethics at Vanderbilt University, “the optics are bad.”

“The legal argument is tenuous,” she said. “Ethically, this is a bad strategy. They need to tell people what they are doing.”

U.S. senators—including Sen. Bill Cassidy, a Louisiana Republican who is a physician—are expressing concern about the program, calling for a moratorium or investigation or proposing legislation.

Again, according to The Wall Street Journal, Google wouldn’t disclose the financial terms of the deal with Ascension. Nor would it say who at Google is allowed to access the data.

Let’s presume the motives of all involved in Project Nightingale are pure. That does not change the fact that Americans do not want their data shared in secret deals. Having this program come to light this way was a mistake by both corporations.

REFERENCE
- Google’s ‘Project Nightingale’ Gather Personal Health Data on Millions of Americans. WSJ Nov 11, 2019
XIIDRA MAY INTERRUPT THE CYCLE OF INFLAMMATION CENTRAL TO DRY EYE DISEASE\textsuperscript{1,2}

The exact mechanism of action of Xiidra in Dry Eye Disease is not known.\textsuperscript{1}

**Indication**

Xiidra\textsuperscript{\textregistered} (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:**

ADVERSE REACTIONS

Clinical Trials Experience

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

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.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

USE IN SPECIFIC POPULATIONS

Pregnancy

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

Animal Data

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

Lactation

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

Pediatric Use

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

CONTRAINdications

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

BRIEF SUMMARY:

Consult the Full Prescribing Information for complete product information.

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

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

CONTRAINDICATIONS

Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients in the formulation.
Holiday cheer as we focus on 2020

Mike Hennessy Sr., Chairman and founder of Ophthalmology Times’ parent company, MJH Life Sciences

The final page on the calendar, December ushers in the holidays and it offers the ophthalmic community an opportunity to both reflect on the year behind us and look ahead to the prospects of a new year. We expect that 2020 will bring increased focus to our industry, and we have some content this month that will help you prepare for the new year.

On the cover of this month’s issue, we feature the latest developments with regard to retromunab, shown in a phase II study to markedly reduce proptosis and diplopia in patients with thyroid eye disease.

In another cover article, we also examine the impact of oxygen on crosslinking. Theo Seiler, MD, PhD, discusses the new understanding of the effect of oxygen on crosslinking which may allow clinicians to compensate for the lack of oxygen.

In surgery, we also focus on lenticules, noting that those obtained during the SMILE procedure are safe to use to treat other corneal disease because there was no evidence of pathogens in the tissue. Gene therapy continues to be a source of innovation and this month we look at AU-011, from Aura Biosciences, a first-in-class drug being investigated as a treatment for choroidal melanoma with promising early results being reported from an ongoing phase Ib/II clinical trial. We also look at two anti-VEGF gene therapies currently being investigated in clinical trials of patients with exudative age-related macular degeneration. According to Szilárd Kiss, MD, initial efficacy and safety results are encouraging.

Imaging of the macula using optical coherence tomography has become nearly indispensable in glaucoma clinical practice, and it is proving particularly useful for examining the RGCs and axons, the cells that are affected by the disease. This month, we also note that current OCT devices provide imaging of the rim and peripapillary retinal nerve fiber layer to aid the diagnosis of glaucoma. Future generations of the technology should be able to visualize the deeper structures of the optic nerve head and reveal existing damage that currently is masked, with the goals of earlier diagnosis and intervention.

As the year comes to a close, we continue to see advances in device technology. The technologies used by retina surgeons are moving ahead at a rapid-fire pace. Dozens of new devices that are smaller (and sometimes larger), shorter, brighter, and lighter have recently become commercially available with the hope of making surgeries easier and more efficient. This could prove to be a critical boost to your practice.

In therapeutics, we look this month at novel drug-delivery technologies that are improving control of pain and inflammation after cataract and other ocular surgeries. Alice Epitropoulos, MD, explains that a number of new advances in drug delivery have been introduced over the past year or two that are helping patients who have undergone cataract surgery and who are having trouble instilling drugs more easily reap the benefits of their prescribed medications.

Clinical diagnosis is seeing advances in artificial intelligence, with screenings that could result in lower costs and quicker treatment of diabetic retinopathy. Srinivas R. Sadda, MD, points out that the availability of artificial intelligence (AI) systems should increase the efficiency of point-of-care DR screening programs. We also offer details on factors that have been connected with lower rates of endophthalmitis, some of which are intuitive and others not so much so.

As we wrap up another successful year, our team at Ophthalmology Times would like to wish you all a happy, healthy, and safe holiday season and a prosperous 2020.
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Recycling lenticules from SMILE offers benefits

Proper processing of materials can result in low infection, rejection risks

By Lynda Charters; Reviewed by Fengju Zhang, MD

The use of lenticular tissue acquired during the SMILE procedure seems to be the same with a minimal risk of infection, and the risk of rejection can be reduced by using an appropriate preservation method.

Myopia has an extremely high incidence in China, and as a result, numerous patients undergo the SMILE procedure, according to Fengju Zhang, MD.

“Because of this, we have accumulated many transparent lenticules after the surgeries and they are being reused in a number of corneal procedures, such as patching corneal perforations and correcting hyperopia, keratoconus, and ectasia after LASIK,” said Dr. Zhang, from the Beijing Tongren Eye Center, Beijing Tongren Hospital, and the Beijing Ophthalmology and Visual Sciences Key Lab, Capital Medical University, Beijing City, China.

However, the recycling of this tissue does not come without inherent risks. Possible infections that can take hold include herpes simplex virus (HSV), which can be latent in corneal stromal tissue for an extended period as well as bacteria, fungi, and Acanthamoeba that may be lurking in the normal conjunctival sac, she explained.

Another potential problem is immunologic rejection following implantation of the lenticules.

One Chinese study reported that at the one-year follow-up of 29 cases (53 eyes) that underwent allelogenic corneal stromal lenticule implantation to treat hyperopia, rejection of the tissue occurred in three eyes (5.66%) of two patients, Dr. Zhang noted.

Clinical Trial

In light of these complications, Dr. Zhang and colleagues undertook a study to detect pathogens and antigens in the fresh lenticules obtained during the SMILE procedure.

A total of 167 patients who underwent the SMILE procedure from October 2018 to April 2019 were chosen randomly. Those included had no systemic diseases, no history of use of systemic hormones or immunosuppressive drugs, no ocular diseases except for a refractive error, no history of ocular surgery or trauma. Patients had a stable refractive with no change exceeding 0.5 D annually for two years.

Patients also could not have used soft spherical contact lenses within one week, toric soft contacts and hard contacts within two weeks, or orthokeratology lenses within three months before surgery.

Any eyes with or suspected of having corneal ectasia, moderate to severe dry eye, severe meibomian gland disease, or an allergy induced by contact lenses were excluded.

SMILE lenticules were collected in 128 eyes of 64 patients with myopia. The donor specimens from each patient were divided into two groups in order to detect pathogens: specimens from 64 eyes (32 left and right eyes) and specimens from 64 eyes (32 left and right right); in the latter group, each specimen was divided into three pieces.

In the first group of 64 eyes, polymerase chain reaction (PCR) was performed to detect HSV-2; in the second group of 64 eyes, cultures were carried out to identify bacterial, fungal, and Acanthamoeba, Dr. Zhang recounted.

The investigators also undertook another experiment to identify antigens. Lenticules were collected during SMILE from 132 eyes of 103 patients with myopia and divided into three groups of 44 specimens each: the fresh group, the −78°C glycerol preservation group, and the 0.1% sodium dodecyl sulfate (SDS) group. All specimens were subjected to immunohistochemistry, Western blot analysis, transmittance electron microscopy (TEM), transmittance, and nanoindentation.

Pathogen, Antigen Detection

PCR showed negative results in all cases for detecting HSV-1 and −2, bacteria, fungi, and Acanthamoeba in both patients with and without a history of contact lens wear.

Regarding antigen detection, in the fresh group, immunohistochemistry showed a positive result for detection of HLA/B/C and HLA-DR. No positive results were seen in the −78°C glycerol preservation and the 0.1% SDS groups.

Western blotting analysis reflected the immunohistochemistry findings. TEM showed collagen fibrils were very regular in the fresh group and the nuclei were intact; in the −78°C glycerol preservation group, the collagen fibrils were regular but the interiors of the nuclei were destroyed; and in the SDS group, both elements were completely destroyed, Dr. Zhang noted.

Regarding transmittance, in the fresh and −78°C glycerol preservation groups, the specimens were transparent, with average transmittance values of 89.32% and 87.94%, respectively; however, in the SDS group the transmittance value was lower at 82.09%.

The nanoindentation curves showed the highest Young’s modulus values in the fresh and glycerol groups, with values of 49.21 and 60.6 kPA, respectively, compared with 24.26 kPA in the SDS group.

Human corneal stromal lenticules from SMILE have a low risk of infection for reuse, Dr. Zhang said. “HLA-I and HLA-II antigens were all expressed in human corneal stromal lenticules from SMILE, and there is a risk of transplant rejection for reuse,” she said.

“An ideal method to reduce the expression of antigen in human corneal stromal lenticules is by using −78°C pure glycerol preservative.”

Deeper

In discussing the negative pathogenic findings of the study, Dr. Zhang said the study subjects were young and healthy with no systemic or ocular diseases.

“Previous studies have reported that HSV-1 was detected mainly in the limbal tissue, while the corneal stromal lenticules were located within the central 6.5-mm diameter of the anterior stroma, which brings us to a advantage of the SMILE procedure,” she said.

“Because no knife is used, no corneal flap is created, and there is no exposed matrix bed, SMILE is unlike the bacteria-carrying corneal layers of LASIK, and the risk of microbial contamination of the conjunctival sac during SMILE is low,” Dr. Zhang said.

She said she considered the sample size to be small. Regarding the results of antigen detection, Dr. Zhang explained that results achieved with the −78°C
C pure glycerol preservation method was preferred because it reduced the antigen expression by rupturing the cells.

“Based on our study results, the human corneal stromal lenticules from SMILE have a low infection risk for reuse,” she said. “HLA-I and HLA-II antigens were both expressed in human corneal stromal lenticules obtained during the SMILE procedure, and there is a risk of transplant rejection for reuse. “The –78°C pure glycerol preservation is an ideal method to reduce the expression of antigen in human corneal stromal lenticules.” Dr. Zhang concluded.

CROSSLINKING

(Continued from page 1)

According to Dr. Seiler, the real bottleneck was found to be the level of interstitial oxygen.

STEP 1

Early in the evolution of CXL, John Kanellopoulous, MD, suggested that the lengthy treatment process comprising 30 minutes each of drops and irradiation be altered to an increased irradiance of 9 mW/cm² to become more practice-friendly.

However, shorter was not better, and actually proved to be less efficient. Other studies also showed that the higher irradiance rates (30 mW/cm²) resulted in a much flatter demarcation line compared with irradiance of 3 mW/cm², Dr. Seiler explained.

A look at the other end of the treatment spectrum, i.e., 1.5 mW/cm² for 60 minutes, found no difference between that lower level and the standard level of 3 mW/cm² and the lower level required twice the time.

The first conclusion that investigators drew was that irradiances higher than 9 mW/cm² cause a significant reduction in the efficacy of CXL.

STEP 2

Investigators then moved on to evaluate the riboflavin dose. The result was similar to that of the irradiance level—more is not necessarily better. The standard dose of 0.1% produced desirable CXL effects to a depth of about 300 µm; increasing the dose to 0.5% resulted in complete absorption within the first 100 µm and there was no volume effect in diseased corneas, according to Dr. Seiler.

The finding that higher concentrations of riboflavin do not increase the efficacy of CXL has been corroborated by other groups of investigators.

TAKE-HOME

The impact of oxygen on crosslinking procedures was not appreciated until recently. New understanding of the effect of oxygen on crosslinking may allow clinicians to compensate for the lack of oxygen.

Investigations carried out by Avedro found immediately after the ultraviolet application, the oxygen in the cornea was consumed; with the 30 mW/cm² protocol, that happened in one second and within about five seconds with the 3 mW/cm² protocol, Dr. Seiler noted. These results begged the question regarding why the irradiance is performed for 30 minutes.

In addition, it also forced investigators to evaluate what happens if more oxygen is added. Dr. Seiler and colleagues added more than 90% oxygen over the cornea and then turned the ultraviolet light on, the oxygen was also consumed rapidly, but 2% to 3% remained.

“This made us hope that there was still oxygen-mediated CXL going on,” Dr. Seiler explained. They found that with use of supplemental oxygen, sufficient oxygen was present even at a corneal depth of 300 µm to initiate CXL.

“Because of this, we believe that supplemental oxygen is the ‘new kid in town’ and likely the most successful factor in improving the efficiency of crosslinking,” Dr. Seiler said. “Interstitial oxygen is the real bottleneck of crosslinking. Adding supplemental oxygen is a simple way to increase the efficiency of the procedure.”

With epi-on procedures, there is far less activity in the cornea because of the lack of oxygen. Dr. Seiler also noted the “dramatic” corneal flattening of 6 D to 8 D in customized CXL procedures in epi-off cases at one month postoperatively.
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INDICATIONS AND USAGE
CEQUA™ (cyclosporine ophthalmic solution) 0.09% is a calcineurin inhibitor immunosuppressant indicated to increase tear production in patients with keratoconjunctivitis sicca (dry eye).

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS
Potential for Eye Injury and Contamination: To avoid the potential for eye injury and contamination, advise patients not to touch the vial tip to the eye or other surfaces.
Use with Contact Lenses: CEQUA should not be administered while wearing contact lenses. If contact lenses are worn, they should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following administration of CEQUA ophthalmic solution.

ADVERSE REACTIONS
The most common adverse reactions reported in greater than 5% of patients were pain on instillation of drops (22%) and conjunctival hyperemia (6%). Other adverse reactions reported in 1% to 5% of patients were blepharitis, eye irritation, headache, and urinary tract infection.

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

Brief Summary of Prescribing Information for
CEQUA™ (cyclosporine ophthalmic solution) 0.09%, for topical ophthalmic use

CEQUA™ (cyclosporine ophthalmic solution) 0.09%
See package insert for Full Prescribing Information.

INDICATIONS AND USAGE
CEQUA ophthalmic solution is a calcineurin inhibitor immunosuppressant indicated to increase tear production in patients with keratoconjunctivitis sicca (dry eye).

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Potential for Eye Injury and Contamination
To avoid the potential for eye injury and contamination, advise patients not to touch the vial tip to the eye or other surfaces.

Use with Contact Lenses
CEQUA should not be administered while wearing contact lenses. If contact lenses are worn, they should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following administration of CEQUA ophthalmic solution.

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

In clinical trials, 769 patients received at least 1 dose of cyclosporine ophthalmic solution. The majority of the treated patients were female (63%).

The most common adverse reactions reported in greater than 5% of patients were pain on instillation of drops (22%) and conjunctival hyperemia (6%). Other adverse reactions reported in 1% to 5% of patients were blepharitis, eye irritation, headache, and urinary tract infection.

USE IN SPECIFIC POPULATIONS
Pregnancy
Risk Summary
There are no adequate and well-controlled studies of CEQUA administration in pregnant women to inform a drug-associated risk. Oral administration of cyclosporine to pregnant rats or rabbits did not produce teratogenicity at clinically relevant doses.

Data
Animal Data
Oral administration of cyclosporine oral solution (USP) to pregnant rats or rabbits was teratogenic at maternally toxic doses of 30 mg/kg/day in rats and 100 mg/kg/day in rabbits, as indicated by increased pre- and postnatal mortality, reduced fetal weight, and skeletal retardations. These doses (normalized to body weight) were approximately 3200 and 21,000 times higher than the maximum recommended human ophthalmic dose (MRHOD) of 1.5 mcg/kg/day, respectively. No adverse embryofetal effects were observed in rats or rabbits receiving cyclosporine during organogenesis at oral doses up to 17 mg/kg/day or 30 mg/kg/day, respectively (approximately 1800 and 6400 times higher than the MRHOD, respectively).

An oral dose of 45 mg/kg/day cyclosporine (approximately 4800 times higher than MRHOD) administered to rats from Day 15 of pregnancy until Day 21 postpartum produced maternal toxicity and an increase in postnatal mortality in offspring. No adverse effects in dams or offspring were observed at oral doses up to 15 mg/kg/day (approximately 1600 times greater than the MRHOD).

Lactation
Risk Summary
Cyclosporine blood concentrations are low following topical ocular administration of CEQUA. There is no information regarding the presence of cyclosporine in human milk following topical administration or on the effects of CEQUA on breastfed infants and milk production. Administration of oral cyclosporine to rats during lactation did not produce adverse effects in offspring at clinically relevant doses. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for CEQUA and any potential adverse effects on the breastfed child from cyclosporine.

Pediatric Use
The safety and efficacy of CEQUA ophthalmic solution have not been established in pediatric patients below the age of 18.

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

PATIENT COUNSELING INFORMATION
Handling the Vial
Advise patients to not allow the tip of the vial to touch the eye or any surface, as this may contaminate the solution. Advise patients also not to touch the vial tip to their eye to avoid the potential for injury to the eye.

Use with Contact Lenses
CEQUA should not be administered while wearing contact lenses. Patients with decreased tear production typically should not wear contact lenses. Advise patients that if contact lenses are worn, they should be removed prior to the administration of the solution. Lenses may be reinserted 15 minutes following administration of CEQUA ophthalmic solution.

Administration
Advise patients that the solution from one individual single-use vial is to be used immediately after opening for administration to one or both eyes, and the remaining contents should be discarded immediately after administration.

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PXR-08050 2018
Light-activated agent novel option for uveal melanoma

Targeted therapy could ultimately prove to be primary treatment for disease

By Cheryl Guttmann Krader, BS, Pharm; Reviewed by Amy Schefler, MD

A U-011 (Aura Biosciences) is a first-in-class drug being investigated as a treatment for choroidal melanoma with promising early results being reported from an ongoing phase Ib/II clinical trial, according to Amy Schefler, MD.

Dr. Schefler is an ocular oncologist in private practice, Retina Consultants of Houston, Houston, TX.

AU-011 is a bioconjugate combining recombinant viral-like particles (VLPs) derived from the human papillomavirus with a small molecule photosensitizer that is activated by 689-nm near infrared light (IR700DX). The VLPs bind selectively to uniquely modified heparan-sulfated proteoglycans that are overexpressed on the membrane of ocular melanoma cells. Laser irradiation with near-infrared light causes focused activation of the bioconjugate, leading to generation of reactive oxygen species that damage the melanoma cell membrane, causing acute tumor cell necrosis.

Damage to healthy surrounding tissue is avoided because of the dual specificity of the investigational agent’s mechanism of action, Dr. Schefler explained.

‘One of the major goals of this treatment is to avoid vision loss that can occur by using brachytherapy to treat tumors located in the fovea and other critical areas.’

— Amy Schefler, MD

‘Its dual specificity and ability to cause targeted necrosis likely confers a safety advantage for AU-011 compared with brachytherapy and explains the findings that are being observed in the clinical trial regarding change in tumor thickness and vision preservation,’ she said.

Safety is being investigated as the primary objective of the phase Ib/II study, which has an ascending single and repeat dose design followed by two expansion cohorts. It initially enrolled patients with small to medium choroidal melanomas that met the clinical diagnosis agreed upon with the FDA and that would have been candidates for plaque brachytherapy. Subsequently, patients with documented tumor growth and thinner tumors were enrolled to better evaluate the safety and efficacy in a broader range of tumor sizes with early stage disease, consisting of subjects with small choroidal melanoma or high-risk melanoma suspects.

In the current cohort, which is the last cohort being enrolled, there is a requirement for documented tumor growth within the past two years. Subjects in this cohort receive two cycles of treatment at an interval of three months. Each cycle consists of three weekly intravitreal injections of AU-011; each injection is followed by two laser light applications.

A total of 46 subjects have been treated in the phase Ib/II clinical trial. Safety data show that AU-011 has been well-tolerated in the majority of subjects.

In the overall population, the most common adverse events were anterior chamber inflammation, posterior chamber inflammation, and increased IOP, all of which are manageable with steroid and/or ocular anti-hypertensive therapy. The intraocular inflammation had a subacute onset, was mostly mild to moderate in severity, and resolved with topical, periocular, or oral steroid treatment.

There was one serious adverse event (SAE) involving acute severe vision loss from pigmentary changes at the edge of the tumor in the area of laser treatment involving the fovea. However, 22 of the subjects enrolled have subfoveal or peri-foveal tumors (within 3.0 mm of the fovea) and 27 of the subjects have tumor within 3.0 mm of the optic nerve and all of these subjects would be considered high risk for vision loss with radiation therapy.

“The protocol for laser application was modified after this event to deliver only one laser spot in the foveal area per treatment, and there have been no other cases of acute vision loss since,” Dr. Schefler said.

Preservation of visual acuity is being analyzed as a secondary outcome measure.

“One of the major goals of this treatment is to avoid the vision loss that can occur using brachytherapy to treat tumors located in the fovea and other critical areas,” Dr. Schefler said. During available follow-up that reaches up to two years, vision loss (≥ 15 ETDRS letters) occurred in three subjects, including the subject with the SAE mentioned above and two subjects who developed subretinal fluid in the fovea.

Vision was preserved in greater than 90% of subjects treated at all doses who did not require rescue with standard of care including those subjects who have received one or two cycles at a full therapeutic dose of AU-011. These subjects were otherwise candidates for brachytherapy and avoided the vision loss and comorbidities of radioactive treatments.

Continues on page 16: Option
Study targets gene therapy for exudative AMD patients

Trial results show promise of transfection with genes for anti-VEGF proteins

By Cheryl Guttman Krader, BS, Pharm; Reviewed by Szilárd Kiss, MD

ANTI-VEGF GENE THERAPY for exudative age-related macular degeneration (AMD) has transformative potential for reducing treatment burden and improving patient outcomes, according to Szilárd Kiss, MD.

Two investigational anti-VEGF gene therapies are currently being investigated in clinical trials – RGX-314 (Regenxbio) and ADVM-022 (Adverum). Dr. Kiss described the two technologies and reviewed some preliminary clinical trial results that support their promise for providing sustained benefit with a single injection.

“Considering the treatment burden of anti-VEGF therapy for other ocular diseases, we can imagine that exudative AMD is just the first indication that will be targeted for anti-VEGF gene therapy,” said Dr. Kiss, chief, Retina Service, associate professor of Ophthalmology, and associate dean at Weill Cornell Medical College, New York, NY.

RGX-314 delivers a gene for an anti-VEGF fab protein that is similar to ranibizumab. It uses adeno-associated virus-8 (AAV8) as a vector and is administered in the operating room as a subretinal injection.

“AAV is the most common viral vector carrier used for gene therapy. Different AAV serotypes have different tissue selectivity,” Dr. Kiss explained. “AAV8 is a wild type AAV that has the propensity for greater transfection of retinal cells compared with AAV2 following subretinal gene therapy delivery.”

Tumor control, defined as change in tumor height ≤ 0.5 mm and in LBD ≤ 1 mm, is currently achieved component of the dead tumor cells.” In addition, acute cellular necrosis is a disease is a small component of the overall lesion, targets only the tumor cells, which in early stage cases with brachytherapy is not completely understood. Probably, however, it is because the treatment only the tumor cells, which in early stage disease is a small component of the overall lesion, not the healthy surrounding tissues,” Dr. Scheffler said. “In addition, acute cellular necrosis is a pro-inflammatory type of cell death and the area of necrosis undergoes fibrosis that will replace a large component of the dead tumor cells.”

Tumor control, defined as change in tumor height ≤ 0.5 mm and in LBD ≤ 1 mm, is currently achieved mild in severity, and there have been no serious drug-related adverse events.

“Fifteen serious adverse events were recorded in nine subjects and there were two deaths, but none were related to the treatment,” Dr. Kiss said.

There has been no observed clinically determined immune responses, drug-related ocular inflammation, or post-surgical inflammation exceeding that expected following routine vitrectomy. Two ocular procedure-related serious adverse events occurred, including a peripheral retinal detachment that was repaired and a case of endophthalmitis following collection of an aqueous humor sample.

In the fourth dose cohort, which included 12 patients, BCVA remained stable through six months and mean CRT improved. Five (42%) patients were injection-free through the six months, requiring no rescue anti-VEGF therapy.

The fifth dose cohort includes 12 patients who have five to six months of available follow-up.

Continues on page 18: AMD
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### WARNINGS/PRECAUTIONS:

- **Careful preoperative evaluation and sound clinical judgment should be used by the surgeon to decide the risk/benefit ratio before implanting a lens in a patient with any of the conditions described in the Directions for Use labeling.**
- **Physicians should target emmetropia and ensure that IOL centration is achieved. For the AcrySof® IQ PanOptix® Trifocal IOL, the lens should not be implanted if the posterior capsule is ruptured, if the zonules are damaged or if a primary posterior capsulotomy is planned. Rotation can reduce astigmatic correction.** If necessary, lens repositioning should occur as early as possible prior to lens encapsulation.
- **Some visual effects may be expected due to the superposition of focused and unfocused multiple images.** These may include some perceptions of halos or starbursts, as well as other visual symptoms. As with other multifocal IOLs, there is a possibility that visual symptoms may be significant enough that the patient will request explant of the multifocal IOL. A reduction in contrast sensitivity as compared to a monofocal IOL may be experienced by some patients and may be more prevalent in low-lighting conditions. Therefore, patients implanted with multifocal IOLs should exercise caution when driving at night or in poor visibility conditions. Patients should be advised that unexpected outcomes could lead to continued spectacle dependence or the need for secondary surgical intervention (e.g., intraocular lens replacement or repositioning). As with other multifocal IOLs, patients may need glasses when reading small print or looking at small objects. Posterior capsule opacification (PCO) may significantly affect the vision of patients with multifocal IOLs sooner in its progression than patients with monofocal IOLs. Prior to surgery, physicians should provide prospective patients with a copy of the Patient Information Brochure, available from Alcon, informing them of possible risks and benefits associated with the AcrySof® IQ PanOptix® Trifocal IOLs.

### ATTENTION:

Reference the Directions for Use labeling for each IOL for a complete listing of indications, warnings and precautions.

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### AMD

(Continued from page 16)

This group also had stable BCVA and improved CRT, and nine of the patients (75%) remained injection-free.

“Standardization, automation, and surgeon skill are critical for the success and safety of subretinal gene therapy,” Dr. Kiss noted. “Surgeons need extensive training that begins in the wet lab and then moves into a virtual reality environment.”

ADVM-022 is an AAV vector encoding aflibercept. It uses a novel AAV-7m8 capsid for gene delivery, which is an engineered vector optimized for strong transfection following in-office intravitreal injection.

### OPTIC TRIAL

OPTIC, the phase 1 clinical trial investigating ADVM-022 in exudative AMD, is evaluating two dose levels of the gene therapy. Eligible subjects must demonstrate a meaningful response to anti-VEGF therapy and are receiving an injection of aflibercept (Eylea, Regeneron) seven to 14 days prior to ADVM-022 injection.

Data from median follow-up of eight months was available for six patients enrolled in OPTIC.

This first cohort had received an average of 6.2 anti-VEGF injections in the eight months prior to study screening and a mean of 35.3 injections since being diagnosed with exudative AMD.

There were some other interesting findings, and patients were requiring few, if any, injections.

Dr. Kiss pointed out that one patient had received 109 previous injections. “Of the 52 rescue injection opportunities during the eight-month follow-up period, zero rescue injections were needed in any of the first six subjects,” he said.

In this small group there have been no serious adverse events nor any adverse events meeting criteria for dose-limiting toxicity.

According to the research, there were 19 ocular adverse events potentially related to the investigational agent, of which 14 were mild and five rated as moderate in severity.

Mild anterior inflammation and vitreous cells were the most common adverse events, and all were well controlled with topical corticosteroids. The research team reported that there were no cases of vasculitis, retinitis, or choroiditis.

Evaluations for efficacy showed BCVA remained stable and CRT improved while all patients remained injection-free.

### RETINAL GENE THERAPY

Gene therapy approaches represent three basic categories, the choice of which depends on the underlying pathology. Both RGX-314 and ADVM-022 are gene augmentation approaches as they are designed to deliver a gene for a functioning protein that is not naturally produced.

Gene augmentation can also be utilized to replace a non-functioning gene, as represented by voretigene nepar-
Imaging of the macula using optical coherence tomography (OCT) has become nearly indispensable in glaucoma clinical practice.

Jullia A. Rosdahl, MD, PhD, demonstrated the importance of the technology for her patients, describing the case of a 69-year-old Caucasian man who she last saw five years earlier, and who did not want treatment at that time. After another physician recommended treatment, he returned for a second opinion for his normal tension glaucoma.

The patient had visual acuities of 20/25 in both eyes and intraocular pressures of 13 mm Hg in both eyes (untreated). He had a paracentral visual field (VF) defect that had not worsened measurably over the five years. Progressive retinal nerve fiber layer (RNFL) thinning was seen on the OCT maps and corresponded to the VF defect. The glaucoma appeared to have progressed. The patient was skeptical.

Dr. Rosdahl is associate professor of ophthalmology, Duke University, Department of Ophthalmology, Chapel Hill, NC.

Macular OCT: A must for treating glaucoma patients

Commercial instruments targeting structure, function correlations

By Lynda Charters; Reviewed by Jullia A. Rosdahl, MD, PhD

Imaging of the macula using optical coherence tomography (OCT) has become an invaluable tool in glaucoma clinical practice. OCT allows physicians to detect defects and other issues more quickly. (Image courtesy of Jullia A. Rosdahl, MD, PhD)
GLAUCOMA MYSTERY: FOCUS ON DEEP OPTIC NERVE STRUCTURES

For earlier detection, technology can help physicians unmask existing damage

By Lynda Charters; Reviewed by Claude F. Burgoyne, MD

CURRENT OPTICAL COHERENCE TOGRAPHY (OCT) devices provide imaging of the rim and peripapillary retinal nerve fiber layer (RNFL) to aid the diagnosis of glaucoma. Future generations of the technology should be able to visualize the deeper structures of the optic nerve head (ONH) and reveal existing damage that currently is masked, with the goals of earlier diagnosis and intervention.

The need for the expanded capabilities of OCT is apparent upon a review of the literature. “Clinicians are highly variable in their assessments of the disc margin and rim width,” said Claude F. Burgoyne, MD, the Van Buskirk Chair for Ophthalmic Research, and director, Optic Nerve Head Research Laboratory, Dovers Eye Institute, Portland, OR.

In a study published by Dr. Burgoyne and colleagues (Am J Ophthalmol 2018;192:65-76), five glaucoma specialists evaluated 214 photographs, and the authors reported the wide variability of the disc margin and rim width. In a follow-up study (Am J Ophthalmol 2019;199:28-43), the authors used a Spectralis device (Heidelberg Engineering) to evaluate a subset comprised of 151 of the 214 photographs in which OCT images were performed on the same day and evaluated how well and consistently suspicious rim tissue could be detected by the OCT instrument. Another study performed by Jean-Claude Mwanza, MD, and colleagues (Am J Ophthalmol 2017;184:183-4) used a Cirrus instrument (Carl Zeiss Meditec) to evaluate the cup-to-disc ratios obtained by the instrument and clinicians.

Continues on page 22: Optic...
INDICATIONS AND USAGE
FLAREX® (fluorometholone acetate ophthalmic suspension) is indicated for use in the treatment of steroid-responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the eye.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS
Contraindicated in acute superfi cial herpes simplex keratitis, vaccinia, varicella, and most other viral diseases of the cornea and conjunctiva; mycobacterial infection of the eye; fungal diseases; acute purulent untreated infections, which like other diseases caused by microorganisms, may be masked or enhanced by the presence of the steroid; and in those persons who have known hypersensitivity to any component of this preparation.

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

STUDY DESIGN:
The efficacy and safety of FLAREX (n=41) vs FML* (n=37) were evaluated in a randomized, double-blind clinical trial in 78 patients with ocular surface infl ammation (eg, conjunctivitis, episcleritis, scleritis) in one or both eyes. In a separate randomized, double-blind clinical trial in 82 patients with ocular surface infl ammation in one or both eyes, the efficacy and safety of FLAREX (n=37) vs prednisolone acetate 1.0% (n=45) were evaluated. In these studies, patients administered either FLAREX or FML*/prednisolone acetate 1.0% every 2 hours for the first 2 days and then every 4 hours thereafter, with signs and symptoms of infl ammation assessed at Days 1, 3, 8, and 13. At each visit, investigators determined if symptoms in the involved eye were resolved (cured), improved, unchanged, or worsened. If a patient was rated as cured before the end of the study, steroid drops were discontinued and the patient was considered to have completed the trial.2

Cost information based on Wholesale Acquisition Cost (WAC), 2019 data.

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FLAREX® (fluorometholone acetate ophthalmic suspension) 0.1% Brief Summary

INDICATIONS AND USAGE
FLAREX® (fluorometholone acetate ophthalmic suspension) is indicated for use in the treatment of steroid-responsive inflammatory conditions of the conjunctiva, cornea, and associated tear film of the eye.

DOSAGE AND ADMINISTRATION
Once a day using a single drop instilled into the conjunctival sac.

CONTRAINDICATIONS
Contaminated in acute superficial herpes simplex keratitis, vernal, vasoconstrictor, and most other viral diseases of the cornea and conjunctiva, mycobacterial infection of the eye, fungal disease, acute purulent uveal infection, which like other diseases caused by microorganisms, may be masked or enhanced by the presence of the steroid, and in those persons who have known hypersensitivity to any component of this preparation.

WARNINGS AND PRECAUTIONS
Topical Ophthalmic Use Only
For topical ophthalmic use only. Not for injection.

Viral Infections
Use in the treatment of herpes simplex infection requires great caution.

Bacterial Infections
Use of corticosteroids may suppress the host response and thus in the establishment of secondary ocular infections. Acute purulent infections may be masked or exacerbated by the presence of the steroid.

Fungal Infections
Topical infections of the cornea are particularly prone to develop coincidently with long-term local steroid application. Fungal infection must be considered in any persistent corneal ulceration where a sterile line has been used or is present.

Contamination
Do not touch dropper tip to any surface, as this may contaminate the suspension.

Contact Lens Wear
Contact lenses should be removed during instillation of FLAREX but may be reinserted 15 minutes after instillation.

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

PATIENT COUNSELING INFORMATION
Risk of Cataracts
Do not touch dropper tip to any surface, as this may contaminate the suspension.

Use with Contact Lenses
The preservation of FLAREX, benzoic acid sodium chloride, may be absorbed by soft contact lenses. Contact lenses should be removed during instillation of FLAREX but may be reinserted 15 minutes after instillation.

Temporary Blurred Vision
Patients should be advised that their vision may be temporarily blunted following dosing with FLAREX. Care should be exercised in operating machinery or driving a motor vehicle.

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Eyers, L. FLAREX (fluorometholone) [package insert]. Fort Worth, TX: Eyevance Pharmaceuticals, Inc.; 2023. Available at: www.eyevance.com/FLAREX.

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CLAUDE F. BURGOYNE, MD
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Heidelberg Engineering. He is also NIH RO1 funded to study the issues presented in this talk. Dr. Burgoyne disclosed that the information about each instrument was provided by the specific manufacturer and should be confirmed by each.

Dr. Burgoyne predicted that ONH anatomy will be integrated with the nerve fiber layer and the macula to increase detection of early glaucoma.

“Both the minimal rim width and peripapillary RNFL thickness are being used and their performance is similar,” he explained. “However, using them together fosters the eventual integration of macular data. OCT angiography may be helpful, but is still early in development.”
New vitreoretinal tools advancing surgical outcomes

Array of instruments available to make retinal surgeries safer, more efficient

By Lynda Charters; Reviewed by David R. Chow, MD, FRCS

Advances in the technologies used by retina surgeons are moving ahead at a rapid-fire pace. Dozens of new devices that are smaller (and sometimes larger), shorter, brighter, and lighter have recently become commercially available with the hope of making surgeries easier and more efficient. David R. Chow, MD, FRCS, detailed several new tools for physicians to consider adding to their practices.

Dr. Chow is assistant professor of ophthalmology, University of Toronto, St. Michael’s Hospital, Toronto Retina Institute, North York, Canada.

VITRECTOMY CUTTERS
Bausch + Lomb has introduced a bi-blade dual-port vitrectomy cutter with an innovative dual-blade design that features a cut rate of 15,000 cuts/minute and is available in three gauges: 23, 25, and 27. The instrument can increase balanced saline flow by 230% and increase vitreous flow by 180%.

Bausch + Lomb also has developed the Visette Hypersonic Vitrectomy probe that boasts a new cutting concept, in that the needle is mounted to a piezoelectric ultrasonic transducer that vibrates harmonically resulting in a cut rate greater than one million cpm. This instrument has been used in more than 200 procedures worldwide with a wide range of vitreoretinal pathologies. It can effectively remove vitreous, lens material, membranes, and silicone oil.

Alcon is offering the Hy permane 27-vitrectomy kit that includes a trocar/cannula, a 48-gauge metal, beveled-tip cannula that is available in 23- or 25-gauge oil-injection devices. It has very thin walls to facilitate injections into the subretinal space.

T A K E - H O M E
› For surgeons, the attention to detail in new technologies being offered today is allowing them to perform safer, more efficient procedures.

INFUSION SYSTEM
Bausch + Lomb has developed the Freeflow infusion device, which is an infusion line that is placed over the infusion cannula to maximize the internal diameter of the cannula. This improves flow rates by up to 40% and will be useful with the bi-blade vitrectomy probe to maintain infusion at high flow rates.

INTERNAL LIMITING MEMBRANE STAIN
DORC is currently trying to bring Brilliant Blue dye to the U.S. market. The dye is currently being reviewed by the FDA.

“...This is potentially the first FDA-approved staining agent for identification of the internal limiting membrane (ILM) intraoperatively,” Dr. Chow commented.

SUBRETINAL RETINAL INJECTION DEVICES
Three new such devices are becoming available this year. Altlaviz is releasing a microvolume injector with dose guidance; it is a self-powered stand-alone device, for use in stem cell and gene therapy. Besides providing visual and audible dose guidance, the injector also allows Bluetooth connectivity that displays the progress of the injection and the metrics.

Another injector from MedOne is the Nano Cannula, a 48-gauge metal, beveled-tip cannula that is specifically designed for use in subretinal procedures. Vortex has designed the Nano Subretinal Gateway Device that is designed to be used in the absence of a vitrectomy. This injector includes a 28-gauge needle, designed for transcleral injections, with an extendable bevel tip, 41-gauge flexible cannula that facilitates injections into the subretinal space.

FORCEPS DEVICE
Larger and smaller forceps handles have been introduced by Alcon, which have been designed for use by surgeons with large and small hands.

The Stiff Dex (Katalyst) is a 19-gauge telescoping stiffening sleeve on a 27-gauge forceps, which allows the forceps to have a much stiffer profile.

The Reddy end-grasping forceps (Bausch + Lomb) features microscorations with a long grasping platform and a window for visualization.

The Sharkskin ILM forceps (Alcon) features laser-ablated microstructures that are 10 x 10 x 5-um teeth that point toward the grasping edge, which increases the kinetic friction between the forceps and tissue. A second feature is a conforming platform that reduces by 50% the indentation force needed to grasp the ILM. Both features increase grasping ability.

CHANDELIER SYSTEM
Vitreq now has the 29-gauge Spotlight directional chandelier system that uses a unique fixation system to the drape above the patients brow to direct a wide-view light beam with a 29-gauge trocar cannula.

CANNULAS
A membrane-peeling Cannula (Katalyst) has burrs on the lateral edges to cut the ILM and a spatula shape with active extrusion to engage and remove the ILM flap. After removing the membrane, the same cannula is used to perform an air/fluid exchange.

MedOne is reintroducing the 27-gauge VFI Cannula with a Luer lock, which is the only all-metal 27-gauge oil-injection device. It has very thin walls to maximize the internal diameter of the cannula for speedy oil injection.

A 38-gauge cannula designed by Carl Claes, MD, has a 38-gauge tapered tip that is available in 23- or 25-gauge that is used to drain or close macular holes under silicone oil with active extrusion.

Continues on page 24: Tools
Harnessing research data for personalized healthcare

Combining information with artificial intelligence algorithms could transform landscape

By Steve Lenier; Reviewed by Jill Hopkins, MD

ONE HEALTHCARE LEADER is making an investment in personalized healthcare, combining the vast amounts of data being collected during clinical trials with artificial intelligence (AI) algorithms. Roche-Genentech sees a transformation on the horizon, based on the ability to use meaningful data on a large scale.

According to Jill Hopkins, MD, global head, ophthalmology personalized health care, Roche-Genentech, the goal of the company’s personalized healthcare initiative is for patients to be identified at earlier stages of disease, and to be able to predict their most likely treatment needs and responses with a large degree of accuracy. There is also potential to build toward a preventive strategy where vision might be preserved.

The company has targeted ophthalmology, oncology, and neuroscience as core focused therapeutic areas for the development of personalized healthcare solutions. The company is considering everything from digital tools to predictive and preventive algorithms of disease to change the way patients in these areas are treated. The question is how to take millions of data points being generated, and add machine learning tools for individualized disease progression and therapy.

Roche-Genentech has much legacy clinical trial data to use from the ranibizumab and lampalizumab trials. The database includes more than 13,000 patients, and around 3 million images. It continues to grow through active phase III programs investigating ranibizumab in the Port Delivery System and faricimab.

“We have worked to optimize the value of the existing data,” Dr. Hopkins said. “It is clinical trial grade data. It is longitudinal, with multimodal imaging, so it really provides a wonderful initial core data set on which to build some of the machine learning and deep learning proof of concept algorithms.”

Dr. Hopkins explained that the first step was to get the data into a format that could be interrogated by the AI tools. An article published in March was the first published as part of the ophthalmology personalized healthcare initiative, and suggests that artificial intelligence could be used to provide widespread, cost-effective eye screenings.1

Dr. Hopkins said the next step is finding how to validate these algorithms on larger, more diverse datasets, which may be best accomplished through collaboration. One of the challenges is to determine how to build and utilize collaborations to start to build larger collections of data, not only in terms of existing disease but also in earlier stages of disease. The organization sees a need for unprecedented levels of collaboration across the healthcare space to get enough data to really be able to answer key scientific questions and to cover enough patients to be generalizable.

One possible model could be a consortia framework, where a combination of pharmaceutical companies, academic institutions, and clinical groups could get together to look at collecting data in an ongoing fashion. The company is currently looking for the best ways to make this data usable, while always remaining sensitive to data privacy, and any other such issues.

The organization sees potential for personalized healthcare solutions—tools that could predict progression of disease and response to treatment as a means of delivering the right therapy at the right time, in the right dose, and with the right delivery system. As algorithms are developed, they must be tested and validated. As the company builds collaborations to build datasets, it will become possible to test an algorithm on a set of tens of thousands of patients.

Dr. Hopkins said because it is a new field, regulatory agencies are thinking carefully about what this will look like in terms of their framework. Roche-Genentech and other companies who are doing work in similar areas are working with the regulatory agencies to determine what makes sense moving forward regarding AI, machine learning, and algorithms to bring meaningful impact to patient care, she said.

REFERENCE

JILL HOPKINS, MD
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Dr. Hopkins is global head, ophthalmology personalized health care at Roche-Genentech. She has no other financial considerations to disclose.

NEW NEEDLE DESIGN
Lyubomyr Lytvynchuk, MD, designed a needle to perform intravitreal injections. It has a solid tip that may require less force during injection, and a proximal injection port that may reduce the amount of cellular tissue that is dragged into the eye during injections.

DAVID R. CHOW, MD, FRCCS
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This article was adapted from Dr. Chow’s presentation at the American Academy of Ophthalmology 2019 annual meeting. Dr. Chow has no financial interest in any aspect of this report.
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Novel delivery systems ease patient pain, inflammation

Physicians turning to new options that sidestep traditional treatments

By Lynda Charters; Reviewed by Alice Epitropoulos, MD

PHYSICIANS HEAR FROM well-intentioned patients all the time about their efforts to instill medications into their eyes perioperatively. The scenarios can vary from instilling too many or too few drops of the correct medications into the eye, forgetting to administer their drops at all, instilling the wrong drugs into the right place, or missing the mark altogether.

The end result is the same: the prescribed drugs are not going where they are intended to go and the desired therapeutic effect, alleviation of pain and inflammation, does not happen.

A number of new advances in drug delivery have been introduced over the past year or two that are helping patients who have undergone cataract surgery and who are having trouble instilling drugs to reap the benefits of their prescribed medications, according to Alice Epitropoulos, MD.

She is clinical assistant professor at The Ohio State University Wexner Medical Center and in private practice in Columbus, OH.

The availability of these formulations in Dr. Epitropoulos’ armamentarium “will elevate the level of patient care by alleviating the age-old problems associated with compliance,” she noted.

“These new drug-delivery systems are a major step forward and will help reduce ocular toxicity and improve patient compliance,” Dr. Epitropoulos said.

A dexamethasone ophthalmic intracameral injection, 0.4 mg (Dextenza, Ocular Therapeutics) was approved in 2018. This device, which is inserted into the punctum after ophthalmic surgery to treat pain and inflammation, is used instead of topical corticosteroid drops during the postoperative period. The insert delivers a sustained release of dexamethasone over a 30-day period.

Dr. Epitropoulos pointed out that in addition to lessening the treatment burden, it also is preservative-free, and prevents exacerbation of ocular surface disease via occlusion of the punctum.

A number of new advances in drug delivery have been introduced over the past year or two that are helping patients who have undergone cataract surgery and who are having trouble instilling drugs to reap the benefits of their prescribed medications, according to Alice Epitropoulos, MD.

Another form of dexamethasone was introduced, in early 2018, i.e., the dexamethasone intraocular suspension 9% (Dexycu, EyePoint Pharmaceuticals). This FDA-approved sustained-release intracameral injection is intended to treat inflammation after ophthalmic surgery. The effect of one injection lasts for 30 days.

STEROID DROPS AND GEL

Other steroid treatments have been engineered to be a step above standard drop therapy with enhanced penetration, which can improve efficacy and help to prevent ocular surface disease from corneal toxicity.

The first, loteprednol etabonate ophthalmic suspension 1% (Inve hostile, Kala Pharmaceuticals), makes use of nanoparticle technology to provide better penetration into the eye following ocular surgeries. The FDA approved this formulation for use after ocular surgery in 2018. The drug achieves improved intraocular penetration as the result of nanoparticle-sized particles that range from 200 to 400 nanomolars.

Dr. Epitropoulos explained that when dosed twice daily, the drug is designed to efficiently penetrate through the mucus barrier on the ocular surface and into the target tissue of the cornea and anterior chamber.

Another novel steroid, flurandrenol etabonate ophthalmic gel 0.38% (Lotemax SM, Bausch + Lomb), received FDA approval in early 2019. This formulation provides two times greater penetration to the aqueous humor as a result of its submicron-particle size. The particles are 80% smaller than those in the Lotemax gel formulation, which allows for more efficient penetration into the target tissues, Dr. Epitropoulos explained.

Lastly, fluorometholone acetate ophthalmic suspension 0.1% (Flares, Eyevance Pharmaceuticals LLC) is being reinvestigated after having been acquired recently by Eyevance Pharmaceuticals. “This topical steroid has the broadest indication of any current branded steroid. It is indicated for conditions of the bulbar and palpebral conjunctiva, the cornea, and anterior segment of the eye with a low incidence of increase in the intraocular pressure. It can be used for induction treatment for dry eye disease or other ocular surface inflammatory conditions, corneal procedures such as LASIK, PRK, keratectomy, corneal-crosslinking, Descemet stripping endothelial keratoplasty, Descemet’s membrane endothelial keratoplasty, and pterygium removal,” she pointed out.

PREVENTING FLOPPY IRIS SYNDROME

Phenylephrine and ketorolac intraocular solution 1%/0.3% (Omidria, Omeros) was FDA approved in 2014 and is indicated for maintaining pupil size and preventing intraoperative miosis during cataract surgery and reducing postoperative ocular pain.

This drug added to the irrigating solution during cataract surgery is particularly beneficial in patients who may have used alpha-blockers such as tamsulosin hydrochloride (Flomax, Sanofi) or other alpha blockers and are at possible risk of iris prolapse or billowing, also known as intraoperative floppy iris syndrome.

“Both Dextenza and Dexycu now have a permanent reimbursement J-code,” she said.

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Dr. Epitropoulos is a speaker and/or consultant for Bausch + Lomb, EyePoint Pharmaceuticals Inc., Kala, Ocular Therapeutics, and Omeros.
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patients, a complication that severely affects patient quality of life and the clinical activity score (CAS), which assesses the activity of TED.

Strabismus and blindness are other potential complications, said Dr. Douglas, professor of surgery, Division of Ophthalmology, and director, Orbital and Thyroid Eye Disease Center, Cedars Sinai Medical Center, Los Angeles. Given the severity of the disease, the need for a treatment is clear—specifically, a treatment that provides molecular targeting of the antigen, he explained.

“It is exciting for me to see that we might have a treatment that could be disease-altering, considering the impact that the disease has on them,” said Dr. Wester, subinvestigator in the OPTIC study, and associate professor of clinical ophthalmology, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami.

TED has an initial active phase followed by a stable phase.

“The ideal treatment would alter that course by altering the disease in the active phase leading to less long-term sequelae,” Dr. Wester said.

Medical treatments used for TED, none of which is FDA approved, include steroids, radiation, topcilizumab, rituximab, and others, and are less than ideal, Dr. Wester noted.

PHASE III STUDY, RESULTS

The study was a multicenter, 24-week, randomized, double-masked, placebo-controlled trial that included patients aged 18 to 80 years who had not undergone a previous treatment for TED and had active disease for less than nine months.

Patients randomly assigned to both active treatment (n = 41) and placebo (n = 42) underwent standardized infusions every three weeks, for a total of eight infusions. The doses begin at 10 mg/kg and go to 20/mg/kg; the first two doses are administered over 90 minutes and subsequent doses are given over 60 minutes.

The primary endpoint was a 2-mm or greater improvement in proptosis at week 24. A total of 39 and 40 patients, respectively, completed the treatment period.

The patients treated with teprotumumab had marked and early improvements in proptosis compared with those randomized to placebo, Dr. Wester noted, with 82.9% meeting the study criterion of greater than 2 mm of improvement, which translated to almost a 75% difference from the placebo group (p < 0.001).

The OPTIC study also showed improvement in the secondary endpoints. “We found that at week 24, 66% of patients treated with teprotumumab had a significant (p = 0.001) improvement from baseline of at least one grade of diplopia, compared to 29% of patients randomized to placebo. This endpoint measured the percentage of patients who reported at least some diplopia at baseline in the study eye and who had a reduction of grade 1 or higher with no correspondingly deteriorating deterioration (≥1 grade worsening) in the fellow eye at week 24,” Dr. Douglas said. The active-treatment group differed from the placebo group by more than 39% in improvement in diplopia.

The results also showed that the active-treatment patients had a significant (p = 0.001) improvement in quality of life of 13.79 measured on the Graves’ Ophthalmopathy Quality of Life scale compared with a change of 4.43 for patients randomized to placebo. He explained that a change of 6 points of the scale is considered clinically significant.

At week 24, the investigators found that 59% of patients randomized to teprotumumab achieved a CAS value of 0 or 1 compared with 21% of those randomized to placebo, a difference that also reached significance (p < 0.001). The CAS scale ranges from 0 to 7, with 0 indicating no swelling or activity.

The phase II study found that adverse events were mild to moderate in intensity and no non-serious events led to discontinuation. In the phase III trial, the safety profile was similar to the phase II study with no new safety observations. The drop-out rate was below 5%.

No deaths were related to treatment.

The most frequent adverse reactions related to teprotumumab were muscle spasms, hyperglycemia, hearing impairment, and infusion-related reaction, all of which resolved by the end of treatment.

These results seem to tick most of the boxes regarding Drs. Douglas and Wester’s definition of an ideal treatment for TED: decreased inflammatory signs, reduced proptosis and underlying pathology, reduced diplopia, improved quality of life, and minimal side effects.

The long-term duration of the responses to teprotumumab remains to be determined. An extension study is currently underway, according to Dr. Wester.

“That study will provide more data on the stability of the response,” she said. “Because I treat many TED patients, I find that we actually have the potential for a therapy that could alter the course of this disease and improve the patients’ quality of life in a much more meaningful way than the previously non-FDA-approved treatments is very exciting to me.”

Dr. Douglas also found the phase III results encouraging.

“This pivotal phase III, placebo-controlled study of teprotumumab demonstrated a significant reduction in proptosis, confirming the phase II study results seen with this targeted IGF-1R inhibitor for treating TED,” he said. “These results confirm that teprotumumab is effective in reducing proptosis, supporting a positive benefit-risk profile in the treatment of TED with apparent disease-modifying activity.”

Teprotumumab has received Priority Review, Orphan Drug, Fast Track, and Breakthrough Therapy designations from the FDA.
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I believe are primary reasons for choosing a TECNIS® IOL. Regarding SA, it has been shown in the laboratory that peak contrast performance is achieved through elimination of SA.8 In contrast to AcrySof® IOLs, only TECNIS® IOLs correct the full SA of the average aging cornea.9 Chromatic aberration is associated with the material of an IOL and corresponds with the Abbe number that is a measure of the material’s dispersion properties.10 A lower Abbe number indicates higher CA and higher light dispersion that can negatively impact image quality and IOL contrast performance.11 Compared with the TECNIS® material, the acrylic material used for AcrySof® IOLs has a lower Abbe number (higher CA), and in the Tecnis Symfony® IOL, CA is further reduced through use of an achromatic diffractive echelle technology.10,11,12

Clinical Outcomes

Studies investigating TECNIS® Personalized Vision combining the TECNIS Symfony® IOL with the TECNIS® Multifocal +3.25 D IOL show that the approach provides excellent outcomes.12,13 One prospective study reporting data from 30 patients followed to 3 months showed that rates of distance UCVA ≥20/20, intermediate UCVA ≥20/25, and near UCVA ≥20/25 were 97%, 97%, and 94%, respectively.12 Since the AcrySof® IQ PanOptix® IOL and TECNIS Personalized Vision are intended to meet the needs of similar patient populations, it is useful to consider results from studies that sought to compare them in subjects undergoing bilateral cataract extraction.

Researchers in one prospective study compared groups of 10 patients each who had bilateral implantation of the AcrySof® IQ PanOptix® IOL or TECNIS® Personalized Vision using the Tecnis Symfony® IOL and the Tecnis Multifocal +4.0 D IOL (Figure 1). Compared with the AcrySof® IQ PanOptix® group, patients who had TECNIS® Personalized Vision had better visual acuity for very short distances, which is not surprising considering use of the TECNIS Multifocal +4.0 D IOL, but also for intermediate and long distances (67 cm to 4 m). They also found that patients with TECNIS® Personalized Vision IOLs had better contrast sensitivity at low frequencies under both mesopic and photopic conditions (Figure 2).

Another prospective study, including 80 eyes of patients, comparing the outcomes with the TECNIS Symfony® IOL, AcrySof® IQ PanOptix®, AcrySof® IQ ReSTOR +3.0 D, and AcrySof® IQ ReSTOR +2.5 D IOLs.14 The results showed that the Tecnis Symfony® IOL had higher tolerance to the distortion and blurriness induced by astigmatism (up to 1.0 D) than the AcrySof® IQ PanOptix® or ReSTOR IOLs (Table 1).

Choosing the Right Lens for Each Patient

I’ve been using the technique of personalization with IOLs from the TECNIS® family for several years and have been extremely surprised and happy with the results. Moreover, and more importantly, in my opinion, my patients have had a much-improved range of vision and a much higher level of satisfaction than I experienced with premium IOLs in the past, and I have tried premium IOLs from all the companies. The personalization approach with TECNIS® IOLs affords a wider range of vision. It also provides some flexibility midstream when patients who have been implanted with either a Tecnis Symfony® or a Tecnis Multifocal in the first eye express a desire for more near vision or more intermediate vision, respectively. I have not had any disappointed patients nor had to explant any IOLs using the personalized approach.

I can offer several tips to success with TECNIS® Personalized Vision. First, if a patient has significant astigmatism in one eye, I choose the Tecnis Symfony® Toric IOL for that eye; surprisingly, dominance doesn’t seem to make a difference in these patients, and so the +3.25 add TECNIS® Multifocal or the Tecnis Symfony® can be placed in the dominant eye.
eye, probably because distance vision will be excellent with both eyes. Next, when implanting a TECNIS Symfony® IOL, I typically aim for emmetropia or the first myopic IOL whereas I will aim for emmetropia or the first hyperopic IOL for the +3.25 add TECNIS® Multifocal. Finally, I recommend using a fourth-generation IOL formula, such as the Barrett Universal, Olsen, or HILL-RBF, to achieve the best refractive results regardless of what IOL is used.

Conclusion

Historically, we used caution against implanting different IOls in fellow eyes, but I can say from my experience that appropriate patients will do extremely well with TECNIS® Personalized Vision. Having witnessed my own patients’ outcomes with TECNIS® Personalized Vision, I remain confident in this approach, but also enthusiastic about other future innovations.

REFERENCES

1. TECNIS Symfony® Extended Range of Vision IOL Directions for Use.

Tecnis Symfony and Tecnis Symfony TORIC EXTENDED RANGE OF VISION IOLs Rx Only

INDICATIONS: The Tecnis Symfony® Extended Range of Vision IOL, Model ZX900, 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 Tecnis Symfony® Toric Extended Range of Vision IOLs, Models ZX150T, ZX225T, ZX300T, and ZX375T, are indicated for primary implantation for the visual correction of aphakia and for reduction of residual refractive astigmatism in adult patients with greater than or equal to 1 diopter of preoperative corneal astigmatism, in whom a cataractous lens has been removed. These models of IOLs, ZX900, ZX150T, ZX225T, ZX300T, and ZX375T, mitigate the effects of presbyopia by providing an extended depth of focus. Compared to an aspheric monofocal IOL, these models of IOLs provide improved intermediate and near visual acuity, while maintaining comparable distance visual acuity. These models of IOLs are 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. Rotation of the Tecnis Symfony® Toric IOLs away from their intended axis can reduce their astigmatic correction, and misalignment >30° may increase postoperative refractive cylinder. If necessary, lens repositioning should occur as early as possible prior to lens encapsulation.

PRECAUTIONS: Interpret results with caution when refraction using autorefractors or wavefront aberrometers that utilize infrared light, or when performing a duochrome test. Confirmation of refraction with maximum plus manifest refraction technique is recommended. The ability to perform some eye treatments (e.g. retinal photocoagulation) may be affected by the optical design. Target emmetropia for optimum visual performance. Care should be taken to achieve IOL centration, as lens decentration may result in a patient experiencing visual disturbances under certain lighting conditions. For the Tecnis Symfony® Toric IOL, variability in any preoperative surgical parameters (e.g. keratometric cylinder, incision location, surgeon’s estimated surgically induced astigmatism and biomey) can influence patient outcomes. Carefully remove all viscoelastic and do not over-inflate the capsular bag at the end of the case to prevent lens rotation.

SERIOUS ADVERSE EVENTS: The most frequently reported serious adverse events that occurred during the clinical trial of the Tecnis Symfony® lens were cystoid macular edema (2 eyes, 0.7%) and surgical re-intervention (treatment injections for cystoid macular edema and endophthalmitis, 2 eyes, 0.7%). No lens-related adverse events occurred during the trial.

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Small changes can help beat endophthalmitis bug

Researchers find that intravitreal injections can have an impact on rate

By Lynda Charters; Reviewed by Sunir J. Garg, MD, FACS

In recent years, various factors have been associated with lower rates of endophthalmitis, some of which are intuitive and others not so much so.

Interestingly, the outcomes of endophthalmitis after intravitreal injections often are worse compared with other intraocular and endophthalmitis mostly because of the roughly three times higher incidence of oral flora, e.g., *Streptococcus viridans*, Sunir J. Garg, MD, FACS, explained. In cases, with infection from this pathogen, the vision often decreases to hand motions.

Dr. Garg is professor of ophthalmology and co-director of retina research, at MidAtlantic Retina, The Retina Service of Wills Eye Hospital, Philadelphia. “We know that the oral flora is from bacterial dispersion from the oropharynx,” he said. “A significant reduction in bacterial dispersion and endophthalmitis resulted from the use of masks and/or implementation of a no talking policy during the procedure by all individuals in the room.”


**PRESENTATION IS EVERYTHING**

Preparation is always important. Ranibizumab (Lucentis, Genentech Inc.) previously was administered in a vial but became available in the United States in a prefilled syringe in 2016. Dr. Garg and colleagues conducted a retrospective study of this change at 10 centers to determine the effect.

The team compared the treatments administered conventionally with those administered via a prefilled syringe. Researchers found that the suspected endophthalmitis rate was reduced with use of the prefilled syringe, although the difference did not reach significance.

The study (*Am J Ophthalmol* [https://doi.org/10.1016/j.ajo.2018.11.023]) included 165,347 conventional injections and 78,407 prefilled syringe injections that were associated, respectively, with 43 and 12 cases of suspected endophthalmitis. These numbers translated to respective incidence rates of 1/3,845 and 1/6,534, Dr. Garg reported.

However, he pointed out, what was more impressive were the culture-positive results, which did reach significance. The respective culture-positive cases were 22 and 2, with incidence rates of 1/7,516 in the conventional group and only 1/39,205 in the prefilled syringe group (p = 0.025).

Another finding was that 27.3% of the conventional cases developed endophthalmitis from oral flora, which was not the case in the prefilled syringe group. This result was directly related to the visual outcomes; the conventional cases lost an average of 4.5 lines of vision compared with a 0.38 line of vision in the prefilled syringe group (p = 0.0062). The average respective visual acuities were 20/250 and 20/50 (p = 0.00039), and more than 25% of conventional patients had counting fingers vision or lower.

**TAKE-HOME**

> Endophthalmitis rates after intravitreal injections can decrease with the implementation of a few relatively easy changes.

The use of topical antibiotics are unnecessary when administering intravitreal injections as confirmed by two studies. The DRCR.net prospective study (*Arch Ophthalmol* 2012;130:809-10; doi: 10.1001/archophthalmol.2012.227) found 6/4,697 with an antibiotic and 1/3,333 without.

Dr. Garg and colleagues conducted a retrospective study (*Ophthalmology* 2014;121:283-9) of 117,000 injections and reported that the routine use of antibiotics increased the incidence of both the suspected and culture-positive cases, the visual outcomes did not improve, and the drugs bred resistance (*Ophthalmology* 2012;119:1420-4. doi: 10.1016/j.ophtha.2012.01.016. Epub 2012 Mar 13).

Povidone iodine 5%, an inexpensive and widely used agent, and is the only agent that has been shown to prevent endophthalmitis. Up to 25% of eyes have preoperative positive cultures right after instillation.

A drawback to its use is that some patients dislike how they feel after instillation. An alternative anti- septic used for other surgical preparation is chlorhexidine gluconate, a broad-spectrum antibiotic, but this should not be used for the ocular surface; however aqueous chlorhexidine can be used for the ocular antiseptic procedure before injections.

A retrospective study of aqueous chlorhexidine (Ophthalmology 2016;123:2588-94) reported that only three cases of endophthalmitis developed in 40,535 cases of intravitreal injections, for a rate of 0.0074%.

A prospective study (*Retina* 2018;38:2064-6) of 40 consecutive patients, 20 each received either povidone iodine or chlorhexidine, reported that pain scores associated with use of povidone iodine were higher than with aqueous chlorhexidine (7/10 versus 2/10, p = 0.001). Culture-positive rates were the same.

In an unpublished study, Dr. Garg and colleagues compared culture rates, corneal epithelium, and patient comfort using the two agents in a prospective study of 100 patients undergoing same-day bilateral intravitreal injections. One eye was randomly administered povidone iodine and the other to aqueous chlorhexidine.

The study showed that pain was greater with povidone iodine immediately after instillation (p = 0.001) but not on day 1 (p = 0.06). Most had no pain with either agent. If they did have pain, it was worse with povidone iodine at both time points.

The Ocular Surface Score, which measures epitheliopathy, was significantly (p < 0.001) better with aqueous chlorhexidine. The culture-positive rates were similar between the two groups.

Some patients may tolerate aqueous chlorhexidine better than povidone iodine, and both agents showed similar antimicrobial efficacy. No random controlled trials have compared the two. Aqueous chlorhexidine is not a standard of care in the United States, is more expensive, and must be obtained from a compounding pharmacy, he noted.

“Masks, no talking, and the use of prefilled syringes are associated with less endophthalmitis,” Dr. Garg concluded. “Routine use of topical antibiotics is useless and potentially harmful. Aqueous chlorhexidine may be a useful alternative to povidone iodine in some eyes.”
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ASSISTANT PROFESSOR/ASSOCIATE PROFESSOR

THE UNIVERSITY OF VERMONT MEDICAL CENTER

The Division of Ophthalmology in the Department of Surgery at the Robert Larner, M.D. College of Medicine at the University of Vermont and its affiliated medical centers, is recruiting a full-time academic Comprehensive Ophthalmologist. This individual must have completed a board approved 3- or 4-year ophthalmology residency, be board certified or board eligible, and eligible for medical licensure in the State of Vermont. The candidate must have demonstrated interest and ability in teaching medical students and residents and be willing to participate in the surgical teaching programs. This academic appointment will be in the non-tenure clinical scholar pathway at the Assistant or Associate Professor level commensurate with experience and training.

This is a full-time, 12-month, salaried, faculty appointment and carries with it attending staff privileges at The University of Vermont Medical Center. Salary is competitive and commensurate with ability and experience.

Located in Burlington, the University of Vermont and the University of Vermont Medical Center serve as Vermont’s only academic medical center. It is the only ACS verified Level I trauma center in the state and provides tertiary care to patients from Vermont and Northern NY. Burlington is a vibrant community located on the shores of Lake Champlain, between the Adirondack and Green Mountains. With year-round recreational opportunities, safe communities and excellent schools, this progressive community has been frequently cited as one of the most livable cities in the U.S.

The University is especially interested in candidates who can contribute to the diversity and excellence of the academic community through their research, teaching, and/or service. Applicants are requested to include in their cover letter information about how they will further this goal.

The University of Vermont is an Equal Opportunity/Affirmative Action Employer. All qualified applicants will receive consideration for employment without regard to race, color, religion, sex, sexual orientation, gender identity, national origin, disability, protected veteran status, or any other category legally protected by federal or state law. The University encourages applications from all individuals who will contribute to the diversity and excellence of the institution.

Interested individuals should apply online at https://www.uvmjobs.com/postings/37767 (position number 00022902).

Inquiries may be directed to Dr. Brian Kim via Kristin Allard at Kristin.Allard@uvmhealth.org
With OXERVATE, up to 72% of patients achieved complete corneal healing at 8 weeks*3

*Complete corneal healing was defined as the absence of staining of the corneal lesion and no persistent staining in the rest of the cornea after 8 weeks of treatment. Based on results from the REDAgP trial (Europe: NGF0212; N=156) and the US trial (NGF0214; N=48).94

Brief Summary of Safety
Consult the full Prescribing Information for complete product information.

INDICATIONS AND USAGE
OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% is indicated for the treatment of neurotrophic keratitis.

DOSAGE AND ADMINISTRATION
Contact lenses should be removed before applying OXERVATE and may be reinserted 15 minutes after administration.

If a dose is missed, treatment should be continued as normal, at the next scheduled administration.

If more than one topical ophthalmic product is being used, administer the eye drops at least 15 minutes apart to avoid diluting products. Administer OXERVATE 15 minutes prior to using any eye ointment, gel or other viscous eye drops.

Recommended Dosage and Dose Administration
Instill one drop of OXERVATE in the affected eye(s), 6 times a day at 2-hour intervals for eight weeks.

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

In two clinical trials of patients with neurotrophic keratitis, a total of 101 patients received cenegermin-bkbj eye drops at 0.02 mg/mL at a frequency of 6 times daily in the affected eye(s) for a duration of 8 weeks. The mean age of the population was 61 to 65 years of age (18 to 95). The majority of the treated patients were female (61%). The most common adverse reaction was eye pain following instillation which was reported in approximately 16% of patients. Other adverse reactions occurring in 1-10% of OXERVATE patients and more frequently than in the vehicle-treated patients included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation and tearing.

USE IN SPECIFIC POPULATIONS
Pregnancy
Risk Summary There are no data from the use of OXERVATE in pregnant women to inform any drug associated risks. Administration of cenegermin-bkbj to pregnant rats or rabbits during the period of organogenesis did not produce adverse fetal effects at clinically relevant doses. In a pre- and postnatal development study, administration of cenegermin-bkbj to pregnant rats throughout gestation and lactation did not produce adverse effects in offspring at clinically relevant doses.

Animal Data
In embryofetal development studies, daily subcutaneous administration of cenegermin-bkbj to pregnant rats and rabbits throughout the period of organogenesis produced a slight increase in post-implantation loss at doses greater than or equal to 42 mcg/kg/day (267 times the MRHOD). A no observed adverse effect level (NOAEL) was not established for post-implantation loss in either species.

In rats, hydrocephaly and ureter anomalies were each observed in one fetus at 267 mcg/kg/day (1709 times the MRHOD). In rabbits, cardiovascular malformations, including ventricular and atrial septal defects, enlarged heart and aortic arch dilation were each observed in one fetus at 83 mcg/kg/day (534 times the MRHOD). No fetal malformations were observed in rats and rabbits at doses of 133 mcg/kg/day and 42 mcg/kg/day, respectively. In a pre- and postnatal development study, daily subcutaneous administration of cenegermin-bkbj to pregnant rats during the period of organogenesis and lactation did not affect parturition and was not associated with adverse toxicity in offspring at doses up to 267 mcg/kg/day. In parental rats and rabbits, an immunogenic response to cenegermin-bkbj was observed. Given that cenegermin-bkbj is a heterologous protein in animals, this response may not be relevant to humans.

Lactation
There are no data on the presence of OXERVATE in human milk, the effects on breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother’s clinical need for OXERVATE, and any potential adverse effects on the breastfed infant from OXERVATE.

Pediatric Use
The safety and effectiveness of OXERVATE have been established in the pediatric population. Use of OXERVATE in this population is supported by evidence from adequate and well-controlled trials of OXERVATE in adults with additional safety data in pediatric patients from 2 years of age and older [see Clinical Studies (14)].

Geriatric Use
Of the total number of subjects in clinical studies of OXERVATE, 43.5% were 65 years old and over. No overall differences in safety or effectiveness were observed between elderly and younger adult patients.

NONCLINICAL TOXICOLOGY
Carcinogenesis and Mutagenesis Animal studies have not been conducted to determine the carcinogenic and mutagenic potential of cenegermin-bkbj.

Impairment of fertility Daily subcutaneous administration of cenegermin-bkbj to male and female rats for at least 14 days prior to mating, and at least 18 days post-coitum had no effect on fertility parameters in male or female rats at doses up to 267 mcg/kg/day (1709 times the MRHOD). In general toxicology studies, subcutaneous and ocular administration of cenegermin-bkbj in females was associated with ovarian findings including persistent estrus, ovarian follicular cysts, atrophy/reduction of corpora lutea, and changes in ovarian weight at doses greater than or equal to 19 mcg/kg/day (119 times the MRHOD).

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TED’S LONG-TERM DAMAGE IS SOMETHING SHE CAN’T COME BACK FROM.

Since there’s a limited window for treating active thyroid eye disease, every moment counts.1,2
To fight back against the impact of this disease, focus on early diagnosis, active monitoring, and prompt medical intervention.1,3-5

To learn more about what to look for, visit TEDimpact.com


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