Gel stent proves value in refractory OAG

Procedure could prove to be alternative to trabeculectomy

By Cheryl Guttman Krader; Reviewed by Davinder S. Grover, MD, MPH

**THE SUBCONJUNCTIVAL GEL-ATIN** stent (Xen45 Gel Stent, Allergan) is a valuable addition to the glaucoma specialist’s surgical armamentarium because it provides a safe, effective and predictable means of creating a new pathway for aqueous humor drainage in eyes with an atrophic collector system, Davinder S. Grover, MD, MPH, said during the 2019 American Academy of Ophthalmology annual meeting.

“Trabeculectomy is not dead, but with the availability of this minimally invasive glaucoma surgery device that creates a new outflow system, I have significantly decreased the number of cases where I need to lean on trabeculectomy and expose patients to the risks associated with a conventional filtering procedure,” said Dr. Grover, attending surgeon and clinician, Glaucoma Associates of Texas, Dallas, TX.

“The stent is made of porcine gel cross-linked with glutaraldehyde. It measures 6 mm in length, has an outer diameter of 210 µm and an inner lumen diameter of 45 µm. In the United States, it is indicated for treatment of refractory open-angle glaucoma, and as with trabeculectomy, patient tolerance of and compliance with complex regimens are key.”

**AAO 2019**

**THE MAGNIFICENT 7: How many glaucoma medications are too many?**

Patient tolerance of and compliance with complex regimens are key

By Lynda Charters; Reviewed by Janet B. Serle, MD

**OPHTHALMOLOGISTS HAVE THE luxury of choosing from among seven current IOP-lowering medications, with doses that range from one to four times daily. The list includes prostaglandin analogs (PGAs), rho kinase inhibitors, beta-blockers, alpha-agonists, carbonic anhydrase inhibitors (CAIs), miotics, and non-selective adrenergic agonists. This may well be an embarrassment of riches, with the ready availability of these options raising interesting questions and prescribing quandaries for physicians.**

“Likely the most important question is what is the optimal tolerated, effective, and reasonable IOP-lowering regimen?” Janet B. Serle, MD, pointed out during a presentation at the 2019 American Academy of Ophthalmology annual meeting.

“We have a great deal of evidence-based facts about medical therapy,” she said. “We know that if a second, third, fourth, or more medications are added to a regimen, typically effic-
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Physicians have to be prepared to deal with patients who may receive misinformation when it comes to efficacy of stem cell therapies.
Fall spotlight shines on innovation

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

AS THE CALENDAR turns to November, we continue to sift through a mountain of information from a busy ophthalmic conference season that recently wrapped up with the American Academy of Ophthalmology (AAO) annual meeting in San Francisco, as well as events in Europe and Canada.

Innovations in several key areas are emerging as primary topics in this issue of Ophthalmology Times. We also are spotlighting a healthy pipeline for new dry eye disease (DED) agents in 2020. Here are some highlights in this issue:

The field of ophthalmology certainly isn’t sitting still, as can be seen on the cover of this issue, with an article adapted from a presentation by Davinder S. Grover, MD, at the AAO meeting focusing on device technology. Dr. Grover describes the surgical technique, patient selection, and outcomes for the subconjunctival gelatin stent, noting that it is a valuable addition to the glaucoma specialist’s surgical armamentarium.

We delve further into device technology with Giacomo Savini, MD, who discusses the accuracy of IOL power calculations, noting that the predictability of refractive outcomes after cataract surgery has improved due in large part to innovative new techniques and technologies. While constant optimization remains key, certain cases present particular challenges.

In clinical diagnosis news, Mita Esmaeli, MD, FAC, discusses efforts to treat conjunctival lymphoproliferative lesions, explaining how clinical recognition of salmon patch infiltrate requires the consideration of a number of factors, and it is the first important step in diagnosing and managing conjunctival lymphoproliferative lesions including marginal zone B-cell lymphoma. Yishay Weill, MD, details a study evaluating the performance of a swept-source optical coherence tomography-based biometry device for identifying macular pathology in patients before cataract surgery, and finds that it helps lower the rate of overlooked macular pathology when combined with dilated biomicroscopy examination.

In the surgical arena, Yonga A. Akova, MD, details a prospective evaluation including 20 eyes, which found that a trifocal IOL effectively reduced astigmatism, had good postoperative rotational stability, provided a full range of excellent uncorrected visual acuity with good contrast sensitivity, caused no significant photic phenomena, and was associated with high patient satisfaction. We also hear from Mark Packer, MD, who outlines a theoretical retrospective study that found the percentage of eyes with ≤0.5 D residual refractive astigmatism after toric IOL implantation improved by 19% using a new vergence-based algorithm for power calculation versus the previous fixed-ratio algorithm.

Therapeutics continue to be one of the most intriguing areas in ophthalmology, and in this issue Alex Huang, MD, PhD, details the union between MIGS and medications. Janet B. Serle, MD, details glaucoma as physicians seek the sweet spot surrounding the number of anti-glaucoma medications to prescribe.

We also focus on imaging, as Dipika V. Patel, MRCPophth, PhD, discusses the cream of the crop of anterior-segment imaging for corneal transplants, noting that with some anterior-segment imaging devices performing better than others in anterior-segment surgeries, surgeons must decide which options are best suited for their practices.

New surgical techniques are offering surgeons improvements in the precision and safety of gene and cell therapy delivery to target tissue. Allen C. Ho, MD, and Ali Khan, MD, discuss research targeting precision dosing for gene and cell therapy.

The pipeline for dry eye appears to be robust as we head toward 2020, and we provide a special section that details DED agents in the pipeline. This includes a brief overview of studies that are nearing completion and some products that have been filed for regulatory approval.

We also offer some advice on practice management from Dianna E. Graves, COMT, who points out that indecision can lead physicians to miss out on the next great opportunity. Matt Rolles offers five steps for practice leaders to follow to achieve revenue clarity.

What’s Trending

See what the ophthalmic community is reading on OphthalmologyTimes.com

1 Keys to integrating, interpreting different types of OCT scans
OphthalmologyTimes.com/OCTscans

2 Considering BID ocular steroid post-cataract surgery
OphthalmologyTimes.com/BIDPostSurgery

3 DMEK versus DSAEK: Debate goes on
OphthalmologyTimes.com/DMEKvsDSAEK

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Video

Eric Donnenfeld, MD
Ophthalmologist, Consultant of Long Island

Eric M. Donnenfeld, MD, shares the take-home message of his poster “The effect of phenylephrine and ketorolac intracameral solution 1%/0.3% on pain and opioid usage during cataract surgery” at the 2019 American Academy of Ophthalmology meeting. Go to OphthalmologyTimes.com/Cataract OMITedlia

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Ars longa, vita brevis
Hippocrates’ work hits mark with modern physicians

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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HIPPOCRATES, THE GREEK
physician, often referred to as the Father of Medicine,
began his medical textbook titled “The Apho-
rismi” with the following preamble that is typi-
cally only partially quoted and almost univer-
sally misinterpreted:

Ο βίος βραχύς,
ἡ δὲ κρίσις χαλεπή,
ἡ δὲ πεῖρα σφαλερή,
ὁ δὲ καιρὸς ὀξύς,
ἡ δὲ τέχνη μακρή,
ハウス βίος βραχύς,
ἡ δὲ κρίσις χαλεπή,
ἡ δὲ πεῖρα σφαλερή,
ἡ δὲ τέχνη μακρή.

Life is short,
and art long,
opportunity fleeting,
experimentations perilous,
and judgment difficult.

The first two lines are well-known, and com-
monly cited by people my age. They are spoken
at certain times, such as at the end of a long
day while sharing a nice bottle of wine. They are
meant to communicate along the lines that one
should try to enjoy life while it lasts. Sort of like
“eat drink and be merry, for tomorrow we may
die.” Others have interpreted the two lines as say-
ing that while our time on this earth is short,
works of art can endure for much longer.

Reading the whole passage and knowing that
Hippocrates was speaking to his fellow physi-
cians and students of medicine makes it clear
that this is not about some philosophical state-
ment about the transcendence of music or poetry.

The meaning of “life is short” is clear, but the
statement about art being long is a reference to
the long amount of time required for a physician
to master his (or her) art or craft. This will res-
sonate with today’s physicians, who are all too
aware of the many, many years of study and de-
layed gratification required to one day become
board-certified. Similarly, we physicians today
use the phrase “state of the art” when we talk
about surgical techniques or advanced medical
therapies, and we are not referring to painting or
music. One scholar suggests that Hippocrates was
telling us that “it takes a long time to master our
medical knowledge and technical expertise, and
then we have a relatively short time left to put
that skill to use.” Those two or three decades of
practice represent our “opportunity fleeting.”

As someone who has been engaged in clini-
cal trials of ophthalmic medications and surgi-
cal devices for two or three decades, I have a spe-
cial affection for the line that speaks to the risks
of human subjects research: “experimentations perilous.” My sense is that many centuries ago,
when medical science was rudimentary and there
were no Institutional Review Boards, it was in-
deed extremely perilous to have a physician ex-
periment with one’s health.

The concluding line—“and judgment difficult”
—is beautiful in its understatement and makes
me think of the times in a physician’s career
when there is no clear scientific data to guide the
care of a patient, but a number of options with
different potential pros and cons. In those situ-
ations the physician or surgeon has to take re-
ponsibility for making a judgment regarding the
best path forward for his or her patient. Taken
as a whole, my assessment of this work by Hip-
pocrates is that he is speaking to his audience
and alerting them to some key challenges that a
physician must face.

Of note, recent work by Pierre Delecto, an ob-
scure and controversial scholar of ancient Greek
working in Baltimore, suggests that fading of the
ink over more than two millennia resulted in the
final line of this introductory paragraph having
been overlooked until now. The addition of this
sixth line, heretofore unknown, truly underscores
Hippocrates’ remarkable knowledge of medical
practice:

Life is short,
and art long,
opportunity fleeting,
experimentations perilous,
and judgment difficult,
and getting reasonable and timely payment
from the insurance companies impossible.

REFERENCE

1. https://www.phrases.org.uk/meanings/ars-longa-vita-
brevis.html
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CENTRAL TO DRY EYE DISEASE

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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.

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

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

References:

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

ADVERSE REACTIONS
Clinical Trials Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In five clinical studies of dry eye disease conducted with 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, dryness, and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus, and sinusitis.

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

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

USE IN SPECIFIC POPULATIONS
Pregnancy
There are no available data on Xiidra use in pregnant women to inform any drug associated risks. Intravenous (IV) administration of 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.

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 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.

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Casting a net to diagnose, treat cancerous lesions

Ultra-low-dose radiation may become effective therapy for low-grade lymphoma

By Lynda Charters; Reviewed by Bita Esmaeli, MD, FACS

Clinical recognition of salmon patch infiltrate requires the consideration of a number of factors, and it is the first important step in diagnosing and managing conjunctival lymphoproliferative lesions including marginal zone B-cell lymphoma. Ophthalmologists should be familiar with the clinical appearance which usually that of a “salmon patch” infiltrate and can affect any part of the ocular surface including the tarsal and palpebral conjunctiva.

This pathology is not limited to one area; the entire ocular surface must be inspected, according to Bita Esmaeli, MD, FACS, professor and director of the Ophthalmic Plastic and Orbit Program, at MD Anderson Cancer Center, Houston.

Eversion of the upper eyelid is important for identifying the full extent of conjunctival lymphomas. Some lesions, she explained, can be very small and limited to the caruncle or a small follicular infiltrate.

Symptoms can include chronic discharge, itchiness, conjunctivitis, and allergic reaction. In some cases, the lesions can be asymptomatic and discovered only coincidentally during the evaluation of other clinical processes.

**BIOPSY IS KEY**

Reactive lymphoid hyperplasia can have an appearance that is similar to lymphoma, indicating that biopsy is a key diagnostic step in ferreting out benign and malignant lesions, Dr. Esmaeli pointed out.

“Biopsy is required to establish the diagnosis of lymphoma and the exact histologic subtype,” she said.

Pathologists often rely on standard morphology, immunohistochemistry, and hematoxylin and eosin staining in cases with conjunctival lesions because the tumor burden may be too small to facilitate flow cytometry, the gold standard for more definitive diagnosis of lymphoma, she pointed out.

Surgeons should also bear in mind that evidence of a lesion on the conjunctiva may be the proverbial tip of the iceberg, that is, the disease can extend well into the orbit.

“For conjunctival lymphoma, the histology is usually very low grade, and more than 90% are likely mucosa-associated lymphoid tissue (MALT) lymphomas,” Dr. Esmaeli said. “Other more aggressive histologic subtypes of lymphoma also can rarely occur, and in most cases they would have an extension into the orbit.”

**AFTER DIAGNOSIS**

At this stage, an important goal is ruling out systemic lymphoma. Positron emission tomography–computed tomography are useful, as are bone marrow biopsy, which are performed at most cancer centers—and even “stage 4” conjunctival MALT lymphoma is possible to be found at initial diagnosis of conjunctival MALT lymphoma with a positive bone marrow involvement.

“That does not necessarily mean that patients need aggressive treatment, but it could be a clue that such patients with a positive bone marrow biopsy will relapse in the future at extraocular sites,” she said.

**TREATMENT**

In cases of ocular surface lymphoma, probably more than 95% of patients undergo radiation therapy because the disease is characteristically low volume and low grade and in most cases does not extend past the ocular surface and is without systemic involvement.

“Radiation has served as the go-to treatment and the most practical solution for ocular surface lymphomas,” Dr. Esmaeli noted.

'Biopsy is required to establish the diagnosis of lymphoma and the exact histologic subtype.'

— Bita Esmaeli, MD, FACS
cases. The late ocular morbidities include cataract development, mild keratitis, and dry eye in about 50% of cases.

More recently, an “ultra-low” dose of 4 Gy of orbital fractionated radiation that is administered in two sessions over two days has gained popularity and is currently being studied in a prospective trial at MD Anderson Cancer Center.

Dr. Esmaeli reported that a retrospective analysis of the results in 23 eyes of 20 patients treated with the ultra-low-dose radiation resulted in responses in all patients, including complete responses in 13 patients (56%) and partial responses in 10 patients (44%) after a median follow-up of 14 months. These early observations were published in 2016. Based on the positive early observations, a prospective trial of the ultra-low dose radiation for orbital and adnexal low-grade lymphomas is underway at MD Anderson with the goal of recruiting 50 patients.

To date, 41 patients have been treated according to the protocol. When combined with the retrospective and off-protocol patients, a total of 70 patients have been treated. Advantages are short treatment duration, lower cost, and lower ocular toxicity. The treatment also can be repeated if needed.

“We are very pleased with the results and this study may lead to a change in the acceptable dose of radiation delivered for low-grade lymphomas of the orbit and ocular surface,” Dr. Esmaeli pointed out, adding that the case of a patient treated in 2013 who responded well to the ultra-low treatment dose and had a prolonged treatment effect with follow-up in 2017.

Other forms of treatment for lymphoma include chemotherapy, combined chemotherapy and radiation, immunotherapy, observation, and oral antibiotics, the last of which have no proven efficacy. These other treatment options may be needed in advanced stages or high-grade lymphoma.

“Clinical recognition of salmon patch infiltrate is the most important first step,” Dr. Esmaeli concluded. “The next step is biopsy to establish the histologic subtype of the lymphoma, which dictates treatment. Staging is vital. For stage 1E disease, very-low dose radiation, even 4 Gy, provides effective local control, convenience, and has low ocular toxicity.”

‘Clinical recognition of salmon patch infiltrate is the most important first step. The next step is biopsy to establish the histologic subtype of the lymphoma, which dictates treatment.’

– Bita Esmaeli, MD, FACS

References:
SS-OCT detecting macular pathology prior to cataract surgery

Tool demonstrates high level of specificity, low sensitivity

By Cheryl Guttman Krader; Reviewed by Yishay Weill, MD

A SWEPt-SOURCE OPTICAL coherence tomography (SS-OCT)-based biometry device (IOL Master 700, Carl Zeiss Meditec) can help with the identification of some significant macular pathologies that otherwise would have been missed using a standard dilated fundus examination for the preoperative evaluation of cataract surgery patients, said Yishay Weill, MD.

Dr. Weill and colleagues at the Shaare Zedek Medical Center, Jerusalem, Israel, undertook a retrospective study to assess the efficacy of the biometer for identifying macular pathology by comparing its findings with those of spectral-domain OCT scans (Spectralis, Heidelberg Engineering) performed on the same day in 460 consecutive eyes of 460 patients.

“Currently, dilated clinical fundus examination is the standard of care for evaluating the macula prior to cataract surgery, but in a previous study we found that it missed more than 50% of existing pathology when the findings were compared with dedicated macular SD-OCT,” said Dr. Weill, refractive surgery and cornea fellow, department of ophthalmology, Shaare Zedek Medical Center. “Macular pathology is important to identify preoperatively because it may affect visual recovery after cataract surgery leading to unmet patient expectations and it may also be worsened by the cataract surgery.”

Dr. Weill noted that the SS-OCT biometer does not substitute for a dedicated SD-OCT macular examination for identifying and diagnosing macular pathology because it is not as sensitive. “Surgeons need to use whatever tools are available to lower the rate of overlooked macular pathology, and the SS-OCT biometer is useful for that purpose,” he said.

The SS-OCT scans were reviewed by a blinded experienced technician and the SD-OCT scans were reviewed independently by a blinded retina specialist. Of the 460 SD-OCT scans, 40 (8.7%) were rated as non-interpretable, 256 (55.6%) were normal, and 164 (35.7%) showed clinically significant pathology. With SS-OCT, 56 (12.2%) scans were non-interpretable, abnormalities were identified in 48 (10.4%) eyes, and 356 (77.4%) scans were considered normal. SD-OCT identified an abnormality in 121 of the 356 scans considered normal on SS-OCT and in 38 of the 48 SS-OCT that were identified as normal.

Analyses of these data showed that SS-OCT had 92% specificity, 23% sensitivity, 67.3% negative predictive value, and 84.4% positive predictive value.

Dr. Weill pointed out that if an abnormality is identified on the SS-OCT foveal printout, there is a high probability that an abnormality exists. “We saw that if we rely solely on dilated fundus biomicroscopy to evaluate the macula before cataract surgery, 52% of pathologies will be overlooked,” he said. “If we also take care to examine the SS-OCT scan from the biometer, the rate dropped to 37%. This is still a high and unacceptable number, but surely an improvement.”

The SS-OCT device performed best in identifying abnormalities associated with macular thickening. Specifically, it identified all cases of vitreomacular traction, 82% of eyes with an epiretinal membrane causing macular thickening, and 52% of eyes with cystoid macular edema. However, it only identified 15% of eyes with dry age-related macular degeneration and none of the eyes with a mild epiretinal membrane without macular thickening.

The difference in performance between the SS-OCT biometer and dedicated macular SD/SS-OCT is explained by the SS-OCT device’s lower resolution (22 versus 5 μm) and imaging of a smaller central area (1x1 mm versus 6x6 mm).

“In the near future, ophthalmologists will have instruments that combine optical biometry and high-resolution macular OCT,” Dr. Weill said.

Although dedicated macular SS/SD-OCT is most reliable for detecting macular pathology, the investigators noted that there is a need to study the cost-effectiveness of incorporating it as a routine component of the preoperative evaluation. “We need to determine the cost of overlooking macular pathology and compare it with the cost of performing macular SD-OCT in every cataract surgery patient,” Dr. Weill concluded. “The device and technician’s time add to the cost of the preop evaluation, and in most cases there is no reimbursement to the surgeon for the testing.”

YISHAY WEILL, MD
E: yishayweill@gmail.com
This article is adapted from Dr. Weill’s presentation at the American Academy of Ophthalmology 2019 annual meeting. Dr. Weill has no relevant financial interests to disclose.
TearCare® is indicated for the application of localized heat when the current medical community recommends the application of a warm compress to the eyelids. Such applications would include Meibomian Gland Dysfunction (MGD), Dry Eye, or Blepharitis.

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Performance of trifocal toric IOL highlighted in tests

Evaluation shows reduction in astigmatism, good postop rotational stability

By Cheryl Guttman Krader; Reviewed by Yonca A. Akova, MD

Findings from a study evaluating postoperative clinical and quality of life outcomes show that an aspheric, nonapodized trifocal toric IOL (AcrySof IQ PanOptix Toric IOL, Alcon) was associated with excellent visual and refractive results, leading to high spectacle independence and patient satisfaction, according to Yonca A. Akova, MD.

“Untreated preexisting corneal astigmatism is an important limiting factor for visual outcomes with multifocal IOL implantation,” said Dr. Akova, professor of ophthalmology, Bayindir Hospital, Ankara, Turkey.

Dr. Akova noted that the study could be among the first reporting clinical outcomes with the toric version of this trifocal IOL.

“The results of this investigation show that the IOL effectively reduced astigmatism, had good rotational stability, and provided excellent visual outcomes at all distances to provide excellent patient satisfaction,” she said.

The trifocal toric IOL has a central trifocal zone of 4.5 mm and 15 diffractive rings. It features a +3.25 D add for near focus and a +2.17 D add for the intermediate focal point (60 cm).

This new trifocal toric IOL technology has brought the intermediate focal point from 80 cm to 60 cm, which aims to provide comfortable vision in daily life.

Dr. Akova conducted the noncomparative study evaluating the trifocal toric IOL with Oya Donmez, MD, ophthalmologist, Bayindir Hospital. It included 20 eyes of 15 patients operated on between April 2018 and June 2018. Eyes were selected for implantation of the toric version of the trifocal IOL based on having ≥1.25 D of with-the-rule astigmatism or ≥0.75 D of against-the-rule astigmatism.

All patients underwent a complete ophthalmological examination preoperatively and three months after surgery. Astigmatism was measured with corneal topography (Sirius, CSO Italia) and optical biometry (IOLMaster 700, Carl Zeiss Meditec). All of the surgeries were done using a femtosecond laser (LenSx, Alcon) for the corneal incisions, anterior capsulotomy, and lens pretreatment followed by phacoemulsification through a 2.2 mm incision (Centurion Vision Systems, Alcon). The patients ranged in age from 46 to 75 years; their mean age was 62 years, and all procedures were for cataract.

Preoperatively, mean corneal astigmatism was 1.8 D (range 0.82 to 4.30 D). Mean predicted residual astigmatism was 0.12 D (range 0.01 to 0.71). The eyes had average axial length (mean 23.9 mm, range 22.16 to 26.99) and anterior chamber depth (mean 3.1 mm, range 2.51 to 3.80).

At three months after surgery, all patients achieved uncorrected visual acuity (VA) of 0.1 logMAR or better at distance, intermediate, and near, and 90% of patients reported complete spectacle independence. Mean logMAR uncorrected VA was 0.005 at distance, 0.06 at intermediate, and 0.05 at near.

Defocus testing was also done over the range of +1.00 to –3.00 D. The curve showed peaks at 0.00 D and -1.50 D. Mean refractive astigmatism was 0.39 ± 0.38 (0-(-)1 D) and mean manifest astigmatism was 0.05 ± 0.22 (0-(-)1 D).

“Refractive astigmatism (This is manifest) was <1 D in all eyes and it was ≤0.50 D in 94% of eyes,” Dr. Akova reported.

Contrast sensitivity testing was also done, and the results showed that all patients maintained normal contrast at all spatial frequencies under both mesopic and photopic conditions. No patients experienced any disturbing optic phenomena. Three patients (15%) reported mild halos, and only one patient (5%) reported glare, which was also mild.

Visual function was also assessed at three months after surgery using the Visual Function Index Test (VF-14). The best possible score on this instrument is 100, and the patients in the study had a mean VF-14 score of 97.63.

Rotational stability was assessed by evaluating IOL alignment at three months after surgery. Mean rotation was 3.3°, and in no case did the IOL rotate >10°.

“We also saw no evidence of posterior capsule opacification, although the follow-up at three months is still a short duration,” Dr. Akova concluded.

Dr. Akova is a consultant to Alcon.

In a prospective evaluation including 20 eyes, a trifocal toric IOL effectively reduced astigmatism, had good postoperative rotational stability, provided a full range of excellent uncorrected visual acuity with good contrast sensitivity, caused no significant photic phenomena, and was associated with high patient satisfaction.

TAKE-HOME

» In a prospective evaluation including 20 eyes, a trifocal toric IOL effectively reduced astigmatism, had good postoperative rotational stability, provided a full range of excellent uncorrected visual acuity with good contrast sensitivity, caused no significant photic phenomena, and was associated with high patient satisfaction.
Advanced toric IOL calculator improves refractive outcomes

A new vergence-based algorithm for power calculation

By Cheryl Guttman Krader; Reviewed by Mark Packer, MD

THE USE OF an advanced vergence-based algorithm to calculate power for the MX60T neutral aspheric monofocal toric IOL (enVista, Bausch + Lomb) significantly improved refractive outcomes when compared with a previous fixed-ratio algorithm, according to Mark Packer, MD.

Dr. Packer, president, Mark Packer, MD Consulting, Boulder, CO, described the new algorithm and presented findings from a theoretical study using historical data to compare predicted residual refractive error and astigmatism using the vergence-based algorithm versus the previous formula. Unlike a fixed-ratio algorithm that assumes the toric power is always in the same place, the new formula takes into account the distance between the corneal plane and the IOL plane.

The new formula incorporates platform-specific inputs for surgically induced astigmatism (SIA) and posterior corneal astigmatism (PCA).

Dr. Packer reported that the outcomes analysis showed that the percentage of eyes predicted to have <1 D residual refractive error improved from 55% using the fixed-ratio algorithm to 74% with the vergence-based formula. The percentage of eyes with residual refractive astigmatism ≥0.5 D also improved from 55% with the fixed-ratio algorithm to 74% using the vergence-based formula.

“The percentage of eyes predicted to be left with 0.5 D or less residual refractive astigmatism with the vergence-based formula approaches the value of 80% that has been reported using other toric IOL formulas that are vergence-based and take into account posterior corneal astigmatism,” said Dr. Packer. “While the new formula seems to achieve its goal in reducing residual astigmatism, it is important to continue this project because I think the results can be further improved.”

DEVELOPING ALGORITHM

Data for the theoretical comparative study and some values for the new algorithm were derived from patients who were implanted with the MX60T or the monofocal nontoric MX60 (enVista, Bausch + Lomb) IOLs in their respective US FDA investigational device exemption clinical trials. A value of 0.46 D at 84.60° was used for SIA and represented the average of SIA values from patients implanted with the MX60 and MX60T IOLs in the clinical trials. The value of PCA was set at 0.3 D at 90°.

To limit influence of biometric errors, the vergence-based portion of the algorithm was developed using values for anterior chamber depth and effective lens position that were derived from optical modeling averaged over the full range of dioptic powers of the toric lens. Then a regression analysis was performed to uncover a scaling factor needed to predict the power relationship between the corneal and IOL planes over the implant’s spherical power range.

FUTURE REFINEMENTS

The predictability of IOL calculation using the vergence-based formula could be improved in the future by using individual measurements for PCA rather than a population average.

“Although SIA is also an important factor to include in toric IOL calculations, the value used has to be based on historical data because patient-specific values are not known until after the operation,” Dr. Packer concluded. “The SIA for each case is multifactorial and depends on incision size, the injector used, incision location, the physical dimensions of the IOL, and corneal healing.”

TAKE-HOME

› A theoretical retrospective study found that the percentage of eyes with ≤0.5 D residual refractive astigmatism after toric IOL implantation improved by 19% using a new vergence-based algorithm for power calculation versus the previous fixed-ratio algorithm.

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This article is adapted from Dr. Packer’s presentation at the American Academy of Ophthalmology 2019 annual meeting. Dr. Packer is a consultant to Bausch + Lomb.
Surgeon provides pearls for handling retinal tears
Approach eliminates need for postoperative prone positioning

By Lynda Charters; Reviewed by Steve Charles, MD

MEDIUM-TERM PERFLUORO-N-DECANE (PFO) without a scleral buckle is the preferred treatment of Steve Charles, MD, for inferior, nasal, and temporal giant breaks as well as inferior retinal detachments. He uses the PFO after vitrectomy as a tamponade and leaves it in place in eyes completely filled with the substance for 14 days.

According to Dr. Charles, clinical professor, University of Tennessee, Memphis, this approach, which he has used in excess of 1,000 cases over almost 20 years, eliminates the need for postoperative prone or face-down positioning and does not limit the patients’ activities or positioning.

such as is associated with the use of gas bubbles as a tamponade.

“I use this for inferior detachments and not for detachments above the horizontal meridian,” he said. “Without the use of scleral buckles, no myopia or strabismus is induced, and there is no pain, ocular surface disorder such as poor conjunctival closure, or corneal damage. This treatment is ideal in phakic and in those with intraocular lenses.”

He also discounted the notion that this tamponade is associated with toxicity.

“In my series of eyes, I have seen no evidence of toxicity associated with the Alcon product which is used off-label,” he stated.

SURGICAL PEARLS
When performing peripheral vitrectomy to repair inferior detachments, Dr. Charles emphasized the importance of removing residual vitreous at the top of the bubble.

“Surgeons must be meticulous about removing vitreous at the point at which the top of the bubble interacts with the superior retina,” he explained. “Don’t be casual about scleral depression and wide-angle visualization to remove superior vitreous.”

Dr. Charles injects PFO, which was developed by Stanley Chang, MD, to treat giant breaks, using a dual-bore cannula (MedOne Surgical Inc.). He advises using the following procedure. Keep the tip of the cannula in contact with the initial bubble made over the optic nerve head, carefully focus and follow that bubble upwards as it expands.

“If method is used, a single bubble will result,” he said. “If multiple small bubbles are created, the chances are higher of one of them going through the break and into the subfoveal space.”

Regarding treating retinal breaks with laser, Dr. Charles has always used confluent laser around the breaks.

“You should never apply multiple rows of spots because of the potential for creation of under lapping, over lapping and larger peripheral field defects,” he said.

Dr. Charles also advises draining subretinal fluid if it persists after PFO is injected.

“If the break is carefully cannulated, the subretinal fluid drainage can be initiated,” he said. “Internal drainage techniques can still be used even in the presence of PFO.”

Dr. Charles noted that if this is done carefully, usually going anteriorly can be avoided as the fluid is forced ante-
When performing an autologous macular patch graft, Dr. Charles uses a procedure developed by Tamer Mahmoud, MD, PhD, to address a macular hole that is under medium-term PFO. The PFO is removed after seven days. The PFO provides better oxygenation than silicone oil and enables the oxygenation from the anterior surface, not just the choriocapillaris.

When performing an autologous macular patch graft, Dr. Charles emphasizes that the cavity is filled with PFO, using less is not as effective. A full fill results in less formation of small bubbles and the advantage, he noted, is that there is no exchange and, therefore, no slippage when managing giant breaks.

“The retina is put back where it belongs,” he said, adding that he has used this technique in pediatric patients with inferotemporal breaks, in whom the PFO was left in the eye for two weeks. In these patients, the lenses remained clear after 15 to 20 years.

An associated point is that vitrectomy does not cause cataracts, vitrectomy causes nuclear sclerotic cataract progression.

“The idea that medium-term PFO should not be used in phakic patients is nonsense,” Dr. Charles stressed.

Removing the PFO in 14 days is mandatory, because of development of a foreign-body reaction in some patients. He uses topical difluprednate twice daily in these cases unless the patient is a steroid responder.

Dr. Charles pointed out that he always excises the anterior flap in giant break cases to avoid its moving forward and causing epipapillary tissue and hypotony.

He again reemphasized the importance of completely tilling the eye with PFO.

“To do this carefully in a phakic eye, the contact lens must be removed,” he said. “Go to the highest magnification right behind the lens, and very carefully remove the last layer of subretinal fluid, infusion fluid, and liquid vitreous that floats up to the top of the PFO to achieve a full fill.”

Dr. Charles also advises a PFO/gas exchange or a PFO/silicone oil exchange for a superior giant retinal tear; he uses silicone oil in eyes with proliferative vitreoretinopathy.

“The technique for the exchange is extremely important,” he said.

Under chandelier illumination, the silicone oil injection VPC is held in one hand and the extrusion cannula without a soft tip in the other hand to remove the PFO. Dr. Charles advises not using the soft-tipped cannula on the optic nerve head to avoid slippage; the cannula should be positioned at the top surface of the outer margin of the PFO.

This position at the periphery facilitates skimming off of any aqueous liquid and not PFO at the top surface. In a phakic eye, care must be taken to not touch the lens with the cannula. The surgeon must remain focused on the cannula tip during the exchange posteriorly to get the best view of the interface. This technique allows all the residual fluids to be removed before the PFO.

A NOVEL TAMPODATE

When performing an autologous macular patch graft, Dr. Charles uses a procedure developed by Tamer Mahmoud, MD, PhD, to address a macular hole that is under medium-term PFO. The PFO is removed after seven days. The PFO provides better oxygenation than silicone oil and enables the oxygenation from the anterior surface, not just the choriocapillaris.
The union between MIGS, medications gaining focus

Researchers find combination offering promising results in glaucoma treatment

By Lynda Charters; Reviewed by Alex Huang, MD, PhD

n the previous 10 to 15 years, a number of new therapies have come through the pipeline to lower IOP in glaucoma, i.e., microinvasive glaucoma surgeries (MIGS) and new medical therapies. The latest effort is combining medicines and MIGS, which may prove to be a positive option with potentially additive effects.

A number of the new therapies, according to Alex Huang, MD, PhD, target the conventional trabecular pathway, and aqueous angiography is one technique which can visualize the impact of MIGS and pharmacological agents on aqueous humor outflow patterns. Dr. Huang, a clinician-scientist and assistant professor, University of California, Los Angeles, and Doheny Eye Institute, Pasadena, CA, described a research collaboration with Lilit Voskanyan, MD, in which indocyanine green (ICG) was introduced into the eye showing regions of poor aqueous outflow. With placement of two aqueous bypass stents (iStent Inject; Glaukos Corporation) in that location, the angiography was able to demonstrate improved aqueous outflow (Figure 1).

Dr. Huang performed a study with Christopher Girkin, MD, in which they injected ICG into an eye to view the aqueous outflow pattern; after Mochol-E (acetylcholine chloride intraocular solution, Bausch + Lomb) was added, improved outflow was again visualized.

LOOKING TO THE FUTURE
Based on these observations, researchers questioned whether MIGS and medications could be combined.

“There are no high-volume, high-quality clinical trials to support combining therapies,” Dr. Huang said. “There is a lot of retrospective, preclinical, and basic translational work that provides a lot of promise.”

Dr. Huang subdivided investigations into three areas: proximal outflow (trabecular meshwork), distal outflow (post-TM), and steroid response concepts.

PROXIMAL OUTFLOW PATHWAY
Regarding the trabecular meshwork, he described microcircus red staining of the collagen in the sclera to demonstrate how the scleral spur lies under the trabecular meshwork and above the ciliary muscle.

“The cross-sectional view teaches how the conventional system works,” Dr. Huang said. “The ciliary muscle grabs the scleral spur and can pull it down or raise it like a lever to control the opening of the trabecular meshwork.”

Dr. Huang pointed out that this biological mechanism became relevant with procedures that were developed to ablate the trabecular meshwork, such as Trabectome (NeoMedix).

Some data have indicated that there is no good evidence to continue the use of pilocarpine after trabecular ablations. A retrospective study by Hamed Esfandian et al. showed that extended muscarinic activation with pharmacologic agents after trabecular ablation made no difference to intraocular pressure lowering or surgical success.

DISTAL OUTFLOW PATHWAY
New drugs, i.e., netarsudil (Rhopressa, Aerie Pharmaceuticals) and latanoprostene bunod (Vyzulta, Bausch + Lomb), a nitric-oxide donating drug, are cytoskeletal relaxing agents that affect the TM and the distal outflow pathway.

Dr. Huang also questioned if the trabecular MIGS work by opening the proximal region and these drugs can impact the distal outflow, would there be a synergistic additive effect. He pointed out that preclinical data on this subject have suggested that there might just be an additive effect.

With Dan Stamer, PhD, they investigated an eye model in which the trabecular meshwork was removed by a 360° trabeculectomy and where changes in outflow facility were measured in response to various drugs with concomitant constriction and relaxation of distal outflow pathway collector channels and aqueous veins. These results opened the idea that drugs could be added after MIGS for positive results.

STEROID RESPONSE
Anecdotal information exists indicating that after trabecular MIGS an aggressive steroid response can still be observed. Thus, despite a lack of carefully performed clinical characterization, the recommendation is to taper the steroid relatively quickly, according to Dr. Huang.

Unlike systemic steroid use or application after cataract surgery, steroid response after glaucoma surgery can be difficult to appreciate. Elevated IOP could be due to steroid response or failure of the glaucoma surgery. Stopping the steroid is the only way to know. When the IOP decreases, this suggests a steroid response.

Dr. Huang concluded that the future ahead is bright. “In some cases, pharmacological medications may be found to assist MIGS, but more data are needed,” he said. “This is already well-known with combining glaucoma medications targeting different pathways although the additive effect may be only 2 + 2 = 3. For medications and MIGS, hopefully the synergy can be greater where 2 + 2 becomes 4 or even 5.”

ALEX HUANG, MD, PhD
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This article is based on Dr. Huang’s presentation at the American Academy of Ophthalmology 2019 annual meeting. Dr. Huang is a consultant/advisor for Aerie Pharmaceuticals, Alcon, and Santen, and receives grant support from Alcon, Glaukos Corp., and Heidelberg Engineering. National Eye Institute, Research to Prevent Blindness, and the National Aeronautics and Space Administration Human Research Program.
INDICATIONS AND USAGE
DUREZOL® (difluprednate ophthalmic emulsion) 0.05% is a topical corticosteroid that is indicated for:

- The treatment of inflammation and pain associated with ocular surgery.
- The treatment of endogenous anterior uveitis.

Dosage and Administration

- For the treatment of inflammation and pain associated with ocular surgery instill one drop into the conjunctival sac of the affected eye four times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the postoperative period, followed by 2 times daily for a week and then a taper based on the response.
- For the treatment of endogenous anterior uveitis, instill one drop into the conjunctival sac of the affected eye 4 times daily for 14 days followed by tapering as clinically indicated.

Most Common Adverse Reactions

- Bacterial infections – Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.
- Viral infections – Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).
- Fungal infections – Fungal infections of the cornea are particularly prone to develop coincidently with long-term local steroid application. Fungal invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use.
- Contact lens wear – DUREZOL® Emulsion should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of DUREZOL® Emulsion. The preservative in DUREZOL® Emulsion may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of DUREZOL® Emulsion.

For additional information about DUREZOL® Emulsion, please see Brief Summary of Prescribing Information on adjacent page.

*Limitations apply. For commercially insured patients. Up to a $155 cap per bottle. Patient will be responsible for any co-pay once limit per bottle is reached. This offer is not valid under Medicare, Medicaid, or any other federal or state program. Not valid for cash-paying patients. Novartis reserves the right to rescind, revoke, or amend this program without notice. Additional terms and conditions apply. Please see co-pay materials for details.

DUREZOL® (difluprednate ophthalmic emulsion) 0.05%  

Initial U.S. Approval: 2008  

BRIEF SUMMARY: Please see package insert for full prescribing information.  

1 INDICATIONS AND USAGE  

1.1 Ocular Surgery  
DUREZOL® (difluprednate ophthalmic emulsion) 0.05%, a topical corticosteroid, is indicated for the treatment of inflammation and pain associated with ocular surgery.  

1.2 Endogenous Anterior Uveitis  
DUREZOL is also indicated for the treatment of endogenous anterior uveitis.  

2 CONTRAINDICATIONS  
The use of DUREZOL, as with other ophthalmic corticosteroids, is contraindicated in instances of active viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal disease of ocular structures.  

3 WARNINGS AND PRECAUTIONS  
5.1 Intraocular pressure (IOP) Increase  
Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. If this product is used for 10 days or longer, IOP should be monitored.  

5.2 Cataracts  
Use of corticosteroids may result in posterior subcapsular cataract formation.  

5.3 Delayed Healing  
The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order beyond 28 days should be made by a physician only after examination of the patient with the aid of magnification such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.  

5.4 Bacterial Infections  
Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection. If signs and symptoms fail to improve after 2 days, the patient should be reevaluated.  

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

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

5.7 Topical Ophthalmic Use Only  
DUREZOL is not indicated for intracocular administration.  

5.8 Contact Lens Wear  
DUREZOL should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of DUREZOL. The preservative in DUREZOL may be absorbed by soft contact lenses. Lenses may be reininserted after 10 minutes following administration of DUREZOL.  

6 ADVERSE REACTIONS  
6.1 Ocular Surgery  
Ocular adverse reactions occurring in 5% to 15% of subjects in clinical studies with DUREZOL included corneal edema, ciliary and conjunctival hyperemia, eye pain, photophobia, posterior capsule opacification, anterior chamber cells, anterior chamber flare, conjunctival edema, and blepharitis. Other ocular adverse reactions occurring in 1% to 5% of subjects included reduced visual acuity, punctate keratitis, eye inflammation, and iritis. Ocular adverse reactions occurring in less than 1% of subjects included application site discomfort or irritation, corneal pigmentation and striae, episceritis, eye pruritis, eyelid irritation and crusting, foreign body sensation, increased lacrimation, macular edema, sclera hyperemia, and uveitis. Most of these reactions may have been the consequence of the surgical procedure.  

6.2 Endogenous Anterior Uveitis  
A total of 200 subjects participated in the clinical trials for endogenous anterior uveitis, of which 106 were exposed to DUREZOL. The most common adverse reactions of those exposed to DUREZOL occurring in 5% to 10% of subjects included blurred vision, eye irritation, eye pain, headache, increased IOP, iritis, limbal and conjunctival hyperemia, punctate keratitis, and uveitis. Adverse reactions occurring in 2% to 5% of subjects included anterior chamber flare, corneal edema, dry eye, infolyphocytis, photophobia, and reduced visual acuity.  

8 USE IN SPECIFIC POPULATIONS  
8.1 Pregnancy Teratogenic Effects  
Pregnancy Category C  
Difluprednate has been shown to be embryotoxic (decrease in embryonic body weight and a delay in embryonic ossification) and teratogenic (cleft palate and skeletal anomalies) when administered subcutaneously to rabbits during organogenesis at a dose of 1-10 mcg/kg/day. The no-observed-effect-level (NOEL) for these effects was 1 mcg/kg/day, and 10 mcg/kg/day was considered to be a teratogenic dose that was concurrently found in the toxic dose range for fetuses and pregnant females. Treatment of rats with 10 mcg/kg/day subcutaneously during organogenesis did not result in any reproductive toxicity, nor was it teratogenic. At 100 mcg/kg/day after subcutaneous administration in rats, there was a decrease in fetal weight and delay in ossification, and effects on weight gain in the pregnant females. It is difficult to extrapolate these doses of difluprednate to maximum daily human doses of DUREZOL, since DUREZOL is administered topically with minimal systemic absorption, and difluprednate blood levels were not measured in the reproductive animal studies. However, since use of difluprednate during human pregnancy has not been evaluated and cannot rule out the possibility of harm, DUREZOL should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or fetus.  

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

8.4 Pediatric Use  
DUREZOL was evaluated in a 3-month, multicenter, double-masked trial in 79 pediatric patients (30 DUREZOL, 40 prednisolone acetate) 0 to 3 years of age for the treatment of inflammation following cataract surgery. A similar safety profile was observed in pediatric patients comparing DUREZOL to prednisolone acetate ophthalmic suspension, 1%.  

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

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iop reductions are not anticipated/obtained compared with when those medications are used as first-line interventions.”

Dr. Serle, professor emeritus, Icahn School of Medicine at Mount Sinai, New York, noted that the duration of efficacy of a second, third, fourth, or more medications may be less and the efficacy tends to wane over time.

Other factors come into play that reduce patient compliance, such as regimen complexity, cost, side effects, age, physical infirmity, changes in mental status, education level, and health literacy. The nighttime efficacy is also less with some drugs, resulting in possible glaucoma progression. Inter-day and intra-day IOP fluctuations also can result in progression.

A study has suggested that combination therapy may actually reduce fluctuations. Chronic medical therapy causes changes in conjunctival tissue that may negatively impact incisonal surgery, and chronic drug dosing contributes to ocular surface disease, Dr. Serle enumerated.

While numerous caveats are related to the decisions to prescribe IOP-lowering medications, Dr. Serle noted that the question is what actually has been happening in medical practice.

A look-back at treatment practices shows a steady rise in the average numbers of medications prescribed over the past three decades. The average number in the Advanced Glaucoma Intervention Study in 1992 indicated that 2.7 drugs were prescribed. This was prior to the advent of the PGAs, topical CAs, and adrenergic agonists. When those drugs became commercially available, the average number of medications rose to 3.0 and 3.2 in major studies from the late 1990s to 2004. By 2006, the average was 3.4, and the current regimens reported in peer review articles have included 3.6 medications; CME case reports have reported use of three to five medications in individual patients, Dr. Serle reported.

A small prospective Japanese study of ripasudil (Glatanec, Kowa Company, Ltd.), a rho kinase inhibitor with twice daily dosing, included 39 patients with a baseline of 3.6 medications; the study found that after 12 months of ripasudil treatment, there was an additional mean 15.5% decrease in IOP in more than two-thirds of patients.

A three-month retrospective study of netarsudil (Rhopressa, Aerie Pharmaceuticals) a rho kinase inhibitor approved in the United States, found an additional 3.9 mmHg IOP decrease in 172 eyes, that was similar in patients regardless of the number of baseline medications.

A retrospective evaluation of brimonidine (Alphagan, Bausch + Lomb) in 53 eyes also showed an additional 20% IOP decrease in 53% of patients after 12 months who had been receiving a mean of three baseline medications.

Many prospective studies of latanoprost (Xalatan and Pharmaclia, Upjohn) have shown a positive additive effect of the drug, with IOP decreases ranging from more than 20% to 36% in patients taking multiple baseline medications, Dr. Serle reported.

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A retrospective evaluation of brimonidine (Alphagan, Bausch + Lomb) in 53 eyes also showed an additional 20% IOP decrease in 53% of patients after 12 months who had been receiving a mean of three baseline medications.

Many prospective studies of latanoprost (Xalatan and Pharmaclia, Upjohn) have shown a positive additive effect of the drug, with IOP decreases ranging from more than 20% to 36% in patients taking multiple baseline medications, Dr. Serle reported.

The question associated with these drugs, which include the co-drug nitric oxide-donating PGA latanoprostene bunod (Vyzulta, Bausch + Lomb), and the FDC netarsudil/latanoprost (Rocklatan, Aerie Pharmaceuticals), brinzolamide/brimonidine (Simbrinzia, Alcon), topical CAI/beta-blocker (Cosopt, Merck Sharp & Dohme), and PGA/beta blocker (Xalacom, Pfizer), is whether the numbers of medications, bottles, or daily drop should be counted, according to Dr. Serle.

Dr. Serle explained that when using the fixed-dose combinations, five medications can be installed with four daily drop instillations, with only three bottles compared with previously when using pilocarpine alone, which was instilled four times daily. So, the consideration here is the level of individual patient tolerance for an ambitious regimen.

Patients can, she believes, instill three, four, or more topical medications daily, and in her practice some do so “reliably and comfortably.” If issues arise, the options include simplification of regimens or moving on to laser or surgery, she noted and pointed to a few red flags indicating when something other than medical therapy may be entertained: the promise of better performance by the patient, IOP variability from visit to visit, running out of or not filling prescriptions, and poor visit compliance.

Dr. Serle pointed out, they address all the caveats mentioned previously. To date, few studies of these drugs have been undertaken.

Regarding the question about how much medication is too much, unfortunately, there is no magic number of medications or daily drops. “One patient’s sweet spot is another patient’s treatment burden,” she said, and the maximal number of medications that is effective, tolerated, and complied with varies markedly. The most efficacious and best-tolerated combinations of medications are unlikely to work for all patients. The bottom line seems to be highly individualized care.

“Make sure the target IOP is achieved, the disease is stable, and the patient is adhering to the regimen. These factors translate to the correct number of drop instillations daily.” Dr. Serle concluded.

Dr. Serle is a consultant to Aerie Pharmaceuticals, Inc., Allergan, and Bausch + Lomb, receives honoraria from Boehringer Ingelheim, and receives lecture fees from Aerie Pharmaceuticals, and Bausch + Lomb. She reported equity ownership in Aerie Pharmaceuticals.
Anti-VEGF injections and glaucoma: Surgeons must watch IOP elevation

With shots, physicians finding they have to pay close attention to levels in patients

By Louise Gagnon; Reviewed by Matthew Schlenker, MD, MSc, FRCPC

ANTI-VEGF INJECTIONS ARE associated with acute IOP spikes and chronic IOP rise in patients, and these increases in IOP need to be acknowledged and managed, according to Matthew Schlenker MD, MSc, FRCPC.

Dr. Schlenker is assistant professor and a University of Toronto, glaucoma, cataract, and anterior segment surgeon, Trillium Health Partners, Kingston Eye Institute, and Toronto Western Hospital, Toronto, Canada.

Speaking at the annual Sally Letson Symposium, Dr. Schlenker discussed whether anti-VEGF injections are treating or causing glaucoma. Dr. Schlenker described instances where VEGF inhibitors have a role and where IOP elevations may be a concern that need to be addressed.

“When you see neovascularization of the iris, these eyes need anti-VEGF (injections) as soon as possible,” said Dr. Schlenker. “This is an opportunity to prevent peripheral anterior synchiae (PAS), and we all know the outcomes are guarded once we have 360° of PAS.”

With respect to wound modulation in filtering surgery, it is complicated to decide whether to use subconjunctival anti-VEGF injections, according to Dr. Schlenker.

“There are plausible mechanisms of action,” he said. “There are some in vitro studies that are promising, and there have been animal studies that are promising. However, the clinical studies have yielded mixed results.”

Dr. Schlenker pointed to some promising data from a prospective, randomized, controlled trial involving 138 patients which found that intracameral injection of bevacizumab improved the outcome of trabeculotomy. Br J Ophthalmol. 2014 Jan;98(1):73-8.

“The data suggested that bevacizumab, administered intracamerally during surgery, was a useful adjunct to mitomycin C,” said Dr. Schlenker. “However, several other studies have been unable to show a benefit.”

In another study, Dr. Schlenker noted that a trial that compared ranibizumab and laser versus laser alone, where the investigators concluded repeated intravitreal injections of ranibizumab may increase the risk of sustained IOP elevation, suggesting a possible need for ocular hypotensive therapy. JAMA Ophthalmol. 2015 May;133(5):589-97.

The investigators concluded that the data indicate IOP be monitored periodically in eyes receiving repeated injections of anti-VEGF therapy, said Dr. Schlenker. “There was not a large number of patients with a problem in these studies; however, these studies mainly included patients who did not have a glaucoma, so may not be generalizable to other patient populations,” he said.

These trials originally reported mean IOPs but did not look specifically at the number of patients with a clinically significant IOP rise over time. In post-hoc analysis, there was a statistically significant difference in patients who had a chronic IOP rise between those receiving injections and those receiving sham injections.

IOP rise can also be a concern in patients with diabetic macular edema receiving injections of VEGF inhibitors.

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Best anterior-segment imaging for corneal transplants

Surgeons must weigh the benefits of range of options available for their patients

By Lynda Charters; Reviewed by Dipika V. Patel, MRCOpht, PhD

A wide range of anterior-segment (AS) imaging technologies are available, but not all of these are of practical benefit for AS surgeons. Some are more useful for diagnosing, managing, and assessing the prognoses of patients undergoing keratoplasty, Dipika V. Patel, MRCOpht, PhD, pointed out. Dr. Patel is a professor of ophthalmology, University of Auckland, Auckland, New Zealand.

**PREOPERATIVE ASSESSMENT**

Ultrasound biomicroscopy (UBM) provides a view of the AS that can be obscured by corneal opacities on slit lamp examination. The surgeon can have a robust view of the anterior chamber depth, angle, lens and anterior capsule, membranes, adhesions, and vitreous in the anterior chamber using UBM, she commented.

The disadvantage of UBM is that the patient must be supine and water immersion is usually needed (although recent models overcome these issues), both of which require patient cooperation or use of general anesthesia.

“Having the knowledge of the status of the eye behind an opaque cornea aids in planning the surgery as well as discussing the prognosis with the patient,” Dr. Patel emphasized.

AS optical coherence tomography (AS-OCT), which is a non-contact technology performed with the patient sitting, allows the surgeon to assess the depth of corneal pathology.

With the information provided by this imaging, the surgeon can select the most appropriate surgical intervention, Dr. Patel noted. She then described a case of stromal haze that developed following implantation of a Kamra inlay (SightLife Surgical) that ultimately was removed.

At the slit-lamp, the depth of the haze could not be clearly ascertained. OCT demonstrated that the haze was maximal at the interface, including the location of the inlay, and extended both anteriorly and posteriorly to the deep stroma.

The disadvantages of AS-OCT include poor visualization of both the ciliary body and through corneal opacities.

**INTRAOPERATIVE OBSERVATION**

*Real-time, high-quality images are now accessible using intraoperative OCT with microscope-integrated OCT devices.*

Dr. Patel noted that the images may be viewed through the surgeon’s microscope on a heads-up display or an external screen.

“The availability of these images affects decision-making intraoperatively and is thought to reduce the length of the surgery,” she explained.

The usefulness of intraoperative OCT technology also was evaluated in a prospective multi-surgeon study that included 244 cases of AS surgery.

The results indicated that the technology influenced surgical decision-making in 43.4% of cases; 78.3% of surgeons preferred real-time to static image acquisition; and 63.1% of surgeons preferred viewing the images on the external screen.

This technology can be applied to deep anterior lamellar keratoplasty (DALK) to evaluate the depth of the needle and dissection, the plane of big-bubble dissection, the residual stromal thickness, and to detect any microperforations.

In Descemet’s stripping automated endothelial keratoplasty (DSAEK) and Descemet’s membrane endothelial keratoplasty (DMEK), intraoperative OCT can evaluate graft-host apposition, assess the interface fluid, check the graft orientation in DMEK, and facilitate faster positioning of the graft with less manipulation.

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**TAKE-HOME**

*There is a wide range of anterior-segment imaging technologies on the market today. Some anterior-segment imaging devices are better than others in anterior-segment surgeries, and surgeons must decide which options are best suited for their practices.*

*Continues on page 28: Anterior-segment*
By Lynda Charters; Reviewed by Carol L. Karp, MD

OCT providing physicians with improved view of ocular surface

Technology helps physicians uncover dangers that can lurk in tissues

NEW TECHNOLOGIES, SUCH as in vivo confocal microscopy, optical coherence tomography (OCT), and ultrasound biomicroscopy, are providing new options for surgeons challenged with diagnosing ocular surface lesions. While some cases may be easier to diagnose, the pathologies in other cases may be shrouded in subtlety or complicated by other diseases.

“These new technologies can assist the ophthalmologist in the diagnosis and management of ocular surface neoplasias,” Carol L. Karp, MD, said. She demonstrated surprising diagnoses that remained undiscovered using conventional diagnostic procedures.

Dr. Karp is professor of ophthalmology, Richard K. Forster Chair in Ophthalmology, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami.

‘High-resolution OCT provides an optical biopsy with excellent correlation to histopathology and has revolutionized my management of ocular surface tumors.’

– Carol L. Karp, MD

OCT showed an abrupt transition to thickened hyperreflective epithelium over a thick area of band keratopathy. A biopsy showed conjunctival intraepithelial neoplasia and band keratopathy. The ocular surface squamous neoplasia (OSSN) was concealed.

Surgeons have a number of possible procedures to use to reach a diagnosis, such as impression cytology, confocal microscopy, and biopsies, but anterior-segment imaging seems more valuable in difficult cases for ferreting out the pathologies lurking on and below the ocular surface. For Dr. Karp, that magical device is high-resolution OCT that has a wavelength of 830 nanometers and axial resolution of 5 to 7 μm.

PTERYGIUM

Dr. Karp recounted another illustrative case of a 64-year-old man with a pterygium. A scan revealed normal dark, thin epithelium and thickened hyperreflective stringy epithelium with an abrupt transition on both sides of the area. The pterygium had normal epithelium. The diagnosis was OSSN adjacent to the pterygium.

A third case was that of a 76-year-old man with rosacea, longstanding trichiasis, and chronic scarring. The patient has been followed for the scar ring, but a granular appearance is raised suspicions. A subsequent scan showed normal epithelium and an abrupt transition to thickened hyperreflective epithelium on the cornea. OSSN was also confirmed to be hiding in this patient.

CORNEAL OSSN

A 57-year-old woman, who was contact lens intolerant, was referred with corneal OSSN. OCT showed normal epithelium with a lesion below. The biopsy revealed a Salzmann’s nodule.

Another patient was referred with a pigmented lesion. The scan showed thin epithelium and multiple subepithelial cysts characteristic of a conjunctival nevus.

PINK SALMON LESION

Another interesting case was that of a pink salmon lesion. Scanning showed normal epithelium and homogeneous hyporeflective dark dots. Biopsy and flow cytometry confirmed lymphoma. After external beam radiation, no dark dots were visualized below the epithelium on OCT.

In another patient referred for lymphoma, the clinical finding was a pink-yellowish lesion. OCT showed a subepithelial lesion with hyperreflective linear opacities that were not homogeneous, thus ruling out lymphoma. The actuality was amyloidosis.

In a final case, a 62-year-old woman presented with a diagnosis of OSSN. A scan showed normal epithelium and thin overlying epithelium over a subepithelial hyperreflective lesion.

This turned out to be an amelanotic melanoma.

Dr. Karp pointed out in OSSN, there is an abrupt transition from normal to abnormal epithelium and thickened hyperreflective epithelium. “With pterygium, the epithelium is thin that may be slightly hyperreflective, but the main lesion is subepithelial, hyperreflective, and stringy,” she said. “Lymphoma is characterized by very homogeneous, dark cellular dots in contrast to amyloid the dots are linear non-homogeneous dots. Cases of melanoma characteristically have normal epithelium with hyperreflective cellular infiltrates and nevi have multiple cysts.”

CONCLUSION

Dr. Karp is using the technology in her own practice, and it allows her to gather more information for some tough cases.

High-resolution OCT is her go-to technology to obtain correct diagnoses in suspicious cases in which a diagnosis may be hidden.

“High-resolution OCT provides an optical biopsy with excellent correlation to histopathology and has revolutionized my management of ocular surface tumors,” she concluded.
THE IMPORTANCE OF the limbal stem cells was never in dispute, and they are fundamental to regeneration of the corneal epithelium. However, the general good health of the cells must be maintained to ensure that regeneration, and uniform guidelines were absent regarding what exactly constituted limbal stem cell disease.

“The stem cells are the source of the regeneration and maintain a healthy phenotype of the corneal epithelium,” Friedrich E. Kruse, MD, explained, underscoring their importance.

In an unhealthy state when the stem cells are not functioning well, the result is conjunctivalization, in which normal corneal epithelium is replaced by conjunctival epithelium.

“When this happens, the characteristic picture of limbal stem cell deficiency arises,” said Dr. Kruse, professor of ophthalmology, Department of Ophthalmology, University of Erlangen-Nuremberg, Erlangen, Germany.

TREATMENTS

The potential treatments for the scenario detailed are limbal stem cell transplantation or ex vivo expanded grafts.

Numerous studies have reported the results of limbal stem cell transplantation, with great variations in the diagnostic criteria, staging systems, and outcome criteria, resulting in marked heterogeneity of the clinical picture of stem cell deficiency and potential confusion with other ocular surface diseases, Dr. Kruse explained.

Recognition of the lack of uniformity in the definition and diagnostic criteria resulted in a consensus conference in which corneal experts ultimately produced two reports, the first of which focuses on definition, classification, diagnosis, and staging of limbal stem cell deficiency.

The committee published a global consensus in Cornea (Deng et al. 2019:38:564-75). The second report on treatment guidelines is currently under review.

NEW DEFINITION

The new definition of limbal stem cell deficiency is that it is “an ocular surface disease caused by a decrease in the population and/or function of corneal epithelial stem/progenitor cells that leads to the inability to sustain normal homeostasis of the corneal epithelium.”

This scenario leads to the clinical picture of conjunctivalization (goblet cells on the ocular surface), signs of epithelial dysfunction or both that include epithelial abnormalities, superficial neovascularization, ocular surface inflammation, and scarring.

However, decreased vision, pain, and negatively impacted quality of life are the frequent results for patients.

INDIRECT EVIDENCE

When goblet cells are present on the corneal surface, changes of the epithelial phenotype provide indirect evidence for the diagnosis of limbal stem cell deficiency: irregularity and hazziness, vascularization, absence of the limbal palisades, persistent and recurrent epithelial defects, and subepithelial fibrosis, according to Dr. Kruse.

The symptoms include pain, foreign-body sensation, photophobia, resulting in decreased vision and quality of life.

The most important diagnostic test is surface late staining with fluorescein; the dye diffuses into the paracellular space of the conjunctivalized surface, and the abnormal delayed staining is seen 10 minutes or longer after fluorescein is instilled on the ocular surface, Dr. Kruse explained.

Other histologic and immunohistochemistry tests, that is, impression cytology and biopsy, also can be performed to diagnosis the presence of limbal stem cell disease.

In vivo imaging also has emerged as a noninvasive tool for patients.

TAKE-HOME

» The lack of consensus regarding limbal stem cell deficiency has been resolved by a panel of experts that provided uniform guidelines for disease diagnosis and staging.

Continues on page 28: Stem Cell
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STEM CELL

(Continued from page 26)

An alternative imaging method is anterior-segment optical coherence tomography, which is also noninvasive and provides a larger field of view.

LIMBAL STEM CELL DEFICIENCY

Acquired limbal stem cell deficiency can result primarily from non-immune causes: chemical, thermal, or radiation injury; contact lens-induced changes; surgery; trachoma and lid disease; and drugs. The immune causes include Stevens-Johnson syndrome, mucous membrane pemphigoid, allergic ocular surface disease, vernal and atomic keratoconjunctivitis, graft-versus-host disease, severe dry eye, and idiopathic problems.

Hereditary limbal stem cell deficiency results from congenital aniridia, dyskeratosis congenita, autoimmune polyglandular syndrome, ectodermal dysplasia, multiple endocrine deficiency, and xeroderma pigmentosum.

STAGING

The expert panel also established a new staging system to guide therapy and surgery.

“Stage I is characterized by healthy corneal epithelium in the center and various degrees of conjunctivalization in the periphery,” Dr. Kruse explained. “In stage II, the corneal center shows signs of disease with various changes in the periphery. Stage III shows complete vascularization of the corneal surface.”

CONCLUSION

Dr. Kruse noted that the panel has established a new definition of limbal stem cell disease.

“We think it is important to look for signs of conjunctivalization on the ocular surface and to prove the existence of goblet cells when invasive therapy is performed.”

- Friedrich E. Kruse, MD

ANTERIOR-SEGMENT

(Continued from page 24)

limited details visible on the heads-up display, light scattering and shadowing from surgical instruments, and cost.

POSTOPERATIVE EXAMINATION

AS-OCT facilitates assessment of grafts in DSAEK and DMEK for thickness, centration, and detachment. This technology influences management considerations such as graft reshaping and repositioning and rebubbling.

“This technology is particularly valuable in cases with an edematous cornea when the view at the slit lamp is poor,” Dr. Patel pointed out.

AS-OCT technology allows the surgeon to assess the graft-host junction after penetrating keratoplasty, in which graft-host malpositioning occurs commonly and is associated with high levels of astigmatism.

Dr. Patel described the case of a patient in whom the vision decreased a few years after deep anterior lamellar keratoplasty due to recurrent granular dystrophy at the interface.

AS-OCT is also useful for evaluating the extent of epithelial ingrowth, albeit rare, following lamellar endothelial keratoplasty.

“This technology is particularly valuable in cases with an edematous cornea when the view at the slit lamp is poor.”

- Dipika V. Patel, MRCoPht, PhD

The technology is also used to monitor patients over time.

IVCM has proven useful to confirm cases of epithelial ingrowth. Dr. Patel described an interesting case in which the IVCM images showed epithelial cells with fibrotic areas in the stroma, where epithelium should not be present, Dr. Patel explained.

IVCM and specular microscopy are both useful technologies that can be used to determine the prognosis as well as the potential for late endothelial graft failure.

Two long-term studies investigating graft failure after full-thickness or endothelial transplants both found that preoperative donor endothelial density is not predictive of failure, but rather, low endothelial cell density (<1,200 cells/mm²) 6 months postoperatively is associated with late endothelial graft failure.

For physicians, AS-OCT is opening new doors to ensure the fast and efficient diagnosis and treatment of patients.

This, according to Dr. Patel, can lead to better outcomes for their vision.

“UBM, AS-OCT, intraoperative OCT, IVCM, and specular microscopy are useful for establishing a diagnosis, directing the management and assessing the prognoses of these patients,” Dr. Patel concluded.

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Dr. Kruse has no financial interest in any aspect of this report.
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SURFING THE DRY EYE PIPELINE

For 2020 and beyond: Dry eye disease agents advance

By Michelle Dalton

Originally believed to be primarily a disease of postmenopausal women with or without autoimmune disorders, it is now recognized that dry eye disease (DED) affects patients of both sexes at younger ages. A chronic inflammatory disease, DED is the most common eye disease. It can have a significant impact on the quality of life of a sufferer. There remains a major unmet medical need for more effective treatments, as currently available treatments for DED have limited efficacy (particularly over the long-term), provide only symptomatic improvement and or are associated with safety and tolerability issues, such as burning or stinging, on instillation that limit their use.

Artificial tears generates close to $540 million in annual sales globally, and the U.S. spends more than $2 billion yearly on pharmaceuticals to treat DED.

Patients with Sjögren’s syndrome dry eye spend 78% more on western medicine than those without the autoimmune disorder DED. There continues to be an unmet need for more effective treatments for DED, as is evidenced from the multitude of clinical studies listed in ClinicalTrials.gov that are under way or not yet recruiting.

Here is an overview of studies nearing completion and products that have been filed for regulatory approval.

ON THE HORIZON

Kala Pharmaceuticals has submitted a new drug application to the FDA for KPI-121 (0.25%) for the treatment of dry eye based on the strength of one phase II trial and two phase III trials, STRIDE 1 and STRIDE 2.

The trials enrolled almost 2,000 patients, and indicated statistical significance for the primary endpoint of conjunctival hyperemia, as well as the primary symptom endpoint of ocular discomfort severity.

If approved, KPI-121 would be first product indicated for the temporary relief of the signs and symptoms of dry eye disease and flares. The agent uses Kala’s AMPPLIFY drug delivery technology to better penetrate the target tissues.

In August, the company received a complete response letter (CRL) from the FDA regarding its new drug application (NDA) for KPI-121.

The STRIDE 3 trial is a multicenter, randomized, double-blind, placebo-controlled, parallel-arm study, comparing KPI-121 0.25% to vehicle (placebo), each dosed four times a day (QID) for two weeks in approximately 900 patients with dry eye disease. Subjects who meet initial screening and inclusion/exclusion criteria undergo a two-week run-in period with vehicle. Subjects who continue to meet inclusion/exclusion criteria after the run-in are randomly assigned to receive either KPI-121 0.25% or vehicle for two weeks.

Data from the phase III clinical trial, STRIDE 3 (ClinicalTrials.gov Identifier: NCT03616899), is expected to be released by the end of the year.

IN THE PIPELINE

Aldeyra Therapeutics is now enrolling patients into the RENEW phase III clinical trial, which will evaluate the efficacy of reproxalap ophthalmic solution (0.25%) versus vehicle in 400 patients with moderate and severe DED. Subjects who meet initial screening and inclusion/exclusion criteria undergo a two-week run-in period with vehicle. Subjects who continue to meet inclusion/exclusion criteria after the run-in are randomly assigned to receive either reproxalap 0.25% or vehicle for two weeks.

Co-primary endpoints are ocular dryness and fluorescein nasal region ocular staining (ClinicalTrials.gov Identifier: NCT03879863). The phase III trial comes on the heels of successful phase Ib trial results, which demonstrated statistical superiority of reproxalap versus vehicle across multiple dry eye signs and symptoms.

In the new study, patients will be randomly assigned to one of four arms: reproxalap 0.25% ad-
administered QID for 12 weeks; reproxalap 0.25% administered QID for four weeks, then BID for eight weeks, or vehicle comparators to each of the active arms. Targeted trial completion is April 2021.

Aurinia Pharmaceuticals recently announced phase II data of its 100-person, double-masked, head-to-head trial comparing voclosporin ophthalmic solution (VOS) to Restasis. Both drugs were well-tolerated and there was no statistical difference between VOS and Restasis for the primary endpoint; both drugs exhibited low drop-discomfort scores. VOS did show statistically significant improvements over Restasis for week 4 for objective tests, including Schirmer’s and fluorescein corneal staining.

Lacripep is currently in a phase II trial to compare its efficacy versus placebo in patients with Sjogren’s syndrome dry eye (ClinicalTrials.gov Identifier: NCT03226444). The primary endpoint is change in fluorescein corneal staining score at week four from baseline. Secondary endpoints include changes in eye dryness, mean SANDE 2 scores, and individual symptom assessments, among others.

Mitotech is developing a few drug formulations of SKQ1, such as Visomitin, which is currently in phase III trials for the treatment of DED (ClinicalTrials.gov Identifier: NCT03764735). Visomitin is already approved for this indication in Russia. Clinical trials have shown that Visomitin is efficacious in improving corneal and conjunctival staining, tear quality, and other DED symptoms.

According to the company website, one part of SKQ1 functions as a molecular “tow truck,” carrying the other part of the molecule—an extremely active antioxidant plastoquinone—into mitochondria. The molecule was designed to act as a mitochondria-targeted ROS scavenger. Mitotech is developing SKQ1 as a potential treatment for uveitis and dry age-related macular degeneration.

Oyster Point Pharma has two nasal spray therapeutics in clinical trial development for the treatment of DED. OC-01 (ClinicalTrials.gov Identifier: NCT03873246) and OC-02 are selective nicotinic acetylcholine receptor (nAChR) agonists that harness the trigeminal parasympathetic pathway to improve tear film production.

The OC-02 RANIER and PEARL studies are complete, but data have not been released. The OC-01 MYSTIC (ClinicalTrials.gov Identifier: NCT03873246) and IMPERIAL (ClinicalTrials.gov Identifier: NCT03688802) studies have an expected completion date in August. ONSET-1 is complete, but data have not been released.

OC-01’s novel mechanism of action re-establishes tear film homeostasis by activating the trigeminal parasympathetic pathway to stimulate the glands and cells responsible for natural tear film production, known as the lacrimal functional unit.

According to the company, in phase IIb clinical studies patients administered either OC-01 or OC-02 experienced rapid and significant improvements in both the signs and symptoms of DED.

Both were well-tolerated with no significant ocular adverse events or drug-related serious adverse events.

Oyster Point in October announced plans for an IPO. The company plans to raise $85 million by offering 5 million shares at a price range of $16 to $18.

ReGenTree will begin enrolling patients into ARISE-3, a phase III trial designed to evaluate RGN-259 for the treatment of DED (ClinicalTrials.gov Identifier: NCT03937882). RGN-259 eye drops contain an active small protein, thymosin beta 4, which is naturally occurring in tears and other body fluids.

The eye drops have demonstrated wide-ranging and multifunctional activities. Such activities underlie the efficacy of RGN-259 eye drops seen to date in alleviating both the signs and symptoms of dry eye.

According to the company, both ARISE-1 and ARISE-2 patients reported minimal ocular discomfort similar to that of the placebo.

A chronic inflammatory disease, dry eye disease is the most common eye disease. It can have a significant impact on the quality of life of a sufferer.

Lacripep is currently in a phase II trial to compare its efficacy versus placebo in patients with Sjogren’s syndrome dry eye (ClinicalTrials.gov Identifier: NCT03226444). The primary endpoint is change in fluorescein corneal staining score at week four from baseline. Secondary endpoints include changes in eye dryness, mean SANDE 2 scores, and individual symptom assessments, among others.

Mitotech is developing a few drug formulations of SKQ1, such as Visomitin, which is currently in phase III trials for the treatment of DED (ClinicalTrials.gov Identifier: NCT03764735). Visomitin is already approved for this indication in Russia. Clinical trials have shown that Visomitin is efficacious in improving corneal and conjunctival staining, tear quality, and other DED symptoms.

According to the company website, one part of SKQ1 functions as a molecular “tow truck,” carrying the other part of the molecule—an extremely active antioxidant plastoquinone—into mitochondria. The molecule was designed to act as a mitochondria-targeted ROS scavenger. Mitotech is developing SKQ1 as a potential treatment for uveitis and dry age-related macular degeneration.

NOValq has two DED products in the pipeline: NOV03 (100% perfluorohexylcaine) and CyclA-Sol (ophthalmic solution of 0.1% cyclosporine A in EyeSol). NOV03 is being developed for evapo-
Challenging conventional wisdom on astigmatism, dry eye disease

Study offers results that diverge from long-held beliefs

By Cynthia Matossian, MD, FACS; Special to Ophthalmology Times

THE CONVENTIONAL WISDOM is that an unstable tear film in patients with dry eye produces pseudo-astigmatism; i.e., that dry, irregular surface makes the eye appear to have more cylinder than it actually does.

Once this is treated, the ocular surface should be smoother and the patient will therefore have less astigmatism.

Or at least that’s how I thought it worked. But in a study I’ve recently conducted, 52% of eyes actually had a higher magnitude of astigmatism when measured six weeks after treatment with thermal pulsation therapy for meibomian gland dysfunction (MGD) than they did before treatment (Figure 1).

Interestingly, we found that we could not predict the magnitude or direction of the cylinder change based on the baseline pre-treatment keratometry.

That’s why it is so important to treat the underlying MGD before performing biometry and IOL power calculations for cataract surgery.

For this study, I evaluated keratometry, refractive error and other measures at baseline and six weeks after a single LipiFlow thermal pulsation treatment (Johnson & Johnson Vision) in patients with MGD who were scheduled for subsequent cataract surgery.

The post-thermal pulsation biometry was used to calculate IOL power and determine my approach to astigmatism management (toric IOL, limbal relaxing incision, or nothing).

Finally, the actual refractive results were compared to those I would have obtained had I relied on the pre-treatment biometry. It turned out that 56% of eyes had less residual refractive astigmatism (i.e., better outcomes) after surgery than they would have had if they had undergone cataract surgery without having the LipiFlow treatment first (Figure 2).

I believe that this is good evidence that treating MGD is important for optimal results during cataract surgery.

Moreover, we cannot assume the “true” astigmatism will always be less than what we see with an unstable tear film.

TAKE-HOME

» Treating meibomian gland dysfunction is important for optimal results during cataract surgery. Physicians cannot assume the “true” astigmatism will always be less than what they see with an unstable tear film.

REFERENCES


Innovative IOL power calculations gain accuracy

Residual refractive error still occurs in clinically significant proportion of normal cases

By Cheryl Gutman Kradar; Reviewed by Giacomo Savini, MD

The accuracy of IOL power calculations continues to improve with the use of modern instruments for biometry, updated formulas, and constant optimization. However, unusual eyes still present a challenge, and residual refractive error still occurs in a clinically significant proportion of normal cases, said Giacomo Savini, MD.

“In my opinion, it is always wise not to overpromise because approximately 15% of eyes may have a prediction error >0.50 D,” said Dr. Savini, private practice, Studio Oculistico d’Azeglio, Bologna, Italy, and researcher, IRCCS GB Bietti Foundation, Rome, Italy. “In particular, surgeons might advise patients who are choosing a multifocal IOL that a laser enhancement may be necessary to reach emmetropia in up to 10% of cases.”

Dr. Savini said that while the available optical biometers represent different technologies, it is not possible to say that one is more accurate than another.

“More or less, the modern biometers are doing the same job, and the choice among them will not affect the final outcome,” he explained. “In studies we did comparing power calculations using data from three different biometers in five different formulas, the results were very close with a prediction error ≤0.5 D achieved in approximately 80% to 90% of eyes.”

Differences

There are differences, however, in the performance of available formulas, and results from various published studies show that better outcomes are achieved by using the newer formulas that take anterior chamber depth into account for the estimation of the IOL position, Dr. Savini said. Some formulas introduced more recently include the Barrett Universal II, EVO, Hill-RBF, Kane, Naeser, Olsen, Panacea, and Pearl-DGS, and most of those can be accessed for free online.

A recent study by Dr. Savini and colleagues compared the accuracy of 15 IOL power calculation formulas, including many of the newer formulas [Savini G, et al. J Cataract Refract Surg. In press https://www.jcrsjournal.org/article/S0886-3350(19)30641-8/fulltext]. Using data from 150 eyes that were all measured with the same biometer, received the same model IOL, and operated on by one of two surgeons, the analyses showed that the prediction error was within 0.5 D in almost 90% of eyes.

“With seven of the formulas, a prediction error ≤0.5 D was achieved in ≥88% of eyes. Even the older formulas did not do so bad because with their use, about 85% of eyes were within 0.5 D of the intended target, which is still a good result,” Dr. Savini said.

Particularly interesting, however, was the finding that a prediction error ≤0.25 D was achieved in the majority of cases (51% to 62%), regardless of the formula used. The best results were achieved with the Kane and Barrett formulas, both of which had a prediction error ≤0.25 D in 62% of eyes.

“As the next frontier, I think we will be classifying performance of IOL calculation formulas by the percentage of eyes with a prediction error lower than 0.25 D instead of ≤0.5 D,” Dr. Savini said.

Special Cases

Nevertheless, it is still necessary to be careful in long and short eyes. In a paper published by Kane et al. [Kane JX, et al. J Cataract Refract Surg. 2016;42(10):1490-1500], a prediction error within 0.5 D of target was achieved in only about 60% of eyes that had an axial length <22 mm or >26 mm. Another recent paper reported that in hyperopic eyes with an axial length <22 mm, the Barrett Universal II was no more accurate than older formulas and resulted in a prediction error ≤0.5 D in less than 50% of eyes [Shrivastava AK, et al. J Cataract Refract Surg. 2018;44(11):1317-1320].

Eyes with keratoconus also present a challenge for achieving accurate refractive outcomes. The problem was highlighted by the findings of a retrospective analysis performed by Dr. Savini and colleagues that compared prediction errors occurring with the Barrett Universal II, Haigis, Holladay 1, Hoffer Q, and SRK/T formulas and dividing eyes according to keratoconus stage [Savini G, et al. J Cataract Refract Surg. 2019;45(5):576-581]. The results showed that all of the formulas were associated with a hyperopic result. The lowest mean arithmetic errors occurred with the SRK/T.

“Although the findings of this study were unexpected, in my opinion, the explanation for why the SRK/T performed best is that it trends toward resulting in a myopic outcome,” Dr. Savini noted. “Therefore, the error with the SRK/T compensates for the hyperopic error that generally occurs in keratoconic eyes.”

Dr. Savini pointed out that a solution will require more sophisticated methods for biometry.

Optimizing Outcomes

Dr. Savini also emphasized the importance of constant optimization for improving refractive outcomes with IOL implantation. The process has been demonstrated to result in an increase in the percentage of eyes with a residual refractive error within 0.5 D of target and in lower overall mean and median absolute errors. Surgeons using published formulas can do the optimization themselves by back-calculating for each patient the constant that would have resulted in zero prediction error and then averaging the constant values for a series of patients. Surgeons using unpublished formulas could contact the developers who may perform the calculations for them.

Most optical biometers have integrated software to perform the calculations, and that involves entry of the IOL power used and the postoperative refraction.

“I suggest all surgeons take the time to optimize their constants so that they can achieve the best outcomes,” Dr. Savini concluded.
Bag-in-the-lens IOL reduces postop issues tied to previous models

Latest option provides near-perfect surgical scenario for physicians, patients

By Lynda Charters; Reviewed by Claus Eckardt, MD

PROVIDING AN OPTION for ease of exchangeability, the Bag-in-the-Lens Intraocular lens (BIL IOL) (Morcher) seems to have overcome a number of the noteworthy problems associated with previous IOL models, including incorrect centering, development of posterior synechiae, and secondary cataract formation.

After what seems to have been a perfect combination surgery of phacoemulsification and IOL implantation, things can go awry in the early postoperative period when the gas bubble can disrupt the centration of the IOL. The result can be an early opacification of the posterior capsule. All IOL types are susceptible to this, and it happens because, at minimum, the haptics are placed in the capsular bag, said Claus Eckardt, MD.

In an effort to overcome postoperative problems, he explained that for the past decade, he and his colleagues have been using an IOL for combined surgery that is designed so that “instead of the lens being placed in the bag, the bag is placed in the lens,” he explained.

‘This IOL eliminates development of posterior synechiae and secondary cataract formation.’

- Claus Eckardt, MD

Implantation of this IOL requires a primary posterior capsulotomy with two rhexes, one of the anterior and one of the posterior capsules. This is an additional surgical step, but it seems to justify the end result, Dr. Eckardt, who is professor of ophthalmology, Klinikum Frankfurt Höchst, Frankfurt, Germany, commented.

The BIL IOL, often referred to as the Tassignon lens for its designer Marie-Jose Tassignon, MD, is made of a hydrophilic acrylic material with two anterior and two posterior haptics, between which is a groove running 360° around the optic into which the edges of the capsules are placed.

“When viewed from the side, it looks like a rim,” Dr. Eckardt noted.

**IMPLANTATION PROCEDURE**

A ring caliper is placed onto the lens to achieve a well-centered 5-mm capsulorhexis. Standard phacoemulsification and cortex removal are performed. The posterior capsule is punctured and a viscoelastic agent is injected into the Berger space both to push the anterior hyaloid back and create a cushion. The posterior capsular rhexis is then created along the anterior rhexis and the BIL IOL is injected. By applying gentle sideward movements and downward pressure on the lens, the edges of the two capsules move almost automatically into the groove, Dr. Eckardt explained.

**ADVANTAGES**

Dr. Eckardt is enthusiastic about the use of the BIL IOL, and he explained there is little change in patients’ eyes over the long term as a result of the primary posterior capsulotomy and implantation of the BIL IOL is not limited to uncomplicated cases.

“These cases did not have only uncomplicated macular puckers and holes but they also had advanced proliferative vitreoretinopathy that needed repeated vitrectomies with gas and oil tamponade,” he said. “Regardless of the vitreoretinal pathology, there is almost guaranteed stable IOL centration.”

In addition to the excellent centration, another advantage is that there is no possibility of development of capsular opacification because the capsule has been removed. “This is particularly advantageous if silicone oil injection is planned, because YAG laser capsulotomy would not be possible,” Dr. Eckardt said.

Notably, posterior synechiae and iris bombe cannot develop, which is important for eyes with uveitis, diabetes, ruberosis, or trauma.

“These complications cannot occur because the remaining posterior and anterior capsules are, in effect, glued together such that the capsular bag is totally closed,” Dr. Eckardt pointed out. “Proliferative lens epithelial cells have no way to come into contact with the iris, and this is also true for severe uveitis in which rapid recurrent synechiae is expected after surgery.”

With this lens, the pupil remains free postoperatively and can regain motility, he explained.

Finally, if needed, the BIL IOL can be exchanged easily; only a spatula is needed to get into the groove and elevate the IOL out from beneath the capsular edge. After cutting and removing the lens, the rhexis can be seen to have remained intact well past the time of implantation.

**DISADVANTAGES**

Dr. Eckardt pointed out that implantation of the BIL IOL becomes more challenging in cases of small pupils and loose zonules. Postoperatively, the pupil should not be dilated excessively during the early postoperative period because of the risk of iris capture, i.e., partly incarcerated in the groove as a result of the pressure of the gas bubble. This can be addressed using a spatula at the slit-lamp.

The chances of calcification of an acrylic lens are the same as with any acrylic IOL after gas tamponade, but after implantation of over 3,000 BIL IOLs, this has not occurred in Frankfurt, Dr. Eckardt reported.

The BIL IOL is more expensive and the surgical duration is three minutes longer than the typical surgery. Dr. Eckardt noted that primary posterior capsulotomy and implantation of the BIL IOL guarantees good IOL centration independent of the tamponade, despite the presence of gas or silicone oil.

“This IOL eliminates development of posterior synechiae and secondary cataract formation. In the event of a refractive error or a refractive change in the fellow eye, the IOL can be exchanged easily, even after the passage of several years postoperatively. This lens is ideal for phaco-vitrectomy.”

**TAKE-HOME**

- The IOL eliminates development of posterior synechiae and secondary cataract formation.
- In the event of a refractive error or a refractive change in the fellow eye, the IOL can be exchanged easily, even after the passage of several years postoperatively. This lens is ideal for phaco-vitrectomy.
GLAUCOMA

(Continued from page 1)

angle glaucoma. The stent can be used regardless of glaucoma stage, and does not have to be combined with cataract surgery.

Traditionally, the stent has been placed in an ab interno procedure with delivery through a 1.8 mm clear corneal incision, but an ab externo approach performed through the conjunctiva or a small peritomy is possible, and the technique appears to be moving in that direction, Dr. Grover said.

Presenting an intraoperative video, he provided this caution, “The surgery is not as easy as it looks, but with experience and proper training, it can be done well and provide a safe and effective surgical treatment for glaucoma.”

“One of the greatest technical challenges is becoming familiar with the ergonomics of the slider and injector used for the procedure.”

Describing his personal ab interno approach, Dr. Grover said the implantation is done under topical anaesthesia. He creates a 1 mm paracentesis in the superior temporal cornea, roughly 90° away from the planned main corneal incision through which to inject a high molecular weight cohesive viscoelastic (Healon GV, Johnson & Johnson Vision). Then he makes the clear corneal incision, and after rotating the globe inferiorly and drying the superior conjunctiva, places a mark 2 mm posterior to the limbus, as a guide to proper subconjunctival and intrascleral positioning of the stent.

“The device is 6 mm long, and in my experience, it ideally should lie 1 mm in the anterior chamber, 2 mm in the scleral wall, and 3 mm in the subconjunctival space,” he explained. Passing the needle tip of the injector system through the corneal wound can be a little difficult but a slight “shimmy” is helpful. Positioning and seating the needle in the superior angle is done under gonioscopic guidance. Dr. Grover noted that placing viscoelastic on the gonioprism is not too difficult but a slight “shimmy” is helpful.”

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According to Dr. Grover, his goal is to seat the needle tip of the injector just slightly anterior to the trabecular meshwork. A key maneuver involves stabilizing the injector while delivering the stent to avoid a “flick” as the needle from the injector disengages from the scleral wall and retracts into the injector.

“This was an initial hurdle for me,” he said.

Once the injector has been fully inserted and the needle tip is tenting up the conjunctiva, Dr. Grover slowly advances the blue slider halfway to insert the gel stent in the subconjunctival space.

“I want to exit right where the 2 mm mark is, and I want to be certain that it is in the subconjunctival space,” he said. “Perforation is possible, but it would be hard to do and is extremely rare.”

If perforation occurs, the surgeon should simply bring the injector back into the anterior chamber, move the needle tip 1 to 2 clock hours to either side, and re-implant.

“The small conjunctival perforation is usually small and does not leak, but make sure it is Seidel negative at the end of the case,” Dr. Grover said.

After implantation, inspection with gonioscopy should confirm that the implant is positioned away from the iris with proper proportions in the anterior chamber and subconjunctival space.

“Using a blunt instrument or the back side of a canula, the surgeon can roll away the chemosis, starting from the limbus towards to fornix, to flatten the conjunctiva and visualize the implant in the subconjunctival space,” Dr. Grover said. “You want to see that the stent is mobile and able to flap freely to the left and right, which is a sign that it is free of any obstruction and not imbedded in Tenon’s capsule.”

Undiluted mitomycin-C (40 to 80 μg) is then injected subconjunctivally in the target quadrant away from the limbus, but first Dr. Grover said he injects a small bolus of 2% lidocaine to improve patient comfort.

“Because the procedure is done under topical anesthesia, patients will feel the burn of the mitomycin-C,” he explained. “A small lidocaine bolus has made a big difference for my patients and for me.”

A low bleb forms with the gelatin stent. Dr. Grover said that postoperative needling with mitomycin-C is needed in about 20% to 30% of cases.

“Knowing how to needle and manipulate the bleb postoperatively is an essential component to success,” he said. “If the idea of a bleb or the need for postoperative manipulation scares you, my advice would be to ask yourself if this is a procedure that you want to learn.”

OUTCOMES

Data from the 510(k) pivotal trial that included 65 eyes of 65 patients showed that at 12 months, 75.4% of eyes had achieved IOP lowering from baseline of at least 20% while being on the same number or fewer medications. Mean baseline IOP was 25 mm Hg and it was reduced by an average of 9.1 mm Hg in the 52 patients who completed the 12-month followup. Mean number of medications was reduced by 50% from 3.5 to 1.7. There were no significant or unexpected complications.


“In general, success rates over time in glaucoma surgery are in the 70-80% range, and so this is a very good result considering that the eyes in the study were very refractory cases with advanced disease,” he said.

PATIENT SELECTION

Dr. Grover said he uses the gel stent when angle surgery cannot be used, has failed, or is not expected to be effective. It can be effective if follow-up is difficult, for example because the patient has a long commute, is expected to be non-compliant, or needs to get back to work quickly; if a patient is on a blood thinner that cannot be discontinued for a few weeks; and when it is important to have a predictable refractive outcome.

Dr. Grover added that he will not use it if there is active inflammation; extensive superior peripheral anterior synechiae; angle closure (unless the procedure is combined with phacoemulsification); neovascular glaucoma; an anterior chamber, unstable posterior chamber, or sutured IOL; or if the patient has irido-corneal endothelial syndrome or is expected to need penetrating keratoplasty.

Dr. Grover provided a caution to consider facial anatomy because the presence of a prominent cheekbone and sunken eye may make surgery more challenging.

“In this situation, try to go as far nasal as possible,” he concluded.
gene therapy

Research targets precision dosing for gene, cell therapy

Subretinal delivery provides direct surgical access, may be key to treating retinal diseases

By Lynda Charters; Reviewed by Allen C. Ho, MD, and M. Ali Khan, MD

Gene therapy is happening today and cell therapy may soon follow, according to Allen C. Ho, MD. Dr. Ho, professor of ophthalmology, Thomas Jefferson University, and director of retina research, Mid Atlantic Retina and Wills Eye Hospital, Philadelphia, and his colleagues have been focusing on improving the consistency and precision of therapeutic delivery to target tissues.

"Subretinal delivery provides direct surgical access to target retinal pigment epithelial cells and retinal photoreceptors," he said. "This direct access may be important for gene and cell therapies for treating retinal diseases."

The first FDA approved gene therapy is voretigene (Luxturna, Spark Therapeutics) for biallelic RPE65 mutation-associated retinal dystrophy. In addition to restoring vision to patients, the studies evaluating the efficacy of voretigene (among other gene therapy studies) have established the safety and feasibility of subretinal delivery of gene therapy.

The use of gene therapy for other retinal diseases, such as neovascular age-related macular degeneration (AMD), are currently in clinical trials. According to Dr. Ho, translational scientists are working on improving viral capsids and transgene selections to improve efficacy. In this aim, Dr. Ho and colleagues are hoping to improve the consistency and precision of delivery systems for gene and cell therapy.

METHODS OF DRUG DELIVERY

Subretinal delivery is achieved in a few ways, the most familiar of these is "transretinal" via pars plana vitrectomy (PPV) and retinotomy using a microcatheter. Another approach is subretinal delivery via the suprachoroidal space.

In this method, Dr. Ho explained, a flexible microcatheter follows the curvature of the sclera and a microneedle, which is under the visual control of the surgeon, enters the subretinal space without the need for a PPV and retinotomy.

"A new intriguing way of transfecting target tissue is suprachoroidal injection therapy," he said. A major advantage of such a treatment would be the potential ability to perform the procedure in the office setting.

GENETHHERAPY CLINICAL TRIALS

A Phase 1/IIa gene therapy clinical trial by RegenexBio for neovascular AMD is currently under way. Enrolled subjects have been treated for neovascular AMD previously and needed frequent anti-VEGF injections over years; he described one subject who needed 23 monthly injections of ranibizumab (Lucentis, Genentech). In the study, a high-affinity AAV8 viral vector that encodes for an anti-vascular endothelial growth factor protein that is similar to ranibizumab is injected into the subretinal space, Dr. Ho explained.

The surgery is performed as follows. A core vitrectomy is performed. A 41-gauge internal diameter microcatheter is then used to deliver the vector into the subretinal space.

This maneuver is performed outside of the macula about two disc areas away from the neovascular lesion. An air-fluid exchange is performed. The traditional eye drops are instilled; no systemic steroids are used in the subretinal injection procedures.

"We have seen very good safety data for this surgical procedure," Dr. Ho reported. Improvement in the precision and control of subretinal delivery has been achieved using a new tool, the Microdose injection kit (MedOne Surgical Inc.) that includes a 1-cc microcalibrated syringe that is hooked up to the viscous fluid injection system.

"The surgeon has foot pedal control of precise volumes of fluid injected into the subretinal space," Dr. Ho noted. "To control any surgeon variability, all procedures, i.e., vitrectomy and subretinal injection, are standardized and automated, and the surgical videos of all surgeons are reviewed in order to improve the techniques and standardize them."

SUPRACHOROIDAL DELIVERY

Cell therapies to replace retinal pigment epithelium cells for the treatment of advanced geographic atrophy in dry AMD are under investigation. Replacement RPE cells may be delivered on a synthetic sheet or in suspension delivered into the subretinal space via a surgical procedure involving PPV and retinotomy formation, according to Dr. Ho.

Potentially complicating these cell therapies is the possibility of scar tissue formation, including epiretinal membrane formation or proliferative vitreoretinopathy-related tractional retinal detachment.

"Complications from proliferative vitreoretinopathy will be a topic of interest for treating retinal specialists. The retina community will be watching this as new cell therapy-related trials are initiated," said M. Ali Khan, MD, assistant professor of ophthalmology,
Thomas Jefferson University and Wills Eye Hospital.

The investigators hypothesized that these complications are the result of egress of delivered cells through the retinotomy on to the surface of the retina.

“That failure stimulated development of multiple approaches to reach the subretinal space. A suprachoroidal microcatheter was developed with a flexible microneedle; this needle emulates the suprachoroidal space to create a detachment and deliver cells.

The advantages are that no vitrectomy and retinotomy are needed, there is no efflux, and as a result the dosing might be more precise and consistent,” Dr. Ho commented.

The procedure begins with insertion of a chandelier light source. A sclerotomy is fashioned 6 mm posterior to the surgical limbus after conjunctival peritomy is performed.

A microcatheter is then inserted via the sclerotomy into the suprachoroidal space after being held in place with scleral sutures (microloops) to stabilize the path of the microcatheter and to reduce the amount of internal catheter movement to avoid damage, Dr. Khan described.

When the microcatheter is visualized to be in the desired location, a microneedle is advanced into the subretinal space. A saline bleb confirms the location.

Cells are then delivered.

‘Subretinal delivery provides direct surgical access to target retinal pigment epithelial cells and retinal photoreceptors.’

- Allen C. Ho, MD

This technology, developed by Gyroscope, has received 2019 FDA approval and is being used in the Lineage (formerly BioTime) cell therapy trial for atrophic AMD.

Dr. Ho pointed out the importance of three-dimensional (3D) imaging in reaching the correct subretinal space with precision and safety. “3D imaging allows measurement of dosing, which is an important metric in a clinical trial,” he commented.

“Gene and cell therapy is happening,” he added. “Subretinal delivery of therapy via a vitrectomy and retinotomy is very familiar.”

However, the dosing can vary and efflux can occur, especially in cell therapy trials.

“The suprachoroidal approach has been approved by the FDA and is being used in an AMD clinical trial. Imaging will be important and we now have three-dimensional imaging to facilitate quantitative dosing,” Dr. Ho summarized.
Individualized patient care gaining traction in glaucoma

Need for new tools, algorithms, and a calculator with integrated genetic data

By Lynda Charters; Reviewed by Fotis Topouzis, MD

GUIDELINES FOR MANAGING glaucoma exist around the world and generally call for either more aggressive or conservative management in subpopulations of glaucoma patients. However, these guidelines do not extend to the level of individual patients, and all clinicians ask for guidance in treating individuals, according to Fotis Topouzis, MD.

Dr. Topouzis is professor of ophthalmology, and chairman, First Department of Ophthalmology, Aristotle University, Thessaloniki, Greece.

STANDARD AND INDIVIDUALIZED CARE

The therapeutic strategies that can be adopted are standard care, either less or more aggressive, and individualized care. The Early Manifest Glaucoma Trial is an example of standard care in which patients received either argon laser trabeculoplasty with betaxolol or no treatment. Interestingly, after six years of follow-up, glaucoma did not progress in 38% of untreated patients but progressed in 45% of treated patients. The latter result raises the question of whether those patients were undertreated, which, according to Dr. Topouzis, was likely for a substantial percentage.

In another example of standard care, in the United Kingdom Glaucoma Treatment Study, patients with open-angle glaucoma were randomly selected for either latanoprost or placebo. After 24 months of follow-up, 15% of treated patients had progressive glaucoma and about 75% randomized to placebo did not progress.

The Collaborative Initial Glaucoma Treatment Study evaluated individualized care. Patients with open-angle glaucoma were randomly selected for either a medical or surgical intervention. Dr. Topouzis explained that the targeted intraocular pressure (IOP) approach was used, which relied on the IOP level and the stage of damage based on the visual field score. After five years of follow-up, the visual field scores remained largely unchanged in both treatment groups; after eight years of follow-up, 21.3% and 25.5% of the surgical and medical groups, respectively, had glaucoma progression. However, the change from the baseline mean deviation was minimal in both groups, with no significant difference between them.

The IOP decrease in the medical group was 35% and 45% in the surgery group. This result raised the question about whether the medical treatment was maximal, which seems the case because maximal medical treatment is expected to yield an IOP decrease of about 38%. When considering the surgery group with its 45% IOP reduction, no benefit was seen from this reduction compared with the medical reduction because the visual field outcomes were similar, which raises the question about whether these patients were over-treated, and this indeed may be the case for a large percentage of these patients, Dr. Topouzis commented.

LESS OR MORE AGGRESSIVE TREATMENT

According to Dr. Topouzis, this presents a conundrum. In many patients in the previously discussed studies, less aggressive treatment resulted in undertreatment, which begs the question about treating patients more aggressively. However, the results of the Collaborative Initial Glaucoma Treatment Study showed that that was not a good choice and resulted in overtreatment. “Strikingly, many glaucoma patients in the United Kingdom glaucoma treatment study and the early manifest glaucoma trial did not progress even without treatment,” he emphasized.

GETTING BACK TO BASICS

Keeping in mind the goals of glaucoma treatment, i.e., maintaining the patient’s visual function and quality of life at a sustainable cost, every treatment has the burden of cost and side effects, the latter of which affect the quality of life. Increased treatment leads to increased side effects and increased effects on the quality of life.

Clinicians currently use the targeted IOP approach to guide treatment decisions for individual patients. “In addition to the stage of damage and the IOP, other factors, such as life expectancy, additional risk factors, such as exfoliation and central corneal thickness, and the rate of progression, also were added to the European Glaucoma Society Terminology and Guidelines for Glaucoma algorithm to achieve more individualized treatment,” Dr. Topouzis explained.

MEASURING PROGRESSION

Measuring the rate of progression is problematic regarding clinical practice, i.e., the slower the rate of progression, the more visual field tests are needed to detect the progression within a given timeframe.

A team of investigators sought to strike a compromise. Chauhan et al. proposed that six visual field measurements be done in the first two years to rule out rapid progression (>2 decibels or more) and establish good baseline data (Br J Ophthalmol 2008;569:73).

“Currently, our best tools, methods, and proposed strategies aiming to detect fast progressors seem inadequate to detect slower rates of progression that would result in visual impairment or blindness during the lifetimes in the majority of patients,” Dr. Topouzis explained.

Dr. Topouzis said this level of screening may be inadequate. A drawback is that currently the rate of progression cannot be predicted. Because of this, the algorithm cannot be used at baseline but later when the progression becomes measurable.

WHAT IS NEEDED

Dr. Topouzis enumerated the tools clinicians need to best serve their glaucoma patients: knowledge of the stage of visual field damage to be prevented; the stage that is tolerable for quality of life may be affected even at an earlier disease stage; strategies and tools to calculate tolerable rates of progression for the individual patient; determination of fast progressors at the individual level, according to their tolerable rates of progression with consideration of their life expectancies and other factors; and strategies and tools to identify fast progressors.

Promising future pathways for individualized management include risk factors/biomarkers for fast progression, candidate biomarkers for angle-based surgeries, and glaucoma risk alleles for glaucoma onset and progression, he pointed out.

“We currently have set targets for IOP in individual patients and reaffirm that target during follow-up,” he concluded. “For the future, we need new tools and algorithms to identify fast progressors. Ideally, we need a calculator for glaucoma progression and fast progression, similar to one we have for ocular hypertension, and potentially with integrated genetic information.”

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Dr. Topouzis has no financial interest in any aspect of this report.
Potential of stem cell therapies offers hope for glaucoma treatment

Caution being urged when it comes to patient-funded trials for developing science

By Louise Gagnon; Reviewed by Leslie Jones, MD

OPHTHALMOLOGISTS SHOULD ADVISE: their patients to perform their due diligence when participating in patient-funded clinical trials on stem cell therapies to treat glaucoma, according to Leslie Jones, MD, chairwoman of Ophthalmology at Howard University in Washington, D.C.

“We need to be aware of what our patients are seeing in the media, that they are being marketed to,” said Dr. Jones, at the annual Sally Letson Symposium. “We have to caution them against things (trials) that are not controlled. They should approach with caution any marketing to participate in patient-funded stem cell trials.”

Dr. Jones noted that patient-funded trials have numerous weaknesses such as the lack of randomization and control arms, a disparity in access to the trials owing to their high fees, and an apparent risk of exploitation of vulnerable patients who are “reaching out for anything to improve their situation.”

Patients need to be informed that a trial appearing on a registry does not guarantee its scientific validity with respect to efficacy and safety, Dr. Jones explained.

According to Dr. Jones, clinicaltrials.gov is a registry that does not ensure that they are doing randomly selected trials or that there is informed consent or a proven effect of the therapy.

Unproven stem cell therapy treatments, often described as “cell therapy,” are readily available in the United States, with 351 businesses and more than 600 clinics, said Dr. Jones, noting the FDA has issued warnings about these treatments and the Federal Trade Commission has taken action as well.

“The availability of these treatments is not limited to the United States, with 351 businesses and more than 600 clinics, said Dr. Jones, noting the FDA has issued warnings about these treatments and the Federal Trade Commission has taken action as well.

The adverse events that have developed after visits to “stem-cell clinics” have been documented and include severe bilateral vision loss subsequent to intravitreal injections of autologous adipose tissue-derived stem cells. N Engl J Med. 2017 Mar 16;376(11):1047-1053.

“They had their own adipose cells removed, and then spun down with various enzymes, and then injected into the vitreous cavity of the eye,” said Dr. Jones, describing in detail the treatment administered to these patients.

“One of the enzymes was so toxic that they caused lysis of zonules,” she added.

Another instance involved a woman who had exudative macular degeneration and underwent bilateral intravitreal injections and later developed retinal detachments in both eyes. Ophthalmic Surg Lasers Imaging Retina. 2017 Sep 1;48(9):772-775.

“The impact of these unproven therapies was very real,” said Dr. Jones, noting patients are paying a minimum of $5,000 per injection per eye.

STEM CELL THERAPIES: GLAUCOMA

The attraction of stem cells, or induced pluripotent cells created by various growth factors and transcription factors, is that they can revert back to the pluripotent state where they can develop into any kind of cell, Dr. Jones pointed out.

Several possible avenues of research are taking hold, such as differentiation of stem cells into trabecular meshwork, with a goal to lowering intraocular pressure and aiming to have the new trabecular meshwork function better than existing trabecular meshwork; use of supportive cells in the retina to protect against degeneration of retinal ganglion cells (RGCs); and differentiation of stem cells into RGCs so that damaged cells in the retina are replaced, with the hope that they would then re-establish axons and reconstitute the optic nerve.


Investigators have successfully transplanted RGCs that have survived, migrated and integrated into the retina in rodent models, but more investigations are needed before this research translates to clinical practice, according to Dr. Jones.

“Is it ready for prime time?” she asked. “There have not been those key trials to move this (candidate therapies) from the bench to the bedside.”

Dr. Jones noted that researchers are much less further along in glaucoma and than researchers in retinal.

“In glaucoma, we do not yet have well-designed clinical trials that are moving stem cell therapies to human testing.”

CONCLUSION

Dr. Jones noted that when it comes to glaucoma, there is not enough known to get these stem-cell therapies to work in vivo in humans.

“What we will need are clinical trials which are randomly selected with a placebo arm, and these are generally very expensive and very slow to start,” she said. “At this point, we are looking at two to three patients in phase I trials to get us going.”

Technologies to image the health of RGCs in vivo are needed, Dr. Jones concluded.

“Candidate therapies that allow us to protect RGCs, rescue injured and dying RGCs, replace non-viable RGCs, and regenerate the optic nerve (are needed), as are randomized, clinical trials with control arms to allow us to test the efficacy of new therapies in humans,” she said.

Leslie Jones, MD

Ph: 202/965-2527

This article is based on Dr. Jones’ presentation at the 52nd Sally Letson Symposium in Ottawa, Ontario, Canada. Dr. Jones is chairwoman of Ophthalmology at Howard University in Washington, D.C. She is director of Glaucoma Services and the department’s residency program. She has no financial disclosures related to her discussion.
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When it comes to complacency, what are you waiting for?

Indecision can result in missing the next great opportunity

Putting It in View By Dianna E. Graves, COMT, BS ED

I WAS AT a conference earlier this year and was wallowing in indecision as to what I wanted to do with the next step of my career/life. I had a job offer from another group and was trying to decide what to do. I felt I had already achieved everything that I could where I was currently working, and desperately needed a change—but I was stuck in the quicksand of indecision, guilt, and fear of leaving the comfortable and moving into the unknown. Then I looked across the patio up where I was sitting and saw the following etched into a stone bench:

“You cannot turn back the hands of the clock; but you can wind it back up again.”

I returned to work the following morning. I gave my notice, accepted the other job and have now begun the process of re-invention.

Careers are made, or lost, in the ability/inability to put one foot in front of the other and continue to grow throughout the years. To always strive for more—whatever your definition of “more” may be. To be able to look in that all too clear mirror and realize that necessity is not the mother of invention but it is re-invention that is the key!

With football season in full swing, I recently was watching the hometown team drive the ball down the field. The crowd was in a frenzy knowing a touchdown was imminent. There was an undercurrent of tension in the stadium. The quarterback unleashed a bomb downfield—the player was wide open. Arms up, ready to catch the ball and be the hero in the end zone. The ball went through his hands and hit him on the top of the helmet.

The play was over. No longer a hero—but definitely the goat.

Someone uttered: “He heard footsteps coming and lost his concentration.”

While we as managers think we are ready to streak down the field in triumph—often we are distracted by “footsteps” preventing us from venturing forward.

We fear the unknown. “If I do this, what might go wrong?” This allows us to stay the course, the safe, well-lit path we often walk. Pretty soon we get so good at following the path that we never venture off the trail. So we never pave a new way—we are simply taking a well, worn route.

There’s no excitement, no challenge, no surprises.

This is what I see so many managers and staff do after being in their roles for awhile. Bored out of our gourds, non—challenged, disgruntled by our inability to climb out of the box we have placed ourselves into—and marking the days on the calendar.

The problems come when the well driven “route” that you take every day all of a sudden has a traffic jam in it and you are now forced to take an alternate route.

Because you have never changed, never varied, you have no alternatives to take and soon get lost. Panic sets in, and your comfort zone erodes as you become more and more unable to get back on track. There is no internal GPS to get us re-centered.

There comes a time when you have to realize that “staying the route” causes a problem that is not “external” (we are not forced to do this route—we choose to do it every day)—but is also internal.

You NEED to hear footsteps behind you to realize that in order for you to re-invent yourself and grow again—you have got to take that first step of the route...and start wandering a new path.

The beginning of the process causes many sleepless nights as you foray into the woods to do something “unknown.”

Soon instead of fear of the unknown, you begin to dream of the possibility that there is something new right around the corner, or maybe the next corner. Your senses perk up, self-awareness kicks in and you begin to believe again that you can do this: you can re-invent yourself and deliver a new view of yourself and your dreams.

When this occurs, you can give this excitement away to others to share with them the ability for them to also re-vitalize themselves. It becomes a contagious process.

The next time you are staring in the mirror and wondering “what happened—when did life become so rote”, allow yourself to look fully through the glass at what is beyond the glass. What is coming next!!

There is an auto-refractor that uses a hot air balloon coming over a barn as a fixation point. Many people tell their patients to look at the balloon as they are taking their measurement. But looking at the balloon still potentially allows the patient’s eyes the possibility to accommodate because they are looking at a fixed point. Not ideally the goal.

Instead, I tell them: “Do you see the balloon? Now I want you to tell me when you see the next balloon.” This puts them at infinity. No balloon is coming— but they search for it to happen. And the journey for their refraction begins.

Viola Davis once said “I guess they say, ‘Necessity is the mother of invention’ because you have two stark choices when you find yourself in a really desperate situation. You can either fold and cave-in to it or you can become really passionate about getting out of it.”

What this tells me is necessity causes us to want to change—to become passionate again. Re-invention of ourselves then allows us to do it!

‘Careers are made, or lost, in the ability/inability to put one foot in front of the other and continue to grow throughout the years.’

- Dianna E. Graves, COMT, BS Ed

**TAKE-HOME**

> Careers are made, or lost, in the ability/inability to put one foot in front of the other and continue to grow throughout the years. Always strive for more—whatever your definition of ‘more’ may be.

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DIANNA E. GRAVES, COMT, BS ED
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Graves is a clinical services manager at St. Paul Eye Clinic PA, in Woodbury, MN. Graves is a graduate of the School of Ophthalmic Medical Technology, St. Paul, MN and has been a member of the teaching faculty since 1983.
Five steps for practice leaders to achieve revenue clarity

Being fiscally proactive can help physicians head off potential problems

By Matt Rolfes

PHYSICIANS AND MEDICAL practice executives don’t always have access to actionable information to identify where they may be falling short in one or more key areas of financial performance. And they often don’t realize it until it’s too late—when cash flow unpredictably drops, and the backlog of unpaid claims reaches crisis mode.

But many times, the main cause of these problems isn’t a lack of discipline on the part of administrators and billing manager—it’s a lack of revenue clarity.

Do you have access to actionable month-end reporting moments after you close? More than just monthly charges, payments, adjustments, and an accounts receivable ledger? Can you review and assess your practice’s financial status in 5 minutes or less? Do you know where you’re leaking money and why? Are you getting paid what you should?

If you answered “I don’t know” to any of those questions, you’re not alone. Many of the physician practice executives we talk to are spending much of their time mining financial and revenue cycle management (RCM) reports and gathering data, which leaves them little time to implement organizational change.

In many cases, by the time they compile the spreadsheets to make decisions from, the data is already outdated. Additionally, with retrospective data analysis, you’re always behind, which makes it nearly impossible to proactively evaluate and plan for changes that lie ahead.

In many cases, meaningful financial evaluation is not what you can see, but what you cannot see. To break the cycle of chasing data and playing catch-up, practices need to bring forward meaningful data that drives good decision making. Follow these five steps to let go of the vague and embrace the clear.

**STEP 1: COMMIT TO IMPROVEMENT.**

Times have changed. If you don’t have a clear and concise monthly reporting package, commit to developing one. You likely know how well your practice is faring in some key performance areas, such as Days in A/R, but do you know your net collection rate? What avoidable write-offs are affecting your cash flow? Has your payer mix changed materially? Are your payers responding as quickly as they were last month? Typically, your standard reports from your practice management system or accounting system will tell you only part of the story. If you commit to a new way forward, gaining clarity into your revenue cycle is key.

**STEP 2: BELIEVE YOU CAN TACKLE THE PROBLEM.**

Once you’ve committed to a new way of doing things, you can begin to let go of what may have been ineffective and time consuming for you.

Evaluate metrics that are meaningful to your practice and can lead to better decisions. Dashboards with relevant KPIs can be created in-house using readily available tools such as Microsoft Excel. However, an increasing number of practices are benefiting from more sophisticated business intelligence and reporting solutions that integrate with their practice management software and automate reporting. These systems offer real-time insight into financial and operational key performance indicators such as provider productivity, charge lag, first-pass resolution rates (by carrier), or patient no-shows by geographic location.

**STEP 3: CONSIDER LEVERAGING TECHNOLOGY.**

Once you realize that a new approach can restore clarity to your medical practice, take a closer look at what tools are available. Analytics solutions can save administrative staff several hours of work each month, and reduce or eliminate time spent gathering multiple reports from disparate sources. Automating your reporting package may allow you to reallocate resources to different areas of your practice where they can make a greater impact.

Furthermore, there are AI-driven workflow automation solutions that enable billing and administrative staff to prioritize tasks more effectively and eliminate the guesswork in managing claims. Economical technology solutions can reduce the burden of reporting, and increase timely access to actionable data.

**STEP 4: TAKE ACTION.**

Once you’ve considered the costs and benefits of various solutions that enhance revenue clarity, it’s time to get moving. If you’re considering a revenue cycle analytics solution, look carefully at capabilities. Is the technology capable of pulling data from multiple sources and synthesizing it into an easy-to-comprehend, dashboard-ready format? Can it derive insights through machine-learning algorithms? Can you benchmark your practice against other medical groups? You may find that you need a third-party consultant or industry expert to review your performance metrics and provide practice-specific recommendations. A good partner will drill down into what the numbers are saying, so you know what changes to make in order to drive improvements.

**STEP 5: CELEBRATE RESULTS.**

By the time you reach this step, you’ve invested in one or more solutions that help you understand performance and boost profit margins. Shift your focus to measuring progress and using the extra time to implement initiatives that drive improvements. For example, if your average days in A/R spikes among the self-pay patient demographic, revamp your collections strategy, so it’s more proactive. You should be collecting most, if not all, of your self-pay dollars up front before the patient even sees the physician.

Walk into your next board meeting with a list of actions and results, not just a stack of reports. Your board will thank you.

Having revenue clarity is the key to creating a sustainable, profitable medical practice. The healthcare industry is complex enough without having to stress about whether you’ll get paid. The more clarity you have, the less you’ll worry about your bottom line.

**EDITOR’S NOTE:** This article appeared in Medical Economics, a sister publication of Ophthalmology Times. Matt Rolfes is the chief financial officer of MedEvolve. He leverages his 13 years of experience in technology and finance to drive and support MedEvolve’s growth and operational success.
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### You can always tell when we have new patients who need glasses.

Artwork by Jon Carter

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### in case you missed it

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**Clinical Trials 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.

The most common ocular adverse reaction observed in controlled clinical studies with RHOPRESSA dosed once daily was conjunctival hyperemia which was reported in 53% of patients. Other common (approximately 20%) ocular adverse reactions reported were: corneal verticillata, instillation site pain, and conjunctival hemorrhage. Instillation site erythema, corneal staining, blurred vision, increased lacrimation, erythema of eyelid, and reduced visual acuity were reported in 5-10% of patients.

**Corneal Verticillata**
Corneal verticillata occurred in approximately 20% of the patients in controlled clinical studies. The corneal verticillata seen in RHOPRESSA-treated patients were first noted at 4 weeks of daily dosing. This reaction did not result in any apparent visual functional changes in patients. Most corneal verticillata resolved upon discontinuation of treatment.

**USE IN SPECIFIC POPULATIONS**

* Pregnancy
  There are no available data on RHOPRESSA use in pregnant women to inform any drug associated risk; however, systemic exposure to netarsudil from ocular administration is low. Intravenous administration of netarsudil to pregnant rats and rabbits during organogenesis did not produce adverse embryofetal effects at clinically relevant systemic exposures.

* Animal Data
  Netarsudil administered daily by intravenous injection to rats during organogenesis caused abortions and embryofetal lethality at doses ≥0.3 mg/kg/day (126-fold the plasma exposure at the recommended human ophthalmic dose [RHOD], based on C_{max}). Malformations were observed at ≥3 mg/kg/day (1330-fold the plasma exposure at the RHOD, based on C_{max}), including thoracogastroschisis, umbilical hernia and absent intermediate lung lobe. The NOAEL for embryofetal development toxicity was 0.1 mg/kg/day (40-fold the plasma exposure at the RHOD, based on C_{max}).

  Netarsudil administered daily by intravenous injection to rabbits during organogenesis caused embryofetal lethality and decreased fetal weight at 5 mg/kg/day (1480-fold the plasma exposure at the RHOD, based on C_{max}) and at 15 mg/kg/day (4440-fold the plasma exposure at the RHOD, based on C_{max}), including aplasia, absent lungs, and abdominal hernias. The NOAEL for embryofetal development toxicity was 0.5 mg/kg/day (214-fold the plasma exposure at the RHOD, based on C_{max}).

* Lactation
  There are no data on the presence of RHOPRESSA in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to netarsudil following topical ocular administration is low, and it is not known whether measurable levels of netarsudil would be present in maternal milk following topical ocular administration. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for RHOPRESSA and any potential adverse effects on the breastfed child from RHOPRESSA.

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

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

**NONCLINICAL TOXICOLOGY**

* Carcinogenesis, Mutagenesis, Impairment of Fertility
  Long-term studies in animals have not been performed to evaluate the carcinogenic potential of netarsudil. Netarsudil was not mutagenic in the Ames test, in the mouse lymphoma test, or in the in vivo rat micronucleus test. Studies to evaluate the effects of netarsudil on male or female fertility in animals have not been performed.

Manufactured for: Aerie Pharmaceuticals, Inc., Irvine, CA 92614, U.S.A.

For more information, go to www.RHOPRESSA.com or call 1-855-AerieRx (1-855-237-4379).

RHOPRESSA is a registered trademark of Aerie Pharmaceuticals, Inc.

U.S. Patent Nos.: 8,450,344; 8,394,826; 9,096,569; 9,415,043
Achieving IOP control

What makes once-daily Rhopressa® different¹

- Consistent IOP reduction up to 5 mmHg in patients across a range of baseline IOPs
- Once-daily dosing to simplify dosing regimens
- Mild ocular adverse events and no known contraindications opens up treatment options
- Unique mechanism of action for patients who may benefit from improved trabecular aqueous outflow

Rhopressa® is covered for the majority of patients nationwide.²

Visit Rhopressa.com to learn more about this innovative IOP-lowering treatment.

INDICATIONS AND USAGE
Rhopressa® (netarsudil ophthalmic solution) 0.02% is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

DOSAGE AND ADMINISTRATION
The recommended dosage is one drop in the affected eye(s) once daily in the evening.

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS
Bacterial Keratitis: There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

Contact Lenses: Contact lenses should be removed prior to instillation of Rhopressa® and may be inserted 15 minutes following its administration.

ADVERSE REACTIONS
The most common ocular adverse reaction observed in controlled clinical studies with Rhopressa® dosed once daily was conjunctival hyperemia, reported in 53% of patients. Other common (approximately 20%) adverse reactions were: corneal verticillata, instillation site pain, and conjunctival hemorrhage. Instillation site erythema, corneal staining, blurred vision, increased lacrimation, erythema of eyelid, and reduced visual acuity were reported in 5-10% of patients.

The corneal verticillata seen in Rhopressa®-treated patients were first noted at 4 weeks of daily dosing. This reaction did not result in any apparent visual functional changes. Most corneal verticillata resolved upon discontinuation of treatment.

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


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