Putting new technologies into practice not perfect science

Ophthalmologists take a wait-and-see approach with latest tools

By Lynda Charters; Reviewed by Ashley R. Brissette, MD, MSc, FRCSC

NEWER DOES NOT necessarily mean better. That can be applied to many things, and it may be especially true in medicine.

New advances in viewing systems, IOLs, and femtosecond laser-assisted cataract surgery (FLACS) should be evaluated before they are incorporated into clinical practice, according to Tetsuro Oshika, MD, PhD, who detailed his views on how these technologies positively and negatively affect practice.

Surgical Viewing Systems

The conventional microscopy system is in some cases being replaced by three-dimensional digitally assisted visualization system, the so-called “heads-up” surgical system, especially during vitreous surgery. Three such systems are currently available: the Ngenuity 3-D system (TrueVision Systems, Alcon), Artevo800 (Carl Zeiss Meditec), and RV800 Viewing System (Leica Microsystems).

“These systems clearly have an advantage in vitreous surgery, in that they provide an enhanced depth of field,” said Dr. Oshika, professor and chairman, Department of Ophthalmology, faculty of medicine, University of Tsukuba, Tsukuba, Ibaraki, Japan. “In addition, the technology is a good educational tool because the systems allows everyone in the operating room to have the same surgical view as that of the surgeon.”

Other advantages in addition to the enhanced depth of field education offered by these systems include a 4,000-pixel monitor, decreased light phototoxicity, digital enhancements, digital filtering, and high dynamic range, Dr. Oshika pointed out.

“These clearly are beneficial for the patients,” he said.

There are some disadvantages that must be addressed, the first of which is latency—the lag in information delivery—that matters more in cataract surgery than in vitrectomy, Dr. Oshika pointed out, because cataract surgery is much faster than vitrectomy.

“Other aspects to consider are the educational benefit and the educational aspect as well,” he said.

While 3D surgery has become a staple in retinal procedures, it has yet to become prevalent in anterior segment surgery. This may change as surgeons become aware of the benefits a 3D system offers.

According to Ashley R. Brissette, MD, MSc, FRCSC, the degree of visualization through the surgical microscope is quite good, which could prove to be beneficial for physicians as they perform challenging procedures.

“I think that there are other benefits to 3D surgery that will become readily apparent over time,” said Dr. Brissette, assistant professor of ophthalmology, Weill Corneal Medicine and New York Presbyterian Hospital, New York.

A number of factors come into play in the quest for ideal intraoperative visualization when using a surgical microscope.

Continues on page 28: Cataract
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**INDICATION**

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

**IMPORTANT SAFETY INFORMATION**

**CONTRAINDICATIONS**

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

**WARNINGS AND PRECAUTIONS**

Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. Intraocular pressure should be monitored during treatment.

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

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

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

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

**ADVERSE REACTIONS**

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

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

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

**References:**


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DEXTENZA is a registered trademark of Ocular Therapeutix, Inc. PP-US-DX-0193
Dextenza®
(dexamethasone ophthalmic insert) 0.4 mg

BRIEF SUMMARY: Please see the DEXTENZA Package Insert for full prescribing information for DEXTENZA (08/2018).

1 INDICATIONS AND USAGE

DEXTENZA® (dexamethasone ophthalmic insert) is a corticosteroid indicated for the treatment of postoperative inflammation and pain following surgical ophthalmic surgery.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Intracameral Pressure Increase

Prolonged use of corticosteroids may result in glaucoma with darkening of the iris, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. Intraocular pressure should be monitored during the course of the treatment.

5.2 Infection

Corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection and enhance existing infection [see Contraindications (4)].

5.3 Viral Infections

Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex) [see Contraindications (4)].

5.4 Fungal Infections

Fungi invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal culture should be taken when appropriate [see Contraindications (4)].

5.5 Delayed Healing

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

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

• Intracameral Pressure Increase [see Warnings and Precautions (5.1)]
• Bacterial Infection [see Warnings and Precautions (5.4)]
• Viral Infection [see Warnings and Precautions (5.3)]
• Fungal Infection [see Warnings and Precautions (5.4)]
• Delayed Healing [see Warnings and Precautions (5.5)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Adverse reactions associated with ophthalmic steroids include increased intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, delayed wound healing; secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the corneal stroma [see Warnings and Precautions (5)].

DEXTENZA was studied in four randomized, vehicle-controlled studies (n = 567). The mean age of the population was 68 years (range 35 to 87 years). 59% were female, and 83% were white. Forty-seven percent had brown iris color and 48% had blue iris color. The most common ocular adverse reactions that occurred in patients treated with DEXTENZA were: anterior chamber inflammation including iritis and iridocyclitis (17%); intraocular pressure increased (6%); visual acuity reduced (2%); eyelid edema (1%); corneal edema (1%); eye pain (1%) and conjunctival hyperemia (1%). The most common non-ocular adverse reaction that occurred in patients treated with DEXTENZA was headache (1%).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate or well-controlled studies with DEXTENZA in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. In animal reproduction studies, administration of topically ocular dexamethasone to pregnant mice and rabbits during organogenesis produced embryotocytic lethality, cleft palate and multiple visceral malformations [see Animal Data].

Data

Animal Data

Topical ocular administration of 0.15% dexamethasone (0.75 mg/day) on gestational days 10 to 15 produced embryotoxic lethality and a high incidence of cleft palate in a mouse study. A daily dose of 0.75 mg/day in the mouse is approximately 5 times the entire dose of dexamethasone in the DEXTENZA product, on a mg/m² basis. Topical ocular administration of 0.1% dexamethasone throughout organogenesis (0.36 mg/day, on gestational day 6 followed by 0.24 mg/day on gestational days 7-18) produced intestinal anomalies, intestinal atresia, gastroschisis and hypoplastic kidneys. A daily dose of 0.24 mg/day is approximately 6 times the entire dose of dexamethasone in the DEXTENZA product, on a mg/m² basis.

8.2 Lactation

Systemically administered corticosteroids appear in human milk and could suppress growth and interfere with endogenous corticosteroid production; however the amount of dexamethasone in the DEXTENZA product, approximately 5 times the entire dose of dexamethasone in the DEXTENZA product, is no information regarding the presence of dexamethasone in human milk, the effects of the drug on the breastfed infant or the effects of the drug on milk production to inform risk of DEXTENZA to an infant during lactation. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DEXTENZA and any potential adverse effects on the breastfeeding child from DEXTENZA.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

No overall differences in safety or effectiveness were observed between elderly (70 years of age and older) and younger patients.

9.3 Carcinogenesis, Mutagenesis, Impairment of Fertility

In fertility studies, females and males of the following species were dosed throughout organogenesis with dexamethasone in the DEXTENZA product, approximately 5 times the entire dose of dexamethasone in the DEXTENZA product, on a mg/m² basis. In a rabbit study, approximately 5 times the entire dose of dexamethasone in the DEXTENZA product, at gestational day 6 followed by 5 times the entire dose of dexamethasone in the DEXTENZA product, at gestational day 10 to 13 produced embryofetal lethality and a high incidence of cleft palate as noted above. Female monkeys dosed at 0.1 mg/kg/day on gestational days 12 to term showed an increased incidence of fetal deaths and a high incidence of cleft palate; however female monkeys dosed at 0.75 mg/kg/day on gestational days 18 to term had no increase in cleft palate. No other relevant findings were noted in any of these studies.

9.4 Human Protein Binding

Systemically administered corticosteroids are known to bind to plasma proteins [see Animal Data]. The magnitude of protein binding is variable. The extent of corticosteroid protein binding is not known in humans.

14.1 Pregnancy

There are no adequate and well-controlled studies in pregnant women to support the use of DEXTENZA during pregnancy. Corticosteroids are able to cross the placental barrier and have been shown to suppress fetal adrenal production, resulting in fetal glucocorticosteroid deficiency. Glucocorticosteroid deficiency in the fetus may lead to withdrawal symptoms in the neonate. The potential effects on the neonate should be considered along with the mother's clinical need for DEXTENZA and any potential adverse effects on the breastfeeding child from DEXTENZA.

14.2 Lactation

Corticosteroids are known to be secreted in human milk. The potential for glucocorticosteroid secretion in breast-fed infants should be considered along with the mother's clinical need for DEXTENZA and any potential adverse effects on the breastfeeding child from DEXTENZA.

17 PATIENT COUNSELING INFORMATION

Advise patients to consult their surgeon if visual acuity or fields of vision are reduced; if eye pain or redness lasting more than 2 or 3 days occurs; if irritation of the eyes does not improve; if the eyes become more inflamed; or if the eyes become more sensitive to light, dryness or irritation, or if the discomfort becomes worse. Advise patients to wash their hands before touching the ocular drug product. Advise patients that the DEXTENZA drug product contains dexamethasone, a potent corticosteroid. Advise patients to consult their surgeon if they have any other concerns.

18 DRUG INTERACTIONS

No interactions have been shown to occur with DEXTENZA.

21 CLINICAL PHARMACOLOGY

21.1 Mechanism of Action

DEXTENZA is a corticosteroid delivered in a sustained-release formulation, which delivers a constant level of dexamethasone for 14 days post application.
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INDICATION FOR USE. The iStent inject® Trabecular Micro-Bypass System Model G2 M-IS is indicated for use in conjunction with cataract surgery for the reduction of intraocular pressure (IOP) in adult patients with mild to moderate primary open-angle glaucoma.

CONTRAINDICATIONS. The iStent inject is contraindicated in eyes with angle-closure glaucoma, traumatic, malignant, uveitic, or neovascular glaucoma, discernible congenital anomalies of the anterior chamber (AC) angle, retrobulbar tumor, thyroid eye disease, or Sturge-Weber Syndrome or any other type of condition that may cause elevated episcleral venous pressure.

WARNINGS. Gonioscopy should be performed prior to surgery to exclude congenital anomalies of the angle, PAS, rubeosis, or conditions that would prohibit adequate visualization of the angle that could lead to improper placement of the stent and pose a hazard.

MRI INFORMATION. The iStent inject is MR-Conditional, i.e., the device is safe for use in a specified MR environment under specified conditions; please see Directions for Use (DFU) label for details.

PRECAUTIONS. The surgeon should monitor the patient postoperatively for proper maintenance of IOP. The safety and effectiveness of the iStent inject have not been established as an alternative to the primary treatment of glaucoma with medications, in children, in eyes with significant prior trauma, abnormal anterior segment, chronic inflammation, prior glaucoma surgery (except SLT performed > 90 days preoperative), glaucoma associated with vascular disorders, pseudophakic, pigmentary or other secondary open-angle glaucomas, pseudophakic eyes, phakic eyes without concomitant cataract surgery or with complicated cataract surgery, eyes with medicated IOP > 24 mmHg or unmedicated IOP < 21 mmHg or > 36 mmHg, or for implantation of more or less than two stents.

ADVERSE EVENTS. Common postoperative adverse events reported in the randomized pivotal trial included stent obstruction (6.2%), intraocular inflammation (5.7% for iStent inject vs. 4.2% for cataract surgery only), secondary surgical intervention (5.4% vs. 5.0%) and BCVA loss ≥ 2 lines ≥ 3 months (2.6% vs. 4.2%). CAUTION: Federal law restricts this device to sale by, or on the order of, a physician. Please see DFU for a complete list of contraindications, warnings, precautions, and adverse events.


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Coronavirus response
Generations react differently to COVID-19

By Peter J. McDonnell, MD
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“THIS CORONAVIRUS THING is certainly a concern,” my physician friend remarked to me.

“Yes, it is worrisome,” I agreed. “But, fortunately for us, it is only really a major problem for old people. So we don’t need to worry much.”

“I’m sorry to tell you this, amigo,” my friend replied, “but you and I qualify as ‘old’ when it comes to this virus.”

Sadly, this is indeed the case. According to the Chinese Center for Disease Control and Prevention, the overall mortality rate from COVID-19 in that country is 2.3%. But for children in the first decade of life, the mortality was 0%. Patients aged 10-19, 20-29 and 30-39 all shared a 0.2% death rate.

And then the age effect begins, with a doubling of the death rate to 0.4% for those in their 40s and a further tripling to 1.3% for patients in their 50s. The death rate continues to increase in patients in their 60s (3.6%), 70s (8.0%) and 80s (14.8%).

So depending on how you look at it, our ability to resist the infection drops as early as the 40s. But even younger people cannot feel “safe,” given that Li Wen-liang, the ophthalmologist who first reported the early stages of the pandemic, was only 34 years of age when he died from the infection.

The demographics of those killed by this pandemic vary distinctly from the 1918-19 so-called “Spanish flu” pandemic that took an estimated 50 million lives and preferentially targeted young individuals (including soldiers, nurses and house officers).

At the same time, news organizations are publishing photographs of bars in various cities filled by millennials after work and hundreds or thousands of college students on spring break in southern beach towns filling bars and crowding together in concerts and other large venues.

Some accuse the young partygoers of irresponsible behavior. When asked why they aren’t heeding the advice of public health experts to stay at home and practice “social distancing,” some of these young folks say that they want to continue living their lives and that social interaction is an important component of that. Also, some say, it is the older “baby boomer” generation that has to fear the virus. In what strikes many as a somewhat callous and perhaps sophomoric twist, these youngsters have used social media to rename the COVID-19 with #BoomerRemover.

According to some pundits in the media, the #BoomerRemover phenomenon is a reflection of the younger generation’s resentment of the problems they attribute to us oldsters: environmental damage, global warming, income inequality, nuclear weapons. They assert that it is time for us older people to step aside and let the younger generation take over and provide better solutions.

On the other hand, I have personally observed younger people looking out for their older friends and neighbors by delivering food and other necessities or running errands for them while the epidemic runs its course.

The demographics of those killed by this pandemic vary distinctly from the 1918-19 so-called “Spanish flu” pandemic that took an estimated 50 million lives and preferentially targeted young individuals (including soldiers, nurses and house officers).

I believe keeping a sense of humor is a good thing, but personally consider it sophomoric behavior to be partying at the beach while using social media cheering on the virus that kills older people. But many of us Baby Boomers were not always kind and respectful of our elders when we were young. Isn’t that why they call them college sophomores?

Keeping a sense of humor is a good thing, but partying on a beach is ‘sophomoric.’

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On the other hand, I have personally observed younger people looking out for their older friends and neighbors by delivering food and other necessities or running errands for them while the epidemic runs its course.

The demographics of those killed by this pandemic vary distinctly from the 1918-19 so-called “Spanish flu” pandemic that took an estimated 50 million lives and preferentially targeted young individuals (including soldiers, nurses and house officers).

I believe keeping a sense of humor is a good thing, but personally consider it sophomoric behavior to be partying at the beach while using social media cheering on the virus that kills older people. But many of us Baby Boomers were not always kind and respectful of our elders when we were young. Isn’t that why they call them college sophomores?
Indication
Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of signs and symptoms of dry eye disease (DED).

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

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

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

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

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

References:

There’s no FDA-approved therapeutic equivalent.2,4 Check out patient resources, insurance coverage, and more at Xiidra-ECP.com
**Special Report**

**OPEN-ANGLE GLAUCOMA**

**PHARMACOLOGIC TREATMENT AN OPTION FOR OPEN-ANGLE GLAUCOMA**

Therapies can help manage disease, lowering and stabilizing IOP

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**XIIDRA®** (lifitegrast ophthalmic solution), for topical ophthalmic use

**Initial U.S. Approval:** 2016

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

**INDICATIONS AND USAGE**

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

**CONTRAINDICATIONS**

Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients in the formulation [see Adverse Reactions (6.2)].

**ADVERSE REACTIONS**

The following serious adverse reactions are described elsewhere in the labeling:

- **Hypersensitivity** [see Contraindications (4)]

**6.1 Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be reliably estimated or establish a causal relationship to drug exposure.

In five clinical studies of DED conducted with lifitegrast ophthalmic solution, 1401 patients received at least one dose of lifitegrast (1267 of which received lifitegrast 5%). The majority of patients (84%) had ≤3 months of treatment exposure. One hundred-seventy two 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, nausea, and decreased visual acuity.

Other adverse reactions reported in 1%-5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased incision, eye discomfort, eye pruritus, and sinusitis.

**6.2 Postmarketing Experience**

The following adverse reactions have been reported voluntarily from a population of uncertain size, it is not 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, swelling tongue, and urticaria have been reported. Eye swelling and rash have been reported [see Contraindications (4)].

**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy**

Risk Summary

There are no available data on Xidra 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 omphalocoele 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 [see Clinical Pharmacology (12.3) in the full prescribing information].

**Data**

Animal Data

Lifitegrast administered daily by IV injection to rats, from pre-mating through gestation Day 17, caused an increased in mean pre-implantation loss and an increased incidence of several minor skeletal anomalies at 30 mg/kg/day, representing five, 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 (46-fold the human plasma exposure at the RHOD, based on AUC). In the rabbit, an increased incidence of omphalocoele 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.

**8.2 Lactation**

Risk Summary

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 [see Clinical Pharmacology (12.3) in the full prescribing information]. 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.

**8.4 Pediatric Use**

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

**8.5 Geriatric Use**

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

Manufactured for:

Novartis Pharmaceuticals Corporation

One Health Plaza

East Hanover, NJ 07936

T2019-110

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**ADVANCES IN TREATMENT OF**

**GLAUCOMA, THE LEADING cause of irreversible blindness in the United States, is caused by ocular hypertension, which damages the optic nerve and results in visual field loss. There is no cure, but the disease can be managed with pharmacologic therapies, among other more invasive treatments, that lower and stabilize intraocular pressure (IOP).**

Joseph F. Panarelli, MD, associate professor in the Department of Ophthalmology at NYU Langone Medical Center, New York, and Sahar Bedrood, MD, PhD, a glaucoma specialist at Acuity Eye Group, and assistant professor of clinical ophthalmology at the USC Roski Eye Institute, Los Angeles, recently spoke on the current state and future of glaucoma therapy and how compliance may not be an issue in the coming years.

**IOP AND GLAUCOMA PROGRESSION**

IOP reduction is the only known modifiable risk factor for open-angle glaucoma. However, studies have shown that disease progression and blindness are still possible even in patients on maximum medical therapy. How IOP factors into visual field loss isn’t entirely clear. According to Dr. Bedrood, one theory—known as the stress/strain model—is that IOP strains the sclera and optic nerve, causing apoptosis and loss of retinal ganglion cells. Another theory—the vascular theory—is when the blood vessels in the optic nerve don’t get enough oxygen, which leads to apoptosis, nerve fiber layer loss, and, eventually, visual field loss.

No two cases of glaucoma are alike, and progression rates vary from person to person.

“Some patients who have a very strong genetic component are going to progress very quickly, and some, not so much,” Dr. Bedrood said.

Co-morbidities such as sleep apnea and IOP fluctuations are other risk factors for visual field progression and greater visual field loss in certain patients.
The causes of IOP fluctuations are multifactorial and can be due to poor treatment compliance, genetics, and a decline in treatment effectiveness over time.4

“After 10-plus years of treatment, some of those treatments that initially worked may not work as well,” Dr. Bedrood said. “Sometimes, patients respond really well in the beginning and then over a couple of months or years they don’t, and then they fluctuate their IOP.”

Over a decade, selective laser trabeculoplasty (SLT) will wear off, requiring patients to have a touchup or a second round of treatment. Patients may develop an allergy or intolerance to glaucoma drops as well.

“Over a course of 10 years, a lot can change,” Dr. Bedrood said. “Their rate of progression can fluctuate. Their tolerance of drugs can fluctuate. Oftentimes after 10, 15, or 20 years, we’re looking at other modalities of treatment like surgery or something that can regulate their pressure a little bit better—other additional drugs, for instance.”

**Personalized Treatment Plan**

Prostaglandin analogues—such as bimatoprost, latanoprost, tafluprost, and travoprost—are common first-line treatments for patients with newly diagnosed glaucoma. They are non-invasive and can reduce IOP by 25% to 30% with once-daily dosing,5 which can be appealing to patients.

Just because they are the most common first-line treatment doesn’t mean they are the best. Clinical trials have shown that SLT is just as safe and effective as drops, with a 20% reduction in IOP that lasts for up to three years without the hassle of daily medication.6

However, patients are often uncomfortable with the idea of a procedure initially and underestimate the burden of daily medication.

Dr. Panarelli believes the pros and cons of SLT versus daily drops is a conversation worth having with patients early on in the treatment process.

“I think it’s worth having a discussion with them [regarding] whether they prefer to start topical therapy or whether they would like to proceed with laser trabeculoplasty, especially now with data from the LiGHT trial,” he said.

Regardless of the initial approach, certain patients will ultimately progress. When it is necessary to advance treatment, these patients may need a more aggressive approach.

“It’s a big decision for me to add another medication,” he said, adding that if a second medication is necessary, his preference is to go straight to a fixed-combination agent for those he suspects are “rapid progressors.”

When selecting a treatment approach, clinicians must consider patient preferences, cost, and other factors impacting compliance. For example, patients with advanced glaucoma may be taking six to 10 drops a day. Drops that contain preservatives may cause ocular surface disease such as dry eye, leading to patient discomfort and decline in quality of life. Drop burden and unwanted side effects all impact compliance rates.

“A lot of us are trying to decrease the number of total drops and maybe even move toward some of the preservative-free agents for a lot of our patients,” Dr. Panarelli said. “I think the medication landscape is changing, but I think the biggest thing we have to keep in mind is cost and compliance with all of our patients. [We’re] trying to find the most effective medicine in the least number of bottles.”

**Newly Approved Agents**

For the first time in decades, two new classes of drugs have been introduced for the treatment of open-angle glaucoma: latanoprostene bunod and netarsudil. The agents have different mechanisms of action and could be disease modifying.

Netarsudil is a Rho-kinase inhibitor that targets the outflow pathway.7,8

Netarsudil is a drug for the treatment of glaucoma. In the United States in 2017, the FDA approved a 0.02% ophthalmic solution for the lowering of elevated IOP in patients with open-angle glaucoma or ocular hypertension, targeting the trabecular meshwork directly.

Netarsudil is unique in that “none of the other medicines out there on the market actually work at the level of the trabecular meshwork,” Dr. Panarelli said. “By inhibiting Rho-kinase, we’re able to relax some of the actin and myosin contractions. By relaxing those contractions, we’re able to enhance outflow through the physiologic outflow pathway.”

It has other mechanisms of action as well and has the potential to lower episcleral venous pressure (EVP). “[This is] something that we do not see with other medication classes,” Dr. Panarelli said. Latanoprostene bunod is a new version of a prostaglandin that also has a nitric oxide donating moiety.9,10

The exact mechanism of action is somewhat complex, according to Dr. Panarelli, but it’s believed to have a number of benefits including smooth muscle relaxation/enhanced outflow through the trabecular pathway as well as increased uveoscleral outflow.

Fixed-combination netarsudil/latanoprost is another new drug on the market, which was approved by the U.S. Food and Drug Administration in 2019.11 The once-daily drug also reduces IOP by enhancing aqueous outflow through both the trabecular and uveoscleral pathways.

“Is unique about the netarsudil/latanoprost combination is this is really one of the first times we actually had a medicine go up against latanoprost alone,” Dr. Panarelli said. “Latanoprost is one of our bigger guns out there, so it is encouraging to see that we have these new medicines, and it’s nice to see data that does support good efficacy with these different agents.”

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**Emerging Therapies**

A number of treatments for glaucoma are not yet approved but currently in development. For example, bimatoprost sustained release (bimatoprost SR) is a first-in-class, sustained-release, investigational, biodegradable implant for the treatment of glaucoma.

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**Special Report**

**Advancements in Treatment of Open-Angle Glaucoma**

‘It is nice to have some new medicines that are out there on the market because I think they all fit into our armamentarium somewhere.’

— Joseph F. Panarelli, MD

Although clinical trial data support the efficacy of these agents, how exactly to use them in the real world and in whom are questions clinicians are currently wrestling with.

“It’s nice to have some new medicines that are out there on the market because I think they all fit into our armamentarium somewhere,” Dr. Panarelli explained. “I think, as clinicians, we are still figuring out exactly how to use these medicines and how to mix them in with our other available agents.”

If a patient is not responding on a prostaglandin analogue, Dr. Panarelli will switch them from either latanoprost to latanoprostene bunod or from latanoprost to combination latanoprost/netarsudil. He also believes there is a place for the medications in patients with low-tension glaucoma, who are traditionally some of the most difficult patients to treat.

Dr. Panarelli has found netarsudil to be particularly useful in these patients because it lowers EVP.

“Some of my patients can get down to that single digit range, which is a number I often cannot get with traditional carbonic anhydrase inhibitors, or alpha-2 agonists, or even beta blockers,” he said.

There are some situations in which Dr. Panarelli will use netarsudil as a first-line agent.

For example, if a patient is uncomfortable with the potential side effects of increased iris pigmentation and periorbital fat atrophy that come with a prostaglandin analogue, he may recommend netarsudil. He may also recommend netarsudil if the patient is already on an oral beta blocker or is hesitant to start on a beta blocker generally.

“I have had several patients where I have talked about having surgery,” he said. “We started netarsudil, and it’s actually been great in that they have gotten to their target IOP without me having to perform a trabeculectomy, which is huge for my patients.”

Continues on page 12: Glaucoma
GLAUCOMA

(Continued from page 11)

of open-angle glaucoma.

If approved, Dr. Panarelli said he believes bimatoprost SR could be “a game-changer” in that it completely takes patient compliance out of the equation and significantly reduces the overall treatment burden glaucoma patients face.

With bimatoprost SR, “all we ask [patients] to do is to come once every several months to get their treatment,” Dr. Panarelli said. “This can have a meaningful impact for our patients. It is one thing to talk to a patient and tell them that they are going to have an injection once every four to six months for the rest of their lives, but if we can give a patient a loading dose of a medicine and not need to reinject them from anywhere from one to (maybe) three years, that will resonate well.”

The big unknown with the implant is safety. Will there be any complications or adverse effects from an injectable form of medicine delivered into the eye every six months? Although data are limited to abstracts presented during conferences such as the Academy of Ophthalmology and American Glaucoma Society, Dr. Panarelli considers the safety and efficacy of bimatoprost SR to be positive so far.12

“We have questions regarding issues with the cornea, and we have concerns about infection,” Dr. Panarelli said. “One of the things that has impressed me most is the fact that a lot of patients (up to 80%) who receive three doses over the first year did not need to be rescued over the next year that they were followed.”

Initially, Dr. Panarelli sees a place for bimatoprost SR as a second-line treatment when a patient is progressing or not achieving the IOP reduction needed on a prostaglandin or after SLT. Once clinicians become more comfortable with the injection and have less concerns about the safety profile, clinicians may start with the injection rather than topical therapy.

“If we can show very good safety profiles for these medicines, I think we are going to see a lot of physicians using this treatment early in their treatment algorithm,” he said.

IMPROVING COMPLIANCE

One of the primary issues in glaucoma is patient compliance. Up to 60% of glaucoma patients are non-compliant with daily drops.13 The reasons for this are multifold. First, glaucoma patients are generally older (people over age 60 are at increased risk for the disease). Second, glaucoma is a life-long disease. Patients may tire of daily drops and may struggle with opening the bottle or even getting the drops in the eye correct as they age.

“They physically have to open up the bottles and place it in their eyes every single day,” Dr. Bedrood said. “That act is very different than taking a pill, and it is oftentimes more difficult for patients.”

Cost is a frequent issue as well, as eye drops are often more expensive than generic medications for other conditions. To address this, Dr. Bedrood suggests providing patients with coupons and enrolling them onto special programs where they can get lower prices.

Glaucoma is also asymptomatic, causing patients to be less aware of their disease.

“[Patients] think, ‘Oh, I am fine. I am not feeling anything, I am not seeing any differently, and I will skip my dose today,’” Dr. Bedrood pointed out.

Dr. Panarelli said ophthalmologists talk about glaucoma being a silent thief. However, it can be an issue for patients.

“That is a big problem for our patients,” he explained. “They don’t physically see the need often to come to these appointments, or they don’t see the need to take their drops quite like some other conditions that are possibly affecting them.”

Dr. Bedrood stresses the importance of having frank conversations with patients on the importance of compliance, and if compliance remains an issue telling them pointblank they could face surgery.

She recommends asking how they’re doing on the medication and if they are able to open the cap. She even asks them to demonstrate how they deliver medications without having the patients perceive their ears up and they say, ‘Oh, wait, I do not want surgery,’” Dr. Bedrood said. “And sometimes it reminds them that maybe it is better for them to use the drops.”

Despite these potential challenges, both physicians agree that, with all the new agents on the horizon, it is an exciting time in the field of glaucoma.

“The sustained release, the implants, the ocular inserts, all of these things promise a way to deliver medications without having the patients do it,” Dr. Bedrood said. “Having it in a very sustained, steady way is a really exciting part of our future in glaucoma. I think that it will really help our patients in the long-term.”

REFERENCES


OMIDRIA® (phenylephrine and ketorolac intraocular solution) 1% / 0.3% is added to ophthalmic irrigating solution used during cataract surgery or intraocular lens replacement and is indicated for maintaining pupil size by preventing intraoperative miosis and reducing postoperative ocular pain.

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References:


Companies unveil customer initiatives, testing options to combat COVID-19 crisis

Medical device providers announce programs to support customers, aid testing efforts

By David Hutton

AS THE COVID-19 pandemic continues to escalate in the United States and across the globe, Topcon Healthcare has announced a series of initiatives and programs designed to support its customers.

Ophthalmologists rely heavily on physical examination during patient consultation, creating some concern for the potential spread of COVID-19 from patients. The ophthalmologist is close to the patient during the slit lamp microscope examination, with droplets from a cough or sneeze easily covering the distance between patient and ophthalmologist.

The American Academy of Ophthalmology (AAO) issued an alert last month suggesting the virus can cause conjunctivitis and could be transmitted through aerosol contact with the conjunctiva, putting ophthalmologists on the front line, potentially being the first healthcare providers to evaluate a patient potentially infected with the disease.

Ophthalmologists and optometrists must be in close contact with patients while performing an exam and are, therefore, unable to maintain the CDC recommended distance of six feet. In order to combat this and prevent the transmission of respiratory illnesses, including COVID-19, Topcon is offering its slit lamp customers a free breath shield that fits onto their instrument and provides a first line of defense for both healthcare providers and patients.

The shields, designed to reduce exposure to airborne contaminants, are available while supplies last. A provider to Avellino's CLIA certified high-complexity testing under CLIA prior to Emergency Use Authorization for Coronavirus Disease-2019 during the Public Health Emergency.

Avellino announced it is adding additional production shifts for its newly developed coronavirus diagnostic, the is in increasing demand by health systems, public health services, and first-responders because of its speed, accuracy, and ability to detect coronavirus in patients who are asymptomatic.

In order to meet growing public health demand, the company is temporarily suspending sequencing operations of its AvaGen genetic test that identifies the risk of developing keratoconus and the presence of corneal dystrophies.

Operations for the AvellinoCoV2 test will expand into the genetic diagnostics lab as used for the company’s newly released AvaGen test used by ophthalmologists and optometrists to diagnose and monitor patients with keratoconus and other corneal dystrophies.

The AvellinoCoV2 test helps clinicians diagnose COVID-19, the disease caused by a SARS-CoV-2 virus infection, by identifying and isolating the genetic markers as approved by the CDC and the FDA.

Avellino Group Chairman Gene Lee noted the company appreciates the support from eye-care professionals who are using the AvaGen genetic test to care for their corneal patients.

“We understand the breakthrough importance of the AvaGen test in treating patients with complex corneal conditions,” he said. “Avellino will restart production of the AvaGen genetic test as soon as we have fulfilled our public health obligation surrounding the coronavirus pandemic.”

On March 5, Avellino completed the validation process for AvellinoCoV2 according to the FDA issued guidance, “Policy for Diagnostics Testing in Laboratories Certified to Perform High-Complexity Testing under CLIA prior to Emergency Use Authorization for Coronavirus Disease-2019 during the Public Health Emergency.”

The test must be ordered by a physician and cannot be made available directly to the public.

The test is performed in the physician’s office or at a public collection facility by collecting cell samples from the back of the patient’s throat and the nose via swabs. Samples are then sent by the healthcare provider to Avellino’s CLIA certified high-complexity molecular testing laboratory facility in Menlo Park, NJ, for testing.

Tests take about 1.5 to 3 hours to perform. Negative results are sent back immediately to the physician and/ or public health officials who ordered the test. Positive results are subject to secondary confirmation testing. Results may be available in as little as six hours or the next day in most cases. A negative result from the rest does not rule out the presence of the coronavirus, which causes COVID-19. This can be the result of potential issues with sample collection and other factors common to all diagnostic tests that can affect results. Clinicians are urged to use clinical observation, patient history, and their best medical judgment in making a final diagnosis and treatment decisions.

Avellino adds shifts

Quidel Corp., a provider of rapid diagnostics testing solutions such as InflammaDry and QuickView Adenoviral Conjunctivitis test, cellular-based assays and molecular diagnostics systems, recently received Emergency Use Authorization from the FDA to market its Lyra SARS-CoV-2 Assay, a real-time RT-PCR test intended for the qualitative detection of nucleic acid from SARS-CoV-2 in nasopharyngeal or oropharyngeal swab specimens from patients suspected of COVID-19 by their healthcare provider.

Testing is limited to laboratories certified under the Clinical Laboratory Improvement Amendments of 1988 to perform high complexity tests. EUAs allow for the early availability of important diagnostic tools.

Douglas Bryant, president and CEO of Quidel, noted that the EAU for the Lyra assay allows the company to join the global fight against the COVID-19 outbreak by providing healthcare workers in highly complex laboratories with a fast, accurate tool to diagnose patients infected with the novel coronavirus.

“The feature benefits of the test system and the Lyra product will contribute substantially to our country’s efforts to fight this pandemic,” he said. “We are proud to have quickly developed this assay in mere weeks, and to have manufactured kits, several of which are in transit to customers. Anticipating significant demand, we are allocating kits across a broad set of customers as we ramp production.”

The Lyra SARS-CoV-2 assay is currently only available for sale in the United States and can be purchased either through Quidel’s salesforce or Cardinal Health.
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Changing focus of accommodating IOLs a new frontier

Lens options available proving a game-changer for ophthalmologists

By Lynda Charters; Reviewed by Stephen D. McLeod, MD

Change is a constant and with change in accommodating IOLs comes potential improvements in vision for presbyopic patients.

True accommodation means that the optic must instantaneously change power from distance to near and back. The most familiar strategy to accomplish this is a change in optic position, but other strategies to produce accommodation are changes in the lens curvature and in the refractive index or optic power, said Stephen D. McLeod, MD, professor and chair of ophthalmology, University of California San Francisco.

STRATEGIC NEAR VISION OPTIONS

Regarding the lens position, surgeons are familiar with both the CrystaLens (Bausch + Lomb) and the Kellan Tetraflex (Lenstec). The Tek-Clear Accommodative Lens (Tekia), a lens with a 360-degree haptic structure and a single optic vault, is a slightly newer IOL than the previous two. But lenses that depend on movement to change accommodation are limited in their ability to do so.

“The issue is that all of these devices are limited by the typical optic powers required by patients who are emmetropic or low and high myopes. When dealing with an optic that moves forward, the degree of that movement is not great, often much less than 1 millimeter, and for most lens powers implanted, the observed degree of movement produces minimal accommodative change proportional to the power of movement that is moving forward,” Dr. McLeod said.

The accommodative IOL models that change lens curvature can more efficiently effect the desired improvements in vision for presbyopic patients. Dr. McLeod pointed out that there are many technologies under development in the accommodate arena.

Accommodative IOLs continue to evolve in promising directions, giving ophthalmologists more options.

“This is a paradigm-shifting lens. The basic mechanism is that the IOL rapidly switches from a monofocal to a multifocal device and back.”

– Stephen D. McLeod, MD

The adjustable focus of the FluidVision IOL (PowerVision, now Alcon), a lens curvature IOL, is one of the older designs with peripheral reservoirs and distensible central optics. When the fluid moves from the reservoir to the center, the curvature changes.

The Opira accommodating IOL (ForSight Labs) is a sulcus-based device for which the haptics are fixed in the capsulorhexis.

“The anterior optic accepts the fluid from the reservoir leading to the change in curvature,” Dr. McLeod said.

The Juvene IOL (LensGen) is based on the same principle as the Opira IOL. “This lens has two compartments,” he said. “The anterior optic is the one that accepts the fluid from the reservoir, and the posterior element remains available for refining the focus power of the eye or for a toric correction.”

Atia Vision has also introduced in 2019 a modular presbyopia correcting IOL with the same basic approach that is comprised of a two-element design. The exception with this IOL is that the posterior element rather than posterior element will undergo the adjustment,” he said. “This lens offers is that if an adjustment of this optic is needed, it is far more accessible since the anterior element is fixed in the capsulorhexis.

The problem with these designs is that with change in optic position, but other strategies to produce accommodation are changes in the lens curvature and in the refractive index or optic power, said Stephen D. McLeod, MD, professor and chair of ophthalmology, University of California San Francisco.

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The Lumina IOL (AkkloLens) is an example of the IOLs that use the third option for accommodating IOLs, i.e., change in the refractive index or lens power. Dr. McLeod noted that this lens is comprised of two elements separated by an interface, a variable curvature cubic optic.

“The anterior and posterior surfaces are displaced relative to each other and this setup changes the power of the intervening space,” he said. “A compressive effect from the ciliary body causes relative motion of the anterior and posterior elements leading to a power change.”

Dr. McLeod further noted that the advantage of this design is the ability to achieve a “substantial change in the focal length with minimal ciliary body effect.”

Because all of these approaches are mechanical, it raises the question about whether microfluidics or microelectronics can be put to better use to develop accommodative IOLs.

The Sapphire AutoFocus IOL (Elenza) may be one answer to that question. This lens changes focus power without moving and relies on a power cell and a chip embedded in the eye. The device has a remote recharging system in goggles that are worn while the patient sleeps.

“This is a paradigm-shifting lens,” Dr. McLeod said, adding that the sensor for the device is that it can detect change in the pupillary diameter, which triggers the electronics to send a signal to introduce a diffractive pattern on the optics.

“The basic mechanism is that the IOL rapidly switches from a monofocal to a multifocal device and back,” he said.

The downsides are the large size, heavy weight and complex electronics, but as Dr. McLeod pointed out, it is showing us the direction in which accommodative IOLs are moving.

Dr. McLeod pointed out that there are many technologies under development in the accommodate arena.

“We are hopefully getting to the point at which we can actively change the true focus power of the system with truly accommodative devices in the reasonably near future,” he concluded.
DEXYCU* (dexamethasone intraocular suspension) 9% is indicated for the treatment of postoperative inflammation.

INDICATION AND USAGE
DEXYCU* (dexamethasone intraocular suspension) 9% is indicated for the treatment of postoperative inflammation.

IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Increase in Intraocular Pressure
- Prolonged use of corticosteroids, including DEXYCU, 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.

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 corticosteroids.

Exacerbation of Infection
- Use of a corticosteroid in the treatment of patients with a history of herpes simplex requires caution and may prolong the course and may exacerbate the severity of many viral infections.
- Fungal infections of the cornea are particularly prone to coincidentally develop with long-term local steroid application and must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal culture should be taken when appropriate.
- 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.

Cataract Progression
- The use of corticosteroids in phakic individuals may promote the development of posterior subcapsular cataracts.

ADVERSE REACTIONS
- The most commonly reported adverse reactions occurred in 5-15% of subjects and included increases in intraocular pressure, corneal edema and iritis.

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

References:
DEXYCU (dexamethasone intraocular suspension) 9%,
for intraocular administration
Initial U.S. Approval: 1958

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

1 INDICATIONS AND USAGE
DEXYCU (dexamethasone intraocular suspension) 9% is indicated for the treatment of postoperative inflammation.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS

5.1 Increase in Intraocular Pressure
Prolonged use of corticosteroids including DEXYCU 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.

5.2 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 corticosteroids.

5.3 Exacerbation of Infection
The use of DEXYCU, as with other ophthalmic corticosteroids, is not recommended in the presence of most 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.

Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires 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 of the cornea are particularly prone to develop coincidently with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal culture should be taken when appropriate.

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.

5.4 Cataract Progression
The use of corticosteroids in phakic individuals may promote the development of posterior subcapsular cataracts.

6 ADVERSE REACTIONS
The following adverse reactions are described elsewhere in the labeling:
• Increase in Intraocular Pressure [see Warning and Precautions (5.1)]
• Delayed Healing [see Warnings and Precautions (5.2)]
• Infection Exacerbation [see Warnings and Precautions (5.3)]
• Cataract Progression [see Warnings and Precautions (5.4)]

6.1 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 following adverse events rates are derived from three clinical trials in which 339 patients received the 517 microgram dose of DEXYCU. The most commonly reported adverse reactions occurred in 5-15% of subjects and included increases in intraocular pressure, corneal edema and iritis. Other ocular adverse reactions occurring in 1-5% of subjects included, corneal endothelial cell loss, blepharitis, eye pain, cystoid macular edema, dry eye, ocular inflammation, posterior capsule opacification, blurred vision, reduced visual acuity, vitreous floaters, foreign body sensation, photophobia, and vitreous detachment.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary
There are no adequate and well-controlled studies of DEXYCU (dexamethasone intraocular suspension) in pregnant women. Topical ocular administration of dexamethasone in mice and rabbits during the period of organogenesis produced cleft palate and embryofetal death in mice and malformations of abdominal wall/intestines and kidneys in rabbits at doses 7 and 5 times higher than the injected recommended human ophthalmic dose (RHOD) of DEXYCU (517 micrograms dexamethasone), respectively [see Data in the full prescribing information].

In the US general population the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

8.2 Lactation
Risk Summary
Systemically administered corticosteroids are present in human milk and can suppress growth, interfere with endogenous corticosteroid production, or cause other unwanted effects. There is no information regarding the presence of injected DEXYCU in human milk, the effects on breastfed infants, or the effects on milk production to inform risk of DEXYCU to an infant during lactation. The developmental and health benefits of breastfeeding should be considered, along with the mother’s clinical need for DEXYCU and any potential adverse effects on the breastfed child from DEXYCU.

8.4 Pediatric Use
Safety and effectiveness of DEXYCU in pediatric patients have not been established.

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

Manufactured for: EyePoint Pharmaceuticals US, Inc. Watertown, MA 02472
ARTIFICIAL INTELLIGENCE (AI) is the subject of numerous articles that tout how well machines function better than human ophthalmologists, but why is this happening?

In April 2018, the first FDA approval of autonomous AI for detecting referable diabetic retinopathy (DR) from fundus photos, the IDx-DR camera system (IDx Technologies, Inc.), legitimized and essentially jump-started AI in ophthalmology, according to Robert T. Chang, MD, associate professor at the Byers Eye Institute of Stanford University, Palo Alto, CA.

“The most important thing to understand if the technology will become widespread is how quickly doctors and patients will trust an AI system such as understanding its strengths and limitations, and how easily the technology will be integrated into current eyecare workflows, especially in terms of liability and business models,” he said.

The FDA was very careful in approving the first specific AI doctorless screening method for detecting DR in fundus images with a heavy emphasis on safety (what could be missed). The IDx-DR breakthrough device prospective multicenter trial included exacting requirements, such as specific camera type, single primary reason for DR screening, a narrow asymptomatic population not previously evaluated for DR, and specific minimal cutoffs for specificity and sensitivity to detect DR that exceeded mild disease, a threshold which likely would not result in a bad outcome given a false negative.

While the narrow confines of the 2017 trial may limit generalizability or slow adoption of telemedicine screening, an AI-driven screening approach may be ideal for ruling out negative disease, which frees up doctor time for positive cases, Dr. Chang explained.

“AI-based screening algorithms can achieve economy of scale and increase access to care at lower cost but high quality, inexpensive image capture remains a barrier,” he said.

Currently, deep learning has been deployed in the case of DR using supervised learning techniques requiring over a 100,000 labelled images (or subimages) to train the algorithm. With such a large number of examples, modern computational power helps finetune a “neural network” mathematical model to detect the most important features within an image to properly classify it with a certain degree of statistical certainty.

“With constant refinement, the model can achieve a performance that is equal or even superior to human pattern recognition, depending on the consensus ground truth (predetermined right answer),” Dr. Chang said. This is in contrast to older AI algorithms in which human expert-driven features of DR were programmed, but these algorithms were not able to achieve superhuman performance.

**OBTAINING DATA SETS**

The rate limiting step in deep learning is clean “Big Data,” that is, sufficient variety and quality of training examples without too many artifacts and ideally the ability to ensure that the AI could calculate the relative risk of misclassification—essentially knowing when not to produce an answer, according to Dr. Chang.

This begs the question: Where does all the data to train algorithms come from? The answer is “de-identified” public data sets that are essentially open sourced by various organizations. Every company is trying to aggregate their own unique or proprietary data set as a competitive advantage since AI algorithm architectures generally are published and cloud computational power is affordable now.

The only real differentiator is the training data quality, quantity, and diversity. Dr. Chang recounted the original Kaggle data science competition in 2014, including more than 600 teams with the aim of training an AI algorithm to screen for DR. The event that kicked off interest in neural networks applied to ophthalmology.

A follow-up similar contest took place last year sponsored by the Fourth Asia Pacific Tele-ophthalmology Society (APTSOS). The data set for this competition was comprised of thousands of images from the Aravind Eye Institute in India, which become public domain when released. More than 3,000 teams were interested in training a better algorithm to screen for DR. However, people quickly realized the definitions of disease in this data set differed subtly from India and models from the prior competition did not achieve similar performance. Humans may not see the small differences, but machines can.

The biggest problem faced in AI is having sufficient longitudinal, real-time, high-quality representative data cleaned up for the appropriate task. The narrower the task, the easier it is to acquire relevant diverse data, but going forward, there is a problem assessing algorithms against each other. Once a validation set is used, it is hard to keep that data private and not become incorporated into training data. Also, data generally are stored all over the place in private data siloes, but ideally, AI needs a globally shared data system to be truly generalizable.

Amassing enough data to garner trust in AI raises all kinds of ethical issues and considerations, including who owns an individual’s health data—the patient, the hospital or hospital system, the insurance company, or the government? And where will all the data be stored securely and who is benefiting from monetizing it.

**Blockchain Technology**

Blockchain technology involves decentralized sharing of information without a centralized owner, such as a Google or Facebook. The first mainstream association of the term blockchain was with bitcoin. However, blockchain is really a platform technology, as Dr. Chang explained.

“Basically, it is a type of shared public database across many computers, with no single owner, that records a series of time-sequenced, permanent transactions, which people can trust to be secure,” he said.

What makes the blockchain technology special is that it is updated in real time across many computer nodes, with a competitive, mathematically based validation system to verify the transactions “AKA blocks.” The trust comes from the fact that it is too expensive for the shared database ledger to be manipulated, and thus the first use case was a decentralized digital currency record-keeping system.

In the healthcare realm, using blockchain platform technology combined with encryption, users can submit private image data, for example, which can be shared without actually becoming public domain. Then, through secure computation, the image data can be used to train or validate AI algorithms without letting any user actually download the original data. This is the concept of the privacy-preserving blockchain as a platform for training and testing AI algorithms. Then a validation set can truly stay private.

“The key factor that attracts people to blockchain...
TECHNOLOGIES

(Continued from page 1)

placed next to the bed and not at the patient’s feet. The surgeon’s sightline is not always straight, which depends on the configuration of the operating room,” Dr. Oshika said.

Dr. Oshika cited a study (Crimean Arch Clin Exp Ophthalmol 2019;257:473-83) of surgeons’ responses to heads-up surgery that reported that the system was best used during retinal procedures, including peeling of internal limiting membranes and removal of epiretinal membranes, and the investigators considered that the procedure for which heads-up surgery was least beneficial was anterior segment surgery.

“Some surgeons jump at the chance to use a new product for the first time and perhaps benefit from opportunities to speak about it,” he said.

Dr. Oshika explained that he is skeptical about new products such as the 3-D system being incorporated into practice until the advantages and disadvantages are weighed and the benefits for patients are clear.

IOLs

A number of new IOLs become commercially available each year. The multifocal IOLs, which have been around for a while, are still associated with unwanted photic phenomena. As a result, the percentage of unhappy patients remains relatively high, with percentages ranging from around 4% to 7% (Am J Ophthalmol 2019;208:133 and J Cataract Refract Surg 2009;35:992 and 2011;37:859). Preoperative examinations cannot predict which patients will experience photic phenomena. Dr. Oshika noted that until recently, he was not a strong advocate of multifocal IOLs.

However, his opinion has been changing with the improvements in the IOL technology. “Newer IOLs are associated with less loss of light energy postoperatively ranging from 14% down to 7%, specifically some trifocal, low-add, extended-depth-of-focus, and dual monofocal IOLs,” he said. “Less loss of light translates to fewer optical problems and better contrast sensitivity.”

Some older products have exhibited up to 22% light loss, Dr. Oshika added. Newer IOLs also have a better defocus curve with a smoother and wider range of focus. Dr. Oshika added that in his current practice he uses a low-add (1.5-D) refractive IOL in the multifocal lens segment and a trifocal IOL in the multifocal lens segment.

FLACS

With its introduction in 2008, surgeons embraced FLACS enthusiastically with the idea that it would become standard practice, as when phacoemulsification supplanted extracapsular cataract extraction. However, over time the incidence of complications associated with FLACS was higher compared with manual phaco.

“There is no clear merit in terms of patient outcomes and cost with the improvements in the IOL technology.” Dr. Oshika said.

There are clear benefits to FLACS in certain clinical scenarios, such as cases with low endothelial cell counts, unstable zonules, displaced and subluxed lenses, and pediatric cataracts. Dr. Oshika also mentioned that the new FEMTIS IOL from Oculentis can be anchored in the perfectly circular capsulorhexis by four additional and specially designed haptics.

An alternative to FLACS is the Zepto capsulotomy system (Mynosys Cellular Devices Inc.), which can precisely create a centered capsulotomy using electrical energy delivered through a nitinol ring, which is a much cheaper version of FLACS, Dr. Oshika said.

However, Dr. Oshika noted that FLACS needs additional improvements in the future. Moreover, Dr. Oshika concluded that newer is not necessarily better.

“The patient benefits should be evaluated before new technologies are incorporated into clinical practice,” he said.

TAKE-HOME

> Ophthalmologists should take a wait-and-see approach before incorporating new technologies into clinical practice.

BLOCKCHAIN

(Continued from page 19)

Technology is that there is no centralized owner, and, thus, information stored on it cannot be manipulated by anyone without taking down the entire system,” Dr. Chang said.

HOW BLOCKCHAIN WORKS

FOR BITCOIN

The first best-known-use case of blockchain was to create an alternate decentralized online payment system, like Bitcoin, in contrast to a centralized electronic payment system, such as Paypal.

Bitcoin transactions or exchanges are stored on a public ledger in real time for all computer nodes to see and verify, and these computers also double as “miners” so there is an incentive to have many participants since the miners supported the nodes also have a chance to win a bitcoin reward. The value of the bitcoin is solely dependent on the supply-demand curve, like digital gold.

“The computation underlying the blockchain communication consists of hash functions or strings of numbers, and the decentralization component makes it difficult to hack all the computers simultaneously,” Dr. Chan said. “While the blockchain public ledger is immutable, hacks can occur at the cryptocurrency digital wallet level, where you hold your bitcoin for example but not at the exchange trading level.”

CONNECTING THE DOTS

Imagine if all the images obtained in ophthalmology clinics were somehow uploaded easily to this decentralized blockchain system, and patients, not hospitals, owned their data. The data then could truly cross systems and borders without fear of loss of privacy, breaking down our current data siloes. In this new system, patients could give permission for any organizations to train or validate off their de-identified data and not worry about whether than can trust the owner (like a Google), Dr. Chang explained.

“There could also be a new data marketplace where secure computing allows data seekers to contract with data providers via a blockchain public ledger,” he said. “This is executed via a process called smart contracts, whereby multiple companies training AI algorithms could access data privately, not needing public domain datasets or data siloes.”

THE FINAL QUESTION

How does the health data get into this secure, decentralized data marketplace for AI training?

Dr. Chang reported that his efforts are focused on speed and ease of use to capture the data, for example by taking a picture of the test result, and immediately labelling it prospectively, rather than going back to export data and label it retrospectively. He suggested that, at the point of care, when patients are receiving their result, they could immediately upload a de-identified test result to the cloud that would be available for AI training through the privacy-preserving blockchain public ledger. This would be the start of a shareable data marketplace without relying on a central owner.

“If enough people worldwide got together and started populating a database like this, it may be faster than trying to fund an international multicenter registry or get organizations to sign data sharing use agreements,” Dr. Chang concluded.
**INDICATIONS AND USAGE**

FLAREX® (fluorometholone acetate ophthalmic suspension) is indicated for use in the treatment of steroid-responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the eye.

**IMPORTANT SAFETY INFORMATION**

**CONTRAINDICATIONS**

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

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

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

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

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FLA-09-12-AD-39

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- The **lowest-cost branded** corticosteroid3,b
- **No generic equivalent**—prescribe FLAREX by name4

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

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

DOSE AND ADMINISTRATION
Shake Well Before Using. One to two drops instilled into the conjunctival sac(s) four times daily. During the initial 24 to 48 hours, the dosage may be safely increased to two drops every two hours. If no improvement after two weeks, consult ophthalmologist. Care should be taken not to discontinue therapy prematurely.

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

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

Intracocular Pressure Increase
Prolonged use may result in glaucoma, damage to the optic nerve, and defects in visual acuity and visual field. It is advisable that the intracocular pressure be checked frequently.

Cataracts
Use of corticosteroids may result in cataract formation.

Delayed Healing
Topical ophthalmic corticosteroids may slow corneal wound healing. In those diseases causing thinning of the cornea or sclera, perforation has been known to occur with chronic use of topical steroids.

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

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

Fungal Infections
Fungal infections of the cornea are particularly prone to develop coincidently with long-term topical steroid application. Fusus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use.

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

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

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

ADVERSE REACTIONS
Clinical Trials Experience
Glaucoma with optic nerve damage, visual acuity and field defects, cataract formation, secondary ocular infection following suppression of host response, and perforation of the globe may occur.

Postmarketing Experience
The following reaction has been identified during postmarketing use of FLAREX in clinical practice. Because reactions are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reaction, which has been chosen for inclusion due to either its seriousness, frequency of reporting, possible causal connection to FLAREX, or a combination of these factors, includes dacygnea.

USE IN SPECIFIC POPULATIONS
Pregnancy
Fluorometholone has been shown to be embryotoxic and teratogenic in rabbits when administered at low multiples of the human ocular dose. Fluorometholone was applied ocellar to rabbits daily on days 6-15 of gestation, and dose-related fetal loss and fetal abnormalities, including cleft palate, deformed rib cage, anomalous limbs, and neural abnormalities, such as encephalocoele, craniorachischisis, and omphalocele, were observed. There are no adequate and well-controlled studies of fluorometholone in pregnant women, and it is not known whether fluorometholone can cause fetal harm when administered to a pregnant woman. Fluorometholone should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation
Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of fluorometholone could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when FLAREX is administered to a nursing woman.

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

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

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
No studies have been conducted in animals or in humans to evaluate the possibility of these effects with fluorometholone.

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

Use with Contact Lenses
The preservative in FLAREX, benzalkonium chloride, may be absorbed by soft or hard contact lenses. Contact lenses should be removed during instillation of FLAREX but may be reininserted 15 minutes after instillation.

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

Rx Only
Distributed by: Eyevance Pharmaceuticals LLC. Fort Worth, TX 76102


GENETIC STUDY
In this case-controlled genetic association study, they took their research a step further in their efforts to clarify the genetic mechanism of the onset and progression of POAG by investigating “the association between the IOP-/non-IOP-related genetic variants and family history of glaucoma as an indicator of the onset of POAG and age at the diagnosis of glaucoma as an indicator of the progression of POAG.”

The investigators reported their findings in the American Journal of Ophthalmology (2020, doi: https://doi.org/10.1016/j.ajo.2020.03.014). The patients were recruited from three hospitals and one clinic in Japan. A total of 505 Japanese patients with POAG (including 264 with HTG and 259 with NTG) and 246 control subjects (mean patient age, 63.7 years; mean control subject age, 67.7 years) were included in the study.

PART OF THE STORY
Dr. Mabuchi and his colleagues, recounted that these factors are only part of the story. According to Dr. Mabuchi and his colleagues, “…cases of POAG caused by these gene mutations account for several percent of all POAG cases, and most POAG is presumed to be a polygenic disease.” Recent genetic analyses, the investigators explained, have reported genetic variants that pre-dispose patients to development of POAG and the additive effect of these variants on POAG, which are classified as two types. The first genetics variants are associated with IOP elevation. The second genetic variants are genetic variables that are not related to the IOP but are associated with optic nerve vulnerability, including apoptosis of the optic nerve, myopia, and optic nerve circulation.

In their previous work, the investigators reported the additive effects of these two types of genetic variants (Am J Ophthalmol 2015;159:437-444 e432; and Plos One 2017;12:e0183709) on the IOP and POAG, including normal-tension and high-tension glaucomas (NTG and HTG, respectively).

TAKE-HOME

» The results indicate that non-IOP-related genetic variants may play an important role in the onset of POAG.

By Lynda Charters
POAG diagnosis and the prevalence of a family history of glaucoma were 56.8 years and 25.5%.

All participants underwent genotyping for 22 genetic variants that predispose to POAG that could be classified into those variants associated with IOP elevation (17 genetic variants) or optic nerve vulnerability independent of the IOP (five genetic variants), Dr. Mabuchi and colleagues explained.

**RESULTS**

The study identified two noteworthy findings. The results showed a significant (P=0.014, odds ratio [OR], 1.26 per GRS) association between the non-IOP-related GRS and a family history of glaucoma. “As the non-IOP-related GRS increased, the risk of a family history of glaucoma increased in patients with POAG,” the investigators reported.

Regarding the association between the GRS and the age at which glaucoma was diagnosed, the investigators reported a significant (p = 0.0014, beta, -0.14) association between the IOP-related GRS and the age at diagnosis of glaucoma. “As the IOP-related GRS increased, the age at the diagnosis of glaucoma decreased,” they stated.

“In summary, a family history of glaucoma in cases of POAG is thought to reflect the influence of genetic variants predisposing to POAG, especially non-IOP-related genetic variants, and therefore accounts for the role of a positive family history of glaucoma as a risk factor for POAG. In contrast, IOP-related rather than non-IOP-related genetic variants were associated with age at the diagnosis of glaucoma, Dr. Mabuchi and colleagues commented.

“These results indicate that optic nerve vulnerability to IOP due to non-IOP-related genetic variants plays an important role in the onset of POAG.”

– Fumihiko Mabuchi, MD, PhD

IOP remains the main risk factor for glaucoma assess and progression. The genetic risk score (GRS) of POAG was calculated, which was comprised of the total number of risk alleles of the 17 IOP-related genetic variants and the five non-IOP-related genetic variants. The investigators then evaluated the associations found between the GRS and the family history of glaucoma, as an indicator of POAG onset, and age at glaucoma diagnosis, as an indicator of POAG progression. Several genes associated with POAG have been identified, though these account for less than 5% of all POAG in the general population.

**RESEARCH HIGHLIGHTS**

+ The researchers evaluated phenotypes using a genetic risk score of primary open-angle glaucoma

+ Non-IOP-related genetic variants are tied to family history of glaucoma

+ IOP-related genetic variants also are linked with a patient’s age at diagnosis

+ Non-IOP-related genetic variants also play an important role in disease onset

+ The research team found that IOP-related genetic variants play an important role in progression

**FUMIHIKO MABUCHI, MD, PhD**

Dr. Mabuchi has no financial disclosures related to this study. The study was supported in part by the Japan Society for the Promotion of Science.

‘These results indicate that optic nerve vulnerability to IOP due to non-IOP-related genetic variants plays an important role in the onset of POAG.’

– Fumihiko Mabuchi, MD, PhD

in case you missed it

Pharmacologic option for open-angle glaucoma PAGE 10

Researchers eye cure, diagnostics for adenoviral conjunctivitis PAGE 32

next issue...

Novel clinical options in pediatric and geriatric patients.

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IMPORTANT SAFETY INFORMATION AND INDICATIONS

CONTRAINDICATIONS
• EYLEA is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

WARNINGS AND PRECAUTIONS
• Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.

• Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.

• There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.
**TRUST ≈8 YEARS** of Extensive Clinical Experience and the Integrity of Data From Large, Well-Controlled Trials

**EYLEA IS THE #1 PRESCRIBED anti-VEGF FDA approved for Wet AMD, DME, and MEfRVO**

*IBM Truven MarketScan data: Number of injections administered from Q4 2017 through Q3 2018; data on file.

**AN ESTIMATED ≈9 MILLION doses administered to ≈790,000 eyes since launch (and counting)²**

**ACROSS ALL APPROVED INDICATIONS 8 PHASE 3 CLINICAL TRIALS including more than 3000 EYLEA–treated patients³**

---

**ADVERSE REACTIONS**

- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.

- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

**INDICATIONS**

EYLEA® (aflibercept) Injection 2 mg (0.05 mL) is indicated for the treatment of patients with Neovascular (Wet) Age-related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR).

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

anti-VEGF = anti–vascular endothelial growth factor; AMD = Age-related Macular Degeneration; DME = Diabetic Macular Edema; MEfRVO = Macular Edema following Retinal Vein Occlusion.

BRIEF SUMMARY—Please see the EYLEA full Prescribing Information available on HCPEYLEA.US for additional product information.

1 INDICATIONS AND USAGE
EYLEA is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of:
Neovascular (Wet) Age-Related Macular Degeneration (AMD); Macular Edema Following Retinal Vein Occlusion (RVO); Diabetic Macular Edema (DME); Diabetic Retinopathy (DR).

4 CONTRAINDICATIONS
4.1 Ocular or Periocular Infections
EYLEA is contraindicated in patients with active or periocular infections.

4.2 Active Intraocular Inflammation
EYLEA is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity
EYLEA is contraindicated in patients with known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as a cutaneous reaction, urticaria, anaphylaxis, or anaphylactoid reactions, or severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS
5.1 Endothelial and Retinal Detachments
Intraocular inflammation, including those with EYLEA, have been associated with endophthalmitis and retinal detachments (see Adverse Reactions (6.2)). Prevention or management technique must be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately (see Patient Counseling Information (17)).

5.2 Increase in Intraocular Pressure
Acute increases in intraocular pressure have been seen within 60 minutes of intraocular injection, including with EYLEA (see Adverse Reactions (6.1)). Sustained increases in intraocular pressure have also been reported after repeated intraocular dosing with vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.

5.3 Thrombembolic Events
There is a potential risk of arterial thromboembolic events (ATEs) following intraocular use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal or fatal stroke, nonfatal myocardial infarction, or vascular death (including deaths due to unknown causes). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.6% (32 out of 1984) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 615) in patients treated with ranibizumab (through week 96). The incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.5% (18 out of 519) in the combined group of patients treated with EYLEA compared with 2.8% (8 of 287) in the control group. From baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (22 out of 527) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

6 ADVERSE REACTIONS
The following potentially serious adverse reactions are described elsewhere in the labeling:
• Hypersensitivity (see Contraindications (4.2)).
• Endophthalmitis and retinal detachments (see Warnings and Precautions (5.1)).
• Increase in intraocular pressure (see Warnings and Precautions (5.2)).

6.1 Clinically Triable Events
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly Compared to rates in other clinical trials of the same drug or another drug may not reflect the rates observed in practice.
A total of 2980 patients treated with EYLEA constituted the safety population in eight phase 3 studies. Among those, 2379 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in 0.1% of intraocular reactions with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, pan, vitreous detachment, vitreous floaters, and injection site hemorrhage.

Neovascular (Wet) Age-Related Macular Degeneration (AMD)
The data described below reflect exposure to EYLEA in 1924 patients with wet AMD, including 1233 patients treated with the 2 mg dose, in 2 double-masked, controlled clinical studies (VIEW1 and VIEW2) for 24 months (with an active control in year 1).
Safety data observed in the EYLEA group in a 52-week, double-masked, Phase 2 study were consistent with these results.

Table 1: Most Common Adverse Reactions (≥1%) in Wet AMD Studies

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Baseline to Week 52</th>
<th>Baseline to Week 96</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EYLEA (N=1924)</td>
<td>Control (N=1047)</td>
</tr>
<tr>
<td></td>
<td>Active Control (ranibizumab) (N=1095)</td>
<td>Control (ranibizumab) (N=1095)</td>
</tr>
<tr>
<td>Conjunctival hemorrhage</td>
<td>22%</td>
<td>21%</td>
</tr>
<tr>
<td>Eye pain</td>
<td>9%</td>
<td>10%</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>9%</td>
<td>11%</td>
</tr>
<tr>
<td>Vitreous detachment</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Vitreous floaters</td>
<td>6%</td>
<td>7%</td>
</tr>
<tr>
<td>Intraocular pressure increased</td>
<td>6%</td>
<td>8%</td>
</tr>
<tr>
<td>Ocular hypertension</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>Corneal epithelium defect</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>Detachment of the retinal pigment epithelium</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Cataract</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Vitreous floaters</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Retinal pigment epithelium tear</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Injection site hemorrhage</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>
| Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal tear, and endophthalmitis.

Macular Edema Following Retinal Vein Occlusion (RVO)
The data described below reflect exposure to EYLEA in a monthly 2 mg dose in 281 patients followed in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following BRVO in one clinical study (VIBRANT).

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Baseline to Week 52</th>
<th>Baseline to Week 96</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EYLEA (N=218)</td>
<td>Control (N=142)</td>
</tr>
<tr>
<td></td>
<td>BRVO (N=92)</td>
<td>Control (N=142)</td>
</tr>
<tr>
<td>Conjunctival hemorrhage</td>
<td>12%</td>
<td>11%</td>
</tr>
<tr>
<td>Intraocular pressure increased</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Vitreous floaters</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>Intraocular pressure increased</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Vitreous floaters</td>
<td>6%</td>
<td>8%</td>
</tr>
<tr>
<td>Intraocular pressure increased</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Vitreous floaters</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Cataract</td>
<td>5%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Less common adverse reactions reported in <1% of the patients treated with EYLEA were conjunctival hemorrhage, eye pain, and endophthalmitis.

Table 2: Most Common Adverse Reactions (≥1%) in RVO Studies

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>EYLEA (N=218)</th>
<th>Control (N=142)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjunctival hemorrhage</td>
<td>12%</td>
<td>11%</td>
</tr>
<tr>
<td>Vitreous floaters</td>
<td>6%</td>
<td>8%</td>
</tr>
<tr>
<td>Cataract</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Vitreous floaters</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Vitreous floaters</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Cataract</td>
<td>5%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Less common adverse reactions reported in <1% of the patients treated with EYLEA were conjunctival hemorrhage, eye pain, and endophthalmitis.

Table 3: Most Common Adverse Reactions (≥1%) in DME Studies

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Baseline to Week 52</th>
<th>Baseline to Week 100</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EYLEA (N=578)</td>
<td>Control (N=287)</td>
</tr>
<tr>
<td></td>
<td>EYLEA (N=578)</td>
<td>Control (N=287)</td>
</tr>
<tr>
<td>Conjunctival hemorrhage</td>
<td>28%</td>
<td>26%</td>
</tr>
<tr>
<td>Cataract</td>
<td>8%</td>
<td>9%</td>
</tr>
<tr>
<td>Vitreous floaters</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Intraocular pressure increased</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Cataract</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Vitreous floaters</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Cataract</td>
<td>5%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Less common adverse reactions reported in <1% of the patients treated with EYLEA were conjunctival hemorrhage, eye pain, and endophthalmitis.

6.2 Lactation
Data
Animal studies
In two embryofetal development studies, aflibercept produced adverse embryofetal effects in rabbits, including external, visceral, and skeletal malformations. A total No Observed Adverse Effect Level (NOAEL) was not identified. At the lowest dose shown to produce adverse embryofetal effects, systemic exposures (AUC) for the active fragment were approximately 2 to 3 times higher than AUC values observed in humans after a single intravitreal treatment at the recommended clinical dose (see Animal Data).

Animal reproduction studies are not always predictive of human response, and it is not known whether EYLEA can cause fetal harm when administered to pregnant women. Based on the anti-VEGF mechanism of action for aflibercept, EYLEA should be used in pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus (see Pregnancy (8.3)).

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the general population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.3 Females and Males of Reproductive Potential

8.4 Pediatric Use.

8.5 Geriatric Use.

9 USE IN SPECIFIC POPULATIONS

9.1 Pregnancy Risk Summary

9.2 Lactation

9.3 Females and Males of Reproductive Potential

9.4 Pediatric Use.

9.5 Geriatric Use.

Manufactured by
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591

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Issue Date: 08/2019
Initial U.S. Approval: 2000
Based on the August 2019 EYLEA (aflibercept) injection full Prescribing Information.
EYL.19.07.0006

Innovations for enucleation: Where can we go from here?

Digital, artificial intelligence may gain traction as options

By Lynda Charters; Reviewed by Jeremiah P. Tao, MD, FACS

Ocular enucleation is inevitable for some patients; but for others, new therapies might spare the eye. If it must happen, there are ways to ease that road for patients. Orbital volume, stability of the implant, and natural-appearing movement of the prosthesis are specific surgeon goals. Digital screens and artificial intelligence (AI) may be the future in optimizing eye prosthetics.

Jeremiah P. Tao, MD, described current and future technologies to assist patients who have undergone enucleation. He is professor of ophthalmology and director of oculo-facial plastic and orbital surgery at the University of California, Irvine.

Avoiding enucleation

Enucleation may not inevitable for some. Some eyes that previously would have had to be removed are being spared as the result of brachytherapy, chemotherapy, laser, and cryotherapy. “Not only are the eyes being spared, but in some cases these eyes even maintain good vision. These treatments are revolutionary,” Dr. Tao said.

One revolution involves the targeted and immune therapies for invasive cancers, he pointed out. “We can now target the cell receptors and molecular mechanisms at the nanoscopic level,” he said, describing the case of a patient with a massive periorbital squamous cell carcinoma that responded amazingly well to pembrolizumab (Keytruda, Merck & Co.).

While the globe in that case was beyond salvage, enucleation might be avoided in other cases, such as those involving invasive squamous cell carcinoma. This patient had a tumor of the lower eyelid that repeatedly recurred and over time invaded the orbit. “As recently as 18 months ago, we would have had to offer an exenteration procedure to eradicate the tumor. These procedures can be devastating to the patient’s physical appearance,” Dr. Tao explained.

However, now, cemiplimab (Libtayo, Sanofi and Regeneron), approved in 2018, resulted in tumor reduction with, in this case, four treatment cycles.

“Not only are the eyes being spared, but in some cases these eyes even maintain good vision. These treatments are revolutionary.”

– Jeremiah P. Tao, MD

Pegs, however, are associated with complications and require a great deal of maintenance even in the best-case scenario. Infection occurs in most cases. Generally, porous implants may be more prone to exposure, inflammation, and infection. Lastly, the motility may not be better, and they are much more expensive than nonporous counterparts, Dr. Tao noted. In contrast, the smooth spheres, which Dr. Tao prefers, are well tolerated and there is less inflammation or scarring; however, migration specific to some implantation techniques can occur.

The enucleation procedure has remained relatively unchanged over the decades. Preservation of the orbit is key during the enucleation process, and harvesting and tagging the extraocular muscles must be done carefully to maintain the anatomy.

“The extraocular muscles should be replaced to their anatomic positions to maintain the physiology,” he said.

While not a recent innovation, he recommends using a snare to sever the optic nerve and last attachments of the eye without bleeding. The snare commonly eliminates the need for aggressive cautery or other coagulation strategies, Dr. Tao reported.

When implanting a silicone sphere, he prefers to wrap it with sclera harvested from the enucleated eye. After inserting the wrapped sphere into the orbit, rectus muscles are sewn back into their natural positions. “The wrap prevents migration of the silicone implant and also decreases exposure by serving as another tissue layer between the implant and the environment,” he explained.

Other options for covering the implant are autologous fascia lata, temporalis fascia, or ear cartilage, but these require a second surgical site. Donor grafts of the same tissues or sclera are options but pose some rejection and disease transmission risks. Synthetic materials such as Gore Tex generally do not integrate well.

Bioengineered acellular dermal matrix may be promising since they purportedly pose low infection risk, though specific implantation techniques can occur.

Innovation: motility

“In the current best-case scenario, some eye movement is achieved with intact rectus muscles under a prosthetic shell, but in the majority, the apparent motility is incompletely satisfactory – the Holy Grail is more full and natural eye movements” he said.

Digital production of prosthetic movement is...
Cataract

(Continued from page 1)

Dr. Brissette pointed out that during cataract surgery, the microscope must be moved to obtain a better view. Some structures are always out of focus, the video and recordings can come in and out of focus because of accommodation especially by trainees, and the illumination and magnification must be optimal.

Ergonomics are important to Dr. Brissette. The careers of many ophthalmologists are truncated by back and neck pain caused by extended periods of surgery and examinations over the years.

3D Technology

Technology is currently available (NGenuity, Alcon, Artvue 300, Zeiss) that provides 4K 3D visualization using 3D glasses. Alcon’s system uses a digital system that processes images and then displays them. The Zeiss system is one of integrated digital optics, featuring intraoperative optical coherence tomography for corneal surgery and will be introducing digital overlays for toric alignment in cataract surgery, Dr. Brissette explained.

Dr. Brissette noted that the new technology offers exciting options for ophthalmologists.

“The three unique advantages of 3D technology are visualization, ergonomics, and education,” she said. “The last has become especially important in anterior segment surgery using the 3D heads-up systems.”

The improvements in visualization seen with 3D technology result from the increased quality of vision to the total operating space and offers high-definition resolution intraoperatively from the nasal to the lateral canthi. This eliminates looking into the microscope and the frequent adjustments needed to obtain clear focus; the entire field is in focus, she emphasized.

Dr. Brissette provided an example of how well 3D technology makes surgery easier. In a patient who is a high myope undergoing cataract surgery the anterior chamber is deep and using a microscope adjusting the focus is needed to see the nuclear fragments. Because of 3D technology, there is no need to adjust the focus intraoperatively to visualize the angle during microinvasive glaucoma procedures and for corneal and conjunctival procedures.

Conclusion

Using 3D systems, surgeons can sit back in the chair and maintain a comfortable position during longer cases and days in the operating room.

“This feature will help to maintain career longevity,” she said.

Education likely is one of the most important benefits of 3D systems. In complicated cases, personnel from different ophthalmic disciplines as well as residents and fellows can view the surgery simultaneously. Nurses viewing the procedures can anticipate the needs of the surgeons intraoperatively.

No refocusing of the field of view is needed as the various surgeons move in and out of the primary position or for teaching opportunities. Surgical skills can be improved by reviewing cases in 3D with residents and fellows.

“The educational component is becoming more and more important with the education of the next generation of ophthalmologists,” Dr. Brissette noted.

• Budding technology may help surgeons extend their careers. Education is one of the most important benefits of 3D systems.

ENUCLEATION

(Continued from page 27)

the latest technology being explored for patients who have undergone enucleation. This involves eye-tracking software that is connected wirelessly to a high-definition miniature screen prosthesis that possibly offers improvements.

This idea is doable albeit complicated and in its infancy.

“We have to ‘read’ the well eye somehow and simultaneously generate the image,” Dr. Tao said and described how in 2015 he and his colleagues constructed a crude prototype with a camera affixed to eyeglass frames. A microchip contact lens could also be used to send a signal to control eye movement. When the movement of the well eye is read, a simultaneous dynamic image of a contralateral eye appeared on a computer screen.

The following year, the investigators built a wearable system for less than $100 with hardware purchased on Amazon. These included a microcamera, a processor was about the size of a credit card and a micro digital display about the size of a watch face.

The shortcomings of these first attempts was that the system captures only very slow eye movement and requires controlled conditions and lighting. Dr. Tao also pointed out that there are problems with glare and interference by eyelashes, among others.

Artificial intelligence (AI) may ultimately play a role in this system. Using AI with its multiple inputs, they then developed a second-generation system that permits much faster and more accurate eye tracking.

Dr. Tao noted that researchers have the technology to do this, but funding is lacking.

“There may not be a large enough market to attract major investments for this project,” he said. “I implore ophthalmologists and ocularists to provide ideas that might make this audacious idea a reality. The dream is to give better eye mobility to patients who are bothered by poor prostheses movement.”

Dr. Tao added that innovation is iteration that begins with ideas.

“Removing the eye is now not necessary in some conditions,” he concluded. “Enucleation techniques have not changed greatly, but they require restoring the anatomy using the best techniques possible. Ophthalmologists should be mindful of the history of implant shapes and materials and which have failed. New bioengineered tissue grafts and wraps have become available that may eliminate some shortcomings with other materials. Digital and AI may be the next frontiers to improve mobility.”

JEREMIAH TAO, MD

j.tao@uci.edu

Dr. Tao is a consultant to Horizon Therapeutics.
INDICATIONS AND USAGE
DURYSTA™ (bimatoprost implant) is indicated for the reduction of intraocular pressure (IOP) in patients with open angle glaucoma (OAG) or ocular hypertension (OHT).

IMPORTANT SAFETY INFORMATION
Contraindications
DURYSTA™ is contraindicated in patients with: active or suspected ocular or periocular infections; corneal endothelial cell dystrophy (e.g., Fuchs’ Dystrophy); prior corneal transplantation or endothelial cell transplants (e.g., Descemet’s Stripping Automated Endothelial Keratoplasty [DSAEK]); absent or ruptured posterior lens capsule, due to the risk of implant migration into the posterior segment; hypersensitivity to bimatoprost or to any other components of the product.

Warnings and Precautions
The presence of DURYSTA™ implants has been associated with corneal adverse reactions and increased risk of corneal endothelial cell loss. Administration of DURYSTA™ should be limited to a single implant per eye without retreatment. Caution should be used when prescribing DURYSTA™ in patients with limited corneal endothelial cell reserve.

DURYSTA™ should be used with caution in patients with narrow iridocorneal angles (Shaffer grade < 3) or anatomical obstruction (e.g., scarring) that may prohibit settling in the inferior angle.

Macular edema, including cystoid macular edema, has been reported during treatment with ophthalmic bimatoprost, including DURYSTA™ intracameral implant. DURYSTA™ should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Prostaglandin analogs, including DURYSTA™, have been reported to cause intraocular inflammation. DURYSTA™ should be used with caution in patients with active intraocular inflammation (e.g., uveitis) because the inflammation may be exacerbated.

Ophthalmic bimatoprost, including DURYSTA™ intracameral implant, has been reported to cause changes to pigmented tissues, such as increased pigmentation of the iris. Pigmentation of the iris is likely to be permanent. Patients who receive treatment should be informed of the possibility of increased pigmentation. While treatment with DURYSTA™ can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

Intraocular surgical procedures and injections have been associated with endophthalmitis. Proper aseptic technique must always be used with administering DURYSTA™, and patients should be monitored following the administration.

Adverse Reactions
In controlled studies, the most common ocular adverse reaction reported by 27% of patients was conjunctival hyperemia. Other common adverse reactions reported in 5%-10% of patients were foreign body sensation, eye pain, photophobia, conjunctival hemorrhage, dry eye, eye irritation, intraocular pressure increased, corneal endothelial cell loss, vision blurred, iritis, and headache.

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


IOP= intraocular pressure.

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The presence of DURYSTA™ implants has been associated with corneal adverse reactions and increased risk of corneal endothelial cell loss. Administration of DURYSTA™ should be limited to a single implant per eye without retreatment. Caution should be used when prescribing DURYSTA™ in patients with limited corneal endothelial cell reserve.

Iridocorneal Angle: Following administration with DURYSTA™, the intracamerai implant is intended to settle within the inferior angle. DURYSTA™ should be used with caution in patients with narrow iridocorneal angles (Shaffer grade ≤ 3) or anatomical obstruction (e.g., scarring) that may prohibit settling in the inferior angle.

Macular Edema: Macular edema, including cystoid macular edema, has been reported in patients with active irritable eye symptoms and in patients with known risk factors for macular edema.

Intraocular Inflammation: Prostaglandin analogs, including DURYSTA™, have been reported to cause irritable eye symptoms, such as increased pigmentation of the iris. Pigmentation of the iris is likely to be permanent. Patients who receive treatment should be informed of the possibility of increased pigmentation. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes.

Pigmentation: Ophthalmic bimatoprost, including DURYSTA™, has been reported to cause changes to pigmented tissues, such as increased pigmentation of the iris. Pigmentation of the iris is likely to be permanent. Patients who receive treatment should be informed of the possibility of increased pigmentation. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes.

Potential for Pigmentation: Advise patients about the potential for increased pigmentation of the iris. Pigmentation of the iris is likely to be permanent. Patients who receive treatment should be informed of the possibility of increased pigmentation. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes.

Contraindications: DURYSTA™ is contraindicated in patients with active or suspected ocular or periocular infections; increased intraocular pressure (OIP); history of or current use of a cycloplegic or anticholinergic agent; history of angle-closure glaucoma, primary open-angle glaucoma, or vertical heterochromia iridis; open-angle glaucoma with pigment dispersion; history of iridocorneal endothelial syndrome, pseudophakic bullous keratopathy, or Behcet’s disease; known hypersensitivity to bimatoprost or any other components of the product; and pregnancy (especially during the first trimester) and lactation.

Warnings and Precautions: The use of DURYSTA™ should be used with caution in patients with active intraocular inflammation (e.g., uveitis) because the inflammation may be exacerbated.

Use in Specific Populations: Pregnancy: There are no adequate and well-controlled studies of DURYSTA™ administration in pregnant women to inform a drug associated risk. Oral administration of bimatoprost to pregnant rats and mice throughout organogenesis did not produce adverse maternal or fetal effects at clinically relevant exposures. Oral administration of bimatoprost to rats from the start of organogenesis to the end of lactation did not produce adverse maternal, fetal or neonatal effects at clinically relevant exposures.

In embryofetal developmental studies in pregnant mice and rats, abortion was observed at doses of bimatoprost which achieved at least 1770 times the maximum human bimatoprost exposure following a single administration of DURYSTA™ (based on plasma Cmax, oral blood-to-plasma partition ratio of 0.858).

In a pre/postnatal development study, oral administration of bimatoprost to pregnant rats from gestation day 7 through lactation resulted in reduced gestation length, increased late resorptions, fetal deaths, and postnatal pup mortality, and reduced pup body weight at 0.3 mg/kg/day (estimated 4.7 times the systemic human exposure to bimatoprost from DURYSTA™, based plasma Cmax, and a blood-to-plasma partition ratio of 0.858). No adverse effects were observed in rat offspring at 0.1 mg/kg/day (estimated 350-times the human systemic exposure to bimatoprost from DURYSTA™, based on plasma Cmax). Lactation: There is no information regarding the presence of bimatoprost in human milk, the effects on the breastfed infants, or the effects on milk production. In animal studies, topical bimatoprost has been shown to be excreted in breast milk. Because many drugs are excreted in human milk, caution should be exercised when DURYSTA™ is administered to a nursing pregnant woman.

Endophthalmitis: Endophthalmitis is a rare but serious complication that can lead to vision loss. DURYSTA™ should be used with caution in patients with limited corneal endothelial cell reserve.

Pediatric Use: DURYSTA™ is not recommended for use in patients who are one year of age or younger. The effects of DURYSTA™ in patients who are one year of age or younger have not been established.

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

Nonclinical Toxicology: Carcinogenesis, Mutagenesis, Impairment of Fertility: Bimatoprost was not mutagenic or clastogenic in the Ames test, mouse micronucleus test, or in the mouse lymphoma assay. Bimatoprost was not clastogenic in the mouse micronucleus test, or in the mouse lymphoma assay. Bimatoprost was not mutagenic in the mouse lymphoma assay, or in the in vivo mouse micronucleus test. Bimatoprost did not impair fertility in male or female rats up to doses of 0.6 mg/kg/day (1770-times the maximum human exposure, based on plasma Cmax, levels; blood-to-plasma partition ratio of 0.858).

Patient Counseling Information: Treatment-related Effects: Advise patients about the potential risk for complications including, but not limited to, the development of corneal adverse events, intraocular inflammation or endophthalmitis. Potential for Pigmentation: Advise patients about the potential for increased pigmentation of the iris, which may be permanent.

When to Seek Physician Advice: Advise patients that if the eye becomes red, sensitive to light, painful, or develops a change in vision, they should seek immediate care from an ophthalmologist.

Rx only

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Robotic technology in surgery: Surgeons’ eye of the future

The time may be right for robotics in corneal, retinal procedures

By Lynda Charters; Reviewed by Jean-Pierre Hubschman, MD

ROBOTIC SURGERY HAS been on its way to becoming an important part of ophthalmic surgical procedures since the Da Vinci Robotic Surgical System (Intuitive) was approved in 2000 for laparoscopic surgery.

Since that time, both the numbers of surgical procedures that benefit from robotics and those of surgical robotic systems have exploded worldwide, according to Jean-Pierre Hubschman, MD, who is associate professor of ophthalmology, Stein Eye Institute, David Geffen School of Medicine, University of California Los Angeles (UCLA).

“Interestingly, the ratio between traditional versus robotic surgery has been evolving quickly,” he said, adding that almost all prostatectomies are assisted by robotics in the United States.

The technology has important advantages, including superhuman dexterity. This enhances precision, maneuverability, control, and improved sensory feedback. These advantages can help to improve traditional ocular surgeries that, he noted, have the disadvantages of limited feedback, limited spatial resolution, depth perception, the absence of tactile feedback, and limited optical coherence tomography (OCT) integration.

In addition, the human factor limitations include physiologic hand tremors make manipulation of delicate tissue challenging.

Our performance can certainly be improved by robotic assistance during ocular surgery by providing better precision and accuracy via filtering of the hand tremors and scaling of motion, and collaborative capabilities can augment the surgeon’s manipulation capabilities,” Dr. Hubschman explained.

Robotics can also provide better feedback to surgeons through augmented sensing of both visualization with enhanced depth perception and augmented reality and haptic/tactile feedback via virtual fixture.

“These augmentations can lead to better surgical outcomes and new surgical manipulations not previously possible,” he said.

LEVELS OF ROBOTIC INVOLVEMENT

In contrast to traditional surgeries, robotic surgeries can be semiautonomous, where both the surgeon and the robot manipulate the tool in the eye simultaneously or fully automated in which the robot is in full control of the tools and supervised by the surgeon.

Regarding retinal surgeries, Dr. Hubschman mentioned different designs potentially used to perform semiautonomous procedures.

One such item is a handheld smart tool in which all the technology will be included in the handle of the tool.

Another design is a co-manipulation system in which a dedicated tool will be controlled simultaneously by the robotic manipulator and the surgeon performing the procedure. Another option is tele-manipulation in which the robotic manipulator is controlled from the robotic controller that is potentially controlled in a surgical cockpit.

TECHNOLOGIC STATUS

To date, the co-manipulation design has been tested successfully in humans at the University of Leuven, Flanders, Belgium, for retinal vein cannulation. The investigators reported their results in the Annals of Biomedical Engineering (2018;46:1676-1685).

“The results show that it is technically feasible to safely inject an anticoagulant into a 100 μm-thick retinal vein of an patient [with retinal vein occlusion] for a period of 10 minutes with the aid of the presented robotic technology and instrumentation,” the investigators wrote.

The tele-manipulation design is used in the Precyeyes Surgical System (Precyeyes BV), which was designed by Marc de Smet, MD. In this system, the instrument is mounted on the robotic arm and controlled from the robotic manipulators by the surgeon. Dr. Hubschman pointed out that this system has received a C mark, is approved in Europe, and is in used in three hospitals.

The system that Dr. Hubschman and colleagues use at UCLA, the Intraocular Robotic Interventional Surgical System (Int J Med Rob 2018;14: e1949, doi: 10.1002/rcs.1949, Epub 2018 Aug 28) has a tele-manipulation design.

“Compared with other systems that provide surgeons with visual feedback only through the surgical microscope, this system has OCT integrated into it. OCT provides real-time acquisition and real-time data processing that allows for enhanced visual feedback as well as tactile feedback through the surgical controllers,” Dr. Hubschman explained.

“This system also can perform semiautomatic tasks via OCT guidance that can define safe trajectory within the working space.”

This system, which was tested during cataract surgery, allowed fully automated lens removal in harvested pig eyes (J Cataract Refract Surg 2019;45:1665-1669. Doi: 10.1016/j.jcrs.2019.06.020), Dr. Hubschman noted.

“We hope that this platform will be ready for a human trial in three years,” he said.

Dr. Hubschman and his colleagues are looking to the future of retinal surgery.

He explained that they envision a semi-autonomous system in which the surgeon will be seated in a surgical cockpit and immersed with sensory feedback both visual and tactile through the robotic controllers.

“We demonstrated recently that adding tactile feedback in addition to the visual feedback facilitated a faster learning curve and safer tissue manipulation,” he said and projected that this platform may be available for human trials in 2024 (Transl Vis Sci Technol 2019:8:2. doi: 10.1167/tvst.8.4.2. eCollection 2019).

CONCLUSION

Dr. Hubschman said robotic surgery is in its infancy in ophthalmology.

“We believe that this robotic technology can provide superhuman capabilities with enhanced capability, efficacy, safety, reliability, and sensing,” he concluded. “The technology has many potential applications, included automation of cataract surgeries and complex membrane dissection and subretinal injection of stem cells and gene therapy in retinal procedures.”

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Dr. Hubschman is the holder of several patents filed through UCLA. He also has received grant support from the National Institutes of Health/NIH/National Eye Institute.
Researchers eye cure, diagnostics for adenoviral conjunctivitis

Molecular testing will provide increased sensitivity for patients

By Lynda Charters; Reviewed by James Chodosh, MD, MPH

adenovirus conjunctivitis, extremely common, extremely contagious, and extremely expensive, is the cause of from 1% to 2% of all visits to primary care providers in the United States, with $430 million spent on diagnosing and treating the infection.

New and repurposed drugs are being explored to address this infection as well as a specific diagnostic test.

“The profound importance of this infection was underscored by a recent outbreak of adenovirus type 3 pneumonia and conjunctivitis in a neonatal intensive care unit that affected 23 neonates and nine adults, of whom four neonates died,” according to James Chodosh, MD, MPH. “This underscores the importance of treatment over and above just red eye.”

Dr. Chodosh referenced a study published in Ophthalmology 2018;Sep 1, pii: S0161-6420(18)31075-3. He is the DC Cogan Professor of Ophthalmology in the Field of Cornea and External Disease, Howe Laboratory, Massachusetts Eye and Ear, Harvard Medical School, Boston.

How Adenovirus Works

The adenovirus succeeds in infecting host cells by binding of the adenovirus’ fiber knob to one of the host cell receptors that include CAR, CD46, MHC class II alpha chain, and in the corneal epithelium, GD1a glycan.

Dr. Chodosh reported that clinical trials are under way that are targeting the adenovirus receptor on the corneal epithelial cells, for example, APD-209 (Adenovir Pharma), a decoy receptor sulfated glycosaminoglycan. In early trials, the drug was shown to be helpful; the investigators reported their findings in Virology 2019;11:E247. The phase III trials are ongoing, he noted.

Dr. Chodosh is hopeful for improved diagnostics and a cure for adenovirus conjunctivitis.

“Considering the avalanche of new molecular diagnostics, eventually we are certain to have rapid, nucleotide-based, in-office testing that works as well as polymerase chain reaction,” he said. “The NovaBay trial confirmed what clinical trialists always knew, that is, that clinical trials are more productive when held in areas where the disease of interest is highly prevalent.”

Dr. Chodosh said if physicians are not sure the patient has the disease and they are enrolled, the value of the trial is diminished.

The potential impact of a drug with efficacy against adenovirus conjunctivitis is high and will continue to attract interest from pharma because companies know that such a drug would be used in a great deal in primary care settings by pediatricians and family care providers and by ophthalmologists, making this a potentially lucrative investment,” he concluded. “FDA-approved drugs repurposed for ocular use continue to be explored. New drug candidates will emerge as our basic understanding of adenovirus increases.”

MOLECULAR DIAGNOSTICS

These are coming. A recent study reported that an in-office molecular test, not a protein-based test, is in the offing (Surv Ophthalmol 2019;64:255-71).

“This type of test would be infinitely more sensitive,” Dr. Chodosh said.

Newly identified antiviral drugs, which include repurposed drugs, also offer hope for a cure. Recently evaluated therapeutics include salicylanilide antihelmintics such as niclosamide, which is FDA-approved (Sci Rep 2019;9:17); mifepristone (Antivirals 2018;159:77-83); and cardiotonic steroids, i.e., digoxin and digitoxin (J Virol 2017;91:e01623-16), he reported.

“Because these drugs are already FDA approved, there is a shorter path to testing and topical use,” Dr. Chodosh said.

Brincidofovir (CMX001, Chimerix, Inc.), an experimental systemic drug of lower toxicity used systemically to treat patients with systemic adenovirus infections who underwent bone marrow transplants, also has shown very promising results in two studies (Biol Blood Marrow Transplant 2017;23:512-21 and J Clin Virol 2017;96:73-9) and may be a candidate for use in the eye.

“If this drug is approved, perhaps it can be re-purposed for ocular use,” Dr. Chodosh suggested.

TAKE-HOME

◗ Adenovirus conjunctivitis is rolling an age-old infection with potentially new diagnostics and cures.

‘FDA-approved drugs repurposed for ocular use continue to be explored. New candidates will emerge as our basic understanding of adenovirus increases.’

– James Chodosh, MD, MPH

According to Dr. Chodosh, successful clinical trials to identify treatments for adenovirus conjunctivitis have been stymied for two reasons. The first is the relatively low positive predictive value (PPV), i.e., 78%, of the only commercially available rapid diagnostic test for adenoviruses that was reported in the clinical trial of Auriclosene (NVC-422, NovaBay Pharmaceuticals) (Ophthalmology 2018;125:1344-53).

“The test did not work in the real world quite as well as we thought it would,” Dr. Chodosh said.

The second reason involves the nonspecific nature of the clinical signs of conjunctivitis, which, Dr. Chodosh noted, when there is no outbreak of the infection and no “truly accurate, rapid diagnostic” test, it is difficult to conduct a clinical trial in the presence of sporadic cases only.

“Clinical trials for this infection are more likely to be successful if instituted during an outbreak,” he said.

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**Scleral Melts: Patching Ultimately May Prove to be Unnecessary**

Necrotizing scleritis can be treated medically; communication with patient key

By Lynda Charters

Dr. Perez described the protocol he abide by when confronted with a patient with a scleral melt.

First, in contrast to many physicians, Dr. Perez said he steps away from the slit-lamp and talks to the patient.

“The clinical history is important,” he said. “I review the bodily systems and medications and perform an external examination, which is crucial for diagnosing all possible diseases that can be associated with the scleral melt.”

Dr. Perez also pointed out that a full ophthalmic examination should include every-thing. He noted that physicians should use their pattern recognition skills.

“We are very good at evaluating the eye and recognizing presentations that can help us with the differential diagnosis,” he said.

Some of those possibilities are mild necrotizing scleritis, severe scleral melt, infectious scleritis, and scleromalacia, which is not an active form of scleritis that rarely needs patching.

**TO TREAT OR NOT TO TREAT**

An illustrative case of a scleral melt caused by a disease is that of a 60-year-old woman who presented with eye pain associated with a scleral lesion.

The patient had rheumatoid arthritis. This scenario, among others, may move physicians to the next step: to patch or not to patch. However, in Dr. Perez’s opinion, the more important consideration is to treat or not to treat.

To address that question, Dr. Perez cited two studies. Watson and Hayreh (Br J Ophthalmol 1976;60:163-91) reported that 29% of patients died within 5 years of the onset of necrotizing scleritis and 67% of those deaths resulted from extraocular vasculitis. Foster et al. (Ophthalmology 1984;10:1253-63) reported that 54% of patients who were not immunosuppressed died.

“Medical therapy, rather than surgery, is always the first line of therapy,” he said.


“Nearly any ocular inflammatory disorder requires chronic systemic steroids,” he said. “These diseases include Behcet’s disease, necrotizing scleritis and vasculitides, birdshot retinochoroidopathy, multifocal choroiditis and panuveitis, serpiginous choroidopathy, mucous membrane pemphigoid, and sympathetic ophthalmitis. Necrotizing scleritis is one of the top candidates for immunosuppression.”

Dr. Perez advised physicians to avoid

**References**

Dry eye cases increase in patients with sleep apnea

Research finds cases of disease increase with mask therapy, gender

By Lynda Charters; Reviewed by Cynthia Matossian, MD

THE INCIDENCE OF dry eye disease (DED) is higher in patients with obstructive sleep apnea treated using a continuous positive airway pressure (CPAP) device or other nasal mask therapy devices. There is also a gender component to this increased incidence of DED, with women with sleep apnea having a higher incidence.

“As eye care providers, we need to start asking our patients whether they use a CPAP device. Dry Eye Disease is prevalent among this subgroup,” said Cynthia Matossian, MD, who is in private practice in Doylestown, PA, and Hopewell, NJ. While the prevalence of DED is considered to be about 6.8% in US adults, the percentage of patients who have been diagnosed clinically with DED is less than half of that. The prevalence of DED among women is almost double that among men, i.e., 8.8% versus 4.5%, respectively. Generally, the prevalence rates increase with age, ranging from 2.7% in persons aged 18 to 34 years up to 18.6% in those 75 years and older, she explained.

Sleep apnea affects both men genders but is substantially among men, 13% to 14% compared with 5% to 6% among women, and the prevalence rates increased markedly from 1994 to 2010. Interestingly, the recommended treatment for sleep apnea is associated with ocular disorders, that is, ocular irritation caused by airflow from a leaky mask or retrograde nasolacrimal escape of air, she noted.

RETROSPECTIVE DESCRIPTIVE ANALYSIS

In light of the statistics, Dr. Matossian and colleagues analyzed data to identify any real-world associations between DED and sleep apnea. The investigators looked at data between Jan. 1, 2013, to June 30, 2018, from the IBM MarketScan Commercial and Medicare Supplemental Databases, both of which contain the inpatient/outpatient prescription drug experience among several million patients covered by a variety of insurance plans.

The study, which was sponsored by Sun Pharma, included adults if they had one or more claims of CPAP or other nasal mask device use during the study period, one or more inpatient/outpatient diagnoses of sleep apnea in the 12 months before the onset of device use, continuous enrollment in a medical or pharmacy insurance program for 12 months or longer before and after the first date of the study, and no diagnosis of DED in the 12 months before onset of device use.

A total of 330,926 patients (median age, 53 years) were included in the study, 65% of whom were men. Overall, 13,176 patients had DED. The most frequent patient comorbidities were diabetes (22%) and chronic obstructive pulmonary disease (COPD) (18%). The most frequently used medications were antihypertensives (58.2%), antidepressants (32.5%), and anxiolytics (31.3%).

Dr. Matossian and colleagues found important associations with the increased incidence of DED in this patient population with use of CPAP devices over time, age, duration of mask use, gender, and certain comorbidities. According to Dr. Matossian, the one-, two-, and three-year DED incidence rates after starting use of CPAP or another nasal mask device were, respectively, 4.0%, 7.3%, and 10.3%. The incidence of DED increased with age; the one-year incidence rates ranged from 1.6% in patients 18 to 24 years old and 11.2% in those aged 75 years and older. The one-year incidence rate in women was higher than in men, 5.6% compared with 3.0%. The presence of specific comorbidities made a difference, that is, the incidence of DED was higher in the presence of psoriasis, with an incidence of DED of 9.1%; COPD, 5.4%; irritable bowel syndrome, 5.3%; diabetes, 5.1%; and rheumatoid arthritis, 5.0%.

The findings were that the incidence of DED was exacerbated both during the second year of use of a device compared with the general incidence of DED among the general population of U.S. adults as well as based on the length of time during which the device is used. Users of the CPAP device who were women, older, or had comorbid inflammatory or metabolic conditions may experience a higher incidence of DED.

TAKE-HOME

• The incidence of dry eye disease increases in patients undergoing treatment for sleep apnea who use mask therapy.

INFECTIOUS KERATITIS

When treating infectious keratitis/keratitis, the potential algorithm is culturing, topical and/or systemic antibiotics and early surgery, which includes cryotherapy with conjunctival resection and antibiotic irrigation and perhaps subpalpebral lavage with an antibiotic or an antifungal with a corneal scleral patch graft.

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Dr. Perez has no financial interests in any aspect of this report.

PATCHING

(Continued from page 34)

jumping immediately to patching. He said it is important to first show how severe the necrotizing scleritis is and look for an infectious necrotizing scleritis. “Do not panic,” he said. “All scleral melts will look emergent, but surgical intervention may not be needed. Always culture the patient and biopsy if necessary.”

TO PATCH OR NOT TO PATCH

When considering surgery, the inflammation or infection must first be controlled. The scleral tissue used can be patch graft or the entire sclera, the latter of which is preferable.

To prepare a patch graft, Dr. Perez likes to use a template to draw the area of scleral necrosis and create a patch graft; healthy tissue must be present in order to suture the graft. The patch graft should be covered with conjunctiva or a mucous membrane graft. The former is the better approach, but in some cases the conjunctiva may have disintegrated.

Dr. Matossian has no financial interest in any aspect of this report.
In many instances, the word “new” can imply good, improved, or progressive, which are all positive attributes. When it is used in conjunction with bacteria, however, it could translate to the description of new drug-resistant microorganisms.

Endophthalmitis, one of the most feared diagnoses in ophthalmology, is often associated with cataract surgery (acute-onset postoperative endophthalmitis) and is caused by coagulase-negative staphylococci, Staphylococcus aureus, Streptococcus species, and gram-negative bacteria. Delayed-onset pseudophakic endophthalmitis is caused by Cutibacterium acnes (formerly called Propionibacterium acnes), coagulase-negative staphylococci, and fungi. Conjunctival filtering bleb-associated endophthalmitis results from Staphylococcus species, Haemophilus influenzae, and Staphylococcus species.

“This classification by etiology allows clinicians to predict the most likely causative organisms,” according to Harry W. Flynn Jr., MD, the J. Donald M. Gass Distinguished Chair and professor of ophthalmology, Bascom Palmer Eye Institute, Miller School of Medicine, University of Miami, during his delivery of the Jones/Smolin lecture.

Less common causes of endophthalmitis are posttraumatic cases (open globe injuries) caused by Bacillus species and Staphylococcus species; keratitis-associated cases caused by Pseudomonas and Staphylococcus; intravitreal injection–associated cases from Staphylococcus and Streptococcus; and endogenous cases from Candida species, S. aureus, and gram-negative species.

According to Dr. Flynn, a fairly consistent rate of moxifloxacin resistance (about 30% to 40%) has been observed at the Bascom Palmer Eye Institute from 1995 through 2018. He added that moxifloxacin is widely used as an intracameral antibiotic during cataract surgery but it provides inconsistent coverage for coagulase-negative staphylococci.

CHALLENGES IN ENDOPHTHALMITIS PROPHYLAXIS

Dr. Flynn said he has encountered a number of cases that were resistant to intracameral moxifloxacin but responded to vancomycin, which is the primary weapon for treating endophthalmitis. However, it is important to recognize that the minimum inhibitory concentration (MIC)90 rates for vancomycin are increasing.

Dr. Flynn also reported on 36 cases in the United States (1 referred to Bascom Palmer) and 23 in Europe. He described a case of hemorrhagic occlusive retinal vasculitis following cataract surgery in which intracameral vancomycin was used.

“This is an immune-mediated response to vancomycin that can cause this disease 7 to 10 days after cataract surgery,” he explained. “This can be a devastating delayed-onset complication.”

Dr. Flynn recounted the case of a patient in whom this complica-
tion developed 10 days after the first cataract surgery but who had undergone the second cataract surgery seven days after the first. The patient developed bilateral disease and hand motion vision in both eyes. At this point, vancomycin is no longer recommended as a prophylactic intracameral antibiotic.

Cefuroxime, an antibiotic used mostly in Europe, requires preparation at a compounding pharmacy in the United States. Dr. Flynn cited a report of 8 patients with endophthalmitis from Fusarium solani caused by contaminated intracameral cefuroxime solution used during cataract surgery.

Following vitrectomy with or without silicone oil and systemic antifungal therapy, the patients’ final visual acuities ranged from 20/100 to light perception.

**ANTIMICROBIAL CHALLENGES**

*Candida auris* is a relatively new pathogen that is resistant to multiple antifungal agents. Worldwide outbreaks have been documented, and the Centers for Disease Control and Prevention has placed it on the list of *Antibiotic Resistance Threats in the United States* report.

In the latest case in New York, a patient with immunosuppression developed endophthalmitis resulting from *C auris* and *Pseudomonas* and ultimately underwent enucleation. A multicenter study in India showed that resistance genes are prevalent in *C auris*; the pathogen can be resistant to multiple drugs. Moreover, 13% of organisms were multi-azole resistant and 8% were resistant to amphotericin B.

*Achromobacter xylosoxidans*, formerly referred to as *Alcaligenes xylosoxidans*, is a gram-negative motile rod that in culture resembles *Pseudomonas*. This pathogen, which may cause delayed-onset endophthalmitis after cataract surgery, responds to ceftazidime and imipenem.

*C acnes* can cause delayed-onset progressive indolent inflammation after cataract surgery. According to Dr. Flynn, removing the intraocular lens may be the best way to eliminate the infection.

Fortunately, the visual outcomes are generally good. *C acnes* has been associated with resistance genes; the mutants *S101L* and *S101W* are always associated with high resistance. He described a patient with *C acnes* endophthalmitis who underwent 2 failed vitrectomies. Later, removal of the entire capsular bag and intraocular lens resulted in elimination of the infection and postoperative vision of 20/25 with an aphakic contact lens.

The eyes can be successfully treated in most cases, but the visual outcomes are often poor. Methicillin-sensitive *S aureus* has a much better visual prognosis. *Trichosporon asahii* endophthalmitis can be devastating in patients who are immunocompromised.

**TAKE-HOME**

» There is still a lot to learn about the use of antibiotics prophylactically and in choosing the right drugs for specific infections.
Dr. Flynn recounted the case of a 37-year-old patient undergoing chemotherapy for acute lymphoblastic leukemia who developed pneumonia and fungemia. His vision decreased and vitreous debris and a subretinal lesion were seen in the right eye. Following 67 intravitreal voriconazole injections over 1 year and systemic micafungin and voriconazole administration, his final vision was 20/20 in the right eye at 1 year. The patient was managed by Royce Chen, MD, the Helen and Martin Kimmel Assistant Professor of Ophthalmology at Columbia University Medical Center and attending ophthalmologist at the New York-Presbyterian Hospital.

NEW TECHNOLOGY
Polymerase chain reaction (PCR) is an example of molecular technology that has evolved into a more clinically useful tool with increased sensitivity and specificity, rapid identification of etiologic agents, and detection of new and emerging pathogens.

According to Flynn, classic PCR technology had nonuniform standards, few commercial kits available, required skilled personnel, and was expensive. Next-generation sequencing, he noted, is more advanced technology utilizing both PCR and whole genome sequencing to identify pathogens causing ocular infections by using microbial DNA in vitreous specimens.

“We are now able to more rapidly and specifically identify the correct causative organism,” he said.

Next-generation sequencing has been reported to identify specific microbes rapidly in twice as many patients compared with traditional cultures (88% vs 44%, respectively). This technology may be very helpful in culture-negative cases in which delayed diagnoses may result in poor visual outcomes.

ANTIFUNGAL THERAPIES
Since 2000, numerous antifungal therapies have been introduced. Flynn and colleagues compared old and new antifungals against 17 Candida isolates.

“We found that voriconazole was still the top anti-fungal agent with an MIC90 of 0.03 µg/mL, followed by amphotericin B with an MIC90 of 0.12 µg/mL. In very severe fungal endophthalmitis cases, I use both agents,” he explained.

When Dr. Flynn and his colleagues undertook an extensive analysis of 47 exogenous fungal endophthalmitis isolates (mold and yeast) and susceptibilities to antifungal agents spanning a 20-year period, they found that voriconazole remained the most potent against these pathogens.

“Intravitreal voriconazole appeared to provide the broadest spectrum of antifungal coverage and may be considered for empiric therapy of endophthalmitis caused by yeast and most are molds (exception fusarium),” the investigators reported (Am J Ophthalmol 2015;159:257-64). Importantly, voriconazole is also the least toxic, Dr. Flynn pointed out.

The altered environmental pool of organisms in turn allows for selection of intrinsically resistant organisms and eventually evolution of more resistant strains, which then forces the use of more antibiotics.

“Obviously, we have a lot to learn about the use of antibiotics prophylactically and in choosing the right drugs for specific infections,” he concluded.

REFERENCES

ENDOPHTHALMITIS
(Continued from page 37)

‘The altered environmental pool of organisms in turn allows for selection of intrinsically resistant organisms and eventually evolution of more resistant strains, which then forces the use of more antibiotics and catches us in a vicious cycle.’

– Harry W. Flynn Jr., MD
IN THE RACE AGAINST GLAUCOMA, DURABILITY WINS

Glaucoma demands outcomes that endure. Results from the largest MIGS pivotal trial to date have shown that the Hydrus® Microstent delivers the greatest improvement compared to cataract surgery alone for IOP reduction and medication elimination at 24 months.1-4,*

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OCTA a hope for diagnosing, managing ophthalamic diseases

Technologies can help ophthalmologists treat challenging cases in young patients

By Lynda Charters; Reviewed by Leah Reznick, MD

Optical coherence tomography angiography (OCTA) may have a bright future in the care of pediatric patients with retinopathy of prematurity (ROP), amблиопия, and glaucoma, offering an increased understanding of disease pathophysiology and aiding in disease diagnosis and management.

OCTA is rapid and noninvasive technology that is advantageous for evaluating the complete microvascular (superficial and deep and choroidal microvascularity) in children. The images obtained are high-resolution, three-dimensional and cross-sectional images with quantifiable metrics. The downsides are the significant artifacts created by motion.

Fluorescein angiography (FA) and indocyanine green angiography (ICGA), both of which require dye injections, provide a wide field of view in contrast to the 30-degree field of view of OCTA and are better suited for evaluating ROP and low-flow vascular lesions. FA and ICGA are limited to visualizing superficial retinal circulation and choroidal vasculature, respectively.

Both types of imaging currently have their place for certain populations and diseases, according to Leah Reznick, MD, associate professor, Casey Eye Institute, Oregon Health Sciences University, Portland.

**OCTA OPTION**

Recent research has indicated the OCTA may be useful to manage ROP and provide a better understanding of how the disease affects the retinal anatomy later in the lives of affected children. OCTA was evaluated fairly recently in babies.

In one study, OCTA visualized hyperreflectivity that corresponded to recurrent extraretinal superficial and deep neovascularization seen on FA in a baby with type 1 ROP after laser treatment who required additional laser (J AAPOS 2016;20:271-278). Another study used a prototype swept-source (SS) OCTA that had been integrated into the operating room microscope and reported the first data from OCTA acquired intraoperatively in two patients (JAMA Ophthalmol 2017;135:483-486).

Neither method is practical for widespread use in ROP screening and diagnosis, but it demonstrates the potential of OCTA for assisting in the diagnosis and management of ROP," said Dr. Reznick.

According to Dr. Reznick, investigators at the Casey Eye Institute have developed a prototype handheld OCTA SS-OCT/OCTA for use in patients with ROP (JAMA Ophthalmol 2017;135:977-81).

"This technology has generated images that provide objective evaluation of ROP zone, stage, and plus disease," she said. "This handheld device is designed to provide a wider field of view from 40 degrees up to 100 degrees using a contact lens-based approach."

Dr. Reznick explained that the researchers, led by J. Peter Campbell, MD, MPH, achieved the wider field of view by adjusting the scanning pattern and tolerating some motion artifact. This technology demonstrates widespread perfusion into zone II and clinicians can see the corresponding retinal structure on OCT.

Another advantage of OCTA is that it can better detect neovascularization than can be accomplished during a clinical examination.

Dr. Reznick described the case of a baby treated with bevacizumab (Avastin, Genentech Inc.) for zone I stage 3 ROP in which the disease appeared on the surface to be clinically regressed; however, OCTA showed in cross-sectional images that there was residual flow above the internal limiting membrane near the border of the perfused and non-perfused retina.

The technology also can identify extraretinal neovascularization and monitor for disease recurrence. "In this way, OCTA can help diagnostically and determine future treatment," she noted.

The technology also can provide a look at the foveas in children with a history of ROP compared with those without ROP. A study published in Eye (Lond) (2019;33:1890-6) reported that 80% of subjects had been treated for ROP and had significantly smaller foveal avascular zones, increased central retinal thickness, and the foveal avascular zone area in the ROP group was associated with gestational age at birth and not birth weight.
A review of the literature showed that the research has focused on the size of the foveal avascular zone and the density of the superficial and deep capillary plexi to identify anatomic differences in eyes with amblyopia.

Small studies have recently reported some mixed results stemming from the different types of amblyopia. Most studies showed no difference in the size of the foveal avascular zone; however, a majority of the studies showed a decreased density of the superficial and deep capillary plexi in patients with amblyopia, she said.

The research suggested some areas for future study, namely, that there needs to be larger scale and prospective studies looking at the retinal microvasculature and foveal avascular zone of anisometropic and strabismic amblyopes to generalize this information and determine its clinical applicability.

Dr. Renick noted that it also raises the interesting question about whether the vascular changes are the cause or the effect of amblyopia.

For pediatric patients with ROP, amblyopia, and glaucoma, OCTA will help us understand underlying pathophysiology and aid in diagnosis and management of disease.’

- Leah Reznick, MD

OCTA IN AMBLYOPIA

‘For pediatric patients with ROP, amblyopia, and glaucoma, OCTA will help us understand underlying pathophysiology and aid in diagnosis and management of disease.’

- Leah Reznick, MD

OCTA AND PEDIATRIC GLAUCOMA

Does pediatric glaucoma work the same way as adult glaucoma?

Dr. Reznick noted that in adults blood flow in the peripapillary microvasculature is lost and that decreased blood flow is correlated with visual field loss.

A study performed at the Casey Eye Institute compared the vascular density in children with juvenile open-angle glaucoma (OAG) with healthy controls using OCTA.

The investigators reported that juvenile OAG patients have decreased peripapillary and macular perfusion (J AAPOS doi: https://doi.org/10.1016/j. jaapos.2019.08.160).

Dr. Reznick also point out that from this initial study, researchers have learned that OCTA use in children is feasible and its use is encouraging as a non-invasive diagnostic tool in children with glaucoma.

‘OCT and OCTA have changed the way we care for adults with a variety of retinal diseases and glaucoma,” she said. ‘For pediatric patients with ROP, amblyopia, and glaucoma, OCTA will help us understand underlying pathophysiology and aid in diagnosis and management of disease. We are in the infancy stage of understanding the applications of OCTA, and significantly more research needs to be performed to understand and validate its applications.”
COVID-19 ‘wake-up’ call: Unexpected advice for happiness from a wealth counselor

Crisis could ultimately prove to be a doorway to peace for your practice

Money Matters By John J., John S., and Traudy Grande, CFPs

UNEXPECTEDLY—SUDDENLY—THERE MAY COME like a thief in the night, a seemingly overwhelming and insurmountable crisis that threatens our very existence.

However, if examined carefully, this crisis can actually be a doorway to peace. At the time of writing this article—and I highly doubt things have changed before publication—our world as we have known it has been turned upside down, and what security we thought we once had, we are suddenly aware was only an illusion.

In a matter of weeks, our financial security, our businesses, our way of life, our world as we knew it, and even our very lives have become threatened.

My profession over the past several decades, blessedly, has been to counsel ophthalmologists around the country in planning for a successful financial life, and a carefree retirement.

My partners and I continue to work with doctors in all phases of their lives, from accumulating assets to withdrawing assets in retirement. Our job was always to plan carefully and prudently to achieve their goals with minimum risk. But, and perhaps because of the very nature of our business, we noticed that there was never a correlation between how much money a person had and how happy they were. This mystery compelled me to search out why this occurred.

So, this article is about our current crisis and happiness, or freedom from the terror of one’s own punishing thoughts.

I have seen it all, or at least I thought I had. But this current financial/health outlier-black swan event is one in which no one can give early predictions as to the impact on our world or domestic economies, or the very survival of our healthcare system. Our family’s and our very own mortality are actually called into question. From nowhere we are now faced with unprecedented challenges. And in many cases overwhelming fear of the unknown.

First, on the financial side, if you are in the accumulation phase of your career, nothing has changed. Unless this is the end of our financial systems as we have always known them, and that is highly unlikely, the companies you have invested in and loved are now at fire-sale prices, provided you are going to hold them long-term. Just keep saving and investing as you have been.

Uncertainty is the last thing Wall Street wants to see. Uncertainty is the last thing any of us wants to see, especially when it comes to our health or financial security. We have, as a team at Grande Financial Services, witnessed more than three decades of ups and downs in the market, and just about every geo-political event imaginable.

This most recent downturn, as severe as it has been, is something that we have not seen before. It is disconcerting, to say the least, to watch your investment holdings lose up to 30% of their value in one week.

However, and yes there is a however, even though we have not seen exactly this particular rapid spiral into a bear market, and a possible recession, we know how it has turned out in the past, which has always been to come back and advance further. This should be no different as the banks are strong and the government is giving its full accommodation to both the virus and the financial markets.

I have witnessed firsthand over the years that fear is the most dangerous emotion when it comes to investing. The feeling of watching your portfolio grow each year is pleasant and rewarding, but does not match the intensity and pain of watching your investments lose value. Presuming that you had a good financial plan laid out, and your exposure to stocks was not more than the absolute minimum risk you had to assume to achieve your financial goals, just stay the course.

You must remember that your stock portfolio represents a long-term strategy, and that you are not to panic and sell out because of fear. Selling out after a large decline in the markets is turning a paper loss into a real loss.

Then comes the problem of getting back before the markets turn upward, possibly as fast as they went down. This is the age of computer trading and things happen very fast, as we have just experienced. This particular downturn may well be the fastest and most severe to date. It gave few investors a chance to trim down their holdings as the markets were down considerably in just one week’s time.

For those ready to retire or in retirement now, it may be a good time to divide your expenses between essential and discretionary. Essentials must be paid, e.g. food, mortgages, property taxes, insurances, gas and electric, cars, etc. The discretionary side would be anything not essential, such as eating out, gifts, travel, etc.

When you calculate what the essential and discretionary costs are, you can divide each number by your investment net-worth, find what the percentage is, and stick to a budget that does not exceed this percentage.

As your portfolio goes down or up and, if the percentage is higher than planned, you may want to cut back on your discretionary spending until the portfolio has recovered again. This will preserve principal and the danger of creating a vicious cycle of depleting your savings when your withdrawal percentage keeps increasing as the portfolio goes down. There are many more strategies to be considered, which will be covered in future articles.

Some examples would be tax-harvesting losses by switching positions on the same day. Thereby, not missing a market upturn if one would occur, but locking in future loss carry-forwards. Also, repositioning portfolios that previously had too much gain to consider a move because of capital gains. There are actually many positive moves one could consider while we are experiencing these depressed markets. Of course, it is imperative that you consult with a tax professional before making these changes.

There is not enough space in this article to fully address the opportunity that presents itself for all of us, but I will give it a try. This shock to our daily lives, in my opinion, is a wake-up call.

It is a time to re-evaluate the reality of the mechanical lives most of us have been guilty of living. We plan and do and do so much every day that most of us miss being in the sacred
moments of being alive. Please excuse me for philosophizing, but the moment seems to call for it. I have watched it my whole career.

Professionals on a treadmill, always looking into the future for when things will really be good, trying to turn "what is" into "what should be"—thereby missing what joy is right in front of them. It is time to come down from our cluttered minds into our hearts and remember the innocence of our childhood. We are more than our money, our professional achievements, our pride. If we look deeper, and this terrible crisis is a perfect opportunity to do so, you will find a peace within you.

Instead of trying to control the future, which we now see we cannot, we can become more grounded in the preciousness of each moment. Just take a look at the fragility of life and what we thought was our security. What have we been missing in an attempt to achieve this illusion? I am not saying not to plan. I am saying to be fully alive while planning. Remember the love we are as human beings. Remember the kindness and compassion that we innately are. There is no such thing as security no matter how much planning we do. There is only now. I urge you, my friends of many decades, to embrace this opportunity to re-evaluate your priorities.

Yes, I said opportunity. Don’t miss it. This crisis will pass, but so will the gift of it to waking up to live the rest of your lives in gratitude and appreciation for each breath you take. Perhaps this sounds like strange advice from a wealth counselor, but I have always loved my profession and my clients and only want them to be whole in life. Integrating their knowledge, intelligence and success without needless suffering. I believe this is a wake-up call. May everyone stay safe.

EDITOR’S NOTE: The views depicted in this material are for information purposes only and should not be considered specific advice or recommendations for any individual. All investing involves risk, including the potential for loss. Past performance is not indicative of future results. No investment strategy can ensure a profit or protect against loss in a declining market.

Zeiss develops measures to protect employees, maintain business continuity

In light of the current situation created by the COVID-19 pandemic, Carl Zeiss Meditec Inc. is focusing on protecting its employees and ensuring smart business continuity to the greatest possible extent.

To continue supporting our customers and partners as best as possible, the company is doing everything it can to protect its employees’ health and safety, as well as maintain production in its plants, and ensure its service operations, the company said in a prepared statement.

In January, a dedicated task force was set up at Zeiss. It reports directly to the Executive Board and oversees the planning and management of the global measures in close collaboration with the regional and functional working groups.

The latest developments are closely assessed with government agencies and health-care authorities on an ongoing basis.

Zeiss also has launched a new website Zeiss Med Support Now. The site will provide easy access to continuing education programs and material, along with information about virtual symposia, interactive technology sessions and clinical insights from peers. Visitors will find guidelines for how to properly disinfect and clean Zeiss devices and how clinicians can order protective breath shields for slit lamps through the Zeiss donation program.

Zeiss said in the statement it would continue to be available for its customers. Some employees in individual areas are currently working remotely, but can still be reached on their usual phone numbers and email addresses.
Physicians can increase value, power when negotiating with payers

Ophthalmologists should find a health plan’s strategic initiatives, focus

By Jordan Rosenfeld

INCREASINGLY, PAYERS ARE adopting a take it or leave it approach in contracts with physicians in the value-based marketplace, putting physicians in a tough spot. What can physicians do to show their value and increase their power in negotiations?

Experts say physicians will have to get creative, by partnering with health plans to achieve common goals, and finding ways to grow market share—and leverage.

“It helps if you can position yourself as a partner versus a vendor,” said Joe Caruncho, JD, CEO of Genuine Health Group in Miami, a management company that helps physicians make the transition to value-based care.

BECOMING A PARTNER

Caruncho pointed out that physicians can achieve that partner status and increase their value by figuring out what the health plan’s strategic initiatives and focus are, and by offering to help the health plan achieve some goals in exchange for a better rate or shared profits.

“These days they are competing on quality measures,” Caruncho said. “It is not about [which payer] can provide the cost for the cheapest.”

Then, he said, the physician and the payer can work together to share in either cost savings or added revenues that result because the physician helped the plan increase its ratings, and as a result, its physicians may be getting more money from Medicare and/or more patients.

Caruncho described this idea of treating the physician payer partnership as “a paradigm shift” from simply expecting payers to pay money for services to one of joining forces with the payer to achieve better results, higher quality, and reduced costs.

“Having a relationship with a health plan where you share in the profits is a lot more lucrative while also practicing great medicine,” he said.

Joe Wagner, director of BRG’s Healthcare Performance Improvement practice, in San Francisco, agreed.
“One thing physicians can do is to demonstrate the ability to improve or work on quality measures that are important either to a commercial payer or to the government,” he said. Wagner explained that this can be done through such means as analytics that identify through their care experience patients that are important for outreach, and patient navigation hubs that direct patients to the right services.

“Patient navigation hubs allow the provider to do outreach with identified patients, where the physician dedicates resources to the important quality measures, schedules appointments based on those measures the program deems are important to quality care of patients and then conducts those services so you actually improve the overall care that has been delivered,” Wagner pointed out.

**TAP EXISTING LEVERAGE**

There are other scenarios where physicians may already have greater leverage than they realize or could build leverage through redesigning their practices.

“Plans need to be compelling to their purchasers, namely individuals and employers. If a health plan is missing a provider that makes it [not compelling], it may not be very viable in the marketplace,” said Adam Powell, PhD, president of Payer+Provider Syndicate, a management advisory and operational consulting firm in Boston.

In some instances a provider may have one of several advantages. First, he noted, the provider may be so highly regarded in a community that it would be difficult for the payer to attract patients to their plan without that provider network.

A provider may have what Dr. Powell called a “local monopoly,” which often happens in rural communities where there aren’t as many options, or a provider who is one of a few offering a specialized service within a certain area. In that case, Dr. Powell said, a health plan is likely to be compelled to contract with the provider because the payer needs to have access to their services in the domains with the monopolies.

Substantial market share gives the provider leverage, Dr. Powell said, because if that organization leaves the network due to failed negotiations with the payer,

“They all those members are going to have to change their family physicians, internists or PCPs and they’re not going to be happy,” he noted.

Since not all physician practices are going to meet either of these criteria, he says, another option is to merge with another provider organization in order to obtain a larger market share.

Dr. Powell explained that many of the small physician practices that have not gone out of business as a result of such pressures have been absorbed by larger entities, though the downsides are real, including loss of control over how medicine is practiced.

“If you have people merging their practices into group practices, there’s better coverage,” Dr. Powell said.

**SIDE HUSTLE**

Lower reimbursement amounts and tough negotiations with payers are pushing more physicians to practice differently in general, says Andria Jacobs, chief operating officer at PCG Software, which develops healthcare applications focused on cost containment, fraud and abuse detection, based in Las Vegas.

“It is a tough environment for physicians,” she says, based on polling done by such groups as the Medical Group Management Association. “Now we have so few payers it is an oligopoly, and the health plans have all the power. Physicians are really unhappy.”

They are also unhappy with the demands of managed care, from the authorization process to quality improvement measures and frustrations with their electronic health records.

As a result, she is seeing physicians either retiring or selling their practices to group practices, or having to get creative.

Other doctors are moving more toward direct pay and concierge options. Jacobs’ own physician has a membership program that ranges from $500 to $1500 per year that gives patients quicker and more consistent access to him.

“Otherwise he cannot stay in business,” she said. “You cannot run your practice like you did in the past where there was always enough money coming in.”

**DIRECT PAY SERVICES**

If negotiations with payers stall or remain unsatisfying, one option is to offer direct pay services to patients, either on the side or as part of a direct pay practice, according to Paula Muto, MD, a surgeon in private practice outside Boston. Dr. Muto founded UBERDOC, a direct pay, direct access healthcare platform.

“Doctors should realize who the payer actually is,” she said. “It is no longer the employer as the burden of payment has dramatically shifted to the patient because of high deductible plans. The patient is the payer.”

With patients facing increasingly higher deductibles they often do not meet in a given year, she sympathizes with their frustration at also receiving bills from their physicians. She believes that price transparency will bring an alternative to the system especially for lower cost routine care, leaving insurance for bigger, more catastrophic services.

“We need to think differently,” Dr. Muto concluded. “I am very excited about bringing the doctor and the patient back together.”

**Editor’s Note:** This article originally appeared in Ophthalmology Times® sister publication, Medical Economics®
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VERMONT

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The Division of Ophthalmology at the University of Vermont College of Medicine, in alliance with the University of Vermont Medical Center, is seeking an academic neuro-opthalmologist. This individual must have completed a board approved 3- or 4-year ophthalmology residency or a 3-year neurology residency and a clinical neuro-opthalmology fellowship, and be board certified or board eligible, and eligible for medical licensure in the State of Vermont. The successful applicant will be appointed at the Assistant/Associate Professor level in the Clinical Scholar Pathway, commensurate with years of experience and accomplishments.

Duties will include providing clinical care to neuro-opthalmology patients, teaching the principles of ophthalmology to medical students and undergraduate students in Allied Health programs, providing teaching experience for residents in training, developing basic and/or clinical research, and performing additional departmental and/or sectional administrative duties as assigned by the Chair of the Department of Surgery.

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Located in Burlington, the University of Vermont Medical Center serves as Vermont’s only academic medical center. Burlington is a vibrant community located on the shores of Lake Champlain, between the Adirondack and Green Mountains. With year-round recreational opportunities, safe communities and excellent schools, this progressive community has been frequently cited as one of the most livable cities in the U.S.

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

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

Interested individuals should apply online at https://www.uvmjobs.com/postings/32453 (position number 006035). Inquiries may be directed to Dr. Brian Kim c/o Kristin Allard at Kristin.Allard@uvmhealth.org.
ASSISTANT PROFESSOR/ASSOCIATE PROFESSOR
COMPREHENSIVE OPHTHALMOLOGIST

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

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

Located in Burlington, the University of Vermont and the University of Vermont Medical Center serve as Vermont’s only academic medical center. It is the only ACS verified Level 1 trauma center in the state and provides tertiary care to patients from Vermont and Northern NY. Burlington is a vibrant community located on the shores of Lake Champlain, between the Adirondack and Green Mountains. With year-round recreational opportunities, safe communities and excellent schools, this progressive community has been frequently cited as one of the most livable cities in the U.S.

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IMPORTANT PRODUCT INFORMATION

Caution: Federal (USA) law restricts this device to sale by, or on the order of, a physician. Indication: The NGENUITY® 3D Visualization System consists of a 3D stereoscopic, high-definition digital video camera and workstation to provide magnified stereoscopic images of objects during micro-surgery. It acts as an adjunct to the surgical microscope during surgery, displaying real-time images or images from recordings. Warnings: The system is not suitable for use in the presence of flammable anesthetics mixture with air or oxygen. There are no known contraindications for use of this device. Precautions: Do not touch any system component and the patient at the same time during a procedure to prevent electric shock. When operating in 3D, to ensure optimal image quality, use only approved passive-polarized glasses. Use of polarized prescription glasses will cause the 3D effect to be distorted. In case of emergency, keep the microscope oculars and mounting accessories in the cart top drawer. If there are any concerns regarding the continued safe use of the NGENUITY® 3D Visualization System, consider returning to using the microscope oculars. Attention: Refer to the User Manual for a complete list of appropriate uses, warnings and precautions.

The CONSTELLATION® Vision System can be connected to the NGENUITY® 3D Digital Visualization System. Please refer to the CONSTELLATION® Vision System user manual for complete instructions, warnings and precautions.