ASCRS and AAO Release Updated Joint Integrated Care Guidelines

The American Society of Cataract and Refractive Surgery (ASCRS) and the American Academy of Ophthalmology (AAO) released updated guidelines about when integrated care is appropriate in certain patients, according to a joint statement from the ophthalmic organizations. The revised statement[1] reportedly is the result of a 2-year discussion between the ASCRS and AAO to modify the original guidance first issued in 2000. The updated document reflects the standards-driven approach in which patients are managed in the current health care environment, and it emphasizes the role of the patient as the ultimate decision maker, with appropriate consideration for quality of care and patients' safety.

In the revised guidance, the ASCRS and AAO focus less on legal and ethical perils, while encouraging ophthalmologists to use professional judgment consistent with applicable ethics and law in interpreting and applying the guidelines to the particular circumstances of their individual practices.

The updated position paper

- Acknowledges that sharing management can serve patients' legitimate interests and can be done appropriately
- Is more appropriate for integrated care systems
- Improves and updates key definitions of terms such as *comanagement* and *transfer* and distinguishes between them
- Removes most references to legal and ethical perils
- Removes a prohibition against routine arrangements and instead emphasizes standards mutually agreed upon
- Adds three categories of circumstances that justify integrated care: barriers to patients' travel, the unavailability of an operating ophthalmologist, and patients' prerogatives
- Adds nine criteria for acceptable arrangements
- Strikes an explicit requirement for written consent and allows verbal consent with documentation

For more information, contact Nancey McCann, ASCRS director of government relations, at (703) 591-2220.

1. Ophthalmic Postoperative Care: a Joint Position Paper of the American Academy of Ophthalmology and the American Society of Cataract and Refractive Surgery. September 9, 2015. http://bit.ly/1UHNhLL. Accessed September 9, 2015.

Allergan to Acquire AqueSys

Allergan has entered into an agreement under which it will acquire AqueSys for $300 million, plus regulatory and commercialization milestone payments related to AqueSys' lead development programs, including the Xen45, according to a company news release.

"The acquisition of AqueSys is part of our larger commitment to being a best-in-class company within eye care, and more specifically with respect to glaucoma," Brent Saunders, president and CEO of Allergan, said in an interview with *Glaucoma Today*. "We have a broad portfolio of pharmacological solutions in glaucoma, and we have some really interesting projects in R&D, most notably bimatoprost (Lumigan) SR, but as we look at the treatment of this disease, it's important to look at more dropless therapies, and by adding a [microinvasive glaucoma surgery] implant to our portfolio, it allows us to have a full range of solutions for physicians and patients with glaucoma."

The acquisition of AqueSys provides Allergan with the Xen45, a soft shunt that is implanted in the subconjunctival space in the eye through a minimally invasive procedure with a single-use, preloaded proprietary injector. The proprietary Xen45 technology facilitates aqueous fluid flow to lower IOP while protecting against the potential for hypotony that is associated with current subconjunctival procedures, according to Allergan.

"We currently have a few drugs on the market for glaucoma, most notably drugs like Alphagan (brimonidine tartrate), Lumigan (bimatoprost), and Combigan (brimonidine tartrate/timolol maleate)," Mr. Saunders said. "When we look at some of the more significant issues that patients with glaucoma face, it has to do with compliance on therapy, or meeting goal of IOP reduction. Many patients are not meeting goal, or they're failing to comply. The combination of our own bimatoprost SR as well as now adding the AqueSys Xen45 into our portfolio gives us the additional complementary products that are dropless, and that will solve for both compliance as well as the potential for reducing pharmacological intervention for those patients not meeting goal."

The Xen45 has received CE Mark approval in the European Union, where it is indicated for the reduction of IOP in patients with primary open-angle glaucoma when previous medical treatments have failed. The CE Mark allows treatment in conjunction with a cataract procedure

Online Survey Results July/August 2015

Do you currently use a team approach to glaucoma management involving MDs and ODs?
Yes 60%
No 40%

or as a standalone procedure. The implant is also approved for use in Turkey, Canada, and Switzerland. AqueSys is pursuing reimbursement in these countries. In the United States, the Xen45 is in late-stage development, with the final US investigational device exemption clinical trial fully enrolled in the second quarter of 2015. Final approval by the FDA is expected by late 2016 or early 2017, according to Allergan.

Pending regulatory approvals, Allergan anticipates closing the transaction in the fourth quarter of 2015.

To see Allergan President and CEO Brent Saunders talking about the acquisition of AqueSys, visit EyewireTV: eyewiretoday.com/tv/eyewiretv-mdash-breaking-industry-news-from-the-escrs-meeting-in-barcelona.

Update on Rhopressa and Roclatan

Aerie reported the results of its second phase 3 trial for Rhopressa, a novel once-daily, triple-action eye drop being tested for its ability to lower IOP in patients with glaucoma or ocular hypertension.

When dosed both once and twice daily, Rhopressa achieved its primary efficacy endpoint of noninferiority compared to twice-daily timolol, according to a news release. The primary efficacy endpoint evaluated subjects with pre-study baseline IOPs ranging from above 20 to below 25 mm Hg. Rhopressa also reportedly demonstrated a consistent level of IOP lowering across all baseline IOPs and throughout the 90-day efficacy period.

The most common adverse event was hyperemia, which was increased in 35% of patients and was scored as mild for 83% of patients dosed once daily. According to the company, the adverse event profile for this arm of the trial was consistent with the results of Rocket 1. Rhopressa dosed twice a day generated a higher incidence of adverse events and was slightly more efficacious when dosed once daily.

Based on these results, Aerie said it expects to file a new drug application for Rhopressa in mid-2016.

"Clinicians have been waiting for an IOP-lowering product that targets the diseased tissue," Richard A. Lewis, MD, Aerie's newly appointed chief medical officer, said in the news release. "None of the treatments currently in the market have this unique function. The Rhopressa efficacy data we see in these Rocket 2 results point to a potential breakthrough for our glaucoma patients."

Dosing commenced for the first patients enrolled in Mercury 1, the company's first phase 3 registration trial of Roclatan, a novel once-daily, quadruple-action fixed-dose combination of Rhopressa and latanoprost. Roclatan is being tested for its ability to lower IOP in patients with glaucoma or ocular hypertension. Aerie said it expects to enroll approximately 690 patients in this three-arm 1-year safety study with a 90-day efficacy readout.

The clinical endpoint of Mercury 1 compares Roclatan for superiority over each of its two components, with all three arms dosed once daily. The range for the primary endpoint evaluates patients with maximum baseline IOPs ranging from above 20 to below 36 mm Hg. Aerie plans to report the 90-day efficacy results in approximately 1 year.

CenterVue Launches Compass Fundus Automated Perimeter

CenterVue released its Compass Fundus Automated Perimetry system in the United States at the Vision Expo West Symposium in Las Vegas at the XXXIII Congress of the European Society of Cataract and Refractive Surgeons in Barcelona, Spain, according to a news release. The platform recently gained 510(k) premarket approval for marketing from the FDA.

According to the company, Compass is the first fundus automated perimetry system capable of providing both standard 24-2 visual field results and true color confocal images of the retina. Compass' real-time retinal tracking, acquired at a rate of 25 images per second, allows precise monitoring of eye movements during visual field testing with corresponding compensation prior to stimulus projection, according to CenterVue. Reportedly with this device, automatic refraction compensation conveniently eliminates the need for a trial lens correction during testing.

Significant IOP Reduction With Ab Interno Canaloplasty

Ellex Medical said it will share the preliminary 6-month case series results for ab interno canaloplasty, known as ABiC at the upcoming European Society of Cataract and Refractive Surgeons annual meeting in Barcelona, Spain.

According to Ellex, ABiC restores the function of the eye's natural outflow system without the need for a scleral incision and is the only minimally invasive glaucoma surgical procedure that successfully and comprehensively

addresses all aspects of potential outflow resistance. The company says this procedure is a simple and quick adjunct to cataract surgery, which conserves the clinically proven benefits of 360º viscodilation of Schlemm canal provided by traditional canaloplasty but via a clear corneal incision.

Based on the preliminary 6-month results of a case series by Mark J. Gallardo, MD, ABiC achieved a significant reduction in IOP of 38% (ie, a reduction of 8.5 mm Hg to achieve an average IOP of 13.3 ±3.2 mm Hg). Additionally, ABiC decreased patients' mean number of glaucoma medications by 50% (from 2 to 1) 6 months postoperatively. Of the 32 patients who reached the 6-month follow-up, 17 recorded a mean IOP of 12.1 ±2.1 mm Hg and no longer required IOP-lowering medication. The average IOP reduction was 44% (ie, a reduction of 9.7 mm Hg) in more than half of the cohort that was also completely off glaucoma medications after this procedure. Patients who underwent selective laser trabeculoplasty prior to ABiC had achieved an average IOP reduction of 65% (ie, a reduction of 12.8 mm Hg with an average IOP of 13.2 ±2.4 mm Hg) at 6 months, in addition to a 33% reduction in medication use.

Patent to Provide Broad Coverage for Steroid Delivered With Iontophoresis

Eyegate Pharmaceuticals received a Notice of Allowance from the US Patent and Trademark Office for a patent application related to its lead product candidate, EGP-437, according to a news release. The patent covers a method of treating eye conditions using EyeGate's proprietary dexamethasone phosphate pharmaceutical formulation delivered by ocular iontophoresis. The patent is not limited to any particular eye condition or to a particular iontophoretic device or method; rather, it is directed at the delivery of this formulation through iontophoresis.

EGP-437, EyeGate's first product in clinical trials, incorporates a reformulated topically active corticosteroid, dexamethasone phosphate, that is delivered into the ocular tissues with the company's proprietary EyeGate II Delivery System. EGP-437 is being evaluated for the treatment of noninfectious anterior uveitis and macular edema.

Glaukos Completes Patient Enrollment in US Pivotal Clinical Trial for iStent Inject

Glaukos completed patient enrollment in its pivotal FDA investigational device exemption (IDE) trial for the iStent Inject Trabecular Micro-Bypass Stent, according to a news release. The device relies on a similar fluidic method of action as the company's iStent Trabecular Micro-Bypass Stent, which was approved by the FDA in 2012. The iStent has been shown to lower IOP in adult cataract patients with mild to moderate open-angle glaucoma.

The iStent Inject is composed of a microneedle that is preloaded with two stents and driven by an auto-inject mechanism for predictable and facile implantation. The device is designed to enable ophthalmic surgeons to inject stents into multiple locations of the trabecular meshwork through a single corneal entry point. The iStent Inject is approximately one-third the size of the iStent, which Glaukos believes is the smallest device ever approved by the FDA.

The prospective, randomized, multicenter clinical trial includes approximately 40 sites and 500 subjects randomized to undergo either implantation of the iStent Inject in combination with cataract surgery or cataract surgery alone. The subjects will be observed for 2 years, with a primary endpoint of a 20% or greater reduction in IOP from baseline. The results of the trial are expected to form the basis for the company's future premarket approval submission to the FDA, the news release said.

The iStent Inject is already approved for commercial use in the European Union, Australia, and Canada, and Glaukos is currently conducting an initial commercial launch of the iStent Inject in Germany. In addition to conducting an iStent Inject US IDE pivotal trial in combined cataract procedures, Glaukos is also conducting an initial US IDE clinical trial to evaluate a second version of the iStent Inject to be used as a standalone procedure in glaucoma patients who are not undergoing concurrent cataract surgery. The objective of this version of the iStent Inject is to make microscale injectable therapy a viable option for a much larger segment of the patient population with open-angle glaucoma.

Iridex Offers iCare Tonometer

Iridex added a tonometer to its suite of commercial products for the global glaucoma market, according to a news release. The new device comes to Iridex through a distribution agreement with iCare Finland, a subsidiary of the Revenio Group, the creator of the iCare tonometer.

The tonometer complements the company's laser platform, Cyclo G6, and its family of single-use disposables as well as the IQ 532 for MicroPulse laser trabeculoplasty. The tonometer includes a disposable device that measures IOP.

Iridex said its sales force has been trained in the use of the tonometer and has begun selling the device globally.

Software Detects Early Stages of Glaucoma

Researchers from the Indian Institute of Science have developed software that can detect glaucoma in its early stages, according to a news release. The investigators

claim that the software is an automated prescreening tool that processes fundus images and is capable of detecting glaucoma with about 90% accuracy.

The software rapidly analyzes hundred of fundus images, which can be obtained with low-cost camera devices fitted onto smartphones as well as tabletop or handheld cameras. The software calculates the cup-to-disc ratio from the fundus images and uses the cup-to-disc ratio and other parameters to classify glaucoma as mild, moderate, or severe. The researchers reportedly are currently converting the software to an Android app.

Short-Duration Chromatic Pupillometry Test May Detect Glaucoma

In glaucomatous eyes, reduced pupillary responses to high-irradiance blue light were associated with greater visual field loss and optic disc cupping, according to a study in *Ophthalmology*.[1]

The cross-sectional study included 161 healthy controls recruited from a community polyclinic (55 men; 151 ethnic Chinese) and 40 patients with primary open-angle glaucoma (POAG) recruited from a glaucoma clinic (22 men; 35 ethnic Chinese) who were 50 years of age or older.

Subjects underwent monocular exposure to narrow-band blue light (469 nm) or red light (631 nm) using a modified Ganzfeld dome. Each light stimulus was increased gradually over 2 minutes to activate sequentially the rods, cones, and intrinsically photosensitive retinal ganglion cells (ipRGCs) that mediate the pupillary light reflex. The investigators used an infrared pupillography system to record pupillary diameter. They compared pupillary responses to blue and red light between control subjects and POAG subjects by constructing dose-response curves across a wide range of corneal irradiances (7-14 log photons/cm^2 per second). In patients with POAG, pupillary responses were evaluated relative to standard automated perimetry testing (Humphrey Visual Field; Carl Zeiss Meditec) and scanning laser ophthalmoscopy parameters (Heidelberg Retinal Tomograph; Heidelberg Engineering).

According to the study, the pupillary light reflex was reduced in patients with POAG only at higher irradiance levels, corresponding to the range of activation of ipRGCs. Pupillary responses to high-irradiance blue light was associated more strongly with disease severity compared with responses to red light, with a significant linear correlation observed between pupillary diameter and Humphrey visual field mean deviation ($r = -0.44$; $P = .005$) as well as Heidelberg Retinal Tomograph linear cup-to-disc ratio ($r = 0.61$; $P < .001$) and several other optic nerve head parameters.

"Our study provides proof of concept that a short-duration chromatic pupillometry test can be used to assess loss of ipRGC function associated with POAG," the investigators said. "In POAG, a short chromatic pupillometry test that evaluates the function of ipRGCs can be used to estimate the degree of damage to retinal ganglion cells that mediate image-forming vision. This approach could prove useful in detecting glaucoma."

1. Rukmini AV, Milea D, Baskaran M, et al. Pupillary responses to high-irradiance blue light correlate with glaucoma severity. *Ophthalmology*. 2015;122(9):1777-1785.

Genetic Interaction May Offer New Therapeutic Approach for Glaucoma

Scientists at the University of California, San Diego School of Medicine have identified a genetic interaction that may be a new therapeutic target for treating glaucoma, according to a study in *Molecular Cell*.[1]

According to the study, variants of gene *SIX6* boost expression of p16INK4a, which in turn accelerates senescence and death of retinal ganglion cells. *SIX1-SIX6* and p16INK4a, are strongly associated with primary open-angle glaucoma. *SIX6* is required for proper eye development, and p16INK4a irreversibly arrests cell growth.

"We also show that high intraocular pressure in glaucoma increases expression of p16INK4a, making it a key integrator of inherent genetic and environmental risk factors that can result in glaucoma," principal investigator Kang Zhang, MD, PhD, said in an interview with Science Daily.[2]

The study's findings suggest that inhibiting p16INK4a could offer a new therapeutic approach for glaucoma, which is currently treated by drugs that lower IOP.

"Although lowering intraocular pressure can slow worsening of the disease, it does not stop it and prevent further cell death or possible blindness," coauthor Robert N. Weinreb, MD, said.

The authors noted that earlier studies in mouse models have shown that selective elimination of p16INK4a-positive senescent cells can prevent or delay age-related tissue deterioration.

The investigators told Science Daily that "the next step is to conduct preclinical studies to assess the efficacy and safety of antisense oligonucleotides—strands of synthesized DNA or RNA that can prevent transfer of genetic information—which might inhibit p16INK4a expression and prevent worsening of glaucoma. If effective, the researchers said they might consider a human trial in the future. ■

1. Skowronska-Krawczyk D, Zhao L, Zhu J, et al. P16INK4a upregulation mediated by SIX6 defines retinal ganglion cell pathogenesis in glaucoma. *Mol Cell*. 2015;59(6):931-940.
2. LaFee Scott. Identified genetic interaction offers possible new target for glaucoma therapy. *Science Daily*. September 10, 2015. http://www.sciencedaily.com/releases/2015/09/150910131759.htm. Accessed September 21, 2015.