In the last two decades, advances in ophthalmology and visual sciences have occurred in leaps and bounds. There are new treatment modalities and different diagnostic management for specific conditions necessitating expensive lasers and other equipment. These advances coincided with innovations in computer imaging and software analyses. As the pathophysiology of different eye conditions are better elucidated and the natural course better understood, specific algorithms have been constructed leading to artificial intelligence that provided more objective measures for diagnosis and monitoring. It is appropriate that these innovations be discussed to update the ophthalmic community of their existence and their role in medical practice.

To provide such a forum, many international meetings have included a section on updates in clinical practice that also discusses problems and controversies. These meetings generally synthesize the current trends and problems in ophthalmology, usually ahead of published studies and reports. In recognition of this, we have included a section on updates and controversies that will provide summaries of new developments in any field in ophthalmology and visual sciences and controversies in the diagnosis and management of specific diseases.

The topics included in this issue were recently debated at the 2nd Asia-Pacific Glaucoma Congress held in Hong Kong in September of this year. These topics were discussed by members of the Philippine Glaucoma Society.

Should Anterior Segment Imaging Devices Replace Gonioscopy?

Discussion by Jovell Ian M. Peregrino, MD and Edgar U. Leuenberger, MD

Glaucoma will continue to be the leading cause of irreversible blindness worldwide.[1,2] A recent meta-analysis done by Tham and coworkers projected an increase of 74% in the total number of people with glaucoma, from 64.3 million in 2013 to 76 million by 2020, and to 111.8 million by the year 2040.[2] With this recent forecast, Asia will have the greatest number of both primary open angle glaucoma and primary angle closure glaucoma (PACG), comprising 18.8 million (79.8%) and 9 million (58.4%) respectively.[2] Since half of the world's PACG will come from Asia, an effective reduction in the real incidence and prevention of visual loss from this devastating disease will depend on the accurate assessment of the anterior chamber angle and early detection of appositional closure.[3]

Advances in imaging technology make it possible to visualize and analyze the anterior segment structures including the angles in an objective manner. Proponents claim that anterior segment imaging devices show reproducible and reliable measurements contributing to a sound diagnosis. Given this modern-day reality, will gonioscopy become obsolete?

Yes, anterior segment imaging can replace gonioscopy.

The kind of goniolens used and the amount of visible light greatly affect the accuracy of gonioscopy. For instance, a Goldmann-type lens has a diameter that is larger than the cornea; as such, inadvertent application of pressure on the limbus or central cornea can alter the angle morphology and appearance with a resultant risk of non-detection of narrow angles.[3,4] Leaving the room lights on and allowing the slit-lamp light to constrict the pupil can make narrow angles look more open. Furthermore, gonioscopy is skill-dependent and is interpreted using several angle-grading schemes.[5,6] Not surprisingly, such variables make room for inconsistencies, disagreements, and ultimately, confusion among clinicians. Lastly, as gonioscopy requires corneal contact, it poses a higher risk of infection and accidental corneal abrasion leading to heightened stress and anxiety among patients.

In contrast to gonioscopy, several imaging

Philipp J Ophthalmol 2014;39:94-100

modalities can image the anterior chamber angle at a higher resolution and deeper penetration. These include the Eyecam by Clarity Medical Systems, ultrasound biomicroscope (UBM), anterior segment time-domain optical coherence tomography (TD-OCT) Visante by Carl Zeiss Meditech, spectral-domain optical coherence tomography (SD-OCT) RTVUE by Optovue, Spectralis by Heidelberg Engineering, and lastly, the swept-source optical coherence tomography (OCT) Casia by Tomey.[6]

The Eyecam, which was originally designed for imaging pediatric fundi with posterior segment diseases, was modified to allow for high-quality direct and colored images of the angles.[3] It provides panoramic visualization that correlates well with gonioscopy in angle closure detection, making it also a good learning tool for patients.[7]

The UBM acquires real-time images of the eye at a high frequency of 50 MHz. It has axial and vertical resolutions of 50 and 25 um respectively, and can penetrate through opaque media and structures. Hence, it is possible to visualize the anterior segment even in the presence of dense corneal opacities. Another advantage of the UBM over gonioscopy is that it allows examination of structures behind the iris, such as the ciliary body and zonules. As such, mechanisms of angle closure such as pupillary block, plateau iris, and iridociliary cyst can be justified with a high degree of certainty.[3,5,6,8]

Anterior segment OCT (AS-OCT) uses low-coherence interferometry to measure the delay and intensity of light reflected from tissue structures, and includes both TD-OCT and SD-OCT. Of the two, the SD-OCT captures images at a faster scanning speed of 26,000 to 40,000 A-scans per second with an axial resolution of 5um. The TD-OCT has an axial resolution of 18um at 2,000 A-scans per second. In contrast to gonioscopy where visible light is needed to visualize the angles, the AS-OCT allows evaluation of the degree of iridotrabecular contact both in the presence or absence of light.[3,5,6,9] It is also useful in monitoring the clinical outcomes of goniosynechialysis and laser iridectomy or iridoplasty procedures. A strong point of the Casia swept-source OCT is its ability to provide a panoramic image of the angles, which facilitates measurement of the degree of peripheral anterior synechiae involvement.[10] Non-contact quantitative and qualitative measurements of the angles and anterior chamber depth are taken via built-in software with the patient in an upright position, making for a fast and easy procedure.[3] In a study by Sakata and associates, gonioscopy paled in comparison to the TD-OCT in the detection of closed angles, especially in the superior and inferior quadrants.[11]

No, gonioscopy is still indispensable.

Despite advances in anterior segment imaging, gonioscopy continues to hold its place as the preferred reference standard for assessing anterior chamber angle configuration and structures. This is largely due to its unique application in differentiating appositional from synechial closure through indentation gonioscopy.

Unlike anterior segment imaging devices, gonioscopy also allows the clinician to detect angle neovascularization, abnormal pigmentation, ghost cells, iridodialysis, hyphema, and angle recession in a manner that is quick, convenient, and inexpensive.[6]

The imaging devices discussed earlier have a downside in comparison to gonioscopy. The Eyecam can only acquire qualitative measurements and may have difficulties discerning angle structures if the trabecular meshwork is lightly pigmented. It is inconvenient, requires the patient to be in a supine position, requires more office space, and is expensive. Furthermore, the bright light used during the procedure may alter the normal behavior of the angles.[3,6] The UBM is operator-dependent, inconvenient, with the patient in supine position, and has the discomfort of a saline bath in contact with the cornea with additional risk for abrasions and infection.[3,5,6,8] The saline bath may also cause inadvertent indentation that may alter the image of the angles. Lastly, AS-OCT has limited visualization of the structures posterior to the iris.[3,5]

CONCLUSION

Anterior segment imaging has been upgraded by new devices with advanced technology that ensure objectivity, reproducibility, rapid image acquisition, image storage, and quantitative analysis, even through opaque corneas. However, each device has its own limitations that need to be addressed. Gonioscopy remains to be the standard for anterior chamber examination when done with proper skill and knowledge. Both old and new devices serve patients best as complementary learning and management tools, especially in challenging cases.

REFERENCES

1. Cheng JW, Zong Y, Zeng YY, Wei RL. The prevalence of primary angle closure glaucoma in adult Asians: a systematic review and meta-analysis. *PLoS One* 2014;9:e103222.
2. Tham YC, Li X, Wong TY, et al. Global prevalence of glaucoma and projections of glaucoma burden through 2040: A systematic review and meta-analysis. *Ophthalmology* 2014;121:2081-2090.
3. Quek DT, Nongpiur ME, Perera SA, Aung T. Angle imaging: advances and challenges. *Indian J Ophthalmol* 2011;59 (Suppl):S69-S75.
4. Friedman DS, He M. Anterior chamber angle assessment techniques. *Surv Ophthalmol* 2008;53:250-273.
5. Quek DT. Innovations in angle imaging. Is gonioscopy obsolete? *CME Newsletter* 2013;August 11.
6. Stuart A. Imaging the angles: anterior segment techniques. *Indian J Ophthalmol* 2011;59:869-875.
7. Perera SA, Baskaran M, Friedman DS, et al, Use of EyeCam for imaging the anterior chamber angle. *Invest Ophthalmol Vis Sci* 2010;51:2993-2997.
8. Barkana Y, Dorairaj SK, Gerber Y, et al. Agreement between gonioscopy and ultrasound biomicroscopy in detecting iridotrabecular apposition. *Arch Ophthalmol* 2007;125:1331-1335.
9. Leung CK, Weinreb RN. Anterior chamber angle imaging with optical coherence tomography. *Eye (Lond)* 2011;25:261-267.
10. Li H, Jhanji V, Dorairaj S, et al. Anterior segment optical coherence tomography and its clinical applications in glaucoma. *J Current Glau Prac* 2012;6:68-74.
11. Sakata LM, Lavanya R, Friedman DS, et al. Comparison of gonioscopy and anterior segment ocular coherence tomography in detecting angle closure in the different quadrants of the anterior chamber angle. *Ophthalmology* 2008;115:769-774.

Should Slow-release Glaucoma Medications Replace Eye Drops?

Discussion by Patricia M. Khu, MD, MS

Instilling glaucoma eye drops has been the mainstay in glaucoma management for many years, be it as initial treatment or as adjunct to laser or filtering surgeries. There are different classes of glaucoma eye drops, with different mechanisms of action to lower the intraocular pressure (IOP), either by improving the outflow facility or by suppressing the aqueous production, singly or as combination therapy. Many of these eye drops can lower the IOP by as much as 35% when given either once or twice a day. Successful treatment outcomes for chronic diseases such as glaucoma, however, require daily use of glaucoma eye drops to minimize disease progression.

To maximize the efficacy of glaucoma eye drops and achieve a high concentration inside the eye requires correct placement of the drop onto the eye, the correct number of administration per day, and the correct time interval between multiple dosing of multiple medications. It also requires diligence and manual dexterity, which many patients find challenging.

Topical eye drops penetrate the cornea but less than 1% reaches the aqueous.[1] Hence, many with glaucoma require multiple eye drops, especially those with advanced disease that necessitate much lower target IOPs. Glaucoma drops also have ocular and systemic side effects that increase with more frequent instillation. Because of the side effects and the inconvenience of frequent instillation, compliance to the prescribed regimen suffers. Moreover, diseases that are asymptomatic, such as glaucoma, are more prone to poor patient adherence and persistence.[2-4] And patients with poor glaucoma medication adherence have been shown to have a higher rate of visual loss.[5,6]

Adherence is a measure of the degree to which the patient followed the prescribed instructions during a defined time period.[2] For prostaglandin that is instilled once a day, the adherence rate over time was 70%; and for medications with twice a day dosing, 54%.[2-4] Persistence, on the other hand, is a measure evaluating the time until the patient first discontinued the use of the eye drop.[2] Several studies have shown that persistence with initial glaucoma medications was as low as 33% to 39% at 1 year.[2-4]

A successful glaucoma management requires minimizing IOP fluctuations and flattening the diurnal curve over the long term. What are, therefore, some of the factors that can cause fluctuating IOPs? Varying efficacies of different medications and their bioavailability inside the eye, specifically to the target site, can cause variable IOPs throughout the day. Improper instillation techniques can also reduce the ocular bioavailability and increase the incidence of systemic side effects. Prolonged fluctuating IOPs or the inability to flatten the diurnal curve over the long term can lead to disease progression.[5-7]

What then are the ideal qualities for a glaucoma drug delivery system? Lavik and coworkers[8] identified the following characteristics: 1) sustained drug delivery to the desired segment of the eye; 2) ability to tailor the drug delivery to the natural progression of the disease; 3) achieve high ocular drug bioavailability; 4) improve local drug activity without causing systemic side effects or complications at the site of administration; 5) non-invasive or minimally invasive drug administration without interfering with vision; and 6) safe, non-toxic drug delivery platforms while ensuring patient acceptance.

While topical eye drops and gels have been the mainstay in glaucoma therapy for decades, the last few years have seen the development of other forms of delivery systems, such as inserts, contact lenses, punctual plugs, liposomes and nanospheres, surgical implants, and injectable systems. They have the capability of delivering the glaucoma drug for several weeks to several months with the intention of reducing the frequency of instillation, improving compliance, and reducing side effects. These slow-release medications are undergoing clinical trials, but should they eventually replace glaucoma eye drops?

Yes, slow-release glaucoma medications should replace eye drops.

Many studies have shown the beneficial effects of lowering the IOP in glaucoma to halt the progression of the disease. The Advanced Glaucoma Intervention Study (AGIS)[9,10] demonstrated that every 1 mmHg higher IOP fluctuation was associated with a 30% higher odds of developing progression. Moreover, eyes with IOP fluctuation less than 3 mmHg remained stable over time, while those with IOP fluctuation greater than or equal to 3 mmHg demonstrated significant progression. This means that it is not enough to lower the IOPs intermittently. To minimize disease progression and possibly effect an improvement in areas of the visual field not yet totally destroyed, a sustained lowering with flattening of the diurnal curve is needed. Adherence and persistence with chronic eye drop therapy is crucial to prevent disease progression.[2,4]

To address this problem, several novel drug delivery systems were developed. They are capable of releasing drugs for several days to several months. Examples of these delivery systems include ocular inserts placed in the lower or upper cul-de-sac of the eye[11], punctual plugs inserted into the lower punctum blocking tear drainage and capable of delivering drugs for 180 days[1], and liposomes which are biocompatible nanocarriers that allow delivery of the drugs for up to 120 to 180 days.[12-14] Some of these devices have completed phase II clinical trials with promising results and manageable side effects.They are well tolerated by patients, providing constant delivery of the glaucoma drugs with resultant persistent lowering of the IOPs.

No, slow-release medications should not replace eye drops.

The concept of a drug reservoir underlies all the newer delivery systems. Sustained release of glaucoma drugs by these reservoirs has been problematic, foremost of which is the control of the release. If the release is too slow, there would be under dosing, and if the release is too rapid, there would be overdosing and increased side effects, some of which can be very serious.

Ocular inserts have been developed that can deliver drugs over multiple days, and the best known and much studied is the Ocusert system delivering pilocarpine for 7 days.[11] Common complaints from patients were difficulty of insertion that required manual dexterity, discomfort, and the insert falling out. Other implants require injection into the vitreous or subconjunctival space which may not be acceptable to patients.[8,12] The punctal plugs and the contact lenses can deliver medications for several weeks but need further improvements in the design to deliver drugs at a constant rate without causing any discomfort or local side effects.[8]

CONCLUSION

There are many effective topical medications currently available for treating glaucoma. However, their clinical efficacy is limited by inefficient delivery systems resulting in poor target bioavailability, increased systemic absorption and side effects, and poor patient adherence.[8] Several slow-release glaucoma medications with improved delivery systems are currently undergoing further studies and provide promise for better patient outcomes. They are options to patient care, but at this time cannot yet replace eye drops.

REFERENCES

1. Gooch N, Molokhia SA, Condie R, et al. Ocular drug delivery for glaucoma management. *Pharmaceutics* 2012;4:197-211.
2. Nordstrom BL, Friedman DS, Mogaffari E, et al. Persistence and adherence with topical glaucoma therapy. *Am J Ophthalmol* 2005;140:598-606.
3. Tsai T, Robin AL, Smith JP. An evaluation of how glaucoma patients use topical medications: a pilot study. *Trans Am Ophthalmol Soc* 2007;105:29-33.
4. Schwartz GF and Quigley HA. Adherence and persistence with glaucoma therapy. *Surv Ophthalmol* 2008;53 (Suppl 1): S57-S68.
5. Kwon YH, Kim YI, Pereira ML, et al. Rate of optic disc cup progression in treated primary open-angle glaucoma. *J Glaucoma* 2003;12:409-416.
6. Quigley HA, Tielsch JM, Katz J, Sommer A. Rate of progression in open-angle glaucoma estimated from cross-sectional prevalence of visual field damage. *Am J Ophthalmol* 1996;122:355-363.
7. Nordmann JP, Auzanneau N, Ricard S, Berdeaux G. Vision-related quality of life and topical glaucoma treatment side effects. *Health Qual Life Outcomes* 2003;1:75.
8. Lavik E, Kuehn MH, Kwon YH. Novel drug delivery systems for glaucoma. *Eye* 2011;25:578-586.
9. The AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. *Am J Ophthalmol* 2000;130:420-440.
10. Nouri-Mahdavi K, Hoffman D, Coleman AL, et al. Predictive factors for glaucomatous visual field deterioration in the Advanced Glaucoma Intervention Study. *Ophthalmology* 2004;111:1627-1635.
11. Saettone MF, Salminen L. Ocular inserts for topical delivery. *Adv Drug Deliv Rev* 1995;16:95-106.
12. Misha GP, Bagui M, Tamboli V, Mitra AK. Recent applications of liposomes in ophthalmic drug delivery. *J Drug Delivery* 2011;2011:863734.
13. Natarajan JV, Ang M, Darwitan A, et al. Nanomedicine for glaucoma: liposomes provide sustained release of latanoprost in the eye. Int J Nanomed 2012;7:123-131.
14. Natarajan JV, Darwitan A, Barathi V, et al. Sustained drug release in nanomedicine: a long-acting nanocarrier-based formulation for glaucoma. *Am Chem* Soc 2014;1:419-429. 419-429.

Will Minimally Invasive Glaucoma Surgery (MIGS) Gain Acceptance and be Adopted in the Asia-Pacific Region?

Discussion by Norman M. Aquino, MD

The options for surgical control of intraocular pressure (IOP) in open-angle glaucoma (OAG) patients are expanding. In the last few years, traditional glaucoma filtration surgery is being challenged with the introduction of new surgical approaches and implants that offer innovative solutions to safely lower IOP in OAG eyes. These new procedures and devises are collectively termed as Minimally Invasive Glaucoma Surgery or MIGS. They involve an ab interno approach and are oftentimes done in conjunction with cataract surgery.

The following techniques and devices fall under the category of MIGS[1]:

1. Ab interno trabeculotomy

The Trabectome (NeoMedix, Tustin, CA, USA) is inserted through a small sideport incision under gonioscopic view. High-frequency electrocautery is used to ablate 90 to 120 circumferential degrees of the trabecular meshwork and the inner wall of Schlemm's canal, areas that are associated with the greatest resistance to aqueous outflow.

2. Drainage into Schlemm's canal

   a. The iStent (Glaukos, Laguna Hills, CA, USA) a trabecular microbypass stent is a device implanted using a disposable insertion instrument through an ab interno gonioscopy-guided approach. It is designed to bypass the trabecular meshwork and create a communication between the anterior chamber and the Schlemm's canal.

   b. The Hydrus (Ivantis Inc., Irvine, CA, USA) is an 8-mm long non-luminal open-design device that is implanted within the Schlemm's canal, oftentimes in conjunction with cataract surgery. It is an intracanalicular scaffold that increases outflow by allowing aqueous to bypass the trabecular meshwork and dilating the lumen of the canal.

3. Drainage into the suprachoroidal space

   a. The iStent Supra (Glaukos, Laguna Hills, CA, USA) is designed to create a patent lumen between the anterior chamber and the

suprachoroidal space. It attempts to harness the potentially vacuum-like effect of the suprachoroidal space by shunting aqueous to the area. It is made of polyethersulfone, has a titanium sleeve, and is heparin-coated. The stent is slightly curved to match the suprachoroidal space and is introduced ab interno and implanted right below the scleral spur. It is advanced into the suprachoroidal space until approximately 0.5 mm of the sleeve is left in the anterior chamber.

b. The CyPass (Transcend Medical, Menlo Park, CA, USA) is a 6.35-mm polyamide tube with an outer diameter of 0.51 mm implanted into the supraciliary space to establish a conduit for aqueous filtration via the uveoscleral pathway. A small guide-wire with a special tip that separates the iris from the scleral spur creates a cleft where the devise is inserted. Once in place, openings along the length of the tube allow aqueous to flow out.

4. Drainage to the subconjunctival space

The Aquesys implant (AqueSys Inc., Aliso Viejo, CA, USA)) consists of a small soft collagen-gelatin implant with an inner diameter of 65 microns. It is positioned into the subconjunctival space using an inserter via an ab interno approach. The objective is to create subconjunctival filtration and subsequent bleb formation without the creation of a conjunctival opening.

Yes, MIGS will be accepted and adopted in the Asia-Pacific region.

MIGS offers the potential to address and avoid most, if not all, the serious and potentially devastating complications associated with the more invasive procedures, like trabeculectomy and glaucoma tube surgery. MIGS procedures are fast to perform, involve much less tissue manipulation, and may have faster visual recovery compared to fistulizing and tube shunt surgery. They are, likewise, antimetabolite-free procedures. As such, MIGS is suitable to be combined with cataract surgery. Studies are currently ongoing to compare the IOP lowering effects of MIGS combined with phacoemulsification surgery versus phacoemulsification surgery alone.

Current available data, though limited and lacking in long-term follow-up, show that MIGS lowers IOP in patients with OAG, but to an extent that is less than that seen with traditional glaucoma surgery. It has also been shown to lower the need for postoperative pressure lowering medications.[2,3,4,5,6,7] Thus, MIGS is often performed to postpone more invasive surgical intervention in cases of early to moderate glaucoma, to prolong the patient's adherence to treatment, and to improve the quality of life.

In the Asia-Pacific region, because of issues related to cost and sustainability of prolonged medical treatment, early glaucoma surgery has become a viable option. MIGS can be adopted to address this concern.

No, MIGS will not be accepted and adopted in the Asia-Pacific region.

The epidemiology of glaucoma in the Asia-Pacific region greatly varies and is different from those in the West.[8] Although MIGS offers great potential in improving treatment outcomes, there is still no available evidence of its applicability and usefulness in patients with angle closure glaucoma, which is the prevalent type of glaucoma in the Asia-Pacific region. The burden of cost and the issue of devise availability will likely make its adaptation difficult and limited. Limited surgical expertise will also be an issue against its widespread use in the region.

CONCLUSION

Although there is a palpable need to develop newer, safer, simpler, and more effective approaches to improve glaucoma surgical outcomes, we should be very critical and circumspect in adopting these new techniques and devises. The key question is whether MIGS adds any further clinical value to currently existing and accepted surgical modalities of treatment. Furthermore, in certain areas of the world, like the Asia-Pacific region, adaptation of these new modalities of treatment will need further consideration as the prevalent type of glaucoma might not be appropriate, and the existing healthcare structure might not be amenable to these new technologies and approaches.

REFERENCES:

1. Brandão LM, Grieshaber MC. Update on Minimally Invasive Glaucoma Surgery (MIGS) and new implants. *J Ophthalmol* 2013;2013:705915.
2. Francis BA. Trabectome combined with phacoemulsification

vs phacoemulsification alone: A prospective non-randomized controlled surgical trial. *Clin Surg J Ophthalmol* 2010;28:1-7.
3. Craven ER, Katz LJ, Wells JM, et al. Cataract surgery with trabecular micro-bypass stent implantation in patients with mild to moderate OAG and cataract: 2-year follow up. *J Cataract Refract Surg* 2012;38:1339-1345.
4. Samuelson TW, Lorenz K, Pfeiffer N, et al. Six-month results from a prospective multicenter study of nickel-titanium Schlemm's canal scaffold for IOP reduction after cataract surgery in OAG. Poster presented at AGS Meeting, March 2012, NY, NY.
5. Hoeh H, Rau M, Reitshamer H, et al. Clinical outcomes of combined cataract surgery and implantation of the CyPass Microstent for the treatment of OAG. Paper presented at the ESCRS Meeting, Sept 2012, Milan, Italy.
6. Hoeh H, Ahmed II, Grisanti S, et al. Early postoperative safety and surgical outcomes after implantation of a suprachoroidal microstent for the treatment of OAG concomitant with cataract surgery. *J Cataract Refract Surg* 2013;39;431-437.
7. Palmberg PF. One-year results with the Aquecentesis procedure. Presented at the 6th International Congress on Glaucoma Surgery, September 2012, Glasgow, Scotland.
8. South East Asia Glaucoma Interest Group. Asia-Pacific Glaucoma Guidelines, 2nd ed. Hong Kong: Asia-Pacific Glaucoma Society, 2008.