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