CrossMark

American Academy of Ophthalmology
The Eye M.D. Association

Special Commentary: Supporting Innovation for Safe and Effective Minimally Invasive Glaucoma Surgery

Summary of a Joint Meeting of the American Glaucoma Society and the Food and Drug Administration, Washington, DC, February 26, 2014

Joseph Caprioli, MD,[1] Julie H. Kim, MD,[2] David S. Friedman, MD, PhD,[3] Tina Kiang, PhD,[2] Marlene R. Moster, MD,[4] Richard K. Parrish II, MD,[5] Eva M. Rorer, MD,[2] Thomas Samuelson, MD,[6] Michelle E. Tarver, MD, PhD,[2] Kuldev Singh, MD, MPH,[7] Malvina B. Eydelman, MD[2]

See editorial on page 1737.

The interest in minimally invasive glaucoma surgical (MIGS) procedures and devices stems from a desire to have a surgical option for the treatment of glaucoma that is associated with less serious risks and fewer complications than established procedures. Furthermore, a relatively simple and safe surgical approach may help to reduce side effects associated with medication use and to reduce the problem of poor adherence with medical therapy in glaucoma patients.

The Food and Drug Administration (FDA) Center for Devices and Radiological Health has received many requests for investigational trials for novel glaucoma surgical devices. Still, there is no consensus regarding the appropriate populations in which to implant these devices, nor are there uniform views by ophthalmologists and researchers concerning the best methods for the assessment of their safety and effectiveness. The FDA and the American Glaucoma Society collaborated in hosting a public meeting on February 26, 2014, in Washington, DC, to discuss guidelines for the evaluation of the safety and effectiveness of MIGS devices. Glaucoma specialists from across the United States and Canada discussed the appropriate clinical trial populations and defined clear and reasonable outcomes for the evaluation of their safety and effectiveness.[1,2]

Food and Drug Administration Regulation of Glaucoma Devices

All medical devices are regulated via a risk-based paradigm, which gives the FDA the flexibility to calibrate its regulatory approach to the level of potential risk posed by new products. This risk-based paradigm is described by the device classification system, which is based on the level of control necessary to demonstrate a reasonable assurance of safety and effectiveness for the device.[3] When evaluating devices, the FDA takes into consideration the intended population with regard to disease severity and prior therapy, as well as the conditions under which the device is being proposed for use (e.g., with or without concomitant cataract surgery). Therapeutic glaucoma devices are categorized as either class II or class III. An implantable glaucoma device is considered class II if it meets the definition identified in 21 Code of Federal Regulations 886.3920, Aqueous Shunt, which states, "An aqueous shunt is an implantable device intended to reduce intraocular pressure in the anterior chamber of the eye in patients with neovascular glaucoma or with glaucoma when medical and conventional surgical treatments have failed." Implantable glaucoma devices, which are intended to treat patients who do not meet this definition, are considered class III.

Furthermore, the FDA has worked with the American National Standard Institute to develop recommendations for conducting premarket studies. The American National Standard Institute published a standard for Ophthalmics—Implantable Glaucoma Devices (American National Standard Institute Z80.27-2014), which has been recognized by FDA subsequent to the workshop. In this document, the patient populations for clinical trials using glaucoma surgical devices are defined as refractory or nonrefractory.[4] The former describes eyes with glaucoma that are uncontrolled by medical therapy and that meet at least 1 of the following criteria: (1) failed 1 or more incisional intraocular glaucoma surgeries (e.g., glaucoma filtering surgery or tube shunt implantation); (2) failed 1 or more cilioablative procedures (e.g., cryotherapy or cyclodiode therapy); (3) have neovascular glaucoma; and (4) have any other ocular condition (e.g., conjunctival scarring or uveitis) in which a conventional incisional glaucoma surgery like trabeculectomy would be more likely to fail than for an eye with uncomplicated primary open-angle glaucoma.

http://dx.doi.org/10.1016/j.ophtha.2015.02.029
ISSN 0161-6420/15

Nonrefractory cases consist of eyes diagnosed with glaucoma that do not meet any of the criteria for refractory glaucoma and include the following characteristics: (1) may or may not have been treated with medications or laser trabeculoplasty; (2) may be candidates for medical therapy, laser trabeculoplasty, and glaucoma filtering surgery; and (3) may have undergone uncomplicated cataract surgery, retinal laser, or extraocular muscle surgery.

Definition of a Minimally Invasive Glaucoma Procedure

There is no single, widely accepted definition of a MIGS procedure. The acronym MIGS was coined initially to represent microinvasive glaucoma surgery,[5] and although it continues to be used in this context, it has also come to represent minimally invasive glaucoma surgery. Although admittedly vague and open to diverse interpretations, this latter representation generally encompasses a diverse group of novel glaucoma surgical procedures and devices that are intended to be safer and cause less tissue disruption than traditional glaucoma filtration surgery. Minimally invasive glaucoma surgery procedures may be categorized further by the recipient structure or space into which aqueous humor is drained (e.g., Schlemm's canal, the suprachoroidal space, or the subconjunctival space).

The definition of MIGS for the purposes of this workshop was the implantation of a surgical device intended to lower intraocular pressure (IOP) via an outflow mechanism with either an ab interno or ab externo approach, associated with very little or no scleral dissection (i.e., needle or device penetration through the sclera allowed, procedures involving significant scleral dissection excluded) and minimal or no conjunctival manipulation (i.e., a limited peritomy or a small incision is allowed). Minimally invasive glaucoma surgery devices can be implanted with or without cataract surgery. Examples of existing MIGS devices that meet and do not meet this definition are shown in Table 1. It is noteworthy that the intent of this workshop was to assess MIGS implantable devices primarily, and procedures such as ab interno trabeculotomy that might be considered MIGS by other criteria were not included, particularly if there was no associated device implanted.

Defining the Patient Population for Clinical Trials

How to Classify Disease Severity in Clinical Trials of New Glaucoma Surgical Devices

The choice of an appropriate population of patients in which to test a new surgical device must be a balance between producing a robust estimate of the device's effectiveness while maintaining patient safety. In addition, the findings must be generalizable to the intended population who will receive the device.

As a severity cutoff for study inclusion, past premarket clinical trials have used Hodapp-Anderson-Parrish visual field criteria as a method of defining the patient population of interest.[7,8] Although many alternative glaucoma classification schemes were discussed at the workshop, no systematic, literature-supported classification method was endorsed by the panel for incorporation in future clinical trials.

Regardless of the method used, members of the panel widely agreed that patients with very mild or severe disease should be excluded from MIGS clinical trials. The rationale for a cutoff at the mild end of the disease spectrum is (1) to prevent recruitment of subjects without definitive disease and (2) to protect subjects from unnecessary glaucoma surgery. The rationale for a cutoff at the severe end of the disease spectrum is (1) to protect patients against a potentially ineffective novel procedure, (2) to allow inclusion of subjects safely in situations where the control treatment is anticipated to result in insufficient IOP reductions given disease severity, and (3) to allow for the safe washout of medications when indicated.

The panel discussed a number of variables typically used to assess glaucoma, including the optic nerve appearance, the retinal nerve fiber layer, and visual fields. It was recommended that new protocols remove certain optic nerve criteria such as cup-to-disc ratio as a requirement for subject inclusion in the trial because of the variability of this measurement. Studies have shown that reading centers also have high interobserver variability when grading the optic nerve, thereby limiting the usefulness of this assessment in clinical

Table 1. Examples of Minimally Invasive Glaucoma Surgery Devices Presented at the Joint American Glaucoma Society and Food and Drug Administration Minimally Invasive Glaucoma Surgery Workshop*

	Category	Approach	Device
MIGS device criteria met	Canal based	Trabecular microbypass stents	Glaukos iStent, Ivantis Hydrus[6]
	Suprachoroidal based	Ab interno suprachoroidal stents	Glaukos iStent, Supra Transcend CyPass
	Subconjunctival based	Ab interno transscleral filtration devices	AqueSys Xen
		Ab externo transscleral filtration devices	InnFocus Microshunt
MIGS device criteria not met	Canal based	Ab interno trabeculectomy	Trabectome
		Ab interno trabeculotomy	iScience catheter
	Suprachoroidal based	Ab externo suprachoroidal stents	Solx Gold Shunt
	Subconjunctival based	Ab externo transscleral filtration devices	Alcon ExPress

MIGS = minimally invasive glaucoma surgery.
*Table presented by Thomas Samuelson at the workshop.