Glaucoma Specialists Outline Clinical Trial Design For Minimally Invasive Surgery Devices

By Lea Radick
March 3, 2014

Executive Summary

FDA and the American Glaucoma Society convened in Washington, D.C., last week in an attempt to define the ideal patient populations for assessing implantable devices used in minimally invasive glaucoma surgery, as well as relevant safety and effectiveness issues.

FDA is soliciting advice from experts to help create guidance on clinical trial design for implantable devices used in minimally invasive glaucoma surgery.

On Feb. 26, physicians, scientists, researchers, educators and FDA staff assembled in Washington, D.C. at a workshop co-sponsored by FDA and the American Glaucoma Society. At the workshop, experts on three panels attempted to define the ideal patient populations for assessing minimally invasive implantable devices for glaucoma, and relevant safety and effectiveness issues.

Malvina Eydelman, director of the division of ophthalmic, neurological and ear, nose and throat devices in CDRH's Office of Device Evaluation, said she hoped discussions held during the workshop would serve as a "foundation for development of a 'leapfrog' guidance for minimally invasive glaucoma surgery devices. That's a mechanism via which we can share our initial thoughts regarding the content of pre-market submissions for such emerging technologies."

According to Eydelman, CDRH has seen an increasing number of submissions for minimally invasive glaucoma surgery devices, but there is no FDA guidance or recognized standard for these devices. "We cannot clearly delineate safety and effectiveness endpoints for investigation of these devices, and we end up having quite extensive discussions with each individual sponsor," she said.

Examples of minimally invasive glaucoma surgery devices include **Glaukos Corp.'s iStent**, **Ivantis Inc.'s Hydrus**, **Transcend Medical Inc.'s CyPass**, **AqueSys Inc.'s Xen gel stent** and InnFocus Inc.'s *Microshunt*.

For the purpose of the workshop, FDA and the glaucoma society defined minimally invasive glaucoma surgery as a procedure to lower intraocular pressure through an outflow mechanism, with either an ab-interno or ab-externo approach, and very limited or no scleral dissection. Although procedures including needle or device penetration/perforation of sclera may count as minimally invasive, procedures requiring significant scleral dissection do not. Also, procedures with more than minimal conjunctival manipulation do not count as minimally invasive, although limited peritomy or small incisions are allowed within this definition.

Defining The Patient Population

Currently, disease severity in clinical trials of new glaucoma surgical procedures is classified by FDA as refractory or nonrefractory. The former describes cases where there is uncontrolled intraocular pressure despite maximal medical treatment, and/or laser surgery and/or incisional glaucoma surgery. In nonrefractory cases, intraocular pressure can be controlled by medical management. The disease is categorized as mild, moderate or severe based on severity of glaucomatous optic nerve damage and visual field loss.

But Rohit Varma, professor and chair of the Illinois Eye and Ear Infirmary in Chicago, thinks the current classification system does not work well. He proposed a new system in which the disease severity for clinical trials of novel glaucoma surgical procedures is classified according to the potential magnitude of intraocular pressure lowering and the potential for pre-, intra- and post-operative risk based on at least one-year of follow-up data. Disease severity is instead grouped by intraocular pressure-lowering level and glaucoma damage levels of minimal, moderate or advanced. (See box)

Proposed Disease Severity Classification in Clinical Trials of New Glaucoma Surgical Procedures

Group	Intraocular Pressure Lowering Level	Glaucoma Damage
1	≤4 mmHg	Minimal
2	≥5 mmHg	Minimal
3	≥5 mmHg	Moderate/Advanced

Source: Rohit Varma, Illinois Eye and Ear Infirmary

Varma's proposed draft classification system incorporates levels of intraocular pressure reduction to help with the selection of future treatment. It also incorporates glaucoma damage, which can prognosticate the future course of action and provides a simple approach to help patients understand management of their disease, he explained at the workshop.

Most panelists liked Varma's plan to classify disease severity for clinical trials in these three groups, but participants believe there is still room to "to tighten up those definitions slightly," according to the summary given by panel co-chair David Friedman, associate professor of ophthalmology at Johns Hopkins University's Wilmer Eye Institute in Baltimore.

The classification of disease severity as refractory versus nonrefractory is "really not understood by clinicians. It's not really something we use clinically," Friedman said.

The panel agreed that an objective measure of optic nerve damage would be needed as a requirement to enter a clinical study.

Some panelists said they are not comfortable with excluding patients who don't have glaucoma from all trials.

Safety Endpoints

Regarding safety endpoints and adverse outcomes, the panel was asked to identify the definitions and relevant clinical findings that should be present to classify certain safety events as adverse outcomes. The discussion covered hypotony, substantial increase in intraocular pressure, and substantial visual field loss.

Most agreed with panelist George Spaeth, a glaucoma specialist at Wills Eye Hospital in Philadelphia, who said that clinical trials have to take into account both the clinical definition of hypotony, which is not based on a specific figure, and the likelihood of patients with low intraocular pressure having "the sort of problems that appear clinically."

Cynthia Mattox, vice chair for clinical services at the New England Eye Center at Tufts Medical Center in Boston, proposed that instead of counting hypotony as a separate complication independent of the other consequences, the most common complications that are causally related to persistent post-operative hypotony should be grouped together.

The panel debated the threshold percentage of the studied population that could have this outcome; Spaeth, who said he hadn't heard a consensus in the first panel regarding the definition of mild and moderate disease severity, said he didn't think any visual decrease should be acceptable. Other panelists said hypotony may be an acceptable outcome if the procedure had a high success rate.

Panelists were less concerned about spikes in intraocular pressure as an adverse outcome than they were about the consequences of hypotony. And most agreed that substantiating visual field loss following surgery as a natural progression of the disease versus untreated progression would be useful as an adverse outcome measure, although some panelists argued there is value in collecting data for visual field loss as entry criteria for the study.

All panelists agreed that one year is sufficient for determining whether there are any severe adverse outcomes associated with using a minimally invasive glaucoma surgery device, but further studies are needed to prove the devices' effectiveness.

Effectiveness Measures

FDA asked a third panel what effectiveness endpoints are necessary to determine study success.

The panel agreed that the procedure should reduce average intraocular pressure by 20 percent or at least create a "robust reduction" in a minority of patients, said panel co-chair Joseph Caprioli, chief of the glaucoma division of the Jules Stein Eye Institute at the University of California, Los Angeles, in summarizing their discussion.

The panel was split on whether the trial should include a composite safety and effectiveness endpoint, rather than separate safety and effectiveness endpoints.

"Composite measures are desirable but yet to be developed and because of the nature of our patients, their variability of severity and their starting points and so forth, it's a fairly complex issue," Caprioli said.

Finally, when asked to consider the appropriate targets for overall study success, the panel concluded that a quality of life measure should be routinely included in any study.

http://www.pharmamedtechbi.com/publications/health-news-daily/2014/3/3/glaucoma-specialists-outline-clinical-trial-design-for-minimally-invasive-surgery-devices