Editorial

MIGS and the FDA: What's in a Name?
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Over the last half century, the treatment of open-angle glaucoma has centered primarily around topical medical therapy with or without laser trabeculoplasty, with traditional filtration surgery reserved for more advanced and worsening disease. Given the potential for serious short-term and long-term complications of trabeculectomy and tube shunts, these are often reserved for much later in the glaucoma treatment paradigm. In fact, the rate of trabeculectomy has declined markedly over the last several years, in part because of the advent of new topical medications. Classic, the regulatory pathway for glaucoma surgical devices has been for use in so-called refractory glaucoma (defined as medically uncontrolled with prior failed surgery or high risk for surgical failure), typically as a class II (higher risk) device, through a premarket notification (510[k]) process demonstrating substantial equivalence to a historical predicate. All aqueous tube-plate shunts currently in use were approved through this pathway. This approach is a reasonable one when considering glaucoma surgery in its traditional role.

Recently, a new class of procedures, termed minimally invasive or minimally invasive glaucoma surgery (MIGS) has emerged. These are designed to improve the safety of surgical intervention for glaucoma. Although initially coined minimally invasive, the term micro seems more appropriate because it truly differentiates these microscopic ophthalmic procedures from other minimally invasive surgical procedures (i.e., general surgery). Most MIGS procedures enhance physiologic outflow and are aimed at a different patient population than traditional filtration surgery. As opposed to competing with traditional filtering surgery, MIGS seems to be more of an alternative to medical therapy in an effort to address adherence challenges, adverse events, and quality-of-life (QOL) issues with topical medications. Thus, MIGS devices often are used earlier in the glaucoma treatment algorithm. This concept has challenged current therapeutic paradigms, as well as raised questions and created uncertainties in the regulatory approval process for these devices. Generally, MIGS devices are considered for nonrefractory glaucoma and thus are classified as class III (highest risk) devices. Class III devices require a more stringent premarket application regulatory process to demonstrate valid evidence of safety and efficacy.

One thing is certain: regulatory approval is a fine and complex balancing act, and there is likely no simple solution to resolve current concerns with it.

Over the last decade, concerns have been expressed about the slowing of the Food and Drug Administration (FDA) approval process. Lengthy timelines may result in delayed access to potentially important medical device innovations for United States citizens, whereas patients in other countries often benefit from these treatments many years earlier. Delays, uncertainty, and the resource intensiveness of the process have some worried that United States–led medical device innovation will be stunted. However, others cite safety concerns and the high number of device recalls to support increased regulation. Indeed, the Government Accountability Office continues to put the FDA on its high-risk list. One thing is certain: regulatory approval is a fine and complex balancing act, and there is likely no simple solution to resolve current concerns with it. Recently, the FDA has taken steps to provide more clarity and consistency around its approval processes.

In an effort to provide guidance on “appropriate clinical trial populations and [to define] clear and reasonable outcomes for the evaluation of [MIGS] safety and effectiveness,” Caprioli et al report on the proceedings of a joint FDA and American Glaucoma Society workshop on this topic. Collaboration between the FDA and the physician community should be applauded, reflecting the desire of all parties to ensure a more efficient approval process of medical devices to the United States consumer. Consensus was achieved on a number of issues; however, many areas remain unresolved.

Confusion starts with how one defines MIGS. A previously proposed definition lists 5 cardinal features of MIGS: an ab interno microincisional approach, minimal trauma to and disruption of normal anatomy and physiology with devices that exhibit a high level of biocompatibility, demonstrable intraocular pressure (IOP) lowering, extremely high safety profile, and rapid recovery. Procedures that involve large conjunctival incisions, scleral dissection, or significant manipulation of ocular tissue are destructive, are nonphysiologic and less likely to be truly considered minimally invasive, or both. By broadening the definition of MIGS too widely, one runs the risk of creating an overly heterogenous group of procedures with wide degrees of IOP lowering and risks. This not only creates difficulties when comparing therapies, but also inappropriately propagates generalizations of efficacy and safety to varying treatment methods. In addition, this creates confusion for patients...
and providers attempting to navigate through the various treatment options.

There is also uncertainty about where MIGS fits in the treatment paradigm and what the appropriate patient populations are to be studied. Should it be based on disease severity? IOP? Medication burden? The answer is likely all three. Excluding patients with mild disease who may have elevated IOP above target, are taking maximal tolerated medications, or both seems unreasonable, whereas excluding the well-controlled advanced patient who seeks to reduce medication burden and side effects while undergoing cataract surgery also seems questionable. Regardless of the optimal study population, we should recognize the gap in interventional options that exists between medical and traditional surgical interventions for patients of all types. As such, the potentially broad population for which MIGS may be useful should be recognized.

Many MIGS procedures have been studied and are used in conjunction with cataract surgery. Many patients (up to 15%-20%) undergoing cataract surgery already have glaucoma. Cataract surgery provides an opportunity to perform a MIGS in which the risks of an intraocular procedure already have been accepted by the patient. Performing an adjunctive MIGS procedure therefore is accomplished with minimal additional risk, thus reducing the risk and costs of these MIGS procedures compared with when they are performed as a stand-alone procedure. However, knowing that phacoemulsification also lowers IOP creates a significant confounder that must be considered when designing studies.

Ultimately, MIGS is predicated on safety, permitting its use in nonrefractory glaucoma and much earlier in the treatment paradigm. So how do we best assess safety, and how long of a follow-up is required? This is where the FDA/American Glaucoma Society workshop found the broadest consensus, agreeing that hypotony, increased IOP, worsening vision, or a combination thereof were important events to monitor for, and that 1 year of monitoring should be sufficient to identify such issues.

Quality-of-life measures are an important metric in assessing the value of MIGS. Unfortunately, most QOL tools address disease-related health quality, but do not address issues directly related to medication use. A glaucoma-specific QOL tool that includes medication use (i.e., Comparison of Ophthalmic Medications for Tolerability [COMTOL]) should be considered to assess adequately the potential benefits of MIGS beyond IOP. Rate of vision recovery, return to baseline activity, and number of physician visits and interventions also are not fully accounted for in currently available tools. Furthermore, if MIGS procedures are able to reduce or eliminate medication burden safely for patients, the resultant improvement in QOL actually should be considered as an effectiveness measure.

A common misperception of MIGS is that it needs to be compared with the gold standard of mitomycin C trabeculectomy to show its effectiveness. This inappropriate interpretation is based on the idea that MIGS procedures are designed to replace conventional filtering surgery. In fact, MIGS devices are designed to address the treatment gap that exists between medical therapy and more aggressive traditional surgical options. We then are left with uncertainty regarding how to assess the IOP-lowering efficacy of these procedures. Should we compare MIGS with phacoemulsification alone? With medications or laser? Do we need an active comparator if MIGS is performed as a standalone procedure? Furthermore, because one of the main thrusts of MIGS is medication reduction or elimination, this factor also needs to be incorporated into study end points. A composite efficacy score (i.e., IOP reduction, medication reduction, and QOL) that uses numerous end points could be used to show overall effectiveness in prospective comparative studies. In addition, postmarket studies can be used provide the necessary follow-up data to address long-term safety and efficacy.

Finally, cost effectiveness and cost utility needs to be addressed and studied to determine the societal and economic impact of MIGS as an option in the treatment of glaucoma. Future studies should incorporate trial-based economic evaluations as a means of estimating costs and effectiveness simultaneously.

Many physicians and patients yearn for a new class of glaucoma interventions that can address an expansive gap in therapy. Ultimately, MIGS may help to fill that void. The first-generation MIGS devices will pave the way for even safer and effective options. However, that journey will require more work to understand, substantiate, and individualize fully the role for MIGS. Basic science, clinical, QOL, and economic evaluations are underway to provide these much-needed data. Collaboration among the FDA, industry, and clinicians is critical to achieve consensus on study end points for MIGS to ensure a transparent and comprehensive evaluation of MIGS devices. Although the future of MIGS and its role in glaucoma management is evolving, certainly a more defined, consistent, and streamlined FDA regulatory process for MIGS seems to be on the horizon.

References


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