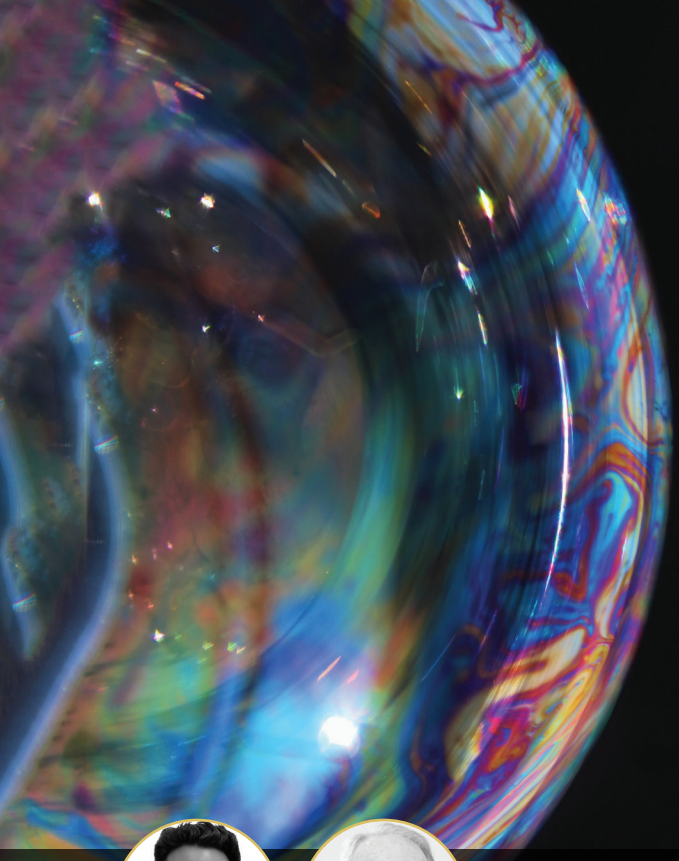

CHOOSING BETWEEN BLEB- AND TRABECULAR MESHWORK–BASED MIGS

The target IOP, disease severity, and risk-benefit ratio all require consideration.

BY VISHAL SHAH, MA, FRCOPHTH, AND KEITH BARTON, MD, FRCP, FRCS

MIGS has increased in popularity around the world,[1] with demand leading to an ever-increasing number of devices coming to market and procedures in development. The widespread appeal of these solutions can be attributed to the perception that they are low-risk and well-tolerated and that they achieve the benefits of lowering IOP, reducing the drop burden, and even halting the progression of mild to moderate glaucoma.

According to the US FDA, MIGS encompasses ab interno, non–bleb-forming procedures and ab externo minimally invasive bleb-forming procedures.[2]

Trabecular meshwork (TM)–based MIGS represents the most popular therapeutic approach. These procedures circumvent the inherent resistance of the TM to access the conventional outflow pathway. The episcleral venous pressure (typically 8–10 mm Hg) provides a ceiling of potential pressure lowering in this setting. Additionally, less quantifiable resistance is provided by the distal outflow system (ie, collector channels) and the veins themselves from segmental flow limitation, distal collector channel collapse, and pressure-dependent variation. TM-based MIGS typically achieves a modest IOP reduction to the midteens.[3,4]

The most relevant ab externo minimally invasive bleb-forming procedure is Preserflo MicroShunt (Santen/Glaukos) implantation. These ab externo procedures are typically augmented with the application of an antifibrotic agent such as mitomycin C (MMC), and they facilitate drainage into the sub-Tenon space, akin to flow through the flap of a trabeculectomy. In creating a new subconjunctival route for aqueous flow, surgery bypasses the conventional pathway completely. In so doing, unlike TM-based options, ab externo minimally invasive bleb-forming procedures can achieve a greater IOP reduction to the low teens.[5] Compared to TM-based options that, as standalone procedures, yield less than a 10% IOP reduction, the Preserflo typically achieves around a 30% IOP reduction.[5]

STANDALONE MIGS VERSUS MIGS COMBINED WITH CATARACT SURGERY: TM-BASED

The Hydrus Microstent (Alcon) and the iStent Inject (Glaukos) are the most well-researched TM-based devices.[6] The HORIZON study provided prospective 5-year randomized controlled trial data on the implantation of the Hydrus in patients with cataract and mild to moderate primary open-angle glaucoma.[3] The iStent Inject pivotal trial provided robust prospective 2-year randomized controlled trial data in a similar patient population.[4, 5]

In both trials, the control arm was defined as cataract surgery alone to allow differences to be attributed to the MIGS device. In the HORIZON study, a 20% or greater reduction

in unmedicated IOP was achieved by 54% of patients who underwent Hydrus implantation combined with cataract surgery versus 33% of those who underwent cataract surgery alone ($P < .001$). In the iStent Inject pivotal trial, the corresponding rates were 76% and 62% ($P = .005$).

Why might these trials have been designed this way? It is well established that cataract surgery reduces IOP. The additional pressure reduction from TM stents, in general, is modest. This trial design maximized the chances of demonstrating a pressure-lowering effect in the combined group, but it also increased the risk of a type 1 error (ie, mistaking a random chance reduction as a real effect). In a subgroup analysis of patients who underwent cataract surgery in the landmark Ocular Hypertension Treatment Study (OHTS), 40% achieved an IOP reduction of 20% or more. An even greater effect was achieved in the patients with the highest preoperative IOP.[7]

The evidence base for the efficacy of standalone TM-based MIGS is sparse by comparison. Katz et al performed a proof-of-principle study more than a decade ago that partially addressed this issue. More than 100 patients with uncontrolled open-angle glaucoma received one to three TM-based MIGS stents (iStent Trabecular Micro-Bypass, Glaukos). The most impressive results were shown in eyes with three stents (n = 35), which achieved a mean IOP reduction of 12.6 mm Hg from baseline at 18 months.[8] The external validity of this study is limited by the fact that it was performed at a single site and all patients were White. Further, the open-label design risked bias.

In the Katz study,[8] all but one participant was phakic. In practice, it is difficult to imagine a scenario in which a phakic patient should undergo standalone TM-based MIGS and not be offered cataract surgery at the same time. Cataract extraction itself facilitates access to the TM, and, with the IOP-lowering effects of phacoemulsification, combined surgery potentially provides a "two-for-one" solution to patients, while minimizing their exposure to the cumulative risks of sequential incisional anterior segment operations.

> "THE CHOICE BETWEEN TM- AND BLEB-BASED MIGS REPRESENTS A TRADE-OFF BETWEEN SAFETY AND EFFICACY. ULTIMATELY, IT COMES DOWN TO WHETHER THE PATIENT REQUIRES IOPS THAT ARE LOWER THAN THE PHYSIOLOGIC LIMITS OF TM-BASED MIGS."

STANDALONE MIGS VERSUS MIGS COMBINED WITH CATARACT SURGERY: BLEB-BASED

The published literature does not support the use of bleb-based MIGS in combination with cataract surgery. In one retrospective study of 58 patients with uncontrolled open-angle glaucoma (baseline IOP of 21–22 mm Hg), no statistically significant differences were observed in IOP lowering between the Preserflo-alone group and the group in which Preserflo implantation was combined with cataract surgery; both treatment arms demonstrated IOPs of 14 to 15 mm Hg at 1 year.[9] This study was retrospective, with a small number of patients and no power calculation. As such, it might well have been underpowered to demonstrate a true difference. Unfortunately, this is endemic to the published research on MIGS.

That said, the Tube Versus Trabeculectomy (TVT) study[10] showed that the success rate of trabeculectomy after phacoemulsification was worse. Given that ab externo MIGS creates a sub-Tenon bleb, much like a trabeculectomy, it is reasonable to assume that Preserflo implantation would be susceptible to similar factors. Further, any procedure combined with cataract surgery may result in intracameral exposure to MMC, the risks of which include corneal toxicity and hypotony.[11]

In contrast to bleb-based MIGS combined with cataract surgery, the evidence base for standalone bleb-based MIGS is robust. Five-year data from Panarelli et al showed that Preserflo implantation yielded an IOP of 14 mm Hg in patients with mild to severe uncontrolled primary open-angle glaucoma, with overall success (at least a 20% IOP reduction without an increase in medication use) achieved in 35%.[12] This outcome may initially sound disappointing, but given the relatively low MMC concentration (0.2 mg/mL) used, higher success rates might be possible; for comparison, 0.4 mg/mL MMC was applied for 2 minutes in the Primary Tube Versus Trabeculectomy (PTVT) study.[13]

Low IOPs after Preserflo implantation have been reported in real-world settings. In one European multicenter retrospective cohort study of 100 consecutive eyes, an IOP of 12 mm Hg or less, with at least a 30% IOP reduction from baseline, was observed in more than 25% of eyes at

1 year.[5] Unfortunately, the MMC dose and duration of application were not captured owing to the retrospective study design.

CLINICAL SAFETY

The TM-based devices have excellent safety profiles. A 5-year follow-up safety study of the 2-year iStent Inject pivotal randomized controlled trial identified no difference in the rate of endothelial cell loss (ECL), which was approximately 14% at 5 years.[14]

The HORIZON data suggest that the Hydrus may have a greater effect on ECL than the iStent Inject. At 5 years, the proportion of eyes with a 30% rate of ECL was almost double in the combined Hydrus-cataract group (20.8%) compared to the group that underwent cataract surgery alone (10.6%). Unfortunately, this difference was not tested in the statistical analysis. A linear regression analysis, however, found that the Hydrus Microstent did not produce a greater rate of ECL than cataract surgery alone ($P = .26$).[15]

In both the HORIZON study and iStent Inject pivotal trial, there were no reported instances of hypotony at 5 years in the device arms.

Bleb-based MIGS has been associated with a greater risk of complications. In one study, 36% of patients who received the Preserflo required at least one glaucoma reoperation, and 9% required at least two reoperations by 5 years postoperatively.[12] The amount of ECL in the Preserflo eyes was around 18% at 5 years, which was similar to that reported for control (trabeculectomy) eyes. The incidences of hypotony and device erosion were 1.8% and 3%, respectively.[12]

CONCLUSION

The choice between TM- and bleb-based MIGS represents a trade-off between safety and efficacy. Ultimately, it comes down to whether the patient requires IOPs that are lower than the physiologic limits of TM-based MIGS.

When the target IOP is not lower than the midteens, a small reduction in the medication burden is desirable, a visually significant cataract is present, and the patient has mild to moderate glaucoma that is not progressing rapidly, TM-based MIGS can provide a well-tolerated solution with an excellent safety profile. When a significant IOP reduction is required, an ab externo bleb-based MIGS procedure is likely the better option, assuming the patient is not at increased risk of failure. In that situation, standalone surgery may be warranted. ■

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