

Rethinking Treatment for Advanced Glaucoma Patients

Overtreatment of early glaucoma and undertreatment of advanced glaucoma is a fundamental problem—at least in the United States,” said Joseph F. Panarelli, MD, at NYU Langone Health. Anthony J. King, MD, FRCOphth agreed. “Many resources have been diverted into screening, detection, and treatment of mild disease, affecting our resources to manage the more complex cases, those most at risk of blindness,” said Prof. King, at Nottingham University Hospital in the United Kingdom.

Is it time to reconsider approaches to treatment of patients with newly diagnosed advanced glaucoma? Recent evidence suggests it may be.

Current Standards

In the United States, ophthalmologists typically use the ICD-10 definition for advanced glaucoma: “evidence of glaucomatous optic disc and visual field loss in both upper and lower hemifields and/or a defect encroaching within 5 degrees of fixation.”¹ “The stakes are higher in this patient population due to their increased risk for lifetime blindness, and the goal is to sufficiently lower pressure to stave off functional vision loss,” said Kateki Vinod, MD, at New York Eye and Ear Infirmary of Mount Sinai in New York City. Maintaining functional vision doesn’t mean that progression of the disease has stopped entirely or that visual fields remain the

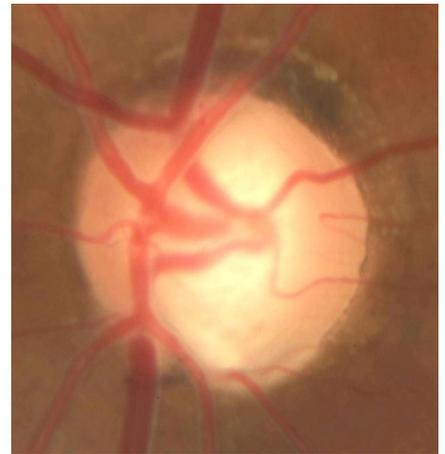
same for 20 years, said Dr. Panarelli. “It means that if you can go to the grocery store or watch your grandkids on your own today, you can continue to do that 20 years from now.”

Current practice. “The traditional approach to treating glaucoma patients, including those with advanced visual field loss, was to use medications first, followed by laser trabeculoplasty, and then to consider incisional surgery,” said Dr. Vinod. However, said Dr. Panarelli, many surgeons currently favor minimally invasive glaucoma surgery (MIGS) and microshunts and are hesitant to operate on patients with advanced disease, mainly because they’re afraid of serious surgical complications associated with trabeculectomy.

Trabeculectomy: Considerations and Risks

Trabeculectomy can allow patients to attain a very low IOP and help halt disease progression, said Dr. Panarelli.

Potential complications. “Trabeculectomy is a high-risk, high-reward procedure—it reflects the trade-off between safety and efficacy inherent in glaucoma surgery,” said Dr. Vinod. Trabeculectomy, she said, runs a higher risk of producing potentially vision-threatening, hypotony-related complications, including serous or hemorrhagic choroidal effusions and hypotony maculopathy, relative to MIGS and carries a lifelong risk of



FUNDUS PHOTO. Optic disc in a patient with advanced glaucoma.

bleb-related complications.

The complication most dreaded by patient and clinician alike is the rare occurrence of “wipe-out”: irreversible, inexplicable, devastating vision loss after surgery. “Understandably, this makes some surgeons reluctant to perform filtering surgery as the first intervention in a patient with advanced field loss,” said Dr. Vinod. “Patients who’ve lost vision after trabeculectomy in one eye may even say that they’d rather go blind ‘naturally’ in their better-seeing eye than accept any risk of hastening vision loss through a surgical intervention.”

Other choices. Given the risks of trabeculectomy, surgeons often opt instead for shunts or MIGS. “Although MIGS devices may not offer as much pressure reduction, many surgeons feel they can get more predictability with these procedures,” said Dr. Panarelli. The challenge with MIGS is the dearth of studies supporting their efficacy

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compared with modern trabeculectomy and their long-term efficacy, which is particularly important for a lifelong condition, said Prof. King.

Intensive follow-up. Other roadblocks to trabeculectomy include what's required after the procedure. "Ideally, you need to see the patient every week for the first month because that's when you make your adjustments to allow for a good long-term outcome," said Prof. King. Depending upon bleb appearance, added Dr. Vinod, you may have to perform interventions like suture lysis and needling with antifibrotics. In addition, because of the potential for late postoperative infections, patients must be counseled about diligent hygiene and symptoms that require immediate evaluation by an ophthalmologist.

Experience and skill. Success with trabeculectomy often comes down to your level of training and experience with the procedure, said Dr. Panarelli. "As a fellowship director, I've found it challenging to make sure our trainees are proficient in performing trabeculectomies and managing the postoperative course with only one year of training."

Prof. King agreed: "This is a complex surgical intervention that takes a significant amount of time to master." Partly because fewer trabeculectomies are being performed overall and partly because of COVID, "there has been a reduction in training opportunities, so there's a generation of surgeons coming through now who have had less exposure to this procedure," he said.

The TAGS Trial: New Evidence in Support of Trabeculectomy

"For several years, the U.K.'s National Institute for Health and Care Excellence [NICE] guidelines² have suggested that we should carry out a primary augmented trabeculectomy for people presenting with advanced glaucomatous visual field loss," said Prof. King, lead author on the Treatment of Advanced Glaucoma Study (TAGS).³ "But very few ophthalmologists have actually followed that guidance, largely due to the lack of a strong evidence base, which is one of the main reasons we conducted the TAGS trial."

Study design. Mimicking standard

care, this pragmatic randomized controlled trial included 453 patients with newly diagnosed advanced open-angle glaucoma, defined according to the Hodapp-Parrish-Anderson (HPA) classification of visual field loss in at least one eye. These criteria include a mean deviation worse than -12 dB, more than 50% of the points in the pattern deviation defective, as well as several other measures of VF loss. Anyone who was in the severe HPA category was eligible for entry into the study, said Prof. King.

At 27 glaucoma departments in the United Kingdom, investigators randomized patients on a 1:1 basis into primary medical treatment or primary surgery. "Primary medical treatment involved starting patients on medications according to NICE guidelines, and subsequent medication was added if deemed necessary by the treating clinician," said Prof. King. "If maximum medical treatment was insufficient, patients were offered trabeculectomy." Primary surgical patients were started on medical treatments and then had a trabeculectomy with mitomycin C (MMC) within three months, he said. "Glaucoma medications were added if the IOP was not lowered sufficiently with trabeculectomy."

Visual results. After 24 months, there was no material difference between the medical and surgical arms for the primary outcome measure, which was the VFQ-25, or for any of the other quality-of-life measures. At 24 months, mean IOP was 12.4 mm Hg in the surgical arm and 15.1 mm Hg in the medical group, said Prof. King. "The visual acuity was slightly better in the medical group, and we speculated that this may be due to the development of some early cataract from trabeculectomy."

Safety. "Probably the most important finding was the very low surgical complication rate, with no statistically significant difference in severe safety outcomes in the two arms," said Prof. King. "Adverse events were generally self-limiting with no long-term consequences. After surgery, there were no episodes of wipe-out. There were two episodes of endophthalmitis, one in the trabeculectomy arm and one in the medical arm in a patient who had had

trabeculectomy for insufficient IOP control. Both patients were treated successfully and returned to preinfection vision levels."

Cost-effectiveness. Medical treatment is more cost-effective, not only because the surgery is expensive but also because multiple postoperative follow-up appointments are necessary in the first year after surgery, said Prof. King. "Those costs evened out after the first year, but we don't yet know the lifetime cost-effectiveness of undertaking early trabeculectomies."

Enough Data to Change Practice?

"Although the current NICE guidelines do recommend primary trabeculectomy, I'm certain the next update will consider the TAGS data, which provides evidence to support it," said Prof. King.

Long-term follow-up. "We felt that two years is probably too short to detect any meaningful visual field change, so we are currently collecting data for five years," said Prof. King.

Dr. Vinod added, "Many complications of trabeculectomy, particularly bleb leak, blebitis, and endophthalmitis, can develop even decades down the line," long after the duration of most randomized clinical trials.

Previous landmark studies. "We've learned valuable lessons from previous randomized clinical trials that enrolled patients with advanced glaucoma, such as the Advanced Glaucoma Intervention Study [AGIS]⁴ and the Collaborative Initial Glaucoma Treatment Study [CIGTS],"⁵ said Dr. Vinod, "and TAGS echoes some of those findings." AGIS taught us that there is a dose-response relationship between IOP and visual field progression in patients with advanced glaucoma, said Dr. Vinod. "From CIGTS, we learned that initial treatment with trabeculectomy is more effective at lowering IOP than medications, which we also saw in TAGS."

But findings from many of the earlier studies have not really changed surgical practice patterns, she said. In fact, as a fellow, Dr. Panarelli conducted an American Glaucoma Society survey that asked whether doctors would choose surgery first based upon these landmark trials.

“The overwhelming answer then was ‘no,’” said Dr. Panarelli.

What’s different now? “TAGS is the only primary treatment trial that has specifically looked at patients presenting with advanced glaucoma,” said Prof. King. TAGS is also important because it represents our more modern approach to trabeculectomy, added Dr. Vinod. “In TAGS, surgeons used MMC in all patients randomized to trabeculectomy.” But in AGIS, the majority of patients did not receive adjunctive antifibrotics at the time of initial trabeculectomy.⁶ And in CIGTS, a large proportion of patients who underwent initial trabeculectomy did not receive intraoperative 5-fluorouracil.⁷

In press. A newer post hoc analysis from TAGS⁸ shows similar rates of visual field progression between the medication and trabeculectomy groups at two years, but a higher proportion of eyes progressing in the medication group, said Dr. Vinod. “In CIGTS, patients with a baseline visual field mean deviation of –10 dB or worse who underwent trabeculectomy showed less visual field progression than those receiving medications.”⁹

To Operate or Not—That Is the Question

Based on our current knowledge, what then is the best approach to treating newly diagnosed advanced glaucoma patients? And how can you best prepare the patient and yourself to optimize outcomes?

Individualize care. “You’ve got to do what you’re comfortable doing,” said Dr. Panarelli. “In truth, it’s hard to generalize the results of any study. Our job is to individualize our patient care and know our limits.”

Consider all your options. How do other surgical procedures such as tube shunts and MIGS fit into this whole picture? “You can debate the value of one procedure over the other, but what we essentially are trying to do is to get substantial IOP reduction with the least amount of risk,” said Dr. Panarelli. “That is the art of glaucoma.”

Dr. Vinod said that doing an angle-based MIGS shouldn’t preclude a future trabeculectomy or tube surgery

or affect their efficacy. However, Prof. King said that in patients most at risk of losing visual function you want to do your best-chance operation as your first intervention.

Prepare patients and families.

“Building rapport over a few preoperative visits is critical,” Dr. Vinod said, given the risks and intense postoperative course of trabeculectomy. “I might add a drop or an oral carbonic anhydrase inhibitor to temporize the IOP as a patient gains more comfort with the idea of surgery.”

In addition, she takes time to educate patients and share results of their glaucoma testing, especially their visual fields. “When their central acuity is still spared, patients may present late because they’re not aware of the extent of their visual field loss.” Dr. Vinod also enlists the support of patients’ loved ones during preoperative discussions and connects patients to low vision services.

But don’t wait too long. “I definitely have a lower threshold for suggesting trabeculectomy for patients with advanced disease than in the past,” said Dr. Panarelli. “What’s hard about these patients is you don’t have the luxury of waiting too long. Losing more visual field may impact their quality of life tremendously.”

Although Dr. Panarelli approaches treatment on a case-by-case basis, he now typically starts patients who have newly diagnosed advanced disease with a prostaglandin analog and adds a fixed-dose combination drop next. If they are not adequately controlled, he moves to surgery. “In the past, I might have added a third, fourth, or fifth bottle and considered laser, and then rechecked pressure. I am less apt to do that now.”

Keep learning. For ophthalmologists who aren’t confident about performing trabeculectomies, try to become as comfortable as you can with all these procedures, advised Dr. Panarelli. “Listen to mentors, go to meetings, ask questions, always keep learning—and know when to ask for help when you have a tough case. If you’re still not comfortable, consider referring a patient to someone who is.” That’s especially critical for



POST-OP EYE. Diffuse trabeculectomy bleb in a patient with advanced glaucoma.

patients with advanced disease, he said.

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