

LANDMARK CLINICAL TRIAL FINDINGS TODAY: AGIS



What are the current applications of the outcomes of the Advanced Glaucoma Intervention Study?

BY FRANK CHIN, MD, AND EYDIE MILLER-ELLIS, MD

The Advanced Glaucoma Intervention Study (AGIS) was a multicenter, randomized controlled clinical trial designed to evaluate two sequences of treatments in patients with advanced, medically uncontrolled open-angle glaucoma. A total of 591 patients (789 eyes) were enrolled and randomly assigned to one of the two sequences: (1) argon laser trabeculoplasty (ALT), followed by trabeculectomy, followed by a second trabeculectomy (ATT), or (2) trabeculectomy, followed by ALT, followed by a second trabeculectomy (TAT).¹

KEY FINDINGS AND EVOLUTIONS IN CARE

AGIS was one of the earliest studies to show that lower IOP was associated with less visual field (VF) progression.² Specifically, eyes with an average IOP of 14 mm Hg or less during the first 18 months after the initial surgical intervention were noted to have less VF progression compared with eyes that had an early average IOP greater than 18 mm Hg. Eyes with an IOP of 18 mm Hg or less at 100% of follow-up visits were noted to have less VF progression than eyes with an IOP of less than 18 mm Hg at less than 50% of follow-up visits.³

AGIS also showed the effect of race on outcomes between the two treatment sequences. Regarding the two main clinical outcomes of visual

acuity and VF loss, Black patients were found to have a lower overall decrease in visual acuity and less VF loss with the ATT sequence, whereas White patients had better outcomes with the TAT sequence.⁴

EVOLUTIONS IN CARE

AGIS patients were recruited approximately 30 years ago, from 1988 to 1992. At that time, medical therapy for glaucoma consisted of beta-blockers, miotics, and oral carbonic anhydrase inhibitors. Since then, the landscape of glaucoma treatment has evolved significantly to include new medications, surgical techniques, and technological advances—most notably, the introduction of prostaglandin analogues, the use of antifibrotic agents in glaucoma filtering surgery, and the development of selective laser trabeculoplasty (SLT).

In AGIS, antifibrotic agents were not typically used during the initial trabeculectomy, but 5-fluorouracil or mitomycin C (MMC) was used if a second trabeculectomy was required.⁵ Overall, only 0.5% of initial trabeculectomies were performed with an antifibrotic agent. This likely contributed to the higher rate of failure in Black patients compared with White patients.⁶ Nowadays, the intraoperative use of MMC for primary trabeculectomy is the standard of care. The limited use of MMC in primary trabeculectomy

at the time AGIS was conducted may account for the higher rate of failure (IOP > 18 mm Hg) and worse outcomes with the TAT sequence in Black patients. There are inherent risks to trabeculectomy, and the magnitude of IOP lowering may not have been sufficient to offset these risks and result in better vision preservation than with initial ALT.

Recent investigations with relevant findings include the Long-Term Outcomes of Augmented Trabeculectomy with 5-Fluorouracil in Nigeria study and the Research into Glaucoma and Ethnicity (REGAE) study, which analyzed the long-term outcomes of trabeculectomy with MMC in African Caribbean patients. In these studies, Black patients experienced good IOP lowering with trabeculectomy when antifibrotic agents were used, with mean IOPs of 15.4 mm Hg and 13.1 mm Hg, respectively, at final follow-up.^{7,8} However, it is important to note that AGIS showed a greater IOP reduction among Black patients with TAT compared with ATT and a greater decrease in visual acuity and VF outcomes with TAT compared with ATT. Visual acuity and VF outcomes were not measured in the more recent studies mentioned.

In today's practice, SLT has surpassed ALT as the preferred treatment option. Although studies have shown similar efficacy between ALT

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and SLT, there are a few notable differences between the two procedures, including the amount of power used, the repeatability of treatment, and the proposed mechanisms of action, which might or might not affect clinical outcomes if AGIS were to be repeated today.⁹ Currently, SLT, which has an excellent safety profile, is used much earlier in the disease course, sometimes before medication; therefore, trabeculectomy would not typically precede SLT in a treatment sequence unless the patient's IOP was significantly elevated to the point that SLT was unlikely to lower IOP enough to prevent glaucomatous progression.

Thirty years of developments in glaucoma management since the publication of AGIS have given ophthalmologists access to a wealth of treatment options. These include a range of medications (prostaglandins, topical carbonic anhydrase inhibitors, alpha-agonists, and Rho kinase inhibitors) and a variety of surgical solutions (glaucoma drainage devices and MIGS devices and procedures) that allow treatment to be tailored to each individual patient. Although several MIGS devices are approved by the FDA for the treatment of mild to moderate glaucoma, subconjunctival microstents (Xen Gel Stent [Allergan] and Preserflo MicroShunt [Santen]) can be used for more advanced disease.

CONCLUSION

If AGIS were to be repeated today, the likely modifications would be to decrease the target IOP to the mid- to low teens because 18 mm Hg is no longer considered the magic number for IOP control; to standardize filtering surgeries with the use of antifibrotic agents, such as MMC with initial trabeculectomy; and to replace ALT with SLT. SLT could be offered earlier in the treatment sequence, but the number of medications available would increase the complexity of stepped management. In addition to standard trabeculectomy, subconjunctival microstents and glaucoma drainage devices could be used. These updates would better reflect the current state of glaucoma practice and help to confirm the best management options for patients with advanced disease.

Additionally, whereas AGIS relied on visual acuity and automated perimetry to assess visual function, OCT could be added to monitor structural parameters of the optic disc and retinal nerve fiber layer. Measurement of central corneal thickness and corneal hysteresis could help with risk stratification and target IOP setting.

Considering the inclusion of patients of other ethnicities, such as Latinos and Asians, would also be beneficial to further understanding of glaucoma management in a manner that reflects

the current patient population in the United States. ■

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FRANK CHIN, MD

- Glaucoma fellow, Scheie Eye Institute, University of Pennsylvania, Philadelphia
- frank.chin@pennmedicine.upenn.edu
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EYDIE MILLER-ELLIS, MD

- Chief of the Glaucoma Service, Vice Chair for Faculty Affairs, Diversity & Inclusion, and Professor of Clinical Ophthalmology, Scheie Eye Institute, University of Pennsylvania, Philadelphia
- eydie.miller@pennmedicine.upenn.edu
- Financial disclosure: None