

Take-Home Messages From the Advanced Glaucoma Intervention Study

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I tasked Leon W. Herndon, MD, and Daniel B. Moore, MD, with a difficult assignment: to answer questions about the Advanced Glaucoma Intervention Study (AGIS). This study is one of the most complex landmark glaucoma studies ever produced, with countless articles stemming from the data. Drs. Herndon and Moore did an admirable job of addressing the questions and explaining the reasons. They summarize that a lower IOP helps to slow down field loss, but how to reduce IOP in each individual patient may need to be modified by countless factors that are addressed in this article.

—Section Editor Ronald L. Fellman, MD

What question was the AGIS designed to answer?

Although it has long been established that patients with advanced glaucoma require aggressive therapy,¹ prior to the AGIS, little was known about the long-term outcomes or effectiveness of surgical treatments in these patients. This study was designed to evaluate two sequences of surgical treatments in patients with medically uncontrolled open-angle glaucoma (OAG). The main outcome measures were visual acuity and progression of visual field loss. The investigators also reported on IOP, complications, time to treatment failure, and the need for adjunctive medications.

How was the study designed to answer the question?

AGIS was a prospective, multicenter, randomized trial that enrolled 591 patients (789 eyes) with uncontrolled

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OAG despite maximum medical therapy between 1988 and 1992 at one of 11 participating clinical centers.² Eligible participants were between 35 and 80 years of age; were diagnosed with OAG in a phakic eye; were on maximum effective, accepted, and tolerated glaucoma medical therapy; had undergone at least one automated field test before the eligibility visual field test; met at least one of nine combinations of criteria for consistently elevated IOP, glaucomatous visual field defect, and optic disc rim deterioration; had a visual acuity score of 56 or better (approximate Snellen equivalent, 20/80); had a visual field score between 1 and 15; and had an eye that was treatable with either argon laser trabeculoplasty (ALT) or trabeculectomy.

Visual acuity, gonioscopy, and fundoscopy were each assessed once, visual field testing was assessed twice, and IOP was assessed three times at baseline. Next, eyes were randomly assigned to one of two sequences of escalating therapy: trabeculectomy, followed by ALT, followed by a second trabeculectomy (TAT) or ALT, followed by trabeculectomy, followed by another trabeculectomy (ATT).

Failure was defined as an eye on maximum medical therapy that met the study's eligibility criteria for elevated IOP, visual field defects, and optic disc rim deterioration. The use of intraoperative antimetabolites was evolving during the study period; prior to 1990, antimetabolites were not used during trabeculectomy, whereas 5-fluorouracil has been used postoperatively since 1990 and mitomycin C intraoperatively since 1991.

IOP was measured 1 and 4 weeks after each operation, and visual acuity, visual fields, and IOP were assessed 3 and 6 months after enrollment and then biannually thereafter. Data collection closed March 31, 2001.³ Because the investigators did not a priori randomize patients stratified by race, there are unequal numbers of patients and eyes in the four arms of the trial. The large sample size, however, makes it possible to statistically compare the results when stratified by race.

With regard to baseline characteristics (AGIS 3) for the study group, what were the most important differences between black and white patients? Interestingly, disc hemorrhages were more common in whites, but glaucoma was more severe in blacks. Why might this occur, considering that disc hemorrhages are usually associated with worsening glaucoma?

Race in the AGIS was characterized as white, black, Hispanic, or other, either by self-report or by study personnel. Of the 581 patients in AGIS 3, 57% were black. This group of patients was younger and had more systemic hypertension and diabetes than white patients. Black patients also had significantly worse visual field defects on average than white patients, although IOP and visual acuity were similar between the two groups. There were only four black patients (all women) who had an observed disc hemorrhage (0.9%), whereas 12 white patients (5 men, 7 women) had disc hemorrhages (3.7%).⁴

The difference in the rate of disc hemorrhages between the two races did not reach statistical significance, but it is an interesting comparison nonetheless. Visual field loss has been reported to occur at an accelerated rate after disc hemorrhages are identified,⁵ but the severity of baseline visual field damage does not seem to be a risk factor for the development of disc hemorrhages.⁶ Although the investigators did not report on specific characteristics of the patients with disc hemorrhages, it is worth noting that variables such as the average IOP or vertical cup-to-disc ratio were similar between the two groups. Optic disc hem-

orrhages have been reported over a wide age range, but advanced age has been reported as a risk factor for visual field progression in patients with disc hemorrhages.⁵ It is possible, therefore, that the significantly older age of the white patients in this study contributed to the finding. Also, as this study evaluated patients with advanced glaucoma, it is important to search for and appropriately consider this finding in all of our glaucoma patients, regardless of the severity of the disease.

What are the most important clinical points regarding the comparison of treatment outcomes in AGIS 4? Even though IOP decreased the most with filtration surgery in both treatment groups, white patients fared better with this treatment modality. What is the most likely cause of this? Could this be because 21% of filters failed in blacks versus only 13% in whites?

AGIS 4, which reported on the 7-year results of the study, is full of acronyms and figures. In essence, the investigators found that, in both black and white patients, the mean IOP was lower in eyes assigned to the TAT sequence, and the cumulative failure of initial therapy was higher with the ATT sequence. When evaluating the preservation of visual field and acuity, black patients fared better with ATT, whereas white patients had a lower cumulative decline with TAT (the first 15 months slightly favored ATT). Despite a greater mean reduction in IOP with the TAT sequence, black patients experienced more rapid visual field deterioration with this sequence compared with ATT. The average visual field defect score actually improved in black patients with the ATT sequence during the first 30 months of follow-up.

Black patients had a higher rate of failure with filtration surgery than did white patients. The reasons for this finding are likely multifactorial, but one important consideration is that an antifibrotic agent was used in only 0.5% of primary filtering surgeries in the AGIS.⁷ Broadway et al⁸ obtained conjunctival biopsies at the time of filtration surgery from 90 patients with glaucoma; 45 patients were black, and 45 were white. Conjunctiva from black patients was found to contain a greater number of macrophages and a smaller number of both mast and goblet cells compared with that of white patients. There was a tendency for the conjunctiva from black patients to contain more fibroblasts. A greater number of conjunctival macrophages and possibly fibroblasts in black patients may partially explain the tendency for a lower success rate with filtration surgery in this group of patients.

AGIS 5 revealed that bleb encapsulation occurred after filtration surgery in 18.5% of eyes with previous ALT and in 14.5% of eyes without ALT. Is bleb encapsulation less of a problem with selective laser trabeculoplasty, or is bleb encapsulation more a function of limbus-based filtration, which is now less common?

AGIS 5 reported on the incidence of encapsulated blebs after trabeculectomy in eyes with and without previous ALT, and the investigators assessed the risk factors for developing an encapsulated bleb.⁹ They found that male gender and high school graduation without further formal education were statistically significant risk factors for bleb encapsulation.

ALT is more destructive to the trabecular tissue than selective laser trabeculoplasty. One report documented elevated levels of TGF-beta 2 in the aqueous of patients with pseudoexfoliation after ALT prior to undergoing trabeculectomy than without prior ALT therapy, and it found that the former were more prone to bleb scarring.¹⁰ It is possible, therefore, that selective laser trabeculoplasty causes less inflammation than ALT, and as such, bleb encapsulation may be less of a concern with that procedure.

AGIS 7 reported the relationship between IOP control and visual field deterioration. What are the most important findings about this relationship? Do the overall AGIS data suggest that diabetic patients are more likely to have trabeculectomy failure or just overall treatment failure? Should glaucoma specialists tell diabetic patients that it might be hard to control their glaucoma?

AGIS 7 evaluated the relationship between IOP and visual field progression over 6 or more years.¹¹ The investigators found with post hoc analysis that eyes with an early average IOP greater than 17.5 mm Hg had significant worsening of visual field progression compared with eyes that had an IOP of less than 14 mm Hg. This difference was even more pronounced after 7 or more years of follow-up compared with 2 years. Furthermore, eyes observed at 100% of follow-up visits to have an IOP of less than 18 mm Hg over 6 years had little to no change in visual field progression, whereas eyes with an IOP of less than 18 mm Hg at fewer than 50% of visits had significant field deterioration. This difference was worse after 7 or more years of follow-up compared with 2 years.

Eyes with an IOP of 17.5 mm Hg or greater had a higher prevalence of diabetes compared with those

that had an IOP between 14 and 17.5 mm Hg or 14 mm Hg and lower. Black patients were more likely to have diabetes compared with white patients.⁴ Diabetic patients did not have a significantly higher rate of bleb encapsulation,⁹ and diabetes was an independent risk factor for cataract progression.¹²

AGIS 11 reported on the association between pre- and postintervention risk factors for treatment failure with trabeculectomy or ALT. Diabetes was associated with an almost threefold risk of trabeculectomy failure as a first or second intervention but not with ALT failure.¹³ Although these results are compelling, they must be interpreted with caution for several important reasons. First, numerous advances have been made in trabeculectomy surgery since the study, including the increased use of releasable sutures, suture lysis, and antifibrotic agents. For example, as mentioned earlier, antifibrotics were used in 0.5% of trabeculectomies as an initial intervention in AGIS and increased to 90% when it was used as the third intervention.⁷ Second, the investigators stratified diabetic patients into an “either/or” category; the disease and its influence on glaucoma is likely more complicated than this distinction. Regardless, patients with diabetes need special consideration, and given these and other data, it is not unreasonable to counsel these patients about the difficulties of managing their glaucoma.

AGIS 9 reemphasizes that, when medical therapy fails to control glaucoma, black patients are better off starting with ALT therapy and white patients are better off starting with trabeculectomy. Have these data changed the way you manage patients? Do you think adjunctive antifibrotic therapy would improve the results of filtration surgery in blacks?

AGIS 9 evaluated treatment outcomes in black versus white patients up to database closure (between 7 and 11 years after enrollment). The investigators found the first intervention failed significantly less often in black patients compared with white patients who underwent the ATT sequence. Black patients had a significantly higher rate of failure, an IOP equal to or greater than 18 mm Hg, and a decline in visual field progression than white patients who underwent the TAT sequence.¹⁴

What this report does not discuss is the rate of complications associated with trabeculectomy as the initial surgical procedure. Given the invasive nature of trabeculectomy and its associated complications, we do not recommend trabeculectomy as a surgical option for either black or white patients before laser trabeculoplasty is offered.

One of the disadvantages of the AGIS is the limited use of antifibrotic agents during trabeculectomy, particularly as a primary intervention. The extended use of these agents has been associated with better results in black patients¹⁵ and is largely the standard of care in our practice.

Thirty percent of black patients who had laser therapy first required a second intervention, and only 18% required a second intervention with a trabeculectomy first. Yet, the AGIS' analysis supports laser treatment first. Why is this?

AGIS 9 reported on 9 years of follow-up with the intent of determining whether the treatment-specific clinical course of advanced glaucoma differed between black and white patients. Due to the numerous tests of statistical significance used in the study, the investigators considered $P < .01$ significant and values between .01 and .05 to be of borderline significance. The eyes of black patients had lower failure rates with initial ALT and higher failure rates with initial trabeculectomy compared with white eyes, which was of borderline significance. Specifically, 30% of black patients' eyes and 39% of white patients' eyes underwent a second intervention in the ATT sequence compared with 18% of black patients' eyes and 13% of white patients' eyes in the TAT sequence.¹⁴ Based on these data alone, black patients had a lower rate of failure than did white patients with ALT first, but this finding seems less convincing when the rate of failure between the two primary interventions in black patients' eyes are compared.

The investigators argue that their data support ALT first in black patients' eyes based on several additional measures. The researchers determined that the odds of achieving an IOP of less than 18 mm Hg was borderline significant and that the risk of visual field loss was significantly greater in blacks compared with whites in the TAT sequence. There was also a trend for a sustained decline in visual field and visual acuity in black patients compared to white patients in the TAT sequence, but this did not reach statistical significance. Taken as a whole, the investigators state the TAT sequence is worse for black patients than white patients, and the researchers suggest ALT first in black patients.

An additional important finding of AGIS 9 was a significantly greater number of prescribed medications for black patients in both the ATT and TAT sequences compared with white patients. The investigators acknowledged that different rates of compliance might contribute to the race-specific outcomes. Although almost 90% of enrolled AGIS patients self-reported

rarely forgetting to take their medications, other research has found that patients often greatly exaggerate compliance.¹⁶

What is the take-home message from this landmark study?

Surgeons need to collate countless variables when tailoring individualized treatment for patients with advanced glaucoma. Two important messages from the AGIS are worth particular consideration: (1) disparate treatment outcomes are associated with race, and (2) regardless of treatment modality, lower IOP is associated with slower visual field progression. ■

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