

Lessons From the AGIS

This study's findings are of practical importance to the clinician.

BY DOUGLAS E. GAASTERLAND, MD

The Advanced Glaucoma Intervention Study (AGIS) was prompted in the early 1980s by the realization that there was a new treatment, argon laser trabeculoplasty (ALT), for glaucoma when IOP-lowering medicines stopped being effective. Most ophthalmologists, myself included, thought the laser procedure was an improvement over filtration surgery. Our bias was that, if ALT failed, we could still perform a trabeculectomy. Like so many new procedures, however, ALT had received endorsements without undergoing any real comparative studies. Several of my colleagues and I decided a study comparing the outcome of ALT versus filtration surgery would be useful. This article highlights many of the study's findings and their practical implications.

PLANNING AND STARTING THE STUDY

I began talking with Fred Ederer, who had recently retired from his position as Director of Biometry and Epidemiology for the NEI of the NIH. We realized we could design a study that incorporated potential treatment failures by planning for a participant to undergo a preplanned, stepwise sequence of glaucoma interventions, as needed. We drew on Mr. Ederer's experience as the principal force behind a number of clinical trials in vascular diseases and in the ocular effects of diabetes.

For this randomized trial, we decided to recruit patients with varying degrees of glaucomatous damage to the optic nerve whose IOP was no longer adequately controlled by medication. One subject group would receive ALT, followed by a filtration procedure if ALT failed and by a second filtration surgery if the first failed. We imagined that only a few would require the third procedure. The second subject group would undergo filtration surgery first, followed by ALT if surgery failed and then by another filtration procedure if laser treatment failed. Because the trial started nearly 5 years before the use of adjunctive antifibrotic agents for filtration surgery was standard practice, we did not initially use them but incorporated these agents into the protocol in the early 1990s.

After creating a rough draft of our plan (a 13-chapter manual of operations), we started gauging the interest of

other glaucoma subspecialists, a number of whom expressed their willingness to participate in the study. We also received an endorsement of our study plan from the NEI, which provided funding in 1987. By our calculations, we needed 790 eyes for the trial. During the next 6 months, we met several times with and trained all of the investigators to perform measurements according to the study's protocols. Enrollment began in April 1988 and concluded in November 1992 (591 patients, 789 eyes). Approximately one-third of the participants needed bilateral surgery at the time of enrollment.

After obtaining baseline measurements, we proceeded with surgery and follow-up, which consisted of post-operative visits in addition to study visits at 3 months, 6 months, and every 6 months thereafter. We had specified the measurements (including a specific method of determining IOP developed by Greg Skuta, MD, one of the AGIS investigators) and examinations to occur at each follow-up visit.

ANALYZING THE DATA

Visual Field Scores

We published only a few reports in the first years of the AGIS. The initial publication outlined the study's design.¹ The second dealt with our efforts to measure visual fields in a way that we could enter into a database.² In the late 1980s, there was no such thing as a visual field score, although something of the sort was in development for StatPac on the Humphrey Visual Field Analyzer (Carl Zeiss Meditec Inc., Dublin, CA). As a result, we worked with Joseph Caprioli, MD, and Michael Patella, OD, who was instrumental in developing visual field assessment for the Humphrey system, to develop an AGIS scoring method. In short, after 10 years, we learned that the scoring method used in the study provided similar results to the mean deviation index in StatPac. We published our method in 1994² and used it throughout the AGIS.

Racial Differences

We noticed differences in the baseline characteristics of self-reported black versus self-reported white subjects.³ After 5 years, we found little difference in outcomes

between patients in the two treatment arms. One of the study's statisticians, E. Kenneth Sullivan, PhD, Mr. Ederer, and I began to examine which factors contributed to a treatment's success or failure. Dr. Sullivan determined that, in self-reported black subjects, the subgroup that began with trabeculectomy did no better during follow-up than those in the subgroup starting with ALT. By contrast, self-reported white subjects in the subgroup starting with trabeculectomy did statistically and clinically significantly better in terms of visual field and IOP outcomes than those in the subgroup starting with ALT.

The discovery of this interaction was startling. It led to the AGIS recommendation that, after the failure of medical treatment, black glaucoma patients receive ALT and white glaucoma patients receive trabeculectomy as their first surgical intervention. Our report on treatment outcomes according to race⁴ was controversial and caused some in the ophthalmic community discomfort. Later in the study period, we were able to compare black and white subjects within treatment groups. After controlling for all variables, the interaction remained.⁵ It may be that race is a surrogate for something else such as corneal thickness. At the time of our analysis, however, we had no such information available.

In addition to the study's analysis of the failure of glaucoma surgeries, Arthur Schwartz, MD, spearheaded an assessment of the encapsulation of blebs during the first year after filtration surgery with and without previous ALT. Although encapsulation occurred in a slightly larger proportion of eyes with previous ALT, Dr. Schwartz found the difference was not statistically significant. Likewise, age, having diabetes, taking systemic beta-blockers, the severity of the glaucoma, and the duration of previous medical treatment had no effect on encapsulation.⁶

Visual Field Progression

Our report on the relationship between controlling IOP and visual field progression was popular.⁷ After analyzing the data by two methods, we found that the preservation of visual fields was more likely in patients with consistently lower versus higher IOPs. Although ophthalmologists had come to believe as much, this report was the first large study to demonstrate indisputably the value of lowering IOP. Further, we found that there were some individuals, even among those who always had an IOP below 18 mm Hg at their study visits, who experienced visual field progression, whereas others did not. This difference suggests that there may have been elevations in IOP between visits or some other cause for worsening. This puzzling observation, particularly a fluctuation of IOP, has fostered further analyses and investigations.⁸

Cataracts

In an analysis of the impact of cataracts on visual field testing results in AGIS patients, we determined that mild nuclear cataracts have little effect on visual fields, whereas dense cataracts cause field depression.⁹ This information is important to practitioners following patients with glaucoma or glaucoma suspects, because many of these individuals are in the cataract age group.

The AGIS allowed us to compare the incidence of cataract formation in patients who first underwent ALT versus trabeculectomy during 7 to 11 years of follow-up.¹⁰ Nearly half of the eyes studied developed cataract. We found that trabeculectomy without complications increased a patient's risk of developing a cataract by 47% compared with those having ALT alone. If the trabeculectomy had serious intra- or postoperative complications (eg, a flat anterior chamber or ciliary body detachment), the risk of developing cataract doubled. These findings confirm earlier reports that filtration surgery increases the risk of cataract formation and provides guidance for surgeons and patients on the outcomes of modern filtration surgery.

Risk Factors

As shown in earlier studies, we confirmed that younger age and higher presurgical IOP increased patients' risk of failed ALT. Further, we identified several baseline risk factors for the failure of trabeculectomy, including younger age, higher IOP at the onset of glaucoma, and diabetes. Moreover, subsequent filtration surgery was more likely to fail if the patient had complications after initial trabeculectomy.¹¹

Regarding visual function, we determined that the patients at high risk of losing visual field due to glaucoma had poorer baseline visual acuity, had fewer baseline visual field defects, were male, or had reported having diabetes.¹² Our findings regarding the worsening of visual acuity during follow-up indicated that better baseline visual acuity, older age, and less formal education were risk factors. This information is distinctly relevant to clinical practice, because it assists the physician in choosing how to manage individual cases of glaucoma.

Results at 10 Years

Follow-up finished in March 2002. By then, of course, some subjects had been lost to follow-up, died, relocated, or become debilitated. Nonetheless, we were still following 80% of eligible subjects, and follow-up ranged from 8.33 to 13 years. Most important about this analysis is that we were able to determine the cumulative probabilities for the failure of interventions, the loss of visual field, and the loss of vision so severe that it constituted legal blindness.¹³

In the long term, black subjects in either arm of the

AGIS had approximately the same proportion (35% at 10 years) experience a decline in visual field. White subjects whose surgical interventions started with ALT had a higher proportion (nearly 40%) with a decline of visual field compared with those who had first undergone trabeculectomy (approximately 28%). After 10 years, in white AGIS subjects, the risk of seriously impaired visual function (visual field or acuity)—as in legal blindness—in one eye was about 30% in the trabeculectomy-first arm of the study. This statistic is lower than the rate reported (46%) at 10 years after filtering surgery in Olmsted County, Minnesota.¹⁴

When developing the protocol, the AGIS investigators wrestled with the decision of what constituted the failure of an intervention. We decided that surgery had failed if the eye again met the AGIS eligibility criteria. In other words, despite medical treatment, an eye with an IOP of 18 to 21 mm Hg had progressive visual field damage, an eye with an IOP higher than 21 mm Hg but still in the lower 20s had severe field damage, and an eye with an IOP greater than 25 mm Hg had mild or moderate field damage.

Based on this definition of failure, initial ALT had failed in 5 years in approximately 30% of the black subjects who had undergone the procedure and 50% in 10 years. When the initial surgery was ALT in white subjects, the failure rate was nearly 40% in 5 years and 55% in 10 years. By contrast, initial trabeculectomy in black patients had a failure rate that was slightly higher than 20% in 5 years and 33% in 10 years versus 10% in 5 years and 17% at 10 years in white subjects.

Although this complex information is potentially confusing, AGIS' long-term results provide statistics to help discuss and plan the management of patients with primary open-angle glaucoma who have failed aggressive medical treatment. Based on the cumulative data presented in the 13th AGIS report, we predict that the majority of patients (black or white) whose glaucoma is out of control are likely to do well for 5 years with either ALT or trabeculectomy.

Thus, physicians should consider ALT for all glaucoma patients (both black and white) whose poor health limits the likelihood of their long-term survival. By contrast, trabeculectomy is likely the better initial surgical intervention with regard to the long-term preservation of visual field in an otherwise healthy white subject.

Visual Field Analysis

In the final report from the AGIS,¹⁵ we analyzed almost 13,000 visual field results from the study and disclosed interesting and useful phenomena. We found that a modest visual defect confirmed at one follow-up visit may

diminish or disappear 6 months later. A review of additional tests, however, showed that patients who recovered in this way often relapsed in later tests. We also learned that it did not take much sustained deterioration to identify eyes in trouble. A falloff of two decibels in the mean deviation index in sequential visual field tests on two different days reliably indicated that the eye's condition had worsened.

CONCLUSION

The goal of the AGIS was to find out what happens to patients who undergo surgery because their IOP is uncontrolled on medication. We wanted to learn which method of management was better for the patient in terms of the long-term outcome. The information on various groups within the study is valuable to the clinician for its statistical applicability to the individual patient. □

Douglas E. Gaasterland, MD, practices at University Ophthalmic Consultants of Washington, and he is clinical Professor of Ophthalmology at George Washington University Medical Center and Georgetown University Medical Center in Washington, DC. Dr. Gaasterland may be reached at (240) 482-1213; degaasterland@uowc.com.



1. The AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 1. Study design and methods and baseline characteristics of study patients. *Control Clin Trials*. 1994;15:299-325.
2. The Advanced Glaucoma Intervention Study investigators. Advanced Glaucoma Intervention Study 2. Visual field test scoring and reliability. *Ophthalmology*. 1994;101:1445-1455.
3. The AGIS investigators. The Advanced Glaucoma Intervention Study (AGIS): 3. Baseline characteristics of black and white patients. *Ophthalmology*. 1998;105:1137-1145.
4. The Advanced Glaucoma Intervention Study (AGIS): 4. Comparison of treatment outcomes within race. Seven-year results. *Ophthalmology*. 1998;105:1146-1164.
5. The AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 9. Comparison of glaucoma outcomes in black and white patients within treatment groups. *Am J Ophthalmol*. 2001;132:311-320.
6. Schwartz AL, Van Vedhuisen PC, Gaasterland DE, et al. The Advanced Glaucoma Intervention Study (AGIS): 5. Encapsulated bleb after initial trabeculectomy. *Am J Ophthalmol*. 1999;127:8-19.
7. The AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. *Am J Ophthalmol*. 2000;130:429-440.
8. Nouri-Mahdavi K, Hoffman D, Coleman AL, et al. Predictive factors for glaucomatous visual field progression in the Advanced Glaucoma Intervention Study. *Ophthalmology*. 2004;111:1627-1635.
9. The AGIS Investigators. The Advanced Glaucoma Intervention Study, 6: effect of cataract on visual field and visual acuity. The AGIS investigators. *Arch Ophthalmol*. 2000;118:1639-1652.
10. The AGIS Investigators. The Advanced Glaucoma Intervention Study: 8. Risk of cataract formation after trabeculectomy. *Arch Ophthalmol*. 2001;119:1771-1779.
11. The AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 11. Risk factors for failure of trabeculectomy and argon laser trabeculoplasty. *Am J Ophthalmol*. 2002;134:481-498.
12. The AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 12. Baseline risk factors for sustained loss of visual field and visual acuity in patients with advanced glaucoma. *Am J Ophthalmol*. 2002;134:499-512.
13. The AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 13. Comparison of treatment outcomes within race: 10-year results. *Ophthalmology*. 2004;111:651-664.
14. Parc CE, Johnson DH, Oliver JE, et al. The long-term outcome of glaucoma filtration surgery. *Am J Ophthalmol*. 2001;132:27-35.
15. The AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 14. Distinguishing progression of glaucoma from visual field fluctuations. *Ophthalmology*. 2004;111:2109-2116.