The Investigators’ Perspective on the Collaborative Initial Glaucoma Treatment Study (CIGTS)

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In the late 1980s, an informal dialogue began between two University of Michigan senior faculty members: one, a glaucoma specialist, and the other, an expert in health behavior. The glaucoma specialist noted that many of his patients who needed a glaucoma-filtering surgery reported how much better they felt following surgery, because their glaucoma medications were no longer needed. A study was suggested to the health behavior expert wherein patients needing glaucoma-filtering surgery would be given a quality of life (QOL) questionnaire preoperatively and then another postoperatively to assess any differences. It was hypothesized that surgery should be offered sooner rather than later in the course of treating glaucoma to improve QOL by reducing the side effects commonly reported with glaucoma medications. But the health behavior expert instead suggested a more rigorous study that would involve patients with newly diagnosed glaucoma being randomized to initial treatment with medications or filtering surgery, with QOL instruments used to assess the patients. In the ophthalmic climate at the time, a study that involved initial treatment with surgery would not be acceptable in the United States without a strong endorsement of such an approach by glaucoma experts. So, a group of 15 to 20 glaucoma experts convened to discuss the idea.

After 3 meetings, the glaucoma experts were unified in their support of such a study. Then, in concert with methodological and QOL experts, they submitted a National Eye Institute (NEI) planning grant and were funded to write the protocol for a randomized, controlled, multicenter clinical trial; the effort was launched on July 1, 1989.

The group discussed work by Smith, Watson and Grierson, Jay and Murray, Jay and Allan, and Migdal and Hitchings, which supported trabeculectomy as an early or even initial intervention for treating glaucoma. The finding by Sherwood et al7 that topical medications had side effects on the conjunctiva that may reduce the success of future trabeculectomy was also considered. One year later, the group submitted a lead grant application with a manual of operations to the NEI, proposing to randomize patients with newly diagnosed open-angle glaucoma to medications or to trabeculectomy and then observe them long-term to determine a person-specific outcome: health-related QOL (HR-QOL). Initially, the secondary outcomes were visual field loss and visual acuity stability. The path to funding was arduous, as several review panels found it hard to envision such a study being accepted by patients and ophthalmologists. Furthermore, study sections felt that within the field of ophthalmology, HR-QOL measurement had not been sufficiently developed and tested for reliability and validity to warrant its position as the primary outcome. This led the researchers to change the primary outcome variable to visual field loss, and QOL became a secondary outcome variable. Through a combination of tenacity and the support of the director of the NEI, grant approval was finally secured. In March 1993, funding was in place for conducting the multi-center, controlled clinical trial.

METHODS

From its onset, the Collaborative Initial Glaucoma Treatment Study (CIGTS) was a complex enterprise to both design and execute. The study name itself evolved from the initial name, Glaucoma Treatment and Quality of Life, to satisfy the concerns of reviewers who felt HR-QOL was, as an outcome, too subjective to be measured validly and reliably. Defining what constituted glaucoma required extensive discussion among glaucoma experts. A definition ultimately was based on a minimum intraocular pressure (IOP) criterion (20 mm Hg), a multifaceted visual field criterion based on Humphrey 24-2 full-threshold testing that became stricter as entry IOP lessened, and an optic nerve criterion based on clinicians’ declaring the nerve appearance to be glaucomatous. Acceptance of not only primary open-angle glaucoma, but also pigmentary and pseudoexfoliative forms of open-angle glaucoma, required group approval. The unit of randomization was the patient, not the eye,
to preserve a patient's assessment of HR-QOL in relation to his or her glaucoma treatment. Therefore, the first treated eye became known in analyses and outcome articles as the study eye. Determining what topical medications would be permitted and their order of administration (eg, a beta blocker or epinephrine derivative was the first topical medication), how standardized the trabeculectomy should be, and what constituted failure of either initial treatment, thereby allowing argon laser trabeculoplasty, were difficult decisions reached by consensus. The extent to which community ophthalmologists could remain involved in the patient care of study participants, an allowance that contributed both to success in enrollment and generalizability of study results, required careful thought. The resulting manual of operations that detailed all protocol matters took up more than 200 pages of text. Staff members at the 11 initial clinical centers were tested on their knowledge of its content before they could initiate study operations. Site visits were conducted at all centers prior to initiating enrollment to certify staff in protocol procedures, such as visual field and acuity testing.

Enrollment of the desired 600 patients, randomized equally to initial medications or initial surgery, took place during a 38-month period. Midway through enrollment, 3 clinical centers were added to augment the rate of enrollment. In April 1997, enrollment ceased with a final tally of 607 patients. This achievement led the study's data and safety monitoring committee (DSMC) to authorize release of baseline characteristics of enrolled patients, which were published in combination with a description of the study's design and methods. Also, the study's approach to measuring HR-QOL and baseline findings from the telephone-administered HR-QOL interviews were published.

On being declared eligible, patients received the randomly assigned treatment and were examined at the clinical center after 3 months, after 6 months, and every 6 months thereafter. Concurrently, they were called at their homes by trained staff at the study's QOL interviewing center. The interview consisted of a comprehensive assessment of their HR-QOL, including both generic and vision-specific measures. Adherence to this protocol yielded thousands of visual field measurements and interviews. The study's coordinating center prompted clinical centers to follow the protocol rigorously; received, audited, and entered all data; conducted the data analyses; and produced study reports. The DSMC met with the operating committee each year to review the annual report and to make recommendations for the following year. As the study progressed, clinical center staff remained masked to outcome data, whereas the study's chairman, resource center staff, and DSMC members were privy to the outcomes by treatment group throughout. The DSMC's recommendations to the NEI were the basis for study continuation.

**SUMMARY OF PRIMARY OUTCOME FINDINGS**

Interim findings from the CIGTS were published in 2 articles that appeared in the journal *Ophthalmology* in 2001. The use of the term *interim* was intentional, because the investigators and the DSMC were convinced that further follow-up was necessary to provide a definitive answer to the study's key questions regarding which initial treatment was better. Even so, with completed follow-up through 4 years and partial follow-up through 5 years after treatment initiation, the findings were deemed important enough to publish. While surgical intervention reduced IOP more substantially than medicine over time, no substantial differences were found in visual field change—the primary outcome variable—between initial medicine and initial surgery groups. The surgery group experienced more cataract extractions than the medicine group and somewhat more loss of visual acuity, even with adjustment for cataract-induced loss. The lack of a substantial visual field difference between groups was considered likely owing to the aggressiveness of IOP control in both treatment arms of the study.

Health-related QOL findings in the 2 groups showed several specific outcomes that were initially better in the medicine group than in the surgery group, of which an increased bother from local eye symptoms was the most substantial. The surgery group also reported more problems with activities related to visual acuity. Overall, though, the effect of the 2 initial treatment approaches on HR-QOL was deemed "remarkably similar."

Support from the NEI continued for further follow-up of the CIGTS cohort through the end of 2004, and further support for follow-up was provided by an unrestricted grant from Allergan Inc (Irvine, California). This has led to a very rich long-term database with important information on how visual field and HR-QOL change over time as well as a large number of secondary outcomes available up to 10 years after treatment initiation. Since the interim reports on clinical and HR-QOL outcomes, 2 reports from the CIGTS group have focused on visual field information. One article addressed factors associated with visual field severity at baseline, of which the more striking (all P<.001) were black race, higher IOP, lower visual acuity, and a center effect. Variability in visual field measurement at baseline was found to be influenced by expected factors (eg, decreased patient alertness and increased age) and an unexpected factor (current smokers had increased variability). The transition to Swedish Interactive Thresholding Algorithm (SITA) from full-threshold visual field testing that occurred later on in CIGTS follow-up permitted us to evaluate similarities and differences in outcome measures from these 2 methods of measuring visual field. A more clinically oriented report addressed the occurrence of complications in the perioperative period after 465 trabeculectomies performed in the 300 patients randomized to the surgery arm. Intraoperative complications were found in 12% of patients, with anterior chamber bleeding as the most frequent (8%). In the first month after trabeculectomy, complications found in more than 10% of operated eyes included a shallow or flat anterior chamber (13%), encapsulated bleb (12%), ptosis (12%), serous choroidal detachment (11%), and anterior chamber bleeding or hyphema (10%). The investigators concluded that among the many complications reported, none were severe or expected to cause sequelae.

**WORK IN PROGRESS**

The wealth of CIGTS data led the NEI to approve 2 data analysis grants: one for extensive data analysis focusing on visual field outcomes and one for HR-QOL outcomes. This grant support has led to additional outcome information that will become available to the public in the coming months. One article addresses factors that influence cataract extraction in the CIGTS as well as the effect of cataract progression and extraction on key...
clinical and HR-QOL outcomes. One study describes the CIGTS patients' fear of blindness at the time of diagnosis and during extended follow-up. Another article addresses depression in the CIGTS patients and a manuscript under development investigates the relationship between driving behavior and clinical outcomes among CIGTS patients. Factors associated with IOP, both at baseline and while under treatment, are the focus of another study. The concurrent measurement of visual functioning and QOL with 2 instruments—the Visual Activities Questionnaire and the NEI Visual Functioning Questionnaire—has led to a manuscript that contrasts outcomes gleaned from these 2 measures.

Of course, a key outcome study that awaits publication deals with how visual field loss has changed during follow-up subsequent to that reported in the interim outcome article, and whether that change differs between the 2 treatment groups. Analyses of these data will also permit us to address factors other than treatment that effect long-term visual field loss, such as the severity of damage at diagnosis and patient age, race, sex, and sociodemographic factors. While this is not an appropriate forum to present preliminary findings, much of the benefit gained from the NEI's long-term support of the CIGTS is yet to come.

Finally, during the course of the study, Marshall Becker, PhD, the health behavior expert alluded to at the beginning of this article, died following an illness that lasted several years. It is important to recognize that this study would never have been performed were it not for the wise counsel and expertise provided by Dr Becker.

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REFERENCES