A Quarter Century’s Progress in the Treatment of Open-Angle Glaucoma
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The publication this month of “A Randomized Trial of a Schlemm’s Canal Microstent with Phacoemulsification for Reducing Intraocular Pressure in Open Angle Glaucoma” by Pfeiffer et al (see http://www.aaojournal.org/article/S0161-6420(15)00315-2/abstract),\(^1\) describing a promising new treatment for glaucoma, has stimulated this reflection of how glaucoma therapy has changed in the past quarter century, roughly the period that I have been in clinical practice.

In 1990, we had not proven to others that glaucoma could be successfully treated, although we behaved as though it were worthwhile. The 3 broad therapeutic avenues back then, as they remain today, were medications, laser, and incisional surgery, and all were directed toward lowering the intraocular pressure (IOP).

Three small randomized trials published approximately 25 years ago addressed the question of whether medical therapy of ocular hypertension could reduce the incidence of glaucoma; 2 demonstrated a beneficial effect,\(^2,3\) but the other failed to do so.\(^4\) These reports did not convince the United States Preventive Health Services Task Force that lowering IOP to either prevent glaucoma or prevent worsening of glaucoma was effective. The glaucoma community was already preparing its response to the report of the task force by designing and conducting larger multicenter randomized trials, including the Collaborative Normal Tension Glaucoma Study (CNTGS),\(^5\) the Ocular Hypertension Treatment Study (OHTS),\(^6\) and the Early Manifest Glaucoma Trial (EMGT).\(^7\) However, it would be a decade before results were published that supported the utility of lowering IOP.

The CNTGS results appearing in 1998 demonstrated a beneficial effect of IOP lowering in eyes with unremarkable IOP and established glaucoma damage. The fact that this effect was uncovered only after eyes with unoperated cataract were removed from the analysis detracted from the validity of the findings. However, with the publication of the results from the OHTS and the EMGT in 2002, we had convincing evidence that lowering IOP was effective in preventing the development of glaucoma in eyes with elevated IOP and in reducing glaucoma worsening in eyes with preexisting disease, respectively.

Several concepts in the management of glaucoma have been popularized in the past 25 years. Paul Palmberg explained the rationale for an individualized “target pressure” in the American Academy of Ophthalmology’s first Preferred Practice Pattern for Primary Open-Angle Glaucoma in 1989. Dr. Palmberg stressed that IOP targets in the low-normal range were indicated for patients with advanced disease. Although there were cries in the wilderness\(^8\) about the influence of central corneal thickness (CCT) on applanation tonometry measurements, it was not until measurement of CCT became part of the OHTS protocol and its role as a risk factor for the development of glaucoma was recognized\(^9\) that pachymetry became standard in the evaluation of individuals with elevated IOP or glaucoma. Another concept that arose from the OHTS was the realization that although, on aggregate, treating individuals with elevated IOP could reduce the risk of developing glaucoma, not all individuals with elevated IOP needed treatment. The art of medicine became deciding which ocular hypertensive patients needed therapy and which did not according to risk factors such as level of IOP and CCT. Kymes et al\(^10\) argued that few ocular hypertensive patients aged 70 years or older needed IOP lowering. A final important idea popularized during this time period was that glaucoma is a heterogeneous disease in terms of its rate of worsening. Anders Heijl\(^11\) eloquently pointed out the importance of distinguishing slowly worsening from rapidly worsening disease and treating accordingly.

Looking back, we can rank the importance of the therapeutic advances in medicines, laser, and incisional surgery for open-angle glaucoma over the last quarter century. In my mind, the most important medical breakthrough was the introduction of Xalatan (latanoprost; Pfizer Inc, New York, NY) in the mid-1990s, which quickly dethroned \(\beta\)-blockers as first-line treatment for lowering IOP. The next largest change occurred in 2011 with the loss of patent protection for Xalatan and the rapid and dominant market penetration of generic latanoprost. Other classes of medications appearing in the past quarter century that have improved the lives of our patients include topical carbonic anhydrase inhibitors and topical alpha-adrenergic agonists; combination therapy, preservative alternatives to benzalkonium chloride, and preservative-free eye drops also have advanced topical glaucoma therapy. The last decade has seen a renaissance in the awareness of the problem of adherence to topical medical regimens and burgeoning research that has demonstrated the ability of educational programs\(^12\) and reminder systems\(^13\) to improve adherence, at least temporarily.

I hope that the next 25 years bring us better medications and a controlled drug-delivery system, neuroprotective agents that can protect the optic nerve, better and longer-lasting laser treatments, and a surgical procedure so safe and effective that it will make eye drops and laser obsolete.

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Advances in laser treatment for open-angle glaucoma have been modest. In 1990, the first results of the Glaucoma Laser Trial\textsuperscript{14} demonstrated that initial laser was safe and at least as effective as initial medications for glaucoma. Selective laser trabeculoplasty became available in the late 1990s and was based on the clever idea that selective absorption of laser energy by the appropriate tissue might result in fewer side effects and greater effectiveness. Selective laser trabeculoplasty almost certainly led to a marked increase in the use of trabeculoplasty in the first years of the 21st century.\textsuperscript{15} However, careful, longitudinal trials suggest that it is no better than the argon laser.\textsuperscript{16}

Turning to the last in the triad of IOP-lowering interventions, trabeculectomy was the mainstay of incision surgery in 1990, and we were using both laser suture lysis and postoperative 5-fluorouracil (5-FU) injections. The 1-year results from the Fluorouracil Filtering Surgery Study\textsuperscript{15} demonstrated the effectiveness of 5-FU over no treatment in eyes at high risk of surgical failure.\textsuperscript{17} At the same time in the late 1980s that 5-FU was being investigated, Chen et al\textsuperscript{18} were experimenting with intraoperative mitomycin C (MMC), which led to small randomized controlled trials in both Japan\textsuperscript{19} and the United States\textsuperscript{20} confirming the effectiveness of MMC in increasing the success rate in eyes with a high likelihood of failure. During the 1990s, we also learned about the downside of MMC. Glaucoma surgeons became acquainted with the phenomenon of hypotony maculopathy and became familiar with consequences of inadequate wound healing, such as bleb leak and endophthalmitis. An editorial in the \textit{Journal of Glaucoma} in 2002 entitled “Late Endophthalmitis–Filtering Surgery Time Bomb”\textsuperscript{21} A randomized trial performed at Aravind Eye Hospital suggested that longer application times did not improve effectiveness but resulted in more cataract worsening than shorter application times.\textsuperscript{22} The hope that other adjuvant agents might be more effective and safer than MMC has not been realized.

On the basis of clinical trials in Scotland and England during the 1980s demonstrating the effectiveness of trabeculectomy as initial treatment for open-angle glaucoma, Lichter et al\textsuperscript{23} launched the Collaborative Initial Glaucoma Treatment Study (CIGTS), comparing initial medical treatment and trabeculectomy. An important aspect of the CIGTS was patient-reported quality of life. The study demonstrated equivalence of the 2 treatments,\textsuperscript{23,24} but because a tie usually goes to the status quo, the CIGTS did not result in more early surgery.

The shortcomings of trabeculectomy led to efforts both to modify trabeculectomy technique and to find other surgical means to lower IOP. Khaw et al\textsuperscript{25} championed the “safer surgery” concept, which espouses a fornix-based conjunctival flap and the application of MMC over a broad area of the sclera during trabeculectomy. Although aqueous drainage devices have been around since the 1970s because of the pioneering work of Tony Molteno, it was not until 1994 and 1995 that the Baerveldt aqueous drainage device and the Ahmed Valve, respectively, were introduced. The utility of these implants was validated in the randomized Trabeculectomy vs. Tube study,\textsuperscript{26} and the implants have also been rigorously compared with one another. Recognizing the filtration bleb as the Achilles’ heel of trabeculectomy, great effort has been expended to develop a blebless operation. Viscocanalostomy, nonpenetrating deep sclerectomy, and most recently canaloplasty purport to decrease resistance into Schlemm’s canal, but all involve conjunctival surgery and are no more effective than trabeculectomy. Avoiding the conjunctiva and using an ab interno approach is the guiding principal of microinvasive glaucoma surgery (MIGS).\textsuperscript{27} MIGS include both technologies that do not involve implantation of a device, such as the trabectome and endocyclophotocoagulation, and those that do. Long-term results of the trabectome, in which trabecular meshwork and the inner wall of Schlemm’s canal are removed with cautery, have been disappointing.\textsuperscript{28} Endocyclophotocoagulation has been around for at least 25 years, but data supporting its effectiveness has not been systematically collected and published.

Among the implantable devices, only the iStent trabecular bypass has been approved by the FDA, with the specific indication of reducing IOP in conjunction with cataract surgery.\textsuperscript{29} Two year data from a multicenter randomized trial of a second implantable device, the HYDRUS Schlemm’s canal microstent, appear in the issue of \textit{Ophthalmology}.\textsuperscript{1} The Cypass suprachoroidal shunt is another MIGS device undergoing phase III trials. As we learn more about the indications for these devices, and hope for FDA approval of those with solid data supporting their safety and effectiveness, we can already make use of convincing data demonstrating that phacoemulsification cataract surgery by itself lowers IOP in many eyes.\textsuperscript{29,30} In fact, a major challenge in demonstrating the utility of new devices is that their effect, when used in conjunction with phacoemulsification, must be greater than phacoemulsification alone.

The last 25 years have witnessed major changes in the medical therapy of glaucoma, incremental improvements in surgery for glaucoma, but only marginal improvements in laser treatment. With the strong interest shown by industry and surgeons, that may be about to change for incisional surgery. I hope that the next 25 years bring us better medications and a controlled drug-delivery system, neuroprotective agents that can protect the optic nerve, better and longer-lasting laser treatments, and a surgical procedure so safe and effective that it will make eye drops and laser obsolete.

References


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