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Therapeutics and Techniques

Medical Treatment of Newly Diagnosed Open-Angle Glaucoma

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The goal of therapy in the treatment of open-angle glaucoma is threefold. First, we strive to prevent the progression of damage to the visual pathways. Success of this endeavor has conventionally been assessed in terms of the stability of the ophthalmoscopic appearance of the optic nerve head and that of the visual field. Currently, numerous other techniques and measures of both anatomic and functional integrity are being vigorously investigated. Second, we attempt to achieve a lowering of intraocular pressure (IOP). This goal has become an accepted short-term focus of therapy even in the absence of signs of progressive damage. The third goal of therapy is to minimize side effects and complications. As in all medical specialties, in planning therapy for glaucoma we must always be thinking of the least invasive and least risky intervention that is likely to achieve the desired level of protection or cure.

This last goal is far from trivial. Consider, as an example, that this is the reason we do not perform, say, cyclodestructive procedures on all newly diagnosed ocular hypertensives, despite the fact that we would likely lower IOP and prevent some visual loss in at least some patients. In other words, the goals of preserving sight and lowering pressure must always be conducted in the context of minimizing the hazard, inconvenience, and cost of therapy.

Arguments favoring filtration surgery as the initial therapy for open-angle glaucoma, as well as those favoring laser trabeculoplasty, have recently been presented (1–6). Portions of this article have been previously published (7). The interested reader may consult these sources for additional perspectives.

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INITIAL THERAPY: FOR WHOM?

As a first step when considering medical treatment as initial therapy for open-angle glaucoma (and equally so for any other treatment modality), one must address the question, Who is the patient requiring *initial* therapy? If we wish to understand the rationale of medical treatment as initial therapy, we must consider not the end-stage patient with uncontrolled IOP, advanced nerve damage, and a deteriorating visual field, but rather the patient who has never received treatment. What is this patient like? What are this patient's needs?

Most patients requiring initial treatment fall into one of two categories. One type is the "glaucoma suspect." Such a patient may have any one of several clinical profiles, and several typical patients may be described. Perhaps there is a strong family history of glaucoma, somewhat anomalous-appearing discs, full visual fields, and borderline IOPs. Or perhaps the discs are normal in appearance, IOPs are mildly elevated, and there is a suggestion of visual field abnormality. Or, again, perhaps the nerve and the field are entirely normal but the IOP is unusually high, say in the upper 30s.

The second common type of patient requiring initial therapy is the newly diagnosed, clear-cut glaucoma patient, usually with mild to moderate dam-

age. This patient may have a typical and confirmed visual field defect, moderate optic disc abnormalities, and modest elevation of IOP. Or perhaps the fields are full, but there is advanced excavation of one or both discs. There may also be asymmetric IOP elevation, perhaps higher on the side with the affected disc.

Thus, the typical patient who unambiguously requires initiation of treatment may have mild signs of optic nerve or visual field damage or both, and perhaps elevated IOP. Only seldom, in our experience, will an untreated, newly diagnosed patient be encountered who has advanced nerve or field damage, although it does happen. It is important to note that the usual patient requiring *initial* treatment for open-angle glaucoma has not been studied extensively with respect to the pressure dependency of their damage (if any), the progressive nature (or otherwise) of their condition, the responsiveness of their IOP to therapy, or their ability to comply with and tolerate various medical regimens.

But each patient, for varying reasons, will have been judged to benefit from the institution of IOP-reducing treatment. Is it reasonable to begin with medical treatment as initial therapy and, indeed, to persist with medical treatment until medical options have been exhausted? Following the principles set forth at the outset of this article, acceptance of the affirmative answer to this question will require that medical therapy can reduce IOP; medical lowering of IOP retards visual damage; other things being equal, the risks of medical therapy are less than those of other approaches. We consider these requirements in turn.

DOES MEDICAL THERAPY LOWER IOP?

All of the classes of medication currently approved for use in treating glaucoma have been shown to lower IOP in controlled clinical trials. In treating an individual patient, however, the results of clinical trials can never be more than a guide. That is, if a drug, such as timolol, has been shown to reduce IOP by, say, 33% on average, can we assume that it will lower IOP by this amount in each patient? Obviously not, and we must evaluate *every* proposed medication in *every* patient whom we wish to treat.

This conclusion brings us to the cornerstone concept of medical therapeutics, considered as a practical rather than theoretical matter: the *therapeutic trial*. In seeking to lower IOP, we choose a medication that is efficacious in most patients, has an acceptable risk of side effects in the patient at hand, and is likely to be tolerable to that patient. β-Blockers and cholinergics are the usual classes that most clinicians use in this regard. After a short trial (on the order of weeks), preferably administered in one eye only, one should assess the results.

At this point, there is essentially a straightforward decision-making process that must be followed. We assess the new IOP. Has it been lowered? If the answer is "yes," we may be satisfied with the new IOP and may obtain an IOP diurnal curve. Or it may be that the new, lower IOP is still not low enough (according to criteria established by the patient's clinical history), in which case we may try an additional or substituted drug or perhaps a change in concentration. If the answer to our question is "no," we must conclude that this particular drug, at the concentration used, is not efficacious for the patient at this time. We do not exclude the possibility that poor compliance is the cause (perhaps because of intolerance to the drug) nor that this drug may yet work in combination with another drug. Nevertheless, our goal is to discover as quickly as possible a regimen that is both tolerated and effective.

Even if the drug is efficacious, we must assess the side effects, if any, that have been experienced. If we foresee a problem with tolerance or with compliance, we address the matter openly and do not hesitate to change medications, noting, for possible future use, the IOP reduction that may have been obtained. Sometimes, we may try a lower concentration of the same drug.

And always, there is the issue of compliance. This problem has been shown to be a major issue (8), and we feel that continuing emphasis to the patient of the importance of regularity in dosing is a central feature of medical therapeutics. However, the fact that strict compliance is a problem for some people does not mean that *all* patients are incapable of compliance. A reasonable principle of therapeutics would be initially to give each patient the benefit of the doubt with regard to compliance and also to give the patient an educated understanding of the critical importance of regular dosing.

Moreover, it seems ethically presumptuous to advocate surgical therapy as advantageous even partly because it does not require compliance with a regimen for its outcome, since it is fair to expect patients to share in the responsibility for their own

therapy and unfair, perhaps, to deny them the opportunity to do so.

In short, medical therapy can lower IOP, but whether it does in any given patient is always an empirical matter. Aggressive attempts to find the right combination of drugs often result in a regimen satisfactory to both the patient and the physician. The therapeutic regimen settled upon will be an idiosyncratic combination of the pressure response of each patient to each drug, the ability of each patient to tolerate an efficacious drug, and the ability and willingness of the patient to comply with the regimen. Only a therapeutic trial conducted with all of these considerations in mind will lead to a successful regimen.

DOES MEDICAL THERAPY RETARD DAMAGE?

The next key question that we wish to answer is: Is the pharmacologic lowering of IOP protective? In phrasing a broad empirical question such as this, one must take great care to bring into sharp focus the thrust of the question. What group of individuals is being considered? How much lowering must be accomplished? How do we define "protective"?

It is helpful to keep these and related questions in mind in considering three recent large, prospective studies of therapy with timolol that have addressed this question. Each study sought to follow a group of patients for ≥5 years, treating half of the enrolled eyes with timolol and the other half with either placebo or no treatment at all. Unfortunately, the results of these carefully conducted studies have not yielded consistent evidence in support of the benefits of medical reduction of IOP as initial therapy, but in some measure this is almost certainly due to the fact that they have not succeeded in properly addressing the question—testimony to the great difficulty involved in studying this problem.

Kass et al. (9) conducted a randomized, double-masked, prospective long-term clinical trial to determine whether topical timolol therapy is effective in delaying the onset of disc or visual field abnormalities in patients with ocular hypertension. Sixty-two patients with bilateral IOPs between 24 and 35 mm Hg were treated with 0.25% timolol in only one eye, chosen at random, and with placebo in the other eye. If an eye showed IOP >20 mm Hg later on, the bottle was changed. In the case of the timolol-treated eye, the new drop was 0.5% timolol, whereas in the case of placebo the "new" drop remained placebo—this maneuver preserved the masking of group assignment.

Because of selection criteria, enrolled patients had a higher than normal vertical cup/disc ratio (average 0.48), unusually low outflow facility (0.12 μl/min/mm Hg), and a markedly high incidence of family history of glaucoma (52%) and of diabetes mellitus (21%). Patients were followed until confirmed visual field loss was present in either eye. The development of optic nerve head changes, as judged from stereoscopic photographs, was noted, but participation in the trial was not altered by these changes. IOP was not used as an end-point in the study. Patients not showing either of the end-point changes were followed for a minimum of 5 years and some for as long as 8 years. Forty-three of the original 62 patients completed the minimum 5 years of follow-up or developed visual field loss.

As expected, timolol therapy significantly lowered IOP in the timolol-treated eye relative to the placebo-treated eye. Reproducible visual field loss occurred in four timolol-treated eyes and in 10 placebo-treated eyes, a significant difference. Changes in cupping of the disc occurred in four timolol-treated eyes and eight placebo-treated eyes, a difference that was not statistically significant. Optic disc pallor was quantitatively assessed from photographs using a computerized image analysis system; all patients followed for ≥4 years had final disc photographs compared against baseline photographs. The increase in pallor in timolol-treated eyes was 0.86%, and in the placebo-treated eyes it was 1.80%, a significant difference.

In a second study on this important topic, Epstein et al. (10) conducted a prospective, randomized trial in which 107 patients with IOP between 22 and 28 mm Hg, but neither disc abnormalities nor Goldmann visual field defects, were either treated with timolol 0.5% twice daily or followed without any treatment. The patients were followed for an average of 4.5 years and were considered to have "failed" the chosen course of treatment if they exhibited IOP >32 mm Hg on two occasions, disc changes (judged in a masked fashion from stereoscopic photographs), or visual field progression.

Again, timolol treatment significantly lessened IOP. During the cumulative follow-up period of the study, 17 of 54 patients (31%) who were untreated failed (i.e., were given a diagnosis of glaucoma), while nine of 53 patients (14%) being treated with timolol failed. However, of the nine treated failures, six had actually discontinued treatment before fail-

ure. The difference between the survival curves of the two groups was significant, indicating a protective effect of timolol. However, when failures were defined only by disc and field criteria and not by IOP-related criteria, the difference between the survival curves was not significant unless patients who stopped timolol were considered to be immediately lost to follow-up (and thus subsequently excluded from the survival curve analysis).

Schulzer et al. (11) conducted a study similar to that of Epstein et al. (10), in which they sought to show a protective effect of IOP reduction by timolol among patients with pressure elevation but no signs of damage at the time of enrollment. They followed 105 patients for a minimum of 6 years or until they showed signs suggestive of glaucoma. All patients initially had an IOP of ≥22 mm Hg, normal visual fields, and no signs of glaucomatous disc damage. Patients had a somewhat higher than usual number of risk factors for glaucoma: 31% had a family history of glaucoma, and 29% had a cup/disc ratio of ≥0.5.

Patients were randomly assigned either to receive no treatment or to receive timolol at a concentration of either 0.25% or 0.5%, as needed. Patients were followed until reaching one of three end points: disc changes, as judged from the masked reading of stereoscopic photographs; disc hemorrhage; or a visual field abnormality. The criteria for a field abnormality were stringent in that a putative defect had to be repeatedly detected on three successive automated tests in order to be confirmed as genuine.

As expected, the timolol-treated eyes had a significant IOP decrease. Of the 105 patients, there were 42 end points reached. Of them, 28 were field defects, eight were disc changes, and six were disc hemorrhages. Of the 28 end points due to field defects, 15 were among the treated patients, and 13 were among the untreated patients. Of the eight patients who had disc changes, two had been treated, and six had been untreated. Finally, of the six patients who had disc hemorrhages, there were three who had been treated and three who had been untreated. It was not stated whether any of these differences (in particular, among the patients who had disc changes) was a statistically significant one. Survival analysis showed that there was no difference in the mean time to failure, from any cause, of treated as compared with untreated patients.

Schulzer et al. (11) concluded that the "pressure reduction obtained may not protect the susceptible individual from the development of localized visual field defects and possible disc changes as well. This cannot be applied in general to pressure reduction, as it may only mean that pressure reduction produced by the nonspecific β-blocker that we used and the pressure level that was obtained does not protect the susceptible individual from visual field defects."

This point was amplified by Javitt et al. (12), who, in a discussion of this study (11), observed that the 4.5 mm Hg IOP decrease achieved nevertheless left treated patients with a mean IOP that was never <21 mm Hg. They noted that this might be regarded as rather mild pressure reduction for a true glaucoma suspect.

These three articles have thus begun the important task of empirically addressing the issue of whether lowering IOP through medication is effective in forestalling the advent of glaucomatous changes in the disc or the visual field. Unfortunately, the results of the studies collectively appear to be inconclusive. One study (9) found a small but significant benefit to treatment. Another study (10) found a small but significant benefit, but it was lost when the data were reanalyzed to disregard those patients who failed only because of pressures that were felt to be too great. The third study (11) failed to find any benefit of treatment. What should we conclude?

First, it should be borne in mind that substantial IOP reduction by surgery has already been shown to reduce the risk of glaucomatous progression. As summarized in the American Academy of Ophthalmology's preferred practice pattern manual for primary open-angle glaucoma (13), there are a number of studies that, taken together, essentially provide a dose–response curve relating IOP to the prognosis for stability of visual field (14–21). Unfortunately, with one exception (21), all of these studies were retrospective. Also it must be emphasized that most patients in these studies had advanced glaucomatous damage, and therefore the results may well not be generalizable to the patient with newly diagnosed glaucoma or to the ocular hypertensive patient.

Second, the group of patients followed in the three timolol versus no treatment studies were, by virtue of the inclusion criteria, ocular hypertensives and not actual glaucoma suspects. Accordingly, many of the studied patients may have had no predisposition to glaucomatous damage, whether treated or not. Therefore, the rate of progression among the study patients may have been too low to discern significant differences between treated and

untreated groups. In many practices, including ours, such patients are followed, not treated, because of the very low chance that they will go on to manifest frank glaucomatous damage. Given our current beliefs about the relationship between IOP and damage, ethical considerations make a long-term, prospective, randomized trial of treatment versus no treatment among glaucoma patients hard to envision, but in our desire to overcome this methodological obstacle, we must not rush to conclude that medical lowering of IOP has no benefit in *glaucoma,* based on studies of rates of progression among those with *ocular hypertension.*

Third, the amount of IOP reduction achieved by these three trials was certainly *statistically* significant but may not have been *clinically* significant. It is as though half of the patients in these studies were assigned to IOP reduction, and then IOP itself was disregarded. In usual practice, given a patient with minimal damage, once the decision to lower IOP has been made, we usually target a particular IOP level within the normal range. If the chosen medication does not lower IOP to that level, it is either supplemented or changed. In other words, a more clinically pertinent comparison of treatment versus no treatment might result from a trial comparing aggressive lowering of IOP against observation among ocular hypertensives. Stated differently, a limitation of these studies is that they were studies of the benefits of timolol treatment. What actually is needed, we believe, are studies of the benefits of significant IOP reduction. Just such a study, the National Eye Institute–sponsored Ocular Hypertension Treatment Study, is being organized, and we may have better information on this topic within the next few years.

Fourth, there is a purely statistical limitation to a negative result, such as that reported by Schulzer et al. (11). Such a result cannot prove that no true difference exists. As pointed out by Javitt et al. (12), there is the "possibility that their negative findings in this small sample of patients may be the result of a type II error (i.e., that they failed to find a true difference between treatment and no treatment in their particular sample of patients)."

Fifth, as pointed out by Schulzer et al. (11), the criteria used by all three studies to detect visual field changes were meant to identify localized scotomas and were insensitive to generalized or diffuse depression. In view of recent evidence (22) that glaucoma patients with higher IOPs have more diffuse damage and those with lower IOPs (low-tension or normotensive glaucoma) have more localized damage, this shortcoming is likely to have had an adverse impact on the ability of the current round of studies to detect a protective effect of IOP reduction among ocular hypertensives.

We began this section by asking, Does the medical lowering of IOP retard visual damage? The question is probably best regarded as not yet having been properly addressed. We can conclude neither that modest reductions of IOP with timolol are clearly beneficial nor that they are not. We must await future studies for proof that medical lowering of IOP is effective. Until such studies are available, we feel it is reasonable to expect that *aggressive* medical lowering of IOP, comparable with aggressive surgical lowering of IOP, will be of benefit to patients with IOP-sensitive glaucomatous damage.

OTHER APPROACHES TO INITIAL THERAPY OF OPEN-ANGLE GLAUCOMA

IOP may be lowered, in general, by any one of three methods: medication, laser trabeculoplasty, or surgery, including filtration and cyclodestruction. Any of the three modalities may result in adequate lowering of IOP, in the sense of achieving a "target pressure" deemed protective for a particular patient at a particular time.

Argon Laser Trabeculoplasty as an Alternative to Medical Therapy

Argon laser trabeculoplasty (ALT) can lower IOP. The main "risk" is that it may not work. Failure of the procedure is increasingly likely with the passage of time (23–26). Shingleton et al. (26), for example, reported that late failure of ALT, as defined by IOP >19 mm Hg, progressive damage, or the need for further surgical therapy, was 23% in the first year and in the range of 7–10% per year thereafter, as shown in Fig. 1. The failure rate at 5 years was 51%. In a more recent report from the same group (27), failure was 70% at 10 years. Ticho and Nesher (28) reported that the failure rate tends toward zero for those whose treatment has succeeded for at least 6 years. Nonetheless, it appears that ~50% of patients will need retreatment and/or supplementary medical therapy to achieve the desired level of control. Retreatment itself has been variously reported to be successful in many cases or in only a few cases (29). The differing results of published studies on this matter may be related to

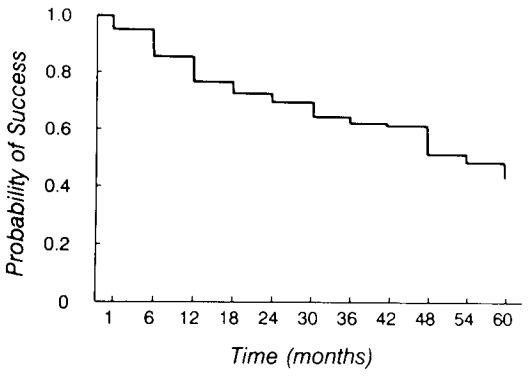

FIG. 1. Survival curve for time to failure after argon laser trabeculoplasty. From reference 26, with permission.

differences in inclusion criteria for study of retreatment, in treatment protocol, and in criteria for failure of initial treatment. In any case, it should be borne in mind that none of these studies was concerned with *newly diagnosed* cases.

However, in the recently completed national Glaucoma Laser Trial (GLT) (30) (discussed below), more than half of the patients who received ALT as initial therapy required medication within the 2-year duration of the study. Overall, ALT can *delay* medical therapy but often does not allow the patient to be *free* of it. Furthermore, ALT frequently has a limited duration of success, which for a chronic, lifelong condition may imply a relatively brief respite from medication.

The GLT was a 2-year, multicenter, randomized, prospective trial (30) in which ALT was compared with medical therapy as the initial step in the treatment of newly diagnosed open-angle glaucoma. Because of the great significance of this large National Eye Institute-funded trial, we will review its design and findings and discuss its conclusions in some detail.

Each eye of 271 patients with elevated IOP and either field or disc abnormalities was assigned to be treated either by ALT, followed if necessary by stepped medical care, or by stepped medical care alone. The protocol called for ~100 laser applications to be placed over 360° of the iridocorneal angle in two sessions, using anterior trabecular meshwork placement and power intensity adjusted to cause blanching. Stepped medical care consisted of 0.5% timolol (step 1), 0.1% dipivefrin (step 2), low-concentration pilocarpine (step 3), high-concentration pilocarpine (step 4), timolol with high-concentration pilocarpine (step 5), and dipivefrin with high-concentration pilocarpine (step 6). If the final step was ineffective in controlling IOP, the patient was treated according to the individual preference of the treating physician (step 7). Steps were mandated if IOP was uncontrolled (defined as IOP >22 mm Hg or IOP <8 mm Hg lower than baseline IOP), if there was confirmed field or disc deterioration, or if there were adverse signs or symptoms, such as blurring, arrhythmias, and so forth. Most patients were followed for ≥2 years. The principal outcome measures were the number of medication steps the patients underwent, change in visual field, change in optic disc, change in IOP, and change in visual acuity.

IOP for the laser-first eyes decreased by 9 mm Hg by 3 months after treatment, while medicine-first eyes showed a 7 mm Hg IOP reduction at this time. This 2 mm Hg difference persisted throughout the 2-year duration of the study and was statistically significant. At 2 years, 44% of the laser-first eyes were controlled without any additional therapy (i.e., any medication), whereas at 2 years 30% of the medicine-first eyes were controlled with the single initial medication, which was timolol. However, at 2 years, 51% of the medicine-first eyes were controlled by steps 1, 2, 3, or 4; that is, with a single medication, though not necessarily timolol.

Visual acuity was stable in both groups. About 85% of the steps to advance therapy in both groups were taken because of uncontrolled IOP. Fourteen percent of the steps in advancing therapy in the laser-first group and 8% in the medicine-first group were implemented because of visual field deterioration. Seven percent of the steps in the medicine-first group and 2% of those in the laser-first group were taken because of adverse signs or symptoms. No eye, in either group, was advanced through the stepped therapy because of disc deterioration. The manifestation of peripheral anterior synechiae (PAS) was a common occurrence among eyes in the laser-first group. Thirty-five percent of these eyes, compared with 3% of eyes in the medicine-first group, developed PAS.

The authors of this study concluded that "fewer medications are needed by [laser-first] eyes than [medicine-first] eyes in all identifiable subgroups" and that "ALT is at least as good as if not better than starting with medications, because in the short term, ALT provides good pressure control and has the advantage of postponing and/or reducing the inconvenience, nuisance, and side effects associated with taking medications."

As have many earlier studies, the GLT has cer-

tainly succeeded in showing the efficacy of ALT as an IOP-lowering treatment. But the stated goal of the study was to "assess the efficacy and safety of argon laser trabeculoplasty (ALT) as an *alternative* to treatment with topical medication" (emphasis ours). Has the GLT shown that initial ALT is comparable to initial medications? Has it shown us that ALT is a viable, perhaps even advantageous, candidate to be the first choice in therapy? Thoughts on these questions have been presented in editorials by Lichter (31) and by Van Buskirk (32), which should be required reading for anyone interested in evaluating this study in detail.

The key outcome measure in the GLT study was the "relative efficacy of ALT versus topical medication for reducing the need for medication," and the trial has indeed confirmed that there is less need for medications in order to control IOP after ALT. Is this not then prima facie evidence that ALT is a rational choice for a first step in therapy? Lichter (31) pointed out that before rushing to this conclusion, it should be noted that the complementary question of whether medication reduces the need for ALT has been neither answered nor even asked in this study, but this is, in fact, one of the crucial comparisons to be made before concluding that initial ALT is superior to initial medications. Lichter stated that he "will look forward to the follow-up results of those medicine-first eyes that underwent ALT after reaching step 7 of the 'stepped medication regimen' as compared with the laser-first eyes that reached step 6."

Lichter also observed that

> if, instead of assessing the efficacy of ALT as compared with topical timolol for initial glaucoma therapy, the study asked whether ALT was as effective as any *single* topical medication in reducing intraocular pressure, the results would have had a different spin. The study showed that a single medication . . . was effective in controlling 51% of the [medicine-first] eyes as compared with ALT alone controlling 44% of the [laser-first] eyes. In other words, if ALT had been the standard therapy and the efficacy of initial medical therapy was being evaluated, medical therapy would have had the edge—at least in terms of the pressure reduction goal used in this study (emphasis ours) (31).

Finally, Lichter drew attention to the "worrisome trend," not statistically significant, evidenced in the finding that "nearly twice as many laser-first eyes as medicine-first eyes required an increase in stepped therapy due to deterioration of the visual field."

Van Buskirk (32), in his editorial, echoed many of the points made by Lichter. He also provided an analysis of the design of the GLT that suggests marked limitations in the practical conclusions that may be drawn. Van Buskirk pointed out that the laser-first eyes really received ALT as a first step in therapy, and the addition of timolol, if and when it came, was really step 2. On the other hand, for medicine-first eyes, step 1 was the institution of timolol, while step 2 was a change to dipivefrin, which has been shown to be, on average, far less effective than timolol as an IOP-lowering agent. Van Buskirk observed that

> in Step 2, the laser-treated eyes had already received laser therapy and were receiving timolol, but the medically treated eyes were receiving dipivefrin alone. . . . In essence, for the laser-treated eyes, Step 2 became a giant step ahead, but, for the non-laser-treated eyes, Step 2 was a leap backward! It should come as no surprise that the medically treated eyes required a move beyond Step 2 to Step 3 or 4, since they had to go all the way to Step 5 before again becoming eligible to receive a significant aqueous humor suppressant. . . . [This design] invalidates using the number of therapy step changes as an index of relative therapeutic efficacy (32).

We must agree with Lichter and Van Buskirk that the results remain inconclusive. We continue to reserve ALT for patients whose IOP cannot be controlled medically and await further long-term comparisons of these modalities before we can recommend the physiologically irreversible step of laser therapy to our patients.

Filtering Surgery As an Alternative to Medical Therapy

As mentioned earlier, surgical filtering procedures have been shown to be capable of dramatically lowering IOP. They also have been shown to be protective of vision. Surgery, however, carries considerable risk of complication, and the complications of intraocular filtration surgery can be substantial (33–38). These risks can be divided into intraoperative, early postoperative, and late postoperative complications. The intraoperative complications include retrobulbar hemorrhage, ocular perforation, local anesthetic-induced allergic or toxic reactions, general anesthetic adverse reactions, conjunctival buttonholes, scleral flap dissection errors, iris bleeding, and vitreous loss.

Early postoperative complications include hypot-

ony (either from hyposecretion or overfiltration), flat anterior chamber, lens–corneal touch, choroidal detachment, suprachoroidal hemorrhage, malignant glaucoma, corneal epithelial defects (especially with adjunct anti-metabolite therapy), hyphema, uveitis, postoperative pressure spike, "snuff-out" of a small central visual island, and endophthalmitis.

Late postoperative complications include most of the early complications and also filtration failure, decreased visual acuity, visual distortions attributable to iridectomy, encapsulated filtering bleb formation, large cystic bleb formation, filtering bleb infection, filtering bleb leak, cataract formation, corneal decompensation, astigmatism, retinal detachment, cystoid macular edema, epithelial or fibrous downgrowth, pupillary distortion, and vitreous hemorrhage.

The severity of the encountered problem may range from the nearly benign to the (rarely) life-threatening. The risk of any specific one of these complications may be reduced to an acceptably low level by meticulous attention to detail in the management of the surgical patient, but it is the rare patient who undergoes surgery without experiencing one or more of these complications. For example, one of the commonly mentioned complications of trabeculectomy is cataract formation. Harding and Egerton (33) studied the histories of 423 adult cataract patients and compared their epidemiologic profiles with those of 608 age- and sex-matched controls. The relative risk of cataract among those with a concurrent diagnosis of glaucoma was 2.9, but among those who had glaucoma surgery, the relative risk was 14.3. About 60% of this risk was attributable to iridectomy, and the rest was associated with trabeculectomy. The next highest relative risk, 4.3, was due to diabetes.

Medical therapy is not without risks as well. However, most of the complications of medical therapy, which have been well described in the literature (39–42), are reversible on discontinuation of treatment.

Furthermore, as with ALT, the success rate of filtering surgery is far from perfect and decreases steadily the longer we follow patients postoperatively. Lamping et al. (43), for example, showed that the success rate declined steadily for up to 5 years after either full-thickness procedures or trabeculectomies (Fig. 2).

Moreover, surgical intervention often must be supplemented by medical therapy in order to achieve the desired final IOP reduction. Thus, improved quality-of-life arguments for surgery, in regard to eliminating the need for medication, will often be rendered moot. In this regard, Lamping et al. (43) also reported that 32% of patients undergoing full-thickness procedures and 49% of patients having trabeculectomies required topical medicines for control after 2–3 years of follow-up. Presumably, because the failure rate increases with the passing of time after surgery, the need for medications also would have increased even more had follow-up been longer.

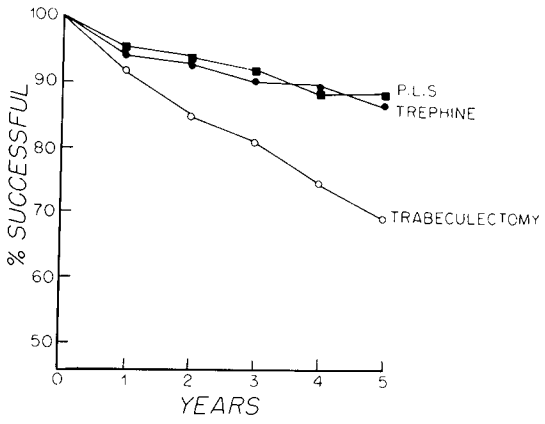

FIG. 2. Survival curve for time to failure after full-thickness procedure with posterior lip sclerectomy (P.L.S.) or with trephine and after trabeculectomy. From reference 43, with permission.

There have been several published studies comparing surgical treatment as initial therapy with medical therapy. In an early study, Demailly et al. (44) randomly and prospectively assigned 60 eyes of newly diagnosed open-angle glaucoma patients to receive either medical treatment only or initial trabeculotomy. After 16 months of follow-up, there were no significant differences between the two groups with respect to overall visual field indices, cupping, incidence of acuity-lowering complications, or IOP. However, 25% of the surgically treated patients were being given medical treatment by 16 months after surgery.

Migdal and Hitchings (45) reported a randomized comparison of ALT, trabeculectomy, and conventional medical treatment in a total of 168 patients with newly diagnosed open-angle glaucoma. All patients had IOPs of $\geq$24 mm Hg, cup/disc ratios of $\geq$0.6 or other glaucomatous disc abnormalities, and visual field loss. The three groups, approximately equal in size, had comparable IOPs at the outset (~34 mm Hg). Eyes in the laser-treated group were

permitted to receive pilocarpine if clinically judged to require lower IOP.

At all times from 6 months to 2 years, trabeculectomy resulted in the lowest IOP. At 2 years, the medically treated group had a mean IOP of 19.2 mm Hg, the laser-treated group had a mean IOP of 18.3 mm Hg, and the surgically treated group had a mean IOP of 15.4 mm Hg. The diurnal variation of IOP was found to be least in the surgically treated group.

Although this study showed that surgery may result in lower IOPs than either ALT or medical treatment, the authors unfortunately did not mention any complications of surgery or of ALT that may have occurred (or any side effects of medication that were encountered), although we must assume there were some. Nor is there mention of what changes, if any, in visual acuity, visual field, or optic nerve head appearance were observed in the three groups over the course of the study. However, they did acknowledge that there is a "known ocular morbidity" of surgery.

In another series from Great Britain, Jay and Murray (1) and Jay and Allan (46) described a randomized, prospective, multicenter trial in which previously undiagnosed patients with IOPs of $\geq$26 mm Hg and visual field loss were treated either medically, followed by trabeculectomy when necessary or with trabeculectomy, followed by medical therapy when necessary. Criteria for failure of medical therapy were largely left to the discretion of the participating physicians: inadequate pressure control and progression of visual field were undefined, and maximal medical therapy consisted of no more than three topical or oral medications. Ninety-nine patients completed at least 1 year in the trial. The group treated medically "showed more frequent and more severe loss of visual field" than the group having early trabeculectomy.

Since various aspects of treatment were discretionary, this study appears to be more a description of a certain practice pattern than a controlled study. For example, one of the main variables was the rate at which those who were initially treated only with medicines went on to trabeculectomy. However, the criteria for this decision were not fixed and were not defined; neither was the degree of aggressiveness of medical therapy. We are thus unable to say whether the results reflect a comparison of the two modes of treatment that would be generalizable to other practices in other centers.

Jay (4) has summarized his view of these issues, stating that a "brief trial of closely supervised medical therapy is clearly the appropriate first line of treatment in the less severe cases" and that trabeculectomy should be performed "without a trial of medical therapy in eyes presenting with pressure over 30 mm Hg and with absolute areas of field loss."

We believe that interpretation of these studies must be undertaken with care, however, since they have shown that surgery, as performed by the respective authors, results in a lower IOP than does medical therapy, as performed by the authors. Moreover, individual patients who are compliant and whose IOPs are responsive to medication may not require surgery to achieve a target pressure, yet initial surgery would prevent these responders from being identified as a subgroup. Nevertheless, we agree that patients whose target pressures cannot be medically achieved, or who continue to show field progression despite IOP reduction, must be rapidly identified and offered surgery to attempt to achieve more aggressive IOP reduction.

Notwithstanding our reservations about these studies, if we accept that lower IOP is of benefit in retarding progression, does it not follow that surgery gives an improved chance of halting progression? Unfortunately, we believe that all that has been shown is that other things being equal, a lower IOP, achieved by any means, is more protective than a higher IOP. It has not been shown that *for equivalently lowered IOP achieved surgically versus medically, there is a benefit to surgical intervention.* In other words, if one could medically lower IOP to the same level as was accomplished through filtration surgery, the apparent greater protection afforded by surgery might be eliminated. In some patients, filtration surgery clearly can lower IOP more than medical therapy. And in some patients, maximally tolerated medical therapy fails to achieve an IOP deemed acceptable.

A more reasonable approach to the question of which modality is "better" might be to compare surgical and medical outcomes, in terms of long-term rate of progression, among patients who have been stratified according to the IOP level achieved. Only in this way would we actually learn whether surgical results, with all the attendant complications, were better than, worse than, or similar to medical results with attendant complications. Neither we nor any other group, to our knowledge, has conducted such a study.

Because of our reservations we are thus unable to agree with the recent conclusion of Sherwood et al.

(2) that "IOP control is significantly better with primary surgery than medical therapy" and that "if the level of IOP is important in the management of open-angle glaucoma, then primary trabeculectomy, by achieving and maintaining the lowest mean IOP with a flatter diurnal pressure curve, best achieves this aim."

Another interesting issue that has been raised is whether long-term medical therapy actually *worsens* the chance of success of later trabeculectomy. Lavin et al. (47) retrospectively reviewed the results of surgery in two groups of patients, one having been medicated for at least 1 year before trabeculectomy, the other having undergone trabeculectomy after an average of only 2 weeks of medical therapy. Those who underwent trabeculectomy after 1 year had previously failed to be controlled with medications alone. Patients were followed for a minimum of 18 months after surgery. Failure of surgery was defined solely by whether there was an IOP of $\geq$21 mm Hg without medical therapy.

Only one of 47 eyes in the early surgery group failed by this criterion, whereas 12 of 34 eyes in the late surgery group failed, a significant difference. One possible flaw in the study, as the authors acknowledged, is that the trabeculectomy group had already failed medical treatment, and they thus may have had a predisposition toward higher IOPs despite attempts at either medical or surgical therapy. However, the authors were unable to identify any variable that differed between the two groups that could account for the difference. They speculated that possible activation of fibroblasts or other inflammatory cells, either by the topical medications themselves or by preservatives in their vehicles, may have contributed.

The series by Jay and associates (1,46) found identical postoperative IOPs in their immediate surgery group and their delayed surgery (after medical treatment) group, although the latter patients had received 2–3 years of medication, while those in the retrospective study of Lavin et al. (47) had received ~6 years of medical therapy.

In a related study, Sherwood et al. (48) compared conjunctiva–Tenon's capsule biopsy specimens taken during trabeculectomy from two groups of patients with open-angle glaucoma, one of which had received early trabeculectomy (after an average of only 3 weeks of medical therapy with pilocarpine after initial diagnosis), and the other of which had undergone an average of 7.7 years of medical therapy with at least two types of medication plus ALT in some cases before surgery. There were significantly more inflammatory cells, including fibroblasts, in the tissues of the long-term medical therapy group as compared with the early surgery group.

Interpretation of these provocative results is clouded first by the fact that the treatment group, as defined in the study, is confounded with the duration of disease, so that those patients who had been treated medically for many years also had been diagnosed with glaucoma for many years, while the early surgery group had had a far briefer duration of disease. It is possible that disease, or high IOP, and not medical therapy may have led to increased numbers of inflammatory cells. Second, the medically treated patients had had ALT as well, and it is possible that this treatment, and not medication, was the cause of the inflammation. Finally, the clinical import of Sherwood et al's. finding (48) is unclear, since no evidence was given that the surgical success rate in the two groups of patients either differed or depended on the type or quantity of cells that were seen at the time of surgery and biopsy.

Moreover, a relevant laboratory study was performed by Williams et al. (49), who investigated whether any of three widely used topical β-adrenergic blocking agents or their preservatives stimulated proliferation of human Tenon's capsule fibroblasts that were grown in culture. Contrary to their promoting proliferation, these drugs were actually toxic to fibroblasts at concentrations even less than, as well as roughly equal to, those found in commercial preparations, and at no concentration did any of the drugs stimulate fibroblast growth.

As the authors acknowledge, comparison of these results with possible in vivo drug actions may be invalid, since, for example, in vivo dosing is transient, while in vitro drug exposure in this study was continuous. It may be that toxicity itself leads to chronic inflammatory cellular activation. Further studies on other classes of drug and using different assays of inflammation are clearly needed.

This provocative and important set of findings regarding the possible adverse consequences of long-term medical therapy clearly deserves further study. It is also to be hoped that further clinical studies of the effects of long-term topical antiglaucoma medications on surgical outcome will soon be available and will be prospective and randomized in nature. Until then, we feel it would be

premature to prognosticate a worsened outcome of later filtering surgery when committing a patient to medical therapy.

CONCLUSION

In the absence of longitudinal, individualized evidence that the degree of IOP reduction achieved using maximally tolerated medical therapy has failed to stabilize the disease, we believe that early surgery submits patients to this irreversible step in advance of evidence that such surgery is required for control of progressive glaucoma. Interestingly, Sherwood et al. (2), at the conclusion of their recent review of the evidence favoring early trabeculectomy as an alternative to medical treatment, state that "it is not suggested, with the evidence currently available, that primary surgery be recommended for all glaucoma patients." It seems that even those who find the arguments for early surgery most compelling are unwilling to commit the patient to surgery until medical options have proved unsatisfactory.

Moreover, we believe that the proper empirical comparison should be between surgical intervention and *optimized* medical intervention. Our wish to avoid the complications of surgery mandates that we exert the fullest possible effort at reduction of IOP using tolerated medicines alone before we reject that course in favor of a filtration procedure. In any individual case, it is always a possibility, until excluded by experience, that more aggressive medical therapy will succeed in reducing IOP to a target level judged to be acceptable. "Aggressive medical therapy," as used here, means frequent monitoring of diurnal variations to assess the peak IOP, stress on compliance, willingness to substitute or retry medications in new combinations, willingness to switch drugs within a class to minimize side effects and/or improve tolerance and compliance, and valid assessment of disease progression.

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