Clinical Ophthalmology

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PERSPECTIVES

Alternatives to Topical Glaucoma Medication for Glaucoma Management

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Abstract: Topical glaucoma medications have favorable safety and efficacy, but their use is limited by factors such as side effects, nonadherence, costs, ocular surface disease, intraocular pressure fluctuations, diminished quality of life, and the inherent difficulty of penetrating the corneal surface. Although traditionally these limitations have been accepted as an inevitable part of glaucoma treatment, a rapidly-evolving arena of minimally invasive surgical and laser interventions has initiated the beginnings of a reevaluation of the glaucoma treatment paradigm. This reevaluation encompasses an overall shift away from the reactive, topical-medication-first default and a shift toward earlier intervention with laser or surgical therapies such as selective laser trabeculoplasty, sustained-release drug delivery, and micro-invasive glaucoma surgery. Aside from favorable safety, these interventions may have clinically important attributes such as consistent IOP control, cost-effectiveness, independence from patient adherence, prevention of disease progression, and improved quality of life.

Keywords: intervention, treatment, sustained release drug delivery, MIGS, medication, selective laser trabeculoplasty

Years of Topical-Medication-First Glaucoma Therapy

Topical medical therapy has been the mainstay of glaucoma therapy for more than 150 years. In that time, multiple classes of drugs have been developed to lower intraocular pressure (IOP) through a variety of mechanisms of action. The regulatory and approval process ensures that the numerous available medications all safely and effectively lower IOP, and major clinical trials have demonstrated that lowering IOP delays or prevents the development and progression of glaucoma,[1–4] reinforcing the medication-first paradigm. Even as new non-medical therapies and procedures such as laser trabeculoplasty and trabeculectomy were developed, they have yet to change the medication-first status quo.[2,5,6] Medical therapy has remained the most common approach to glaucoma treatment despite multiple important limitations, which have been tolerated in part due to lack of viable alternatives and easier accessibility.

In more recent years, newer therapeutic options, including selective laser trabeculoplasty (SLT), sustained-release drug delivery (SRDD) platforms, and minimally invasive glaucoma surgeries (MIGS), have renewed scrutiny of the medication-first approach to glaucoma. The overall rationale for this paradigm shift was presented in the recent paper by Radcliffe et al,[7] which noted the high rates of medication nonadherence, side effects, quality-of-life consequences, costs, and diminished efficacy observed with medication therapy. These limitations were juxtaposed with the availability of newer therapies such as selective laser trabeculoplasty and minimally invasive procedures. Together, these factors prompt a reevaluation of the existing stepwise medication-first treatment algorithm. In the present paper, we will specifically review the limitations of topical medical therapy and discuss treatment alternatives that overcome these limitations.

Limitations of Topical Medical Therapy

The pharmaceutical agents in topical anti-glaucoma medications are effective in lowering IOP, especially in patients with elevated IOP. However, they are challenged in their current form of topical administration in three notable ways: a)

Received: 9 September 2023
Accepted: 22 November 2023
Published: 14 December 2023

patient nonadherence, b) side effects due to toxicity, and c) difficulty in penetrating the corneal surface, the eye's natural barrier, to deliver an appropriate amount of drug in a 24/7 consistent manner.

A central limitation of topical medical therapy is nonadherence. Medications only work if patients take them, and many do not: for example, Nordstrom et al showed that 90% or more of patients did not refill their topical medications continuously over a period of 3 years, and approximately 50% of patients stopped taking their prescribed medications within 6 months.[8] Other studies have confirmed that 30–80% of patients are nonadherent to their glaucoma therapy.[9–13] Nonadherence, in turn, increases the risk of progression over time.[9,10,14,15] Nonadherence is a complex and multifactorial behavior.[16–18] Physical factors (for example, tremor or arthritis of the hand)[19,20] and cognitive factors (for example, forgetfulness or dementia)[19,21–23] can lead to unintentional nonadherence. Difficulty with self-administration of eye drop medications is also a common cause of unintentional nonadherence.[24] Most patients prescribed eye drop medications are not provided with instruction on proper instillation technique,[25,26] and 13–91% of patients make one or more mistakes when instilling eye drops,[26–30] which includes the 10–76% of patients who miss the eye entirely when attempting to take their medication.[25,27,28,31] Unintentional nonadherence accounts for the majority of all nonadherence (66–83%).[32]

Intentional nonadherence is less common (17–34%)[32] and can often be related to a belief that therapy is unnecessary or unhelpful or to avoid unwanted side effects.[33] Furthermore, approximately half of glaucoma patients require more than 1 medication for adequate IOP control.[1,34–38] These multi-drop regimens—often requiring several drops per day from multiple bottles—are associated with greater nonadherence related both to the complexity of the dosing regimen[39] and the increased rate of side effects arising from greater BAK exposure.[40–46] This sets up a vicious cycle in which nonadherence leads to elevated IOP, prompting addition of more medications, producing more side effects and greater nonadherence, ultimately resulting in disease progression and the need for more invasive, higher-risk interventions.

As noted above, side effects are also a significant limitation of topical medical therapy. The side effect profiles of glaucoma medications vary by drug class and can range from mild and transient effects such as stinging, unpleasant taste, and blurred vision, all of which are common with topical carbonic anhydrase inhibitors, to more significant effects such as periocular hyperpigmentation and hair growth and periorbitopathy associated with prostaglandin analogues (PGAs).[47] In addition to the side effects of active ingredients delivered topically, excipient ingredients can also produce adverse effects. Most glaucoma products, like most ophthalmic formulations in general, are preserved with benzalkonium chloride (BAK).[48,49] BAK is cytotoxic to ocular surface cells including conjunctival and corneal epithelial cells as well as goblet cells.[50,51] It is also known to be cytotoxic to intraocular tissues fundamental to the regulation of intraocular pressure, including the ciliary body and trabecular meshwork.[52,53]

With chronic exposure to BAK in glaucoma medications, 30–70% of patients will develop signs and symptoms of ocular surface disease over time,[40–46] which increases the risk of nonadherence[54] and decreases quality of life.[55,56] Furthermore, chronic exposure to topical glaucoma medication increases the risk of failure of future glaucoma surgeries.[47,49,57] And lastly, although systemic side effects of topical medications are uncommon, they can be very serious.[58,59]

In addition to side effects and nonadherence, topical medical therapy is limited by the inherent difficulty of penetrating the corneal surface, the eye's natural barrier, to deliver medication in a consistent 24/7 manner. This difficulty may contribute to the fact that although all glaucoma medications have proven IOP-lowering efficacy, they are still not a sure-fire way to eliminate the risk of glaucoma progression. In clinical trials, 25–27% of patients receiving topical medical therapy experienced disease progression over 6–8 years despite protocols that mandated the addition of adjunctive medications if target IOP was not achieved.[2,60] The landmark population-based study from Olmsted County, MN, showed that despite being prescribed glaucoma medications, there was a 13.5% unilateral and 4.3% bilateral blindness rate in patients over the course of 20 years, with average time to blindness of 5.8 years.[61] In such studies, the fact that glaucoma progressed despite topical medical therapy underscores some of the fundamental limitations observed with topical agents: for example, the self-reinforcing negative cycle (discussed previously) that transpires from nonadherence, medication side effects, elevated IOP, dosage escalation, and invasive interventions; and the IOP fluctuations (peaks and troughs) of topical medications,[62,63] which increase risk of glaucoma progression.[64–69] Regarding this latter point about IOP fluctuation, it is not surprising that studies have consistently shown less IOP variability and lower disease progression with procedural rather than topical medication-based treatments.[70–72]

Additionally, the costs of medications can be an important limitation of their utility. For example, some patients may have medical insurance that covers procedures but not certain medications, making a procedural intervention a more viable option. In fact, cost-related nonadherence has been reported to affect ~8% of the general population[73] and approaches 20% in high-risk Black and Hispanic populations.[74] Not surprisingly, in low-resource settings where the affordability of any aspect of health care is challenging, SLT and trabecular micro-bypass stents have been shown to be cost-effective over medical therapy for glaucoma.[75,76] Medications also have ongoing monthly or quarterly costs that procedures usually do not have.

Ultimately, regardless of which treatment is chosen, one must be cognizant that patients are dealing with a chronic, often asymptomatic, gradually progressive disease that does not have many near-term feedback points to motivate patient adherence. This, combined with the reality of medications' many downsides (such as side effects, bothersome dosing regimens, etc.), means that improving medication adherence is an inherently uphill battle – one that even significant patient education can only improve modestly.

The Rationale for an Interventional Approach to Glaucoma

Topical medical therapy historically has remained the starting point for glaucoma treatment because, despite its limitations, the alternatives were worse. However, that may no longer be the case. The evolution of laser technology from ALT to SLT, the development of SRDD platforms, and the proliferation of MIGS procedures all potentiate a tectonic shift in our approach to treating glaucoma. The attributes of these newer therapies overcome many or even most of the limitations of topical medical therapy and represent opportunities to concurrently preserve both visual function and quality of life for patients with glaucoma.

SLT vs Topical Medications

Selective laser trabeculoplasty utilizes the concept of selective photothermolysis to heat and thermally disrupt pigmented cells of the trabecular meshwork (TM) with a short burst of laser energy without damaging neighboring nonpigmented cells.[77,78] The platform developed for ophthalmic use is a Q-switched, frequency-doubled, 532-nm Nd:YAG laser that delivers a 400 micron diameter treatment spot in 3 nanoseconds.[79] The SLT procedure itself is a noninvasive office procedure performed at the slit lamp under topical anesthesia with minimal discomfort.

Efficacy. Several early, small, single-center studies demonstrated that SLT lowered IOP equivalently to a PGA.[80–82] The SLT MED study was the first multicenter trial to compare IOP reduction after SLT versus medical therapy (initial PGA with other medications added as needed).[35] The study enrolled patients with open-angle glaucoma (OAG) after washout of topical medical therapy (as this was not a study of primary SLT in treatment-naïve patients). Although the study was terminated before completion due to insufficient enrollment, results after 9 months suggested similar mean IOP reductions between groups.

More recently, the Laser in Glaucoma and Ocular Hypertension (LiGHT) trial compared initial SLT to initial medical therapy in randomized fashion in newly diagnosed and treatment-naïve OAG or ocular hypertension patients.[34,60] In this trial, 78% of eyes receiving primary SLT remained medication-free at 3 years and 70% were medication-free at 6 years; in the majority of these eyes (77% at 3 years and 56% at 6 years), only a single SLT treatment was required. Interestingly, while the mean IOP was slightly higher in the SLT group compared to the medication group at 6 years (16.3 mmHg vs 15.4 mmHg, respectively; $p < 0.001$), numerous important outcomes were better in the SLT group, including lower rates of glaucoma progression (20% vs 27%, $p = 0.01$), lower rates of trabeculectomy (2.4% vs 5.8%, $p < 0.001$), and lower rates of cataract surgery (10% vs 17%, $p = 0.03$). Better outcomes despite higher IOP are likely attributable to adherence issues, as study patients may have missed doses between visits (thereby allowing for progression) despite being faithful with dosing around the time of study visits. In contrast, SLT patients, like all patients undergoing a procedural intervention, were not dependent on adherence for the IOP-lowering effect.

Safety. SLT is among the safest therapies available for glaucoma. Common side effects include transient anterior chamber inflammation (not requiring routine prophylactic anti-inflammatory therapy[83]) and transient IOP elevations (which are usually reduced or prevented with prophylactic short-acting IOP-lowering therapy).[84–86] The incidence of IOP elevations has been reported to be 5–25% depending on the magnitude of IOP elevation.[85] However, these values come

largely from studies of adjunctive or replacement SLT and may not be representative of the risk in primary SLT, as the LiGHT study reported only a single IOP elevation requiring treatment among 776 primary-SLT treatments in the first 3 years of the study.[34] Another potential complication is idiopathic corneal edema,[87] which is thought to be rare but may be underrecognized. Overall, sight-threatening complications after SLT are rare and mostly self-limited.[86] There were no such complications reported in the LiGHT study.[34,60]

Adherence. The IOP reduction after a procedural intervention as primary treatment (such as after SLT in this case) lessens or eliminates the need for adherence with topical medical therapy. For patients undergoing SLT to reduce medication burden, the simplification of the drug regimen would be expected to improve symptoms associated with ocular surface disease (the severity of which is proportional to the number of medications used and drops administered per day[40–46]) and to improve adherence to remaining medications.[39–46]

Quality of Life. Intuitively, the benefits of a procedural intervention over medical therapy would be expected to translate into improvement in quality of life. These benefits can include freedom from the responsibility of daily eye drop administration by the patient or caregiver, elimination of the side effects of topical therapy, lower rates of glaucoma progression and glaucoma surgery, and lower risk of later filtering surgery failure.[47] In a prospective randomized study comparing SLT to continued medical therapy in medically treated patients, SLT patients reported consistently better outcomes on the Treatment Satisfaction Survey, which assesses items such as perceived effectiveness of therapy, convenience of use, and side effects, among others.[88] In another prospective randomized trial comparing SLT to topical therapy in treatment-naïve patients, SLT provided greater improvements in social well-being than medical therapy.[89] Interestingly, a consistently discernable difference in quality of life, measured by existing instruments, between the SLT and medication groups was not observed in the LiGHT study.[34,60] This finding is consistent with other studies of medication versus observation or placebo that found equivocal or minimal quality of life benefit to becoming topical medication-free.[90–92] This nonintuitive finding may be attributed to the nature of available quality-of-life instruments, which are designed to measure the impact of glaucoma or overall health status (and not the impact of treatment) on quality of life. There remains a significant unmet need for a standardized, validated instrument to assess the impact of various treatment modalities on the quality of life in glaucoma.

Cost Effectiveness. Glaucoma treatment is expensive. In 2017, Medicare spent nearly $1.1 billion on topical PGA therapy alone.[93] Multiple studies have demonstrated that SLT is cost-effective versus medical therapy,[60,75,94] with the LiGHT study showing a ~$3700 lifetime saving per newly-diagnosed patient receiving primary SLT versus medications. Given an estimated 3 million people with glaucoma in the United States[95] and a median survival time of 16 years from glaucoma diagnosis to death,[96] this savings translates to nearly $700 million annually (more than 60% of the total annual expenditure for topical PGA therapy[93]).

Disadvantages. A well-known limitation of SLT is that its effectiveness wears off over time, with the duration of effectiveness varying from patient to patient. For example, in the LiGHT study, 23% of eyes at 3 years and 44% at 6 years needed repeat SLT.[46] In other studies of SLT as primary or monotherapy, the median time to retreatment after initial SLT was approximately 7 years.[97,98]

Future Directions. Two developments will potentially further increase SLT utilization. First is the development of direct SLT, a procedure performed with a proprietary device to deliver SLT energy trans-sclerally via an ab externo approach rather than via a gonioprism via an ab interno approach. The device has recently completed a head-to-head trial versus standard SLT with comparable efficacy and safety.[99] The second development is the potential shift from standard-energy SLT (repeated as needed) to low-energy SLT (repeated annually) in newly-diagnosed patients with mild-moderate POAG or high-risk ocular hypertension.[100] This latter shift is the subject of the ongoing head-to-head Clarifying the Optimal Application of SLT Therapy (COAST) trial, which compares the two treatment protocols with regard to the primary outcome of long-term medication-free IOP control.

In addition to SLT, other laser-based therapies such as cyclomodulating procedures have been introduced. Cyclomodulating procedures can be completed alone or in combination with other procedures to augment IOP reduction. Examples include traditional laser transscleral cyclophotocoagulation or endoscopic cyclophotocoagulation, which act by decreasing aqueous production. While these traditional cyclomodulating procedures are often reserved for more moderate or advanced stages of glaucoma, newer subthreshold techniques such as micropulse laser (either micropulse laser

trabeculoplasty or micropulse transscleral cyclophotocoagulation) may sometimes be considered in milder cases due to a better safety profile while maintaining adequate efficacy.[101]

Paradigm Shift. In recent years, and potentiated by the LiGHT Study, there has been increasing interest in using SLT (rather than topical medication) as primary therapy. In the US and Europe, glaucoma treatment guidelines have been revised to support or encourage the use of SLT as primary therapy,[89,90] in some cases officially recommending SLT as the appropriate primary treatment for newly-diagnosed patients with glaucoma.[102]

Sustained Release Medical Therapy vs Topical Medications

Sustained-release drug delivery (SRDD) refers to variety of technologies, delivered via various routes of administration, that share in common a depot of active drug that is released gradually over time to provide continuous therapy over an extended period of time. Numerous products for a variety of ocular conditions have been developed and commercialized,[103] many of which have been steroid-containing devices intended for the treatment of posterior segment inflammatory conditions.[104] In glaucoma, the historical Ocusert was placed in the conjunctival fornix and released pilocarpine for up to one week. More recently, there has been significant research and development on a variety of innovative platforms.[105] These have generally fallen into the following broad categories: punctal plugs (eg, Mati, Ocular Therapeutix), subconjunctival injections (eg, Anecortave, GrayBug), ocular surface inserts (eg, Helios, contact lenses), and intraocular depots (eg, Bimatoprost SR, Aerie, iDose). The only currently available SRDD implant in the US is the bimatoprost sustained-release (SR) anterior chamber intraocular implant (Durysta, Allergan, an AbbVie Company),[106] while the iDose TR travoprost intraocular implant (Glaukos Corp.) is in the late stages of FDA review. These novel SRDD technologies may create opportunities to intervene earlier in the glaucoma treatment algorithm, potentially prompting clinicians to reevaluate long-assumed topical-medication-first treatment plans.

Efficacy. A key aspect of SRDD in glaucoma management is the consistency of IOP control achieved via reduction or elimination of nonadherence (see below). Also, the steady and continuous release of drug over time provides consistency of exposure and can eliminate peak and trough dosing effects of intermittently applied topical therapy.[70,107] Such consistency may help prevent the glaucoma progression known to occur with IOP fluctuations,[64–69] a finding that has been confirmed by studies showing less IOP variability and lower disease progression with procedural rather than topical medication-based treatments.[72]

The ocular surface—both the cornea and the conjunctiva/sclera—poses multiple barriers to the penetration of topically applied drugs into the intraocular space, including anatomic barriers, physiological barriers, and drug- and formulation-specific factors.[108] Intraocular delivery of active drug may enhance efficacy by increasing bioavailability at the target tissues to up to 100%.[109] In actual patient usage, an intraocular travoprost-eluting implant currently under late FDA review showed that 69% of eyes were well controlled on the same or fewer topical medications at 3 years, and 81% of eyes were topical medication-free at 12 months.[110–112]

Safety. A central safety benefit of delivering glaucoma medications via intraocular drug delivery is the avoidance of ocular surface side effects, such as the ocular surface disease seen with chronic topical medical therapy.[40–46] In a beagle model, use of the intracameral bimatoprost SR implant significantly reduced off-target tissue exposure (such as exposure of the cornea and conjunctiva) compared to topical bimatoprost dosing.[113] The bimatoprost SR implant, intraocular drug delivery platforms for other diseases, and platforms in development for glaucoma therapy are all preservative-free. This is especially important because BAK is well known to be cytotoxic not only to ocular surface cells but also to intraocular tissues fundamental to the regulation of intraocular pressure, including the ciliary body and trabecular meshwork.[52,53] One potential risk considered for intraocular drug delivery is corneal endothelial damage, which contributed to the current intracameral bimatoprost SR implant being approved for only a single administration. In contrast, the aforementioned intraocular travoprost-eluting implant under late FDA review showed no corneal endothelial damage after readministration procedure, with total follow-up duration of 5.2 years from the initial surgery.[114] Two other potential risks inherent to any intraocular intervention are intraocular inflammation and endophthalmitis. For example, inflammation in the form of iritis was reported in 0.5–5.1% of eyes in the Durysta and iDose pivotal trials (vs 0–0.5% of control eyes). Meanwhile, endophthalmitis was not reported in any eyes in the pivotal trials for either device, although it remains an intrinsic theoretical possibility.

Adherence. A key benefit of SRDD is that it takes the responsibility out of patients' hands and puts it in the hands of the surgeon, thereby delivering medicine, a highly effective and proven solution, directly into the eye. When seen from a patient perspective, the average glaucoma patient would need to administer approximately 2190 topical drops over 3 years,[115] as compared to receiving one long-acting SRDD (such as in the case of iDose, currently in late-stage FDA review). Such a direct form of administration, in addition to improving adherence, allows the medication to bypass the corneal surface and thus helps avoid the side effects and minimal corneal penetration associated with topical administration. As noted previously, medication nonadherence is a key obstacle to topical medication therapy, with data showing that 90% or more of patients do not refill their topical medications over a 3-year period and approximately half stop taking medications within 6 months.[8] An SRDD offers freedom from the responsibility of daily self-dosing and eliminates nonadherence in patients on topical monotherapy. Even patients who subsequently require a multi-drug regimen for glaucoma management can enjoy the topical medication-free period of time following diagnosis during which SRDD monotherapy is sufficient. Additionally, if additional medication is ultimately needed, the overall drop regimen would be expected to be lower than without an SRDD implant. As noted previously, up to half of glaucoma patients require 2 or more medications for adequate IOP control, so SRDD platforms may need to adapt to incorporate multiple medications so that these multi-drug patients can derive maximal long-term benefits afforded by SRDD therapy. Indeed, there is already considerable interest in developing such SRDD platforms.[116]

With any SRDD implant, there remains the theoretical risk of nonadherence with follow-up and redosing upon drug depletion and loss of efficacy. However, this would be expected to be similar in prevalence to the loss to follow-up after other interventional glaucoma therapies such as SLT and surgery, which the literature has not reported to be as problematic as topical medications.

Quality of Life. Intuitively, freedom from the responsibility for daily self-dosing, as well as the elimination of ocular surface side effects, would have beneficial effects on quality of life. As discussed above, however, these benefits are difficult to measure in the absence of instruments designed to assess treatment effects on quality of life.

Disadvantages of SRDDs. As noted above, the only currently available SRDD implant in the US is the bimatoprost sustained-release (SR) anterior chamber intraocular implant. One disadvantage of this device is the potential for complications like the ones discussed in the safety section above. Another disadvantage is the need for repeat administrations, which the implant is not approved for and may result in accumulation of structural remnants. Depending on design and choice of polymers for drug encapsulation, SRDD implants may eventually biodegrade completely or leave behind structural remnants that accumulate with repeated dosing.[117] In the Phase 3 trials of the bimatoprost SR implant administered three times 4 months apart, the degree of biodegradation varied at each time point between patients; the proportion of implants that were absent or <25% of initial size was 82% at month 12 (4 months following last administration) and 95% by month 20 (1 year following last administration).[118] It may be reasonable to think that complications related to readministration, if present, potentially could be minimized by longer-acting implants and/or implants with different designs, sizes, placement methods, or implantation locations.

Future Directions. Growing interest in sustained-release drug delivery in glaucoma mirrors an overall growing interest in ocular drug delivery.[119–121] Many novel platforms for sustained-release delivery of glaucoma drugs are in various stages of clinical development. These can include extraocular approaches such as contact lenses (eg, theranostic smart contact lenses, with both diagnostic and therapeutic capabilities); intracanalicular punctal plugs [OTX-TP (Ocular Therapeutix), Evolute (Mati Therapeutics)]; ocular rings placed in the inferior or superior fornices [Bimatoprost Ocular Ring (Allergan, an AbbVie Company)]; and nanotechnologies such as polymeric hydrogels (including microspheres and dendrimer nanofibers), microemulsions, and nanoemulsions.[122] SRDD treatments under development also include intraocular devices such as intracameral implants [OTX-TIC (Ocular Therapeutix)]; implants placed in the iridocorneal angle [ENV515 (Envisia), latanoprost free acid SR (PolyActiva)]; implants mounted on intraocular lenses [Spyglass Pharma Drug Delivery Platform (Spyglass Pharma)]; and scleral-affixed implants secreting ciliary neurotrophic growth factor [NT-501 CNTF].[105] Many of these devices elute travoprost, latanoprost, or bimatoprost.[122] In addition to reformulating existing topical therapies into SRDD platforms, technologies that bypass the ocular surface may offer the potential for new therapeutics that cannot be formulated for topical delivery—for instance, those with physicochemical properties that preclude formulation tolerability or ocular surface penetration.

MIGS vs Topical Medications

Historically, incisional surgical interventions for glaucoma included trabeculectomy and tube-shunt implantation. These procedures are highly effective in lowering IOP but have safety profiles that include numerous vision-threatening complications.[123–125] Accordingly, these procedures have historically been reserved for patients who need large IOP reductions or very low target IOP such that the risks of surgery are justified by the need for great efficacy. Given the use of filtration surgery in these more advanced cases, it is not surprising that clinical trials exploring the role of filtration surgery as primary treatment have had mixed results and thus did not support a surgery-first paradigm shift.[2,5]

Over the past one to two decades, a growing family of related procedures—collectively called micro-invasive glaucoma surgeries or MIGS—has been developed to provide moderate IOP reductions with greater safety and faster visual recovery than traditional procedures. Accounting for nearly no procedures a decade ago, MIGS procedures now comprise a significant majority of glaucoma surgeries and have come to be accepted as standard of care.[126] The most longstanding MIGS devices have amassed over 12 years of history in over a million implants and have considerable scientific evidence supporting their usage.[127]

The benefit-to-risk tradeoff of MIGS procedures is especially appealing in patients who would benefit from surgical intervention but whose therapeutic goals do not justify the risks of traditional surgery.[128] In general, MIGS procedures produce less dramatic IOP reduction but are significantly safer than traditional filtration surgery.[129–131] Potential mechanisms of action of MIGS can include incision or excision of the trabecular meshwork, stents to bypass the meshwork, and implants to expand the canal of Schlemm using viscodilation or implantation of a scaffolding device.[132,133] Additionally, some MIGS procedures rely on subconjunctival filtration and bleb formation, more narrowly bridging the gap between MIGS and traditional surgeries.[132,133] Depending on country and clinical context, some procedures are performed as standalone therapy, while others are performed at the time of cataract surgery.[134]

The favorable safety profile of MIGS, coupled with the moderate IOP reductions appropriate for many patients with early-moderate POAG, has led to interest in early surgery for patients with glaucoma, not necessarily as primary therapy, but rather as an early adjunct to primary SLT and/or SRDD therapy and before the use of topical medical therapy or to replace poorly tolerated topical therapy.[134–136] The rationale for such an approach is described below.

Efficacy. As an alternative to topical medical therapy as the next therapeutic step in patients who have already received SLT and/or SRDD therapy, the various MIGS procedures offer the potential for meaningful IOP reduction. Robust meta-analyses and systematic literature reviews of the MIGS family of surgeries collectively as a class have demonstrated significant reductions in both IOP and the need for IOP-lowering therapy when performed as standalone procedures or combined with cataract surgery.[137–140] These reviews report mean IOP reductions across the MIGS family in the 25–35% range, which is consistent with the expectations of primary topical medical therapy with a PGA. The fact that these MIGS IOP reductions are often accompanied by reductions in medication use—with meaningful proportions of patients being medication-free many years after surgery—suggests that the IOP reductions in non-medicated eyes could be even greater if medications were to be reintroduced.

Safety. Complications of MIGS usually occur in the perioperative period (late complications are uncommon), and sight-threatening complications are rare. Adverse events differ based on which MIGS procedure is completed. For example, hyphema is more commonly associated with trabectome (23–48% of eyes), gonioscopy-assisted transluminal trabeculotomy (30–40% of eyes), or Kahook Dual Blade (6–19% of eyes);[130] peripheral anterior synechiae (6–15%),[130] intraocular inflammation (4–6%)[130] and ≥30% endothelial cell loss (21% of eyes)[141] have been associated with Hydrus; and IOP elevation can be seen with all MIGS procedures, including iStent (1–2% of eyes),[142] iStent inject (2% of eyes),[143] and OMNI (5–7% of eyes).[144–146] Pivotal trials for some MIGS devices have shown some of them to have similar safety profiles vs cataract surgery alone.[142,143,147] In comparison, the side effects of medical therapy are chronic and persist throughout the long-term course of therapy. Again, sight-threatening complications with topical medications are rare, but some common side effects—such as dry eye, which occurs in 30–70% of patients on chronic topical medical therapy[40–46]—can have significant negative impacts on adherence[54] and quality of life[55,56] as noted previously.

Adherence. MIGS—like other provider-administered therapy such as SLT or SRDD—would eliminate nonadherence for the patients in whom it successfully controls IOP without the need for supplemental topical medication. In eyes that require medical therapy adjunctively to MIGS, the medication burden would be expected to be lower than for eyes that

have not undergone MIGS. A lower medication burden would be expected to improve adherence, as adherence is known to decline with additional medications due to aforementioned factors such as complex dosing regimens[39] and BAK-related side effects.[40–46]

Quality of Life. Intuitively, patients who undergo MIGS in lieu of topical medical therapy would be expected to attain an improvement in quality of life associated with the freedom from daily medication administration and dosing complexities, as well as diminished side effects and significantly improved ocular surface health.[55,56] In the iStent inject trabecular micro-bypass pivotal trial, decreased medication dependence in the bypass group versus the cataract-alone group was indeed associated with greater improvement in quality of life.[148] Although iStent inject is the only MIGS pivotal trial to-date with published QoL data, the positive association between medication reduction and quality of life improvement has been seen in real-world studies of various MIGS procedures.[149,150]

Cost-effectiveness. Phacoemulsification alone can lower IOP,[151] but numerous meta-analyses and systematic literature reviews have demonstrated that MIGS combined with phacoemulsification provides additional IOP reduction that is cost-effective compared to phacoemulsification alone.[152–155] Other data support the cost-effectiveness of standalone MIGS.[156] And consistent with the shift toward earlier intervention, one study suggested that the cost-effectiveness of MIGS could be improved by intervening at the moderate disease stage rather than waiting for advanced glaucoma to develop.[155]

Disadvantages. Any surgery, even the most micro-invasive MIGS procedure, carries unique risks that topical therapy may not. However, the rate of sight-threatening complications of MIGS is low, vs the rate of quality-of-life-limiting side effects of topical medications is high. There is presently no theoretical framework for comparing these two treatment options, either from the objective perspective (the nature and frequency of adverse events) or the subjective perspective (quality of life and patient preference). The ability to quantify the risk threshold that patients would accept to remain free of topical therapy is an unmet need that would facilitate individualized care planning for glaucoma.

Future Directions. Long-term data for existing MIGS procedures and short-term data for new procedures continue to emerge. These data will further characterize the efficacy and safety profiles of these procedures and aid in the selection of the best procedure for each patient based on individual characteristics. There is also growing interest in regulatory change to broaden the availability of MIGS procedures for standalone use. Many pseudophakic patients would benefit from standalone MIGS surgery, and the options in this setting are limited.[134]

Another area of keen interest, as discussed in this paper, is sustained-release drug delivery devices, which are in various stages of development. In addition, there are a number of minimally invasive interventions not based on medications: for example, a multi-pressure dial (MPD) with negative pressure application;[157] electromagnetic therapy to induce beneficial inflammation;[158] focused ultrasound therapy to decrease aqueous production and increase outflow;[159] the Cilio-Scleral Inter-Positioning Device [CID Implant (Ciliatech)] placed between the ciliary body and sclera to enhance uveoscleral outflow; polyzwitterion hydrogel injection into the suprachoroidal space to enhance uveovortex outflow; and OCT-guided femtosecond laser [ViaLuxe Laser System (ViaLase)] to create drainage channels through the trabecular meshwork.

Conclusion

The topical medication-first glaucoma treatment paradigm does not reflect the current array of treatments available to prevent vision loss and blindness. Topical medical therapy has many important limitations that compromise its utility, including poor adherence, side effects, limited ocular surface penetration, suboptimal consistency of IOP control, costs, and diminished quality of life. A slate of newer procedural alternatives to topical medical therapy, including SLT, current and emerging sustained-release medical therapy platforms, and a wide assortment of MIGS procedures may offer important advantages vs topical medical therapy for long-term glaucoma management. For example, a procedure-based intervention is fundamentally removed from the need for patient adherence, while it also may produce more 24/7 consistency of IOP control than the peaks and troughs of medications; such consistency in turn can help slow disease progression. In addition, reducing topical medication burden improves patient quality of life, reduces local and systemic side effects, and preserves the health of the ocular surface. In light of these benefits, an evidence-based assessment of the

advantages and disadvantages of the various modalities may indeed support the adoption of a new glaucoma treatment paradigm that does not prioritize topical medical therapy as primary treatment.

Data Sharing Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Acknowledgment

Editorial assistance (Dana M. Hornbeak, MD, MPH; Tony Realini, MD, MPH) was provided by Glaukos Corporation.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

No funding was provided for the creation of this manuscript. Publication fees were provided by Glaukos Corporation.

Disclosure

SB: Allergan: speaker, consultant; Glaukos: Speaker, consultant; Thea Laboratories: consultant; Ocular Therapeutix: consultant; BVI: consultant; MST: consultant; Belkin: consultant; Elios Vision: consultant. JB: AbbVie (C, L); Aerie (C); Aerpio (C); Alcon (C, L); Aldeyra (C); Aurea Medical (C)

Aurion Biotech/CorneaG (C, O); Balance Ophthalmics (C); Bausch + Lomb (C); Dakota Lions Eye Bank (C); Elios Vision INC (C); Equinox (C, O); Expert Opinion (C, O); Glaukos (C, L); Gore (C); Iacta Pharmaceuticals (C); Imprimis (C, P); Interfeen (C); iRenix (C); IVERIC Bio, Inc (C); Johnson & Johnson (C); Kala (C); Kedalion (C); MELT Pharmaceuticals (C); MicroOptx (C); New World Medical (C); Ocular Surgical Data (C, O); Ocular Theraputix (C); Omega Ophthalmic (C, O); Orasis (C); Oyster Point (C); RxSight (C); Santen (C); Sight Sciences (C); Surface Inc (C, O); Tarsus (C); Tear Clear (C); RxSight (C); Vance Thompson Vision (C, O); Verana Health (O); Versea Biologics (C); Vertex Ventures (C); ViaLase (C); Visionary Ventures (C); Visus (C); VittamedB40 (C); Zeiss (C, O). A.S. reports the following disclosures: Alcon, Nova Eye, AbbVie, and Glaukos. IPS is a speaker and consultant for Glaukos, Allergan, BVI, New World Medical, Ivantis, Sight Sciences, Ocular Therapeutix, Sun Pharmaceuticals, Novartis, Nova Eye, Bausch + Lomb, Kala Pharmaceuticals, and EyePoint Pharmaceuticals. The authors report no other conflicts of interest in this work.

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