CURRENT & EMERGING TREATMENT APPROACHES
ADDRESS UNMET NEEDS IN GLAUCOMA CARE
Sustained-release implants and micro- or minimally invasive glaucoma surgeries (MIGS) are emerging therapies that address key unmet needs in glaucoma treatment. By broadening the spectrum of interventions, these therapies allow glaucoma specialists to consider more measured approaches earlier in disease progression, with a view to delay as well as safeguard the possibility of further invasive surgeries.

Drs. Herbert Reitsamer, Andrew Tatham, and Iqbal Ike K. Ahmed discuss how patient compliance impacts glaucoma progression, the role of sustained-release drug delivery and MIGS in alleviating patient treatment burden, the use of MIGS in combination with cataract surgery, and how these therapies can be incorporated into the treatment paradigm.

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PATIENT COMPLIANCE IN GLAUCOMA

Poor Adherence to Medication Exacerbates Progression

On average, ophthalmologists see 30 glaucoma patients per month, according to the European Society of Cataract and Refractive Surgeons (ESCRS) 2020 Clinical Survey results. While medical management of glaucoma is first-line therapy to control intraocular pressure (IOP) and prevent disease progression, the modality is not without problems. Andrew Tatham, MD, noted, “Non-adherence to treatment is the most common problem. It is a major barrier to effective glaucoma treatment, and we probably under-recognize it. Studies show that up to one-third of people prescribed eye drops, for the first time, discontinue the collection of their prescriptions within a year”. Indeed, a systematic literature review of 58 articles showed that compliance and persistence are particularly challenging for patients new to therapy.

Iqbal Ike K. Ahmed, MD, agreed, stating, “Every published study has shown poor adherence, globally. This is correlated to the number of drops, complexity of the treatment regimen, and the presence of ocular surface disease, which is very common in people with glaucoma and further exacerbated by drops.” Herbert Reitsamer, MD, echoed these sentiments, observing that compliance becomes particularly problematic when patients are prescribed a third eye drop. Unsurprisingly, respondents to the ESCRs 2020 Clinical Survey believed that, on average, 22% of patients prescribed one or two medications were not compliant (Figure 1). This figure increased to 28% when patients were prescribed three or more medications.

Dr. Tatham. Qualitative research has shown that in addition to knowledge gaps, and physical, economic and psychological barriers, there is insufficient patient education around proper eye drop instillation, with the combination of factors resulting in poor compliance. Moreover, even when using electronic monitoring devices, up to half of all patients remain poorly adherent.

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Non-adherence is underscored by the difficulty in quantifying it in clinical practice. “Compliance is an issue of any chronic disease; however, in glaucoma, there is the added difficulty of administering the medication – putting a drop into the eye”, explained.

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Eye drops remain the cornerstone of glaucoma therapy; however, a variety of factors, including complex regimens, ocular side effects, gaps in disease knowledge, financial burden of long-term treatment, cognitive impairment, proper eye drop instillation, and formulary restrictions, impinge on medical adherence and consequently, lead to poorer patient outcomes. While behavioral interventions have been employed to improve adherence, medical glaucoma management is also shifting towards patient-independent drug delivery in the form of sustained-release implants.

ADDRESSING AN UNMET NEED

‘White coat’ adherence, whereby patients increase treatment adherence around clinic visits means that adherence rates in clinical studies provide an inaccurate reflection of patient compliance in real world settings. Additionally, IOP fluctuations are common. The primary draw of sustained-release devices is the potential to provide continued and reliable IOP control and reduce IOP fluctuations. “Sustained-release drug delivery is the Holy Grail of medical glaucoma. It delivers the drug to the target tissue, eliminates local side effects, and addresses adherence”, said Iqbal Ike K. Ahmed, MD. Moreover, advances in home tonometry and implantable IOP sensors could round out effective disease management. He added, “If we had a feedback cycle with IOP monitoring, then drug delivery, and even an outflow device, that would be the ultimate glaucoma intervention”.

Sustained-release devices including external ocular inserts, contact lenses, intracameral depots, punctal plugs, and injectables hold great promise for glaucoma patients. Andrew Tatham, MD, highlighted biodegradable implants as more advanced, less invasive, and less complex (Figure 2). Pharmacokinetic studies suggest that the therapeutic effect of certain implants could extend beyond active release of the drug. “The real value-add is the ease of administration, i.e., a limbal injection done at the slit lamp. It is a fairly universal, low risk technique”, noted Dr. Ahmed (Figure 3). As the implantation is easier than that of MIGS devices, Dr. Tatham predicted that the procedure could be performed by non-ophthalmologists, albeit those with intraocular surgical experience, drawing parallels with the UK nurse practitioners who administer intravitreal injections.

An attractive aspect of the implants is the large patient base they can serve, specifically those that struggle with eye drops, have ocular side effects, and known compliance issues. In recent clinical studies, most patients who were suitable candidates for the implants said that they welcomed another implantation procedure (82.9%) and would recommend it to others with the same condition (88.6%).

“We are still figuring out the duration of some of these products. Some last months, others can last even longer. This is important to determine re-dosing and the associated safety.” – Iqbal Ike K. Ahmed, MD

CONSIDERATIONS FOR SUSTAINED-RELEASE IMPLANTS

As with any treatment, there are pros and cons associated with sustained-release implants. “We are still figuring out the duration of some of these products. Some last months, others can last even longer. This is important to determine re-dosing and the associated safety”, cautioned Dr. Ahmed. Herbert Reitsamer, MD, added, “Ask yourselves, what can I achieve, what is the target IOP, and are there medications that the patient cannot tolerate?”.

Furthermore, these implants require anatomical considerations when placed within the anterior chamber. Dr. Tatham advised, “Patients will need to have an open angle. There should be sufficient space...
for the implant to rest without encountering corneal endothelium. It is also unclear whether patients who have had previous glaucoma surgeries or iridectomies are suitable candidates. With non-anchored devices, the device may block or migrate to the opening”.

Moreover, reports of corneal endothelial loss associated with anterior chamber implants warrant additional investigation in real world settings1. Although endothelial cell counts prior to implantation could prove useful, Dr. Ahmed stated, “It is not always necessary. Our current treatment approach and labeling work just fine and the data, so far, are reasonable. However, our understanding of these implants with respect to anatomy, patient selection, and re-dosing is constantly evolving, and we should balance risk and benefit. Overall, sustained-release drug delivery addresses compliance, IOP fluctuation, and local side effects with minimal risk. This is the kind of interventional pharmacology we are moving towards for glaucoma”.

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EARLY SURGICAL INTERVENTION IN GLAUCOMA
MIGS Has a Place on the Mantle

Medication and surgery have traditionally been bookends of the glaucoma treatment paradigm, with prevailing practice delaying surgery until glaucoma is advanced. Indeed, 48% of respondents to the 2020 ESCRS Clinical Survey preferred to wait until three or more medications failed, before initiating surgical intervention1. Furthermore, most respondents maintained a medical glaucoma practice and only 26% performed surgical interventions (Figure 4)1.

The continued development of MIGS has been revolutionary for the treatment paradigm, bridging the gap between medication and more invasive surgeries, and expanding the glaucoma armamentarium that can be offered to patients.

“We often do not have the luxury of treating early glaucoma, simply due to late referrals.” – Herbert A. Reitsamer, MD

TREAT EARLIER, TREAT LOWER
This is the idiom that glaucoma specialists should follow, according to Iqbal Ike K. Ahmed, MD, saying, “We need to be proactive. We now have better tools, with improved risk and postoperative recovery profiles, to treat disease progression in a safer way while addressing adherence”. Herbert Reitsamer, MD, agreed, emphasizing that reducing and stabilizing IOP, without titrating levels, was the most effective strategy for any disease progression.

“There is growing evidence that early glaucoma or even a glaucoma diagnosis can reduce quality of life...
due, partly, to the topical medications but also the disease itself. For example, we know that glaucoma increases the risk of falls and the likelihood that a patient will need to stop driving⁴, observed Andrew Tatham, MD. Moreover, years of topical therapy can take a toll on the conjunctiva, severely limiting the efficacy of subsequent glaucoma surgery.

In choosing between MIGS procedures and implants, Dr. Ahmed weighs risk, benefit, and effort by considering potency, disease severity, medication tolerability, IOP, and coexisting cataracts. According to Dr. Tatham, restoring physiologic outflow (versus subconjunctival) with MIGS, early in glaucoma, is not only attractive but also feasible, commenting, “It is important to intervene early in the course of the disease to reduce the impact of glaucoma, and glaucoma treatments, on quality of life. We are fortunate to have a wide range of MIGS procedures available, either aiming to restore physiological outflow pathways, or for greater IOP reduction, to shunt aqueous into the subconjunctival space”.

SHIFTING THE CULTURAL PARADIGM
Dr. Reitsamer noted, “We often do not have the luxury of treating early glaucoma, simply due to late referrals”. A study by the European Glaucoma Society revealed that most referrals for primary glaucoma surgery were either suboptimal or too late². He highlighted that some European Union (EU) countries tended to have longer median non-surgical treatment periods than other or non-EU countries, suggesting that paradigms needed to be revisited. Indeed, a 2017 survey of the American Glaucoma Society also showed that trabeculectomies remained the most popular primary glaucoma surgery⁵.

Though MIGS are still developing, raising awareness that other surgical options, besides trabeculectomy, exist and can be introduced earlier in treatment is important. Early referrals can potentially help preserve the conjunctiva and consequently, preserve sight. Interestingly, cognitive biases in surgical decision-making may also play a role in the glaucoma surgeon’s choice between MIGS and more invasive surgeries⁴. Physician education programs will be crucial to not only familiarize a broader audience with the capabilities and efficacies of MIGS, but also induce a shift in mind-set. “Selective trabecuoplasty, for example, was typically a pre-surgical treatment in the past. It has now moved up to become first-line therapy. Surgery is also moving in this direction, and it is important to understand the role of the referring physician and general ophthalmologist in these treatment options”, said Dr. Ahmed.

COMBINING MIGS WITH CATARACT SURGERY
An Exercise in Balancing Efficacy, Convenience, Cost, and Safety

Cataracts and glaucoma tend to coexist in the elderly population. The ESCRS 2020 Clinical Survey reported that approximately 11% of all cataract patients had glaucoma¹. Although there are established practice patterns for treating each disease separately, co-management can be challenging.

Up to 12% of cataract patients, currently on topical glaucoma therapy, were believed to be candidates for MIGS, according to the 2020 ESCRS Clinical Survey (Figure 5). The continued refinement of MIGS now begs the question of, not only combining surgeries, but also treatment individualization, particularly in this cohort.

WHAT ARE THE BENEFITS?
Though not feasible or appropriate for all patients, combined phacoemulsification and MIGS should, at least, be considered in cataract patients with glaucoma. “The opportunity to further reduce IOP and the number of medications, together with better postoperative compliance, is a strong reason to consider combining surgeries. Many MIGS procedures are very safe and have minimal impact on the recovery and refractive status after cataract surgery”, said Iqbal Ike K. Ahmed, MD. He believes

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What % of your cataract surgery patients, currently on topical therapy for glaucoma, would you estimate are candidates for a Minimally Invasive Glaucoma Surgery (MIGS) device? (Even if you do not perform MIGS)

![Graph showing distribution of responses](image-url)
that the benefits of combined surgeries can far outweigh the risks. In fact, MIGS combined with cataract surgery can also reduce the likelihood of requiring secondary invasive glaucoma surgeries, compared to cataract surgery alone².

Andrew Tatham, MD, added, “In addition to the early stages, canal-based MIGS may also be beneficial in later stages of the disease by avoiding more complex, high-risk surgery. We also improve conjunctival health by reducing the number of medications, which is particularly helpful if we suspect a bleb-based procedure to be necessary down the road”.

While cost and access challenges can be prohibitive, Herbert Reitsamer, MD, remarked, “A comprehensive cost evaluation has never been done”, suggesting that the cost of long-term glaucoma medications, their conjunctival toll, and the reduced likelihood of future surgical success could paint a more favorable picture of the cost-utility of combined procedures.

THE ORDER OF THINGS IN ANTERIOR SEGMENT SURGERY
The order of procedures typically depends on the outflow pathway being enhanced. Canal-based MIGS are best performed before phacoemulsification while the globe is firm, the view is ideal, and there is lower blood reflux. Dr. Tatham said, “This is particularly important in high myopes where there may be anterior chamber instability following phacoemulsification”. Dr. Ahmed added that, if preferred, capsulorrhexis could precede the MIGS procedure.

In contrast, subconjunctival MIGS are best performed after phacoemulsification to account for the greater outflow in the region. Implant insertion before phacoemulsification could lead to anterior chamber instability and chemosis. Subconjunctival MIGS are particularly successful in myopic patients as the controlled outflow prevents hypotony, reduces the risk of hypotony maculopathy, and eliminates the need for scleral flaps or suture tension, which are typically difficult to achieve in the thin sclera of myopic patients.

THERE IS NO ‘PLUG-AND-PLAY’ APPROACH
A growing number of studies are demonstrating that subconjunctival MIGS combined with cataract surgery can be as successful as canal-based procedures (Figure 6)³. However, like the decision to combine surgeries, the surgeon must consider the patient themselves and disease progression when choosing between MIGS. Dr. Reitsamer noted, “There is not enough clinical trial data to support the merits or pitfalls of these therapies. Whether performed individually or in combination, they require different strategies”.

For example, both Drs. Tatham and Ahmed prefer not to combine bleb-based MIGS with cataract surgery as the high degree of intraocular inflammation could lead to bleb failure. However, studies and anecdotal experiences have shown that, if surgeries are combined, failure can be mitigated with a comprehensive treatment plan including preoperative oral acetazolamide and steroids, halting preoperative topical therapy to optimize the conjunctiva, additional needlings, sufficient use of anti-fibrotics, and longer postoperative steroid use. As more data becomes available, surgical practices and preferences may shift.

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As an irreversible, variably progressive, chronic disease, several therapies and surgical procedures have emerged to treat glaucoma, each with their own risks and benefits. As treatments evolve, so must practice patterns. Continuing physician education will provide surgeons with the tools to more effectively manage and personalize glaucoma treatment, thereby addressing pain points in the patient’s journey as well as, ultimately, maintaining healthy vision for longer.

CONCLUSION

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