Ophthalmology® ROUNDS

Volume 14, Issue 4

AS PRESENTED IN THE ROUNDS OF THE DEPARTMENT OF OPHTHALMOLOGY AND VISION SCIENCES, FACULTY OF MEDICINE, UNIVERSITY OF TORONTO

Glaucoma in 2021 – Advances in Medical, Laser, and Surgical Treatment

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Ongoing efforts to develop therapeutic approaches to glaucoma, the most common cause of irreversible vision loss worldwide, have resulted in new medications and laser and surgical techniques. This array of treatment options assists the physician to make the best management decisions based on each patient's unique clinical profile. This issue of *Ophthalmology Rounds* reviews several options in these 3 categories that are either approved in Canada or potentially available in the near future.

Glaucoma is the world's leading cause of irreversible vision loss.[1] Currently, the only available treatments are measures to lower intraocular pressure (IOP),[2] which have consistently shown benefit in multiple clinical trials involving patients with conditions ranging from ocular hypertension to advanced glaucoma.[3-9] Present treatment methods fall broadly within 3 groups: medication, laser, and surgery. This paper will review new options in all 3 categories.

Medications (Table 1)

Newer versions of familiar drugs include preservative-free latanoprost 0.005%, bimatoprost administered via an intracameral implant, and latanoprostene bunod. Agents that are available in the United States (US) but not yet in Canada include the rho kinase (ROCK) inhibitor netarsudil and combination netarsudil-latanoprost. The clinical characteristics of each will be reviewed.

Preservative-free latanoprost

The preservative-free formulation of latanoprost was approved by Health Canada in 2018.[10] Its efficacy is similar to latanoprost,[11] but there are significant advantages to the minimum unit dose application for some patients. Multiple-drop use[12] and cumulative exposure to benzalkonium chloride have been shown to negatively affect both the outcomes of glaucoma surgery and ocular surface health.[13,14] Other preservative-free options are available in Canada, including dorzolamide hydrochloride and combination dorzolamide hydrochloride-timolol maleate.

Bimatoprost implant

Adherence to glaucoma therapy is a major cause for treatment failure.[15-17] An injectable, biodegradable bimatoprost implant approved by the US Food and Drug Administration is intended to provide long-term IOP lowering.[18] The implant is delivered through clear cornea via a preloaded injector,[19] and typically floats to the 6 o'clock position of the anterior chamber, where it remains stable. The implant first enlarges and then biodegrades as the drug elutes and eventually disappears. IOP reduction at 16 weeks was statistically and clinically significant, with mean decreases of 7.2, 7.4, 8.1, and 9.5 mm Hg with different implant doses versus 8.4 mm Hg in topical bimatoprost-treated control eyes.[19] Most of the ocular adverse events were transient and related to the injection; cataract was reported in 1 study eye, there were no reports of cystoid macular edema or endophthalmitis.

Latanoprostene bunod (LBN)

LBN is a novel drug with a double action: it has the same base molecular structure as latanoprost, but also has a butanediol mononitrate moiety that releases nitric oxide (NO).[20]

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Table 1. Current topical medications for the reduction of intraocular pressure

Class	Mechanism	Examples	Adverse effects
Prostaglandin agonists	Improved uveoscleral outflow	Travoprost 0.003% or 0.004% Latanoprost 0.005% Preservative-free Bimatoprost 0.01% or 0.03%	Change colour of iris Hypertrichiasis Hyperemia – conjunctival and periocular
Prostaglandin agonists + nitrous oxide moiety	Improved uveoscleral outflow + lower episcleral venous pressure	Latanoprostene bunod	Change colour of iris Hypertrichiasis Hyperemia – conjunctival and periocular
ROCK inhibitors	Improved trabecular outflow	Netarsudil	Conjunctival hyperemia Petechial hemorrhages Corneal verticillata
ROCK inhibitors + PGA	Improved trabecular and uveoscleral outflow	Netarsudil + latanoprost	Conjunctival hyperemia Petechial hemorrhages Corneal verticillata
Beta-blockers	Decreased aqueous production	Timolol 0.25% or 0.5% Betaxolol 0.25%	Slow heart rate Fatigue Trouble breathing Irregular heartbeat Decreased libido
Alpha-adrenergic agonists	Decreased aqueous production, some uveoscleral outflow improvement	Brimonidine tartrate 0.2% Apraclonidine 0.5% or 1.0%	Burning Conjunctival hyperemia Hypertension Tachycardia Arrhythmia
CAI	Decreased aqueous production	Brinzolamide 1% Dorzolamide 2%	Should not be used in renal failure Paresthesia Fatigue Renal calculi
Combinations	CAI + beta blocker Alpha agonist + beta blocker CAI + Alpha agonist PGA + beta blocker	Dorzolamide 2% + timolol 0.5% Brinzolamide 1% + timolol 0.5% Brimonidine 0.2% + timolol 0.5% Brinzolamide + brimonidine Latanoprost 0.005% + timolol 0.5% Travoprost 0.004% + timolol 0.5%	

CAI, Carbonic anhydrase inhibitor; PGA, prostaglandin analogue; ROCK, Rho kinase

Once released, NO relaxes the trabecular meshwork, improving conventional outflow by widening intercellular spaces. LBN, therefore, improves outflow by affecting both conventional and uveoscleral outflow. The APOLLO and LUNAR studies showed that once-daily LBN 0.024% was associated with a significantly greater reduction in mean IOP than twice-daily timolol,[21,22] and the VOYAGER study showed LBN to be more effective than latanoprost.[23] Safety was similar between the 2 groups. For either treatment, >1% of subjects experienced mild to moderate adverse events, such as eye irritation, conjunctival hyperemia, dry eye, and instillation-site pain. Severe or serious nonocular adverse events were rare, and none were considered to be treatment related.

ROCK inhibitors

ROCK inhibitors decrease actin-myosin contraction, relaxing the trabecular meshwork, and have 3 main mechanisms of action: improved conventional outflow, decreased episcleral venous pressure, and decreased aqueous production.[24,25] The Phase III ROCKET-1 and ROCKET-2 trials reported that once- and twice-daily administration of netarsudil were noninferior to timolol in significantly reducing IOP from baseline at all time points in the study groups with a maximum baseline IOP of <25 mm Hg.[26] Likewise, ROCKET-4 showed noninferiority at all time points between netarsudil and timolol in a population with a wider IOP inclusion range of >20-< 30 mm Hg.[27] The authors concluded that netarsudil lowers IOP irrespective of baseline pressure, unlike timolol where the degree of pressure lowering is greater with a higher baseline. Safety data were similar across these studies; conjunctival hyperemia and hemorrhage were reported significantly more in the netarsudil-treated groups (47.9%–53.2%) versus timolol (8.2%–10.8%). Conjunctival hemorrhage was

generally due to small petechiae and self-resolved. Corneal verticillata were seen in the netarsudil groups (5.4%–24.5%) with an onset at 6–13 weeks. Visual acuity was not affected, and a long-term follow-up report is planned.

Combination netarsudil-latanoprost was shown to be statistically superior to the individual components in 2 Phase III trials.[28] Mean diurnal IOPs at 2 weeks for the combination, netarsudil-only, and latanoprost-only groups were 15.3 mm Hg, 18.1 mm Hg, and 17.5 mm Hg, respectively, versus baseline mean diurnal IOPs of 23.6 mm Hg, 23.6 mm Hg, and 23.5 mm Hg, respectively. These between-group differences were maintained at 6 and 12 weeks ($P<0.0001$ at all time points). A ≥40% reduction in IOP was found in 30.9% of the combination group versus 5.9% with netarsudil and 8.5% with latanoprost. Conjunctival hyperemia and corneal verticillata were seen in the netarsudil-treated groups at a greater frequency than the latanoprost group.

Lasers

Current laser therapies can be used in several ways to treat glaucoma. The therapeutic applications for the 3 discussed here include targeting the trabecular meshwork to increase aqueous outflow, ablating the ciliary processes to reduce production of aqueous humour, and performing laser peripheral iridotomy to prevent pupillary block.

Laser trabeculoplasty

Selective laser trabeculoplasty (SLT) is currently the most widely used laser therapy for open-angle glaucoma (OAG), and has superseded argon laser trabeculoplasty (ALT).[29-31] SLT is effective in reducing IOP by ≥20% below baseline in 40%–85% of eyes at 2 years.[32] The IOP-lowering effect of SLT is similar to medical treatment, thus it can reduce or delay the need for antiglaucoma medication use, improving patient convenience, adherence, comfort, and appearance. It is, therefore, increasingly used earlier in the glaucoma treatment algorithm, prior to maximal medical management and even as first-line therapy. A large-scale prospective study (LiGHT) examining SLT as initial treatment found that 75% of patients were drop-free at 3 years.[33] The economics of SLT are also favourable when compared to medical therapy as primary treatment for OAG. Allowing for repetition of SLT every 2 years, 6-year cost savings versus monotherapy and triple-drug therapy were calculated to be $206.45 and $2992.67 per patient, respectively, in our Canadian healthcare system.[34]

Another new laser that targets the trabecular meshwork is micropulse laser trabeculoplasty (MLT), which was first described in 2005.[35] Using a diode laser, microsecond pulses of repetitive energy are delivered to the trabecular meshwork, spaced apart with periods of rest time to reduce heat build-up and associated collateral thermal damage.[36] The mechanism of MLT's subthreshold energy treatment remains poorly understood, causing neither thermal damage (as with ALT) nor cellular damage (as with SLT).[37] There are no observable treatment endpoints with this treatment; the laser energy is generally titrated down if the patient experiences pain. Laser settings vary between studies, and lack of a standard MLT protocol is a drawback to this technique's widespread clinical application. There is currently a lack of well-powered prospective studies comparing MLT with more conventional laser trabeculoplasty techniques; however, promising initial results found that MLT can reduce IOP by 17%[38] to 21%,[39] with effects sustained for 6 months. There are no MLT-related significant, sight-threatening complications in the literature,[40] and it is hoped that MLT can prove to have equal efficacy but an even safer profile compared to SLT.

Cyclophotocoagulation

Another target of glaucoma laser therapy is the aqueous humour-producing ciliary processes. Transscleral cyclophotocoagulation (TCP) was introduced in the 1970s and has traditionally been reserved for refractory glaucoma patients with poor visual potential. Newer procedures, such as micropulse cyclophotocoagulation (MCP) and endoscopic cyclophotocoagulation (ECP), may expand available options for patients with moderate to severe glaucoma, and may even be considered in eyes with good visual potential.

Micropulse cyclophotocoagulation delivers pulsatile laser energy to the ciliary body. The "on" cycle delivers 810 nm of thermal energy and causes photocoagulative thermal damage, while the "off" phase allows adjacent structures to cool, reducing damage to collateral tissues.[41] One study comparing MPC with conventional TCP found both modalities were effective with a 45% reduction from baseline IOP at 18 months.[42] However, serious complications were observed more frequently in the TCP (60%) than the MPC (12%) group, which could be attributed to the minimal damage to the surrounding structures associated with MPC. MPC has the potential to be a safer alternative to traditional TCP, with similar efficacy but a lower complication rate;[41] however, concerns over post-MPC visual decline and persistent anterior chamber inflammation remain.[43]

ECP, developed in 1992, is an intraocular approach whereby diode laser energy is applied directly to the ciliary processes under endoscopic visualization.[44] This potentially decreases the risk of overtreatment and has a better safety profile than conventional TCP.[45] ECP is relatively invasive, performed through a limbal or pars plana approach, and is often conducted with phacoemulsification. There is evidence that concurrently performing the 2 procedures can lower IOP and allow a reduction in antiglaucoma medications.[46-48]

Laser peripheral iridotomy

Laser peripheral iridotomy (LPI) has been established as first-line intervention for acute primary angle closure (PAC) and there is strong consensus that laser iridotomy is beneficial in fellow eyes of patients who have suffered an acute attack of angle closure.[49] The role of prophylactic LPI in the management of asymptomatic PAC suspects (PACS) is uncertain, with current evidence for both the risks and benefits appearing weaker than had been previously believed.[50,51] The Zhongshan Angle-

closure Prophylaxis trial provided robust evidence that rate of conversion from PACS to acute angle-closure was very low, with an annual incidence of <1%, and concluded that the overall benefit of LPI in preventing significant loss of vision was modest.[51] Age-related growth of the lens is a major contributing factor to primary angle closure. Anterior-segment optical coherence tomography showed a significant increase in angle-width parameters in patients before and after cataract extraction compared to LPI.[52] The EAGLE study, a large, multicentre randomized trial, compared clear-lens extraction with LPI as the initial treatment for either primary angle closure with IOP >30 mm Hg or primary angle-closure glaucoma.[53] Results supported phacoemulsification as a primary treatment option for those meeting study criteria, with improved patient-reported quality of life, reduced need for medication, and fewer surgeries. Increasing knowledge of the mechanisms leading to angle-closure glaucoma may prompt questioning the utility of prophylactic LPI and adopting lens extraction earlier in the treatment algorithm.

Surgery

Trabeculectomy with mitomycin C (MMC) and glaucoma drainage devices (Ahmed®, Ahmed Clearpath™ or Baerveldt® implants) remain the gold-standard modalities for surgical glaucoma in achieving low IOP.[54] The Ahmed implant is valved and the Clearpath and Baerveldt implants are nonvalved. These surgeries have relatively long recovery periods and the risk of serious complications.[55] Moreover, their indication leaves important gaps in the surgical paradigm for early to moderate disease. A variety of small implants and surgical techniques have emerged since early 2000 to try to address these issues. These techniques, collectively known as less invasive, minimally, or microinvasive glaucoma surgery (MIGS),[56] show modest IOP lowering with a high safety profile. MIGS options can be classified by the anatomical pathway used to facilitate aqueous outflow. The Schlemm canal bypasses trabecular meshwork (TM) outflow, either with an implant or by excising tissue. The suprachoroidal space is not currently used. The subconjunctival space creates a bleb forming outflow pathway for aqueous humour. This section will discuss the major available MIGS procedures and the evidence for their efficacy.

Trabecular bypass - implant
iStent®

The iStent and iStent inject® are placed through the TM to shunt aqueous directly into the Schlemm canal. The central outlet of the newer iStent inject is 80 µm in diameter with an outer flange of 230 µm, the head has 4 side flow outlets, and the stent is 360 µm long. A recent prospective, randomized, controlled trial compared the iStent inject plus phacoemulsification to phacoemulsification alone in patients with mild to moderate primary OAG (POAG).[57] At 24 months, 76% of stent-implanted eyes experienced a 20% reduction of unmedicated diurnal IOP (mean 6.9 mm Hg) versus 62% of control (mean 5.4 mm Hg). The safety profile was similar in both groups. A 2019 Cochrane review showed very low-quality evidence that treatment with iStent in combination with phacoemulsification compared to phacoemulsification alone or iStent compared to medical therapy resulted in higher proportions of patients no longer needing drops or achieving better IOP control in the short, medium, or long term.[58]

Hydrus®

The Hydrus microstent is an 8-mm trimodal device: the tail end in the anterior chamber allows flow into the Schlemm canal and the body of the stent maintains patency and tension in the canal, improving outflow. The HORIZON study compared the Hydrus microstent plus phacoemulsification to phacoemulsification alone. At 24 months, 77% of the Hydrus group had 20% reduction in diurnal IOP (mean -7.6 mmHg) compared to 58% (mean -5.3 mmHg) of the phacoemulsification group.[59] The COMPARE study, comparing Hydrus to 2 iStent devices stent over 12 months, showed higher surgical success rate and fewer medications with Hydrus, with similar safety profiles.[60]

Trabecular bypass – excision

The Kahook Dual Blade® (KDB), Trabectome, TrabEX™, TrabEX+™, and gonioscopy-assisted transluminal trabeculotomy (GATT) are a group of devices that deroof the TM and improve conventional outflow. The KDB and TrabEX are blades, the Trabectome uses electrocautery, and GATT can be performed with either a light-emitting diode fibre or a 6-0 prolene suture.

A 1-year prospective study of goniotomy performed using the KDB combined with phacoemulsification in POAG patients showed a 26% reduction in IOP and a 50.0% reduction in mean topical IOP-lowering medication usage.[61] A retrospective chart review for 2 years after 360° GATT indicated that the procedure was associated with a decrease in IOP of 9.2 mm Hg (14%–37% decrease from baseline) and an average reduction of 1.43 glaucoma medications in both primary and secondary glaucoma patients.[62] Hyphema was the main intra- and post-operative complication in about 30% of cases. In a systematic review study, GATT achieved both a significant IOP lowering of 10 mm Hg and a pooled medication burden decrease of 1.7.[63]

According to a 1-year prospective randomized controlled study, POAG patients treated with

phacoemulsification-Trabectome achieved similar IOP lowering to those who received phacoemulsification-trabeculectomy with MMC (20.0±5.3 baseline to 16.8±2.7 mm Hg versus 23.1±6.4 to 17.1±5.0 mm Hg, respectively) with a similar number of glaucoma medications used.[64] The 1-year mean IOP of 17.1±5.0 mm Hg in the phacoemulsification-trabeculectomy group was higher than expected, but the phacoemulsification-Trabectome group had an increased incidence of long-term PAS compared to control.

Subconjunctival bleb forming

The XEN® Gel Stent and PreserFlo™ microshunt are bleb-forming devices that bypass conventional outflow pathways, travelling through scleral tissue to connect the anterior chamber and subconjunctival space. As with trabeculectomy, these require subconjunctival injection of MMC.

The XEN Gel Stent is 6 mm in length with inner and outer diameters of 45 μm and 150 μm. The on-label use is an ab interno insertion, but an ab externo approach is also used. The 2-year results of a multicentre study of the XEN Gel Stent with and without phacoemulsification found that a ≥20% reduction in mean IOP from baseline was achieved in 65.8% of eyes and 44.7% were medication-free for both groups; 24.2% of eyes achieved IOP ≤12 mmHg. Complications were similar to the trabeculectomy profile; however, the rate of bleb needling was 41.1%.[65]

The PreserFlo Microshunt is a bio-inert polystyrene tube implanted ab externo, with the long end subconjunctival and the short end inserted into the anterior chamber. The device has a luminal diameter of 70 μm and a length of 8.5 mm. Several early studies have shown good IOP and medication lowering effects with a low risk of serious complications.[66] Long-term analysis is ongoing.

The MIGS umbrella comprises several devices with a variety of potentially clinical applications, mechanisms of action, and success rates. Cost and access to these devices remain considerable issues. The Canadian Agency for Drugs and Technologies in Health Report concluded in 2019 that there was insufficient evidence to make recommendations specific to the optimal use and funding of MIGS in Canada due to existing knowledge gaps, and recommended additional high-quality evidence.[67] These devices still have an important role in surgical glaucoma management in our aging population, aiming for a faster visual recovery and better safety profile than the conventional surgeries.

Conclusion

The different treatment options for glaucoma vary widely with respect to their ease of use, efficacy, and safety. New developments in medications, lasers, and surgery all improve the flexibility of our therapeutic armamentarium. The best treatment for any given patient, therefore, will depend on the unique clinical situation of the individual patient.

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The authors state that they have no disclosures to report in association with the contents of this issue.

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Ophthalmology Rounds is made possible through educational funding from the following industry co-sponsors:

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