Recent Advances in the Management of Glaucoma

Dr. J.S. Bhalla MS, DNB, MNAMS, **Dr. Himani Anchal** MS

Department of Ophthalmology, D.D.U. Hospital, New Delhi, India

Glaucoma is the leading cause of irreversible blindness in the world[1]. In India, estimated number of cases of glaucoma is around 12 million, and an equal proportion of open and closed angle glaucoma is seen[2].

Glaucoma is defined as a group of chronically progressive optic neuropathies characterized by atrophy of optic nerve, visual field defects and characteristic optic nerve head changes[3]. Risk factors include advanced age, African race, a positive family history of glaucoma, severe myopia and ocular risk factors, such as increased IOP, morphological features of optic disc and thinness of cornea[4,5,6].

The established treatment protocol has been concentrated on lowering IOP to a level at which the progression of glaucomatous damage can be delayed or halted. In recent years, however, a more aggressive treatment approach has been adopted. This change is due to both the availability of more powerful ocular hypotensive agents as well as to the increased understanding of the need to achieve the lowest possible pressure to preserve the visual field.

ADVANCES IN THE MEDICAL MANAGEMENT OF GLAUCOMA

Latanoprostene bunod

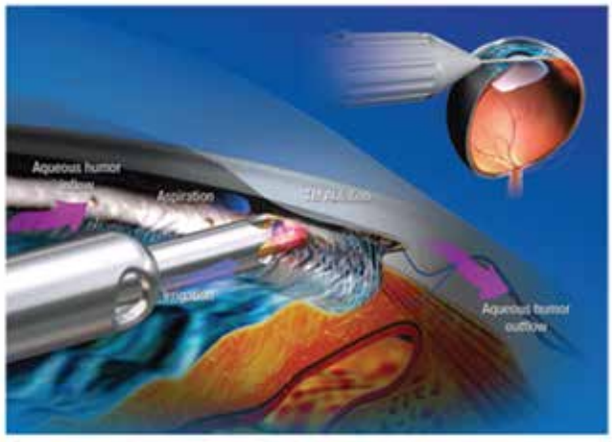
Latanoprostene bunod (LBN) is a nitric oxide (NO) donating prostanoid FP receptor agonist. It is rapidly metabolized in the eye into lataoprost acid, a F2α prostaglandin analogue, and butanediol mononitrate, which subsequently releases NO in conjunction with butanediol, an inactive metabolite[7,8]. Latanoprost acid causes remodelling of the extracellular matrix in the ciliary body, thereby increasing aqueous humor outflow through the uveoscleral pathway and thus decreases the IOP[9,10,11,12]. NO causes relaxation of the trabecular meshwork and Schlemm's canal, resulting in increased aqueous humor outflow[13,14,15,16].

The VOYAGER study, a well-controlled phase 2 study in 413 patients with open angle glaucoma (OAG) or ocular hypertension (OHT) demonstrated a significantly greater reduction in mean diurnal IOP after 28 days of treatment with LBN 0.024% compared with latanoprost 0.005%[17].

Another randomized controlled study (APOLLO study) demonstrated that LBN 0.024% resulted in significantly greater IOP lowering compared with Timolol 0.5%[18].

Rho kinase inhibitor

Rho kinase (ROCK 1 and ROCK 2) is a serine/ threonione kinase that serves as an important downstream effector of RhoGTPase, and plays a role in the regulation of contractile tone of smooth muscle tissue in a calcium independent manner. Modulation of ROCK activity within the aqueous humor outflow pathway using selective inhibitors can be used in the treatment of glaucoma.



The Trabectome tip, moving through Schlemm's canal, ablates trabecular and juxtacanalicular tissues to improve aqueous access to outflow channels and lower IOP.

Figure 1: *Glaucoma surgery using Trabectome*

Inhibitors of ROCK and Rho kinase increase aqueous humor drainage through the trabecular meshwork, leading to decrease in IOP. Further they have been shown to increase the ocular blood flow, retinal ganglion cell survival and axonal regeneration.

A double masked randomized controlled trial in 89 patients with OAG or OHT demonstrated a statistically significant ocular hypotensive effect of 0.05%, 0.1% and 0.25% AR12286, a Rho kinase inhibitor[19].

Another phase 2 randomized clinical study of a Rho kinase inhibitor, K-115, showed a significant ocular hypotensive effect in OAG and OHT[20].

Sustained release drugs

Daily application of topical medications have a negative impact on patient compliance due to poor bioavailability and other long term side effects such as allergy and intolerance to medications, which leads to suboptimal medical management of the disease resulting in poor IOP control[21]. The use of liposomes as biocompatible nanocarriers allows delivery of lipophilic as well as hydrophilic drug molecules, due to its physical structure of a polar core and lipophilic bilayer[22]. Topical application of liposomes have demonstrated poor penetration into the eye[23]. Subconjunctival injections, however, have shown limited sustainability[24].

A study by Natrajan JV et al has revealed that a single subconjunctival injection of latanoprost-loaded Egg PC liposomes effectively lowered IOP in rabbit eyes for at least 90 days[25].

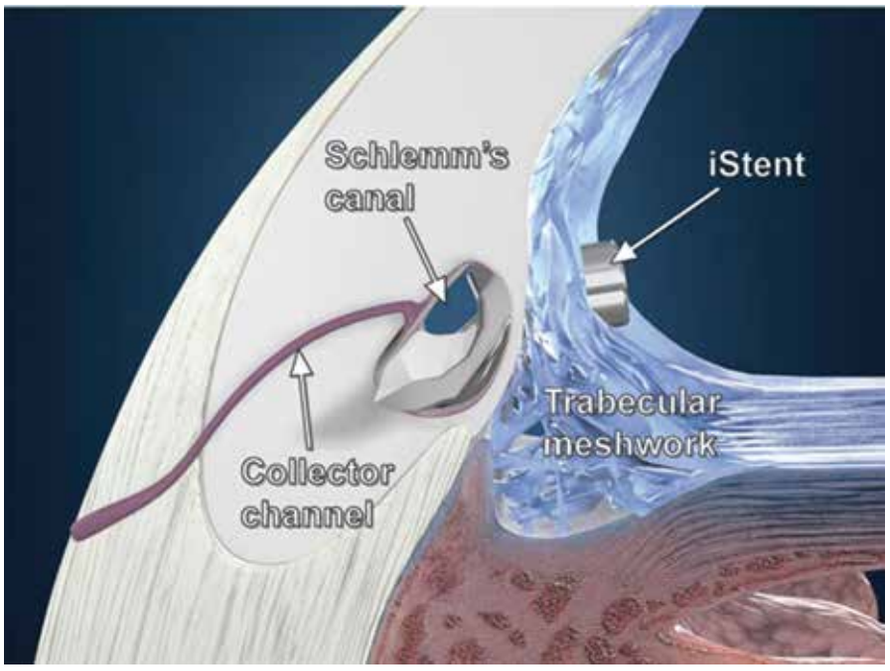


Figure 2: *Glaucoma surgery showing iStent*

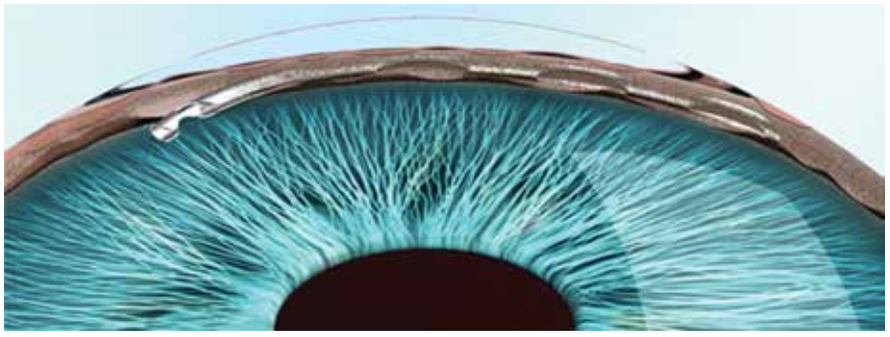


Figure 3: *Hydrus microstent placed in the Schlemm's canal*

Nicotinamide

Recently, the differences in gene expression and total NAD levels have been proposed to affect the functioning of retinal ganglion cells. Williams et al hypothesized that reduced levels do destabilize metabolism during periods of stress and that the age-dependent decline in NAD levels, when combined with stress from elevated intraocular pressure, has a negative effect on mitochondrial function. This compromise in function leads to increases in the metabolism of fatty acids and the generation of free radicals, and thus an impaired response to metabolic stress, which in turn leads to loss of retinal ganglion cells. To test the "NAD-deficit" hypothesis, Williams et al. supplemented the mouse diet with nicotinamide (the amide of vitamin B3 and a precursor to NAD+) to enhance cellular energy production. At the lowest dose studied (equivalent to about 2.5 g per day for a person weighing 60 kg), the authors found that nicotinamide prevented the structural and functional loss of retinal ganglion cells despite the continued elevation of intraocular pressure[26].

ADVANCES IN SURGICAL MANAGEMENT OF GLAUCOMA

Microinvasive Glaucoma Surgery (MIGS)

Traditionally, invasive surgical management of glaucoma is recommended when medication and or laser trabeculoplasty fail to control IOP. Filtering procedures such as trabeculectomy and glaucoma drainage devices, are effective in lowering IOP, but are associated with significant adverse effects and high rates of failure.

MIGS procedures have a higher safety profile with a fewer complications and a more rapid recovery time than other invasive techniques.

MIGS APPROACHES

1. Increasing trabecular outflow
   - Trabectome
   - Istent
   - Hydrus stent
   - Gonioscopy associated transluminal trabeculotomy
   - Excimer laser trabeculotomy
2. Suprachoroidal shunts
   - Cypass microstent
3. Reducing aqueous production
   - Endocytophotocoagulation
4. Subconjunctival filteration
   - XEN gel implant

TRABECTOME

The Trabectome system performs a trabeculotomy via an internal approach. Under the guidance of intraoperative gonioscopy, a disposable 19.5-gauge handpiece with an insulated footplate containing electro cautery, irrigation, and aspiration functions is inserted into the anterior chamber and then through the TM into Schlemm's canal. The device moves along the TM, removing both a strip of TM and the inner wall of Schlemm's canal. Thus a pathway for aqueous outflow from the anterior chamber directly into the collector channels is created[27].

Maeda et al evaluated the outcome of surgeries using Trabectome in 80 eyes of 69 patients. A mean preoperative IOP of 26.6 ± 8.1 mmHg was found to decrease to a mean postoperative IOP of 17.4 ± 3.4 mmHg within 6 months after the surgery. Average number of medications also decreased from 4.0 ± 1.4 to 2.3±1.2 at 6 months[28].

ISTENT IMPLANT

The iStent is a trabecular micro-bypass product that directly connects the anterior chamber to Schlemm's canal and creates a permanent opening into Schlemm's canal. The device is composed of a heparin-coated, non-ferromagnetic, titanium stent, approximately 1×0.3 mm in size, that connects at a right angle to the canal-implanted portion, which has a pointed end. It comes with an inserter, which is guided into a corneal wound, at least 1.7 mm in size, and into the anterior chamber under ophthalmic viscoelastic device (OVD). With the help of a surgical gonioscopy lens, it is implanted into Schlemm's canal with a sideways sliding technique. Like the Trabectome, the iStent reduces resistance in the juxtacanalicular TM.

A prospective randomized clinical trial demonstrated a significant reduction in the mean diurnal IOP and the number of medications[29].

Figure 4: *Gonioscopy assisted transluminal trabeculotomy*

phacoemulsification combined with XEN45 implant surgery in 30 eyes and reported a significant decrease in IOP and the number of medications over a period of 12 months[32].

MINIATURIZED HIGH INTENSITY FOCUSED ULTRASOUND

The ciliary body ablation is still considered as a last resort treatment to reduce the intraocular pressure (IOP) in uncontrolled glaucoma. Several ablation techniques have been proposed over the years, all presenting a high rate of complications, nonselectivity for the target organ, and unpredictable dose-effect relationship. These drawbacks limited the application of cyclodestructive procedures almost exclusively to refractory glaucoma. High-intensity focused ultrasound (HIFU), proposed in the early 1980s and later abandoned because of the complexity and side effects of the procedure, was recently reconsidered in a new approach to destroy the ciliary body.

Several mechanisms of action were proposed to explain the final IOP lowering after HIFU, such as localized destruction of the ciliary-pigmented and nonpigmented epithelium, atrophy of the ciliary muscle, cyclodialysis cleft, and scleral thinning[33,34,35]. Despite encouraging initial evidence, the ultrasound cyclodestruction was used only in advanced and refractory glaucoma, because of the significant risk of complications (scleral staphyloma, corneal thinning, persistent hypotony, phthisis bulbi, and loss of the visual acuity).

Ultrasound circular cyclocoagulation (UC3), by using miniaturized transducers embedded in a dedicated circular-shaped device, permits to selectively treat the ciliary body in a one-step, computer-assisted, and non-operator-dependent procedure. UC3 shows a high level of safety along with a predictable and sustained IOP reduction in patients with refractory glaucoma. Recent studies in patients with refractory glaucoma report encouraging results after UC3 in terms of both IOP reduction and safety of the procedure[36,37,38].

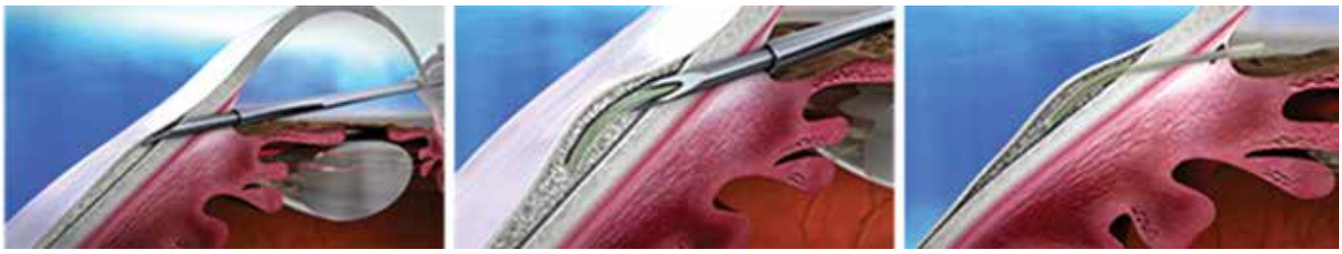


Figure 5: *Placement of a XEN GEL implant in the eye*

HYDRUS IMPLANT

The device is inserted into the Schlemm's canal via a 1-1.5mm clear corneal incision. It dilates the canal by 4-5 times the natural width, thus maintaining patency and establishing outflow.

A study by Pfeiffer et al compared Hydrus microstent with concurrent cataract surgery and cataract surgery alone, and reported that 86% of Hydrus patients had a 20% reduction in the washed out IOP compared to 46% of patients undergoing cataract surgery alone[30].

GONIOSCOPY ASSISSTED TRANSLUMINAL TRABECULOTOMY (GATT)

GATT is a sutureless and conjunctival sparing technique. Under the guidance of gonioscopy lens, a goniotomy is made in the nasal trabecular meshwork through which a microcatheter is inserted. Microsurgical forceps are used to advance the microcatheter in the Schlemm's canal circumferentially 360 degrees. The catheter is then externalized to create a 360 degree trabeculotomy.

Grover et al reported a significant IOP decrease in patients with primary OAG and secondary glaucoma[31].

XEN GEL IMPLANT

It is an ab interno gelatin stent implanted via a clear corneal incision without conjunctival dissection. The stent follows Poisueille's law of laminar flow where the length and the inner diameter of tube manages the rate of flow.

Perez-Torregrosa et al performed

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Correspondence to:
Dr. J.S. Bhalla
Department of Ophthalmology,
D.D.U. Hospital, New Delhi, India