

Recent Updates on Medical Management of Glaucoma

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Abstract

Glaucoma is the leading cause of irreversible blindness worldwide. It is estimated to affect more than 110 million people globally by the year 2040. The disease is characterized by progressive loss of the retinal ganglion cells resulting in characteristic visual field defects. Modulating intraocular pressure is a widely accepted and practiced strategy in managing glaucoma. While most available drugs either suppressed aqueous formation or shunted it across the uveo-scleral pathways, rho kinase inhibitors have been introduced targeting the trabecular meshwork. Latanoprostene Bunod and its combination with Latanoprost and Omidenepeg Isopropyl are new additions soon to be available in India. Durysta, a sustained-release Bimatoprost implant, is already approved in the United States; other implants involving Travoprost are in the pipeline. Neuroprotection is the ultimate goal in glaucoma management and recent trials with neurotrophic factors, glutamate antagonists, stem cells and antioxidant therapy have been encouraging. Co-enzyme Q10 with vitamin E combination (Coqun) eye drops have demonstrated efficacy as an adjunct antiglaucoma therapy. While Brain Derived Neurotrophic factor have demonstrated efficacy in animal studies, experimental study with Nerve Growth Factor eye drops have shown promising results in humans. Stem cell research has a great potential in neuroprotection but still is in infancy. Concerns such as mode of delivery, graft survival and potential side effects remain to be known before stem cell therapy comes to the fore of clinical management of glaucoma. The present article provides an overview of the recent developments in the wide arena of medical management of glaucoma.

Keywords: Rho-kinase inhibitors, Latanoprostene Bunod, Omidenepeg Isopropyl, Durysta implant, Neurotrophic factors, glaucoma.

INTRODUCTION

Glaucoma is a neurodegenerative disorder characterised by progressive loss of the Retinal Ganglion Cells (RGC) leading to characteristic optic disc cupping and visual field defects. It is the leading cause of irreversible blindness worldwide. The global estimates point to more than 75 million people in age group between 40 to 80 years to already have been affected by glaucoma by the year 2020 and this figure is expected to cross 110 million by the year 2040. Over the past few decades, efforts are being made to gain deeper insights into the disease pathology and innovate ways to halt or reverse the glaucomatous damage. In spite of our evolving understanding, most of our treatment modalities still revolve around altering the intraocular pressures. Newer molecules are now available to provide more options for effective intraocular pressure (IOP) control. Advances in drug delivery systems have improved the drug bio-availability and the overall efficacy of medical management. However, effective neuroprotection

and possible neuro-regeneration remains to be an elusive holy grail in glaucoma management. The present article aims to provide an overview of the recent developments in the medical management of glaucoma. (Figure 1)

Rho Kinase Inhibitors

By 1990s, most of the available anti-glaucoma medications reduced the IOP by either suppressing the aqueous formation or by shunting it through the uveo-scleral pathway. It was well understood that altered trabecular meshwork (TM) structure and function was the underlying mechanism for causing a rise

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Newer Drugs	Sustained Release Drug Implants	Neuroprotection
<ul style="list-style-type: none"> •*ROCK Inhibitors •Latanoprost+Netarsudil (Rocklatan) •Latanoprostene Bunod •Omidenepeg Isopropyl 	<ul style="list-style-type: none"> •Durysta (Bimatoprost) Implant •Bimatoprost Ocular Rings •i-Dose Travoprost Implant •Travoprost Punctal Plugs 	<ul style="list-style-type: none"> •Memantine •Neurotrophic Factors •Co-enzyme Q10 •Ginkgo Biloba Extract

Figure 1: Recent developments in medical management of glaucoma (Green denotes 'commercially available' Red denotes 'experimental stages', *Rho-kinase)

in IOP, yet there was no antiglaucoma medication targeting the TM. In 1993, new research molecules were discovered which facilitated the aqueous outflow across the TM- the Rho Kinase Inhibitors popularly known as the ROCK- inhibitors.

The Rho family (RhoA, RhoB, RhoC) are small G-proteins that are active when bound to guanosine triphosphate (GTP) and inactive when bound to guanosine diphosphate (GDP). They regulate cell morphology, polarity, proliferation, adhesion, motion, cytokinesis, and apoptosis along with smooth muscle contraction and neurite elongation. Rho Kinases (isoforms 1 and 2) phosphorylates Guanosine-diphosphate (GDP) to Guanosine-triphosphate (GTP) and thereby activates Rho proteins. The activated Rho proteins lead to contraction of actin-myosin chains in the smooth muscles resulting in increased tone and stiffness of the TM and reduced conductance of the Schlemm's canal (SC). Rho-kinase Inhibitors on the other hand facilitate the aqueous outflow by relaxing the stiffness of TM and enhancing the pore formation in the SC.⁵ It also alters the SC cytoskeleton to reduce cellular adhesions in the juxtacanalicular TM.

In addition to the abovementioned effects, ROCK inhibitors result in activation of Nitric Oxide Synthetase (NOS) which enhances Nitric Oxide (NO) production. NO is a potent vasodilator and an anti-apoptotic agent and is proposed to promote Retinal ganglion cell survival. Furthermore, ROCK inhibitors may potentially enhance bleb longevity by reducing the trans-differentiation of human Tenon's fibroblast into myofibroblast and prevent bleb scarring.

Ripasudil (Glanatec)

Ripasudil is nonspecific inhibitor of both Rho kinase 1 & 2 (ROCK 1 & 2) and was first approved in Japan for treatment of Glaucoma and Ocular Hypertension (OHT) in 2014. Ripasudil 0.4% solution in BID doses has been found effective in lowering IOP by 2 to 4 mm Hg in among glaucoma and OHT patients. Additionally, it has also been found to be a safe option for IOP lowering in ocular hypertension with uveitis. Recent phase 3 trials have also reported its efficacy as an add on anti-glaucoma medication with other first line anti-glaucoma medications such as Timolol and Latanoprost. Ripasudil along with Timolol combination is reported to result in greater lowering of IOP than with Latanoprost 0.005% combination when compared to placebo. Conjunctival hyperaemia is by far the commonest ocular adverse effect reported with Ripasudil use.¹⁵ The hyperaemia is usually observed to peak within 15 minutes of drug instillation before gradually resolving over next two hours. Other significant ocular adverse effects reported with Ripasudil include blepharitis

and allergic conjunctivitis.⁵ *Netarsudil (Rhopressa) and Fixed Combination Netarsudil-Latanoprost (FCNL)*

Netarsudil was first launched in United States in 2017 as a non-specific ROCK inhibitor having an additional norepinephrine transporter inhibitor property. It has 20 times more potent inhibitory action compared to other ROCK inhibitors. The drug not only facilitates the outflow across the TM but additionally reduces aqueous production and episcleral venous pressure. The additional effects are brought about by its norepinephrine transporter inhibitor action. This dual action makes it a unique antiglaucoma medication.

Commercially, the drug is available in 0.02% formulation with QD dose recommendation. The drug is metabolised to its active metabolite Netarsudil-M1 by corneal esterase which is almost 5 times more potent ROCK inhibitor compared to Netarsudil itself.¹⁷ Past double masked randomised control trials including ROCKET 1 & 2 have found Netarsudil 0.02% in QD and BID doses to be non-inferior to Latanoprost 0.005% and Timolol 0.5% respectively. The trials highlighted better IOP lowering effect of the drug especially in patients with lower baseline IOPs perhaps secondary to its episcleral venous pressure lowering property. As an add on anti-glaucoma therapy to Latanoprost, both MERCURY 1 & 2 trials have reported greater efficacy of a fixed dose combination of Netarsudil 0.02% with Latanoprost 0.005% compared to monotherapy alone. Latanoprost increases aqueous outflow through the uveo-scleral pathway whereas Netarsudil enhances TM outflow in addition to reducing aqueous production and episcleral venous pressure making it an ideal combination. A fixed dose combination of Netarsudil (0.02%) and Latanoprost 0.005% (FCNL)-Rocklatan was recently FDA approved for management of POAG and OHT.

Similar to Ripasudil, conjunctival hyperaemia is the commonest ocular adverse effect reported with Netarsudil. Other common adverse effects reported include subconjunctival haemorrhages described as 'small perilimbal micro-haemorrhages' and cornea verticillata.⁴ Cornea verticillata observed with Netarsudil commonly occurred 2-13 weeks of initiation of the drug and was similar to observed with systemic medications like Amiodarone. Greater incidence of these adverse effects was observed when the drug was used in higher concentrations or frequency and were reversible upon cessation of therapy. Recently a couple of studies have also reported reticulate corneal oedema with Netarsudil usage. These were observed in patients with poor endothelial count.

The safety and efficacy of Netarsudil in children (<18 years) and pregnant women is yet to be ascertained. Netarsudil has been found to be teratogenic in animal studies, however, these effects were observed with concentrations almost 126 times recommended in humans. With extremely low systemic absorption after ocular instillation, the drug is unlikely to cause any adverse effects in breast fed infants. The drug should however be used with caution during lactation.

Fasudil

Fasudil is another non-specific Rho-kinase inhibitor which is presently approved in Japan and China for treatment of cerebral vasospasm. Recently it was reported to lower IOP by 8-9 mmHg in end stage POAG patients. Further research is awaited before it can be made available for treatment of glaucoma.

Latanoprostene Bunod

Latanoprostene Bunod (LBN) is essentially a modified prostaglandin F_{2α} analogue with Nitric Oxide (NO) donating property.²³ The drug is presently approved in US markets for treatment of POAG & OHT. NO is endogenously produced using NO synthetases. The NO produced regulates the blood flow in the tissues by relaxing the vascular smooth muscle cells. NO synthetase in eye is mainly found in anterior segment, non-pigmented epithelium of ciliary processes, ciliary muscle, TM, SC, and collector channels and is proposed to play a vital role in aqueous humour dynamics and IOP control.²³ NO also regulates ocular blood flow and is vital for the functioning and survival of the retinal ganglion cells. Additionally, it is thought to relax the smooth muscles in TM and facilitate aqueous outflow.

LBN is hydrolysed by corneal esterase to latanoprost acid (active metabolite) and butanediol mononitrate, which is further metabolized to 1,4-butanediol (inactive metabolite) and NO (active metabolite).²³ It combines the IOP lowering effect of Latanoprost via the uveo-scleral pathway with NO mediated TM outflow making it an ideal combination. The VOYAGER trial reported greater IOP lowering effect of 0.024% LBN ophthalmic solution compared to Latanoprost in QD doses in POAG and OHT patients. Furthermore, the CONSTELLATION and APOLLO trial found LBN (0.024% QD dose) to provide better day and night time IOP control compared timolol. LBN also resulted in better ocular perfusion pressures compared to Timolol both during the day and night time. The JUPITER trial evaluated the long-term efficacy of LBN over a period of 52 weeks. It reported a 22% reduction in IOP by the end of first month with persistent IOP lowering effects reaching up to 26% from the baseline among POAG and OHT patients.

The ocular adverse effects profile of LBN is similar to those observed with prostaglandin analogues. The common adverse effects observed with LBN include conjunctival hyperaemia, growth of eyelashes, eye irritation, eye pain and increase in iris pigmentation.²³

Omidenepeg Isopropyl (OMDI)

Ever since the rise of prostaglandin analogues (PGA) as the first line anti-glaucoma therapy, Prostaglandin Associated Periorbitopathy (PAP) secondary to stimulation of F-Prostanoid (FP) receptors has been a major cause of concern. Not only does this contribute to major cosmetic blemish for patients, PAP also hinders glaucoma management. Difficulties in IOP assessment, failure of trabeculectomy and

reduced compliance have all been related to PAP. Recent researches have pointed to new molecules which modulate prostaglandin signalling by acting upon E-prostanoid receptors (EP receptors) to lower IOP without causing adverse effects as observed with traditional PG analogues which act upon FP receptors.

Omidenepeg Isopropyl is a selective EP2 receptor agonist with a non-prostaglandin structure. The molecule was co-developed by Ube Industries Ltd. (Tokyo, Japan) and Santen Pharmaceutical Co. Ltd. (Osaka, Japan). In 2018, 0.002% OMDI ophthalmic solution was approved as world's first selective EP-2 receptor agonist in management of OAG and OHT in Japan. Subsequently, the drug has also been approved in Singapore, Taiwan and South Korea. The drug is yet to obtain regulatory approvals in India and United States.²⁷ OMDI is an isopropyl ester prodrug that undergoes hydrolysis to its active metabolite (omidenepeg, OMD) during corneal penetration. It selectively acts upon EP-2 receptor which is a Gs-coupled transmembrane receptor found in the ciliary body and trabecular meshwork. EP-2 receptor agonists decrease IOP by increasing both trabecular and uveo-scleral outflow by stimulating a Gs-protein-mediated elevations in intracellular adenosine 3',5-cyclic monophosphate (cAMP) levels and various signalling cascades in the ciliary body and trabecular meshwork. PAP and other ocular adverse effects are not observed with OMDI due to poor affinity to FP receptors.²⁷

The AYAME study from Japan reported OMDI 0.002% ophthalmic solution in QD dose to be non-inferior to Latanoprost 0.005% and reduced IOP by 5.93 mmHg from the baseline in POAG and OHT. These results were also reflected in a larger multicentre study involving India. Thus, OMDI became the first drug to show non-inferiority to Latanoprost in last 20 years. Additionally, the drug was also found to be useful in patients who were initially non responsive to PGA therapy. As a combination therapy, the RENGE trial demonstrated that the IOP lowering efficacy of OMDI improved with addition of Timolol making it an effective combination. Thus, with an advantage of QD dosing regime and almost equal efficacy to PGA, OMDI is a promising alternative to PGA as first line therapy in POAG and OHT. The common ocular adverse effects reported with OMDI include conjunctival hyperaemia, corneal thickening, eye pain, photophobia and cystoid macular oedema. Most instances of macular or cystoid macular oedema with OMDI were observed in pseudophakic patients and the drug has been contraindicated in patients with pseudophakia or aphakia.²⁸ The mechanism of action of the abovementioned drugs is summarised in figure 2.

Sustained Release Implants

Life-long regular use of glaucoma medications is a daunting task for any patient. Multiple factors such as cost of therapy, associated adverse effects, patients' lack of understanding and forgetfulness etc. have been found to affect the continuity

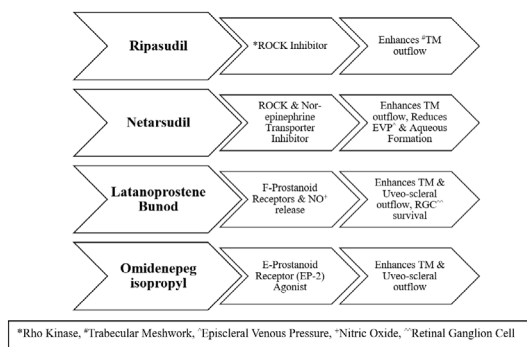


Figure 2: Newer anti-glaucoma drugs and their mechanism of action

of glaucoma treatment. All these factors contribute to poor compliance and worsening of glaucoma among patients. Efforts have been made in past to develop sustained release glaucoma medications to overcome the challenges posed by long term glaucoma treatment. Among the many potential candidates, Durysta-a Bimatoprost sustained release implant is only currently available commercially in US markets.

Bimatoprost Sustained Release Implants

Durysta is the first Bimatoprost sustained released intraocular implant approved by the United State Food and Drug Administration (FDA) for treatment of OAG and OHT in the year 2020.³¹ The implant consists of a 10- μ g dose of bimatoprost, released in a non-pulsatile, steady-state fashion, held within a rod-shaped poly-D,L-sustained lactide-co-glycolide (PLGA) polymer matrix drug delivery system based on Allergan's NOVADUR platform.³⁰ The biodegradable implant is placed intracamerally at the iridocorneal angle to provide a lasting therapy for more than 4 months. Both 10 and 15 μ g strength of Bimatoprost implant were found to be non-inferior to Timolol 0.5% providing 30% IOP lowering from the baseline at 12 weeks. However, the safety with Bimatoprost 10 μ g SR implant was more favourable. The major adverse effect observed with implant was a drop in corneal endothelial cell count. Other common adverse effect seen in patients included conjunctival hyperaemia. Based upon the adverse effect profile, FDA recommends the implant to be used only for one time in a patient to avoid corneal endothelial cell loss.

Bimatoprost Ocular Ring made up of silicon and polypropylene is an extraocular insert impregnated with 13 mg of Bimatoprost. The implant can be placed in superior and inferior fornices to provide sustained drug availability for about 6 months. Presently, the implant has undergone phase 2 of clinical trials and has been found to have a retention rate of 88.5% at 6 months. In terms of efficacy, it was found to be non-inferior to Timolol 0.5%. Punctate keratitis, eye pain and discharge were the commonest adverse effects reported with Bimatoprost rings. More than 80% of the patients were comfortable with the implant. On repeated application every 6 months, the implant was found to be safe and provided sustained IOP reduction over a period of 19 months. The implant is not yet available for commercial use.

Travoprost Sustained Release Implant (Under Trial)

ENV515 is a biodegradable Travoprost sustained-release implant for intracameral implantation.³¹ The implant is placed at the iridocorneal angle to target continuous drug delivery for 6 to 12 months. A Phase 2 clinical trial demonstrated non-inferiority of the implant to Timolol 0.5% causing 25% reduction in IOP from the baseline. Conjunctival hyperemia was the commonest adverse effect reported with implant use.

i-Dose is a titanium-based intraocular Travoprost eluting intracameral implant. The implant is produced by Glaukos Corporation (San Clemente, California). It is surgically inserted into the sclera through the TM and requires surgical removal at the end of the drug elution process. A phase 2 trial has compared two different rates of drug elution with Timolol 0.5%. Both the slow-release and fast-release *i-Dose* implants displayed comparable efficacy with 7.4 and 7.9 mmHg reductions in IOP from the baseline at 24 months. There was no loss of corneal endothelial cells, conjunctival hyperemia or any other corneal adverse effect reported with either of the drug-eluting implants. The results of the Phase 3 trials with the implants are awaited.

Travoprost Intracanalicular Punctal Plugs under development by Ocular Therapeutix (OTX) (Bedford, Massachusetts, USA) is an extraocular implant for providing sustained delivery of Travoprost.³¹ It is a hydrogel based implant which is placed in the canalicular space to release the drug over a period of 90 days. The implant was found to have lower IOP lowering effect compared to Timolol 0.5%. Dacryocanalculitis was the main adverse effect observed with this implant.

Neuroprotection in Glaucoma

Retinal ganglion cell death is the common underlying patho-mechanism observed in glaucoma. Both mechanical (raised IOP) and vascular (reduced optic nerve head perfusion) factors have been implicated in progressive RGC loss. On a molecular level, deprivation of neurotrophic factors, elevated levels of excitatory amino acids such as glutamate and oxidative stress lead to apoptosis and progressive RGC loss.³² Neuroprotection in glaucoma primarily aims at preventing RGC apoptosis by measures other than IOP modulation. Most of the neuroprotective agents have shown promising results in preclinical and selected clinical trials, their official approval in glaucoma management is still awaited.

Glutamate Antagonist

Glutamate-induced excitotoxicity has been implicated in RGC loss leading to glaucomatous optic neuropathy. Glutamate acts upon the N-methyl-D-aspartate (NMDA) receptors on RGCs, which in turn causes intracellular calcium influx leading to the activation of a complex cascade which attacks cell components and produces free radicals, followed by programmed cell death or apoptosis.⁴¹ Memantine & MK801 (dizocilpine maleate) are non-selective NMDA receptors

antagonists tried in glaucoma.⁴¹ Promising results were seen with Memantine in preclinical studies, however, a recent phase 3 randomized placebo-controlled clinical trial failed to show any efficacy of Memantine as a neuroprotective agent. The efficacy of Memantine in glaucoma management thus remains unproven.

Neurotrophic Factors

Most of the ganglions including the RGCs express receptors for various neurotrophic factors. Stimulation of these receptors by neurotrophic factors plays an important role in promoting survival of injured ganglion cells. Brain Derived Neurotrophic Factor (BDNF), human Ciliary Neurotrophic Factor (CNTF) and Nerve growth Factor (NGF) were found to have a protective role and promoted the survival of RGCs.^{42,43} While most of the studies have been conducted on transected or crushed optic nerves in animals, there is a paucity of data on the effect of exogenous neurotrophic factors in glaucomatous optic neuropathy. Interestingly, an experimental study reported success of murine NGF eye drops in treatment of glaucoma. Patients treated with NGF demonstrated long lasting improvements in visual field, optic nerve function, contrast sensitivity, and visual acuity. The authors proposed NGF to be used as an adjunct therapy in management of glaucoma.⁴⁵

Ginkgo biloba Extract

The extract from the leaves of *Gingo Biloba* has medicinal property and has been traditionally used in management of several medical conditions. Ginkgo contains certain substances, including poly-phenolic flavonoids which may theoretically prevent oxidative stress in the mitochondria and thereby protect RGCs.⁴⁶ Past studies have demonstrated improvement in visual functions in normal tension glaucoma patients treated with *Ginkgo Biloba* extract. The extract has been reported to be used as an adjunct therapy in management of normal tension glaucoma, however there is no conclusive evidence to prove its neuroprotection in glaucoma.⁴⁷

Vitamin E & Co-enzyme Q 10

Antioxidants aim to counter the oxidative stress caused by reactive oxygen species (ROS) and prevent RGCs from undergoing apoptosis. Animal studies have demonstrated vitamin E and Co-enzyme Q 10's protective role in preventing RGC apoptosis. Topically used Coqun eye drops (co-enzyme Q10 combined with vitamin E) in glaucoma patients was reported to have a beneficial effect on inner retinal function as measured by pattern ERG with consequent improvement of visual cortical responses assessed by visually evoked potentials (VEPs).⁴⁸ These studies have favored the use of antioxidants as adjunct glaucoma medications.

Brimonidine and calcium channel blockers (CCB) are thought to provide neuroprotection by preventing glutamate-induced toxicity. Brimonidine acts upon the alpha 2 receptors to reduce the amount of glutamate, whereas CCB reduces intracellular calcium influx and prevents apoptosis.

Stem Cell Therapy

It is hypothesized that intraocular implantation of stem cells may play a beneficiary role in preventing RGC apoptosis and promoting their survival. Stem cells may be used as vectors for regular production of various biological factors, including neurotrophins which can promote RGC longevity.⁴⁹ However, various concerns such as stem cell graft survival, induction of retinal gliosis, tumorigenesis and uncertainties in the expression of desired bio-active factor may limit its utility for now.⁵⁰ Stem cell research is still in its infancy and there is a long way ahead before viable treatment options for glaucoma can be made commercially available.

CONCLUSION

The ongoing research in various spheres of glaucoma management has brought us closer to finding an appropriate cure for the dreaded disease. Commercial use of ROCK inhibitors in India have added to the armamentarium of glaucoma specialist. Soon anti-glaucoma medications approved in other countries shall be available in India too. In the meanwhile, we all strive to find newer avenues to upgrade glaucoma management, provide better care and perhaps find the holy grail of glaucoma treatment.

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