Recent Advances in Pharmacotherapy for Glaucoma Management

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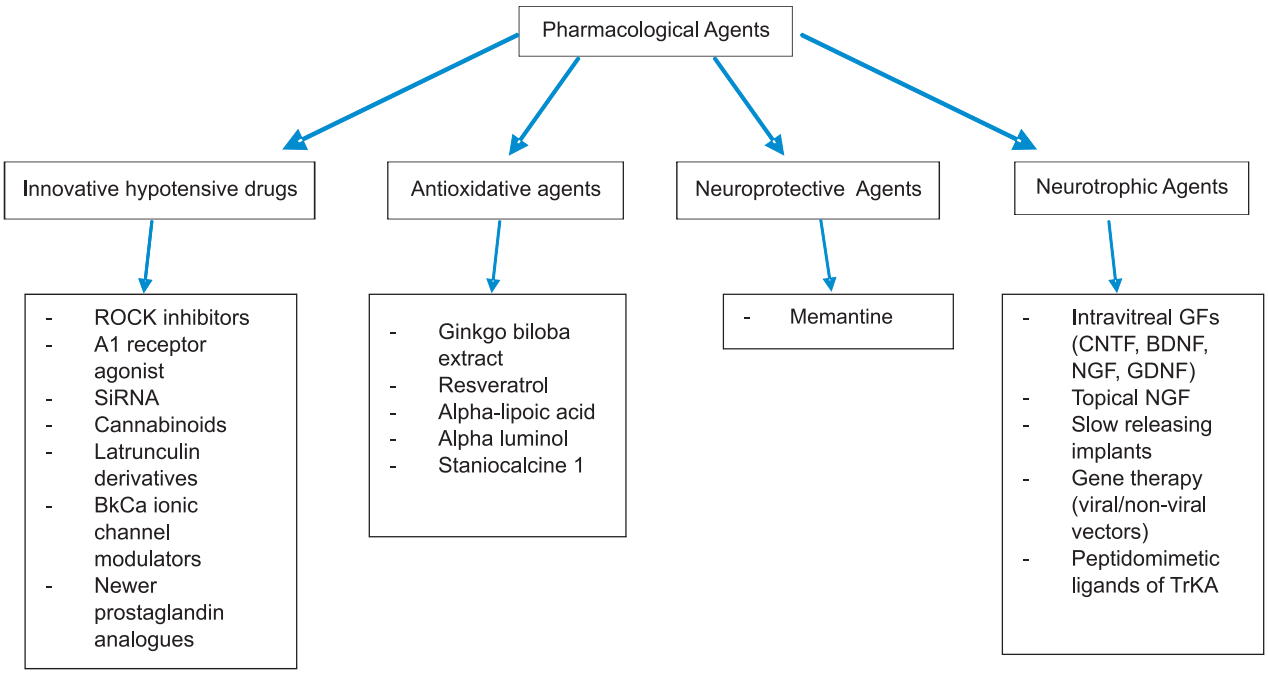
Introduction:

Glaucoma is a chronic progressive optic neuropathy caused by a group of ocular conditions, leading to damage of optic nerve with loss of vision, the most common risk factor being raised intra-ocular pressure.[1] It is a leading cause of irreversible blindness and the second leading cause of blindness worldwide.[2,3] Estimated global burden induced by glaucoma is 76 million in 2020 and expected to increase upto 111.8 million by 2040 majorly affecting the Asian and Africans .[2,4] Out of which open angle glaucoma (OAG) accounts for 70 percent of all the glaucoma.[2,5]

Axons of retinal ganglion cells are damaged leading to an earlyapoptosis and hence irreversible vision loss.[6] As the disease is mostly asymptomatic its often very late by when the diagnosis is made butpermanent visual disabilitycan be prevented by early diagnosis, appropriate management. The mainstay of treatment lies in strict intra-ocular pressure control primarily by medical management .[2,7] Multiple factors aid poor adherence and failure in management of glaucoma i.e. lack education about the disease, poor communication between patient and doctor, lifelong follow-up, timely and repetitive evaluation, complex and multi-drug therapy and financial constraints. [2,8,9]

It is necessary to understand and assess the benefit- risk ratio of medical management to achieve the target pressure without hampering the health-related quality of life (HRQL) and improve patient adherence. Hence the need for more research and introduction of newer drugs with mild or no side effects, better IOP lowering and neuroprotection.



NEWER PHARMACOLOGICAL AGENTS

A. INNOVATIVE HYPOTENSIVE DRUGS:

- **ROCK inhibitors (RHO kinase inhibitors):** The Rho family consists of guanosine triphosphate-binding protein which plays a vital role in regulating cell shape, motility, contractility, proliferation, and apoptosis.[2] Rho-associated coiled-coil-forming protein kinase (ROCK) regulates the actin-myosin proteins that promote cellular contraction in smooth muscle and also promotes the production of extracellular matrix proteins which are responsible for anchoring of cells to their substrate. The cells oftrabecular meshwork (TM) contains smooth muscle like properties and

the resistance to aqueous drainage is controlled by the contraction of cells of TM and production of extracellular matrix components. ROCK inhibitors block the TM cell contraction and decrease the production of the extracellular matrix substance hence increasing the aqueous outflow thus reduces the IOP [10]

1. **Ripasudil-**was approved in Japan for the treatment of glaucoma and OHT in September 2014. Phase 1 and phase 2clinical trials(Mono drug), demonstrated ripasudil (0.4%) twice daily provided reduction of 2 to 4.4 mmHg of IOP from the baseline.[11-13] Phase 3 trial demonstrated ripasudil (0.4%) when used along with timolol maleate (0.5%)twice daily gave an additional lowering in IOP of 0.9 to 1.6 mmHg.The most common side effect was conjunctival hyperemia which was observed in all the phases of clinical trial.[14]
2. **Netarsudil-** It is a Rho kinase inhibitor and norepinephrine transporter inhibitor whichwas approved in 2017 for use in United States of America for management of glaucoma and OHT. It had a longer duration of action than few drugs in this category.[15] Animal trials demonstrated additional action of decreased aqueous production and additional action of decrease in episcleral venous pressure was noted in humans and rabbits too and differentiating this drug from the other drugs in this class .[16,17] In a clinical trial of single daily dose Netarsudil (0.01% and 0.02%) an average of 5.5 and 5.7 mmHg IOP lowering from the baseline was noted. Conjunctival hyperemia, increased lacrimation were few side effects of the drug. The study concluded that if used with latanoprost 0.005% provided good results. Also, the drug showed better results in patients with lower mean IOP from the baseline .[18]

- **Adenosine receptor agonist:** Various physiological and biochemical pathways in the body are facilitated through G protein-coupled adenosine receptors. Secretion of matrix metalloproteins (MMP) in the endothelial cells of TM is stimulated by these receptors leading to shrinkage of cell volume and extracellular matrix remodeling, ultimately facilitating the conventional aqueous outflow.[2] Trabodenoson is a highly selective adenosine A1 receptor agonist that causes an upregulation of protease A and matrix metalloproteinase-2 (MMP-2) in target cells. A phase 2 study on patients with POAG and OHT of Trabodenoson reported that it was well tolerated by the study group at a dose of 500 micrograms twice daily with no systemic side effects. The average IOP lowering was 4.1 mmHg .[19]

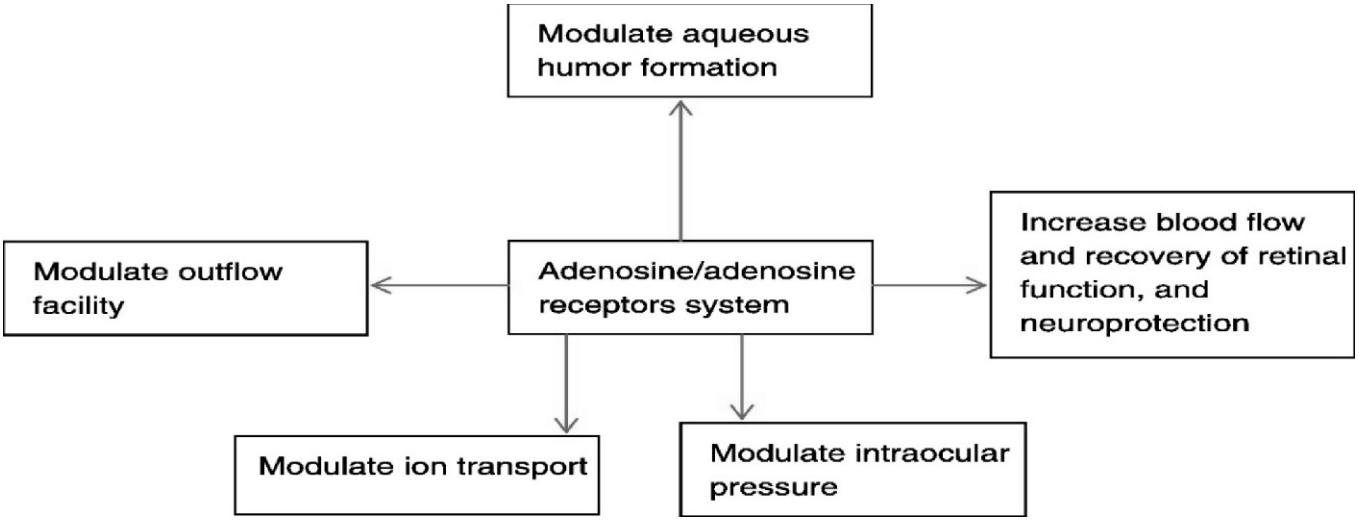


Figure 1 : Mechanism of action of Adenosine receptor agonist [20]

- **Small interference RNA (siRNA):** siRNA are small nucleotides able to interfere with mRNA translation protein. Bamosiran is a naked double stranded siRNA, it acts as agene silencer and blocks the beta-2 adrenergic receptor thus decreases the aqueous production by the ciliary body. As the drug gets absorbed very quickly in the anterior chamber, no systemic absorption of the topical drug has not been reported yet .[21] Phase 1 clinical trial have shown that 600 µg/eye/day of the Bamosiran was well tolerated with 20% IOP reduction from base line. Few animal studies have also reported neuro protective properties as well .[10] A multicenter randomized placebo controlled parallel design phase 2 trial of 89 patients revealed that 300 µg/eye/day caused statistically significant IOP reduction and was well tolerated by 80% of the patients and only one serious complication of hyponatremia was noted .[22]
- **Cannabinoids:** They not only reduce IOP but also possess neuro protective properties as well agents .[10] The presence of cannabinoid receptor 1 was seen in the TM and ciliary epithelium. They have a direct effect on the ciliary process and dilating blood vessels contributing to its property of altering aqueous humor dynamics. They also induce COX-2, PG E2 and MMP 1,3 and 9 expression adding to IOP

reduction property.[23]

- **Nitrogen Mono-oxide (NO) donors :** Nitric oxide using cGMP initiates a series of events causing structural and functional changes leading to overall relaxation of TM an inner wall of Schlemm's canal.[24] Latanoprostene bunod (0.0024%) aka LBN is a nitrous oxide donating compound which is metabolized in situ and converted to latanoprost acid and butanediol mono nitrate a NO donating species. LBN causes lowering of IOP by dual action primarily it increases the uveoscleral outflow and secondly it causes the relaxation of TM and SC leading to increased drainage of aqueous humor. Various studies comparing the efficacy of LBN (0.024%) with timolol maleate (0.5%) have been done. Studies like LUNAR and APOLLO demonstrated that LBN once daily dose of LBN (0.024%) was not inferior to timolol maleate 0.5% and was well tolerate in study group. Another study VOYEGAR concluded that the LBN 0.024% had better IOP reduction than latanoprost (i.e. 1mmHg more than Latanoprost).Some newer drugs NCX 667 (Nicox) and NCX 470 are also in the pipeline and under going animal trial .[25-29]
- **Newer Prostaglandin Analogues:**

1. **Tafluprost :** it is a newer prostaglandin analogue available in 0.0015% conc. for the management of glaucoma. The mechanism of action is same as that of latanoprost and other drugs in this class, but it has pro stanoid FP- receptor affinity 12 times greater than latanoprost .[30] Preservative free tafluprost has been developed for patient with sensitivity against the BAC and other preservatives. A study by Hommer et al. done in 544 patients to evaluate the efficacy and tolerability of preservative tafluprost 0.0015%. The subjects for the study were on antiglaucoma drugs and tafluprost was used as an adjunct therapy or in combination with pre-existing treatment. The study found that preservative free tafluprost 0.0015% caused significant reduction in IOP from baseline. In 79.5% eyes IOP <= 18 mmHg was achieved. An overall reduction of IOP in all patients (N = 544) from 19.4 +/- 5.0 mmHg at baseline to 15.7 +/- 4.1 mmHg after 4 to 6 weeks and to 15.3 +/- 3.5 mmHg after 12 weeks. Both values were significantly lower than treated baseline IOP ($p < 0.001$) was noted.[31] Another study Tumbocon JA et al. reported preservative free tafluprost (0.0015%) to be safe and effective IOP lowering agent in routine clinical setup. The study was conducted in 329 eyes of 177 patients. Most common diagnosis was primary open-angle glaucoma (POAG) (34.9%), followed by primary angle-closure (PAC) glaucoma post-laser iridotomy (24.0%), PAC post-laser iridotomy (15.5%), ocular hypertension (OHT) (14.6%), secondary glaucoma (6.7%), and normal-tension glaucoma (4.3%). Mean IOP change at month 3 was 6.18 mmHg (SD 4.06), a 26.37% reduction ($p<0.001$) and IOP reduction was sustained throughout the study period. Conjunctival hyperemia was noted in 15% patients in the study.[30]
2. **Unoprostone:** IOP-lowering docosanoid and belongs to the of a family of lipid IOP-lowering agents. It is commercially available as Unoprostone Isopropyl (0.012%) ophthalmic solution. Although the mechanism of action of unoprostone may be controversial as earlier the mechanism of IOP lowering was thought to be same as latanoprost i.e. IOP lowering by increasing the uveo-scleral outflow. But according to new research it acts on BK channels which, upon activation cause cell hyperpolarization. Endothelin-1 (ET-1) in the TM induce contractility of cells which is mediated via glutamate-associated increase in intracellular Ca2+. Through BK channel activation, unoprostone is believed to block this increase in intracellular Ca2+ in TM cells leading to increased trabecular meshwork outflow and IOP reduction .[32] Unoprostone typically lowers IOP by 10%–25% from baseline, with a duration of effect of 2–5 hours .[33] Sponsel et al [34] compared the IOP-lowering and hydrodynamic effects of unoprostone and latanoprost in 25 patients with open-angle glaucoma or ocular hypertension. After one month of therapy, both agents produced significant reductions in IOP and increases in pulsatile ocular blood flow, although the changes seen with latanoprost were nearly two-fold greater than those seen with unoprostone, which was statistically significant. Another study by Nordmann et al [35] in, double-masked, randomized trial of 556 patients with glaucoma orocular hypertension receiving either unoprostone, betaxolol, or timolol twice daily for 6 months, found similar mean diurnal IOP-lowering efficacy between betaxolol and unoprostone monotherapy. When used as adjunct therapy with timolol it has shown to provide an additional 2-3 mmHg fall in IOP

B. ANTIOXIDANTS:

Under stressful conditions like OHT/ glaucoma there are micro-alterations in the blood ocular barrier as well as there is transient and prolonged ischemia this results in release of inflammatory factors and free radicals which further leads to glaucomatous neurode generation. The free radicals generated may directly or indirectly damage the astrocytes and muller cells of the retina further causing NMDA receptor hyperactivity seconded by retinal ganglion cell cytotoxicity. Mitochondrial dysfunction induced due to ischemia may also lead to RGC viability.Reducing the oxidative stress could be helpful in achieving neuro protection. Antioxidants like alpha-luminol, Ginkgo biloba extracts, resveratrol, stanniocalcine-1 and alpha-lipoic acid have been evaluated in mouse models, proving to be effective in RGC protection. [23]

C. NEUROPROTECTIVE AGENT (MEMANTINE):

Another molecule that has been evaluated for neuro protection. It is a receptor antagonist for NMDA glutamatergic and acts by blocking the exocytotoxic process mediated by glutamate .[36] It prevented retinal ganglion cell loss in animal trials but in human trials the results were not very satisfying when compared to the placebo group. [23]

D. NEUROTROPHIC AGENTS:

Ciliary neurotrophic factor (CNTF), Brain derived neurotrophic factor (BDNF) Neurotrophic factors, neuronal growth factor (NGF) and the glial cell line-derived

neurotrophic factor (GDNF) are produced by cells within the retina. In chronic conditions the intrinsic growth factors are not enough and can be administered via exogenous route.[23] intravitreal injections of 5 micrograms of BDNF and 2 µg of CNTF have reduced the death of RGC in animal models by 8 and 22% respectively after 1 month, but the effect was not sustained and the need of repetitive inject was required. Another study reported that topical administration of NGF qid for 7 weeks increases the density of ganglion cells by 37%. Functional improvements detected with electro retinography, visual evoked potentials and computerized visual field, as it was carried out in small number of patients it was still carried and in the absence of a control group the efficacy is doubtful .[37-39] The gene therapy approach to elevate endogenous retinal production of neurotrophic factors prevents the undesirable complications and problems associated with the in vivo delivery, showing good efficacy in pre-clinical trials. Furthermore, research is required for development of this approach to get desirable results with minimal side-effects.[40]

Conclusion:

As it is proven fact that glaucoma is the leading cause of irreversible blindness severely affecting the health quality of life. Its timely diagnosis and management is even more difficult due to lifelong treatment and poor patient adherence. Various drugs for glaucoma management in the pipeline are undergoing trials. Few of which like siRNA (Bamosiran), RHO Kinase Inhibitors (Ripasudil, Netarsudil), Nitrogen Mono oxide donor (LBN) and Tafluprost have shown promising results either as mono therapy, adjunct therapy or in combination with older drugs. These results have provided a ray of hope that glaucoma management wouldn't be atedious process for the patient and improvement in compliance to treatment can be seen. Although a more extensive and aggressive approach may be required for the future.

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Pirfenidone Inhibits Post-Traumatic Proliferative Vitreoretinopathy

B N M K Khanum, R Guha, V P Sur, S Nandi, S K Basak, A Konar and S Hazra Eye (Lond). 2017 Sep; 31(9): 1317–1328.

Purpose: The purpose of the study was to evaluate the efficacy and safety of intravitreal pirfenidone for inhibition of proliferative vitreoretinopathy (PVR) in a model of penetrating ocular injury.

Patients and methods: Penetrating trauma was induced on the retina of rabbit and treated either with 0.1ml of phosphate-buffered saline (PBS) or 0.1ml of 0.5% pirfenidone, and development of PVR was evaluated clinically and graded after 1 month. Histopathology and immunohistochemistry with transforming growth factor beta (TGFβ), alpha smooth muscle actin (αSMA), and collagen-1 were performed to assess the fibrotic changes. Expression of cytokines in the vitro-retinal tissues at different time points following pirfenidone and PBS injection was examined by RT-PCR. Availability of pirfenidone in the vitreous of rabbit at various time points was determined by high-performance liquid chromatography following injection of 0.1ml of 0.5% pirfenidone. In normal rabbit eye, 0.1ml of 0.5% pirfenidone was injected to evaluate any toxic effect.

Results: Clinical assessment and grading revealed prevention of PVR formation in pirfenidone-treated animals, gross histology, and histopathology confirmed the observation. Immunohistochemistry showed prevention in the expression of collagen-I, αSMA, and TGFβ in the pirfenidone-treated eyes compared to the PBS-treated eyes. Pirfenidone inhibited increased gene expression of cytokines observed in control eyes. Pirfenidone could be detected up to 48h in the vitreous of rabbit eye following single intravitreal injection. Pirfenidone did not show any adverse effect following intravitreal injection; eyes were devoid of any abnormal clinical sign, intraocular pressure, and electroretinography did not show any significant change and histology of retina remained unchanged.

Conclusion: This animal study shows that pirfenidone might be a potential therapy for PVR. Further clinical study will be useful to evaluate the clinical application of pirfenidone.