Review Article

Newer advances in medical management of glaucoma

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The burden of irreversible vision loss from Glaucoma continues to rise. While the disease pathogenesis is not well understood, intraocular pressure (IOP) is the only modifiable risk factor identified to prevent glaucomatous vision loss. Medical management remains the first-line of treatment in most adult glaucomas and the evolution of medical therapy for glaucoma has followed an exponential curve. This review tracks the rapid development of new medications and drug delivery systems in the recent years. Introduction of Rho kinase inhibitors with an entirely new mechanism of action from that of the currently used anti glaucoma medications has been a significant milestone. Latanoprostene Bunod is a novel, single molecule which provides two active metabolites that work through two different pathways for reducing intra ocular pressure. Bimatoprost implants and travoprost punctum plugs attempt to ease chronic medication use in glaucoma patients. Nanotechnology is an evolving route of drug delivery. Role of cannabinoids in medical management of glaucoma remain equivocal. The relatively short term effect on IOP, the risks of developing tolerance and side effects impacting patients' neurocognitive health greatly outweigh the potential benefit. Research on Latrunculin B, Adenosine receptor agonists, Specific gene silencing and Stem cell therapy are poised to make an impact on glaucoma treatment. While there is some evidence to support the role of Brimonidine in neuroprotection, further research is needed to clarify the role of Memantine and Neurotrophins. Evidence for benefit from dietary supplementation with Alpha lipoic acid, Forskolin , and Ginko Biloba is limited

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The global burden of irreversible vision loss from glaucoma continues to rise as the population ages. It was estimated to affect 64.3 million people aged 40–80 years in 2013, 76 million in 2020 with estimates increasing to 111.8 million in 2040.[1] While the disease pathogenesis is not well understood, intraocular pressure (IOP) is the only modifiable risk factor identified to prevent glaucomatous vision loss. Medical management remains the first-line of treatment in most adult glaucomas which has been helped by the rapid development of unique agents in the last 50 years.

This paper provides an extensive review of the newer glaucoma medications available on the market today, as well as newer methods of drug delivery and drugs that may potentially be available in the future.

Rho Kinase Inhibitors

In 1993, researchers discovered the role of cytoskeletally active agents, such as Rho kinase, in regulating trabecular outflow.[2] Rho A, Rho B and Rho C are a family of G proteins which are active when bound to guanosisne triphosphate (GTP) and inactive when bound to guanosine diphosphate (GDP). The two Rho kinase isoforms (ROCK 1 and ROCK 2) are the effectors of the Rho family.[3]

Rho kinase inhibitors increase aqueous outflow and decrease outflow resistance by increasing the ability of the Schlemm's canal endothelial cells to form pores. Another hypothesis is that Rho kinase inhibitors cause relaxation of the smooth muscle fibers in the trabecular meshwork and thereby increase outflow.[4] Experimental evidence also supports changes in Schlemm's canal cytoskeleton causing decrease in focal adhesions in the juxtacanalicular meshwork.[5]

Ripasudil and netarsudil are the two commercially available formulations of Rho kinase inhibitors, both of which work on ROCK1 and ROCK 2 receptors. Ripasudil hydrochloride hydrate (Glanatec®) 0.4% reduced IOP by 2.6 mm of Hg at trough and 3.7 mm of Hg at peak in patients with primary open angle glaucoma (POAG) and ocular hypertension (OHT).[6] The most commonly reported adverse events included conjunctival hyperemia (76%), blepharitis (21%),

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and allergic conjunctivitis (20%). Additive IOP lowering effect of ripasudil 0.4% with timolol maleate 0.5% was found to be 1.6 mm of Hg at peak and 0.9 mm of Hg at trough.[7] The additive effect with latanoprost 0.005% was a reduction of 1.4 mm of Hg at peak but no significant reduction in IOP at trough,[7]

Netarsudil (Rhopressa®) is a Rho kinase inhibitor and nor-epinephrine transporter inhibitor which decreases IOP by decreasing the outflow resistance. In addition, netarsudil caused reduction in aqueous humor production in animal studies and decrease in episcleral venous pressure in animal and human studies.[8,9] This has been linked to the nor-epinephrine transporter inhibitor activity of netarsudil.

A double-masked randomized controlled trial (RCT) compared the efficacy of netarsudil 0.01%, netarsudil 0.02%, and latanoprost 0.005%, all dosed once daily, in reducing IOP in patients with OHT and POAG with IOP ≥24 and <36 mmHg. Reduction in IOP on day 28 was 5.5, 5.7, and 6.8 mmHg in the netarsudil 0.01%, netarsudil 0.02%, and latanoprost 0.005% groups, respectively.[10] Both concentrations of netarsudil did not meet the noninferiority criteria compared to latanoprost. When the subgroup of patients with IOP ≤26 mmHg was analyzed separately, netarsudil 0.02% was statistically noninferior to latanoprost 0.005%. Netarsudil was, therefore, thought to be more effective in patients with lower baseline IOP. The most commonly reported adverse event was conjunctival hyperemia, which was more common with netarsudil compared to latanoprost.

Following this, two RCTs evaluated the noninferiority of netarsudil 0.02% with timolol maleate 0.5% in patients with a lower baseline IOP of <27 mm of Hg after washout.[11] Both the studies found netarsudil to be statistically noninferior to timolol 0.05% in the subgroup of patients with IOP <25 mm of Hg. The same was not true for the entire cohort. Conjunctival hyperemia was again the most common adverse event reported at 50–53% with netarsudil dosed daily, 59% with netarsudil dosed twice daily, and 8–10% with timolol dosed twice daily. Perilimbal conjunctival micro hemorrhages were reported in 13–17% patients, and cornea verticillata were reported in 9–15% of the patients on netarsudil versus less than 1% patients in the timolol only group. All the adverse effects reversed after cessation of medications. Two recent case series reported a reticular pattern of corneal edema in patients on netarsudil, causing decrease in visual acuity, unlike the earlier reported adverse events.[12,13] Most of these, though not all, have been in eyes with decompensated corneas and resolved on cessation of the drug. The mechanism of this is not yet fully understood.

Mercury -1 and 2 trials reported on the efficacy of a fixed drug combination of netarsudil 0.02% and latanoprost 0.005% (FCNL) dosed once daily, compared to monotherapy with netarsudil 0.02% or latanoprost 0.005%.[14] The mean baseline IOP was 23.6, 23.6, and 23.5 mmHg in the FCNL, netarsudil, and latanoprost groups, respectively. Both studies showed that the FCNL provided higher mean IOP reduction compared with monotherapy. The most common adverse events were conjunctival hyperemia, cornea verticillata, and subconjunctival hemorrhage. The rate of conjunctival hyperaemia was noted to be 58.7, 47.0, and 22.1% in the FCNL, netarsudil, and latanoprost groups, respectively. In the follow up period, 5% of patients in both the FCNL and Netarsudil groups, and 0.2% participants in the latanoprost group discontinued treatment due to conjunctival hyperaemia. The incidence of cornea verticillata was 15.4 and 11.6% in patients who received FCNL and netarsudil, respectively. There were no reports of cornea verticillata in patients receiving latanoprost. Less than 1% participants discontinued treatment because of cornea verticillata. Subconjunctival hemorrhage was found in 10.8, 14.5, and 1.0% in the FCNL, netarsudil, and latanoprost groups, respectively. A Phase 3 clinical trial comparing the efficacy of FCNL to the fixed drug combination of bimatoprost 0.03% and timolol 0.5% is ongoing.[15]

Finally, fasudil is a newer Rho kinase inhibitor which has been studied in a few eyes with end-stage glaucoma with promising results.[16] Table 1 summarizes the major clinical trials on Rho kinase inhibitors.

The value of Rho kinase inhibitors as an adjunctive therapy is significant because the mechanism of action is different from that of the currently used medications. The side-effect profile with a relatively high incidence of conjunctival hyperemia and subconjunctival hemorrhages, however, may prove to be a deterrent to long-term compliance with these medications. The safety and efficacy of Rhokinase inhibitors in individuals below 18 years of age, pregnant, and lactating women is not known. Animal studies with systemic administration of the drugs have not demonstrated harmful effects on the fetus.

While most studies have reported on the role of Rho kinase inhibitors in treating patients with OHT or POAG, the role of Rho kinase inhibitors in the treatment of different types of glaucoma needs further investigation. A prospective observational study of ripasudil found statistically significant drop in IOP in patients with POAG, uveitic glaucoma, and steroid induced glaucoma but not neovasular glaucoma.[21] Other potential areas of investigation include the role of Rho kinase in neuroprotection via increased blood flow to the optic nerve and its proposed role in preventing postsurgical scarring by inhibiting TGF-β-mediated activation of fibroblasts.[22,23]

Latanoprostene Bunod

Latanoprostene bunod 0.024% (LBN) [Vyzulta™] is a unique nitric oxide (NO) donating Prostaglandin F2 alpha analogue.

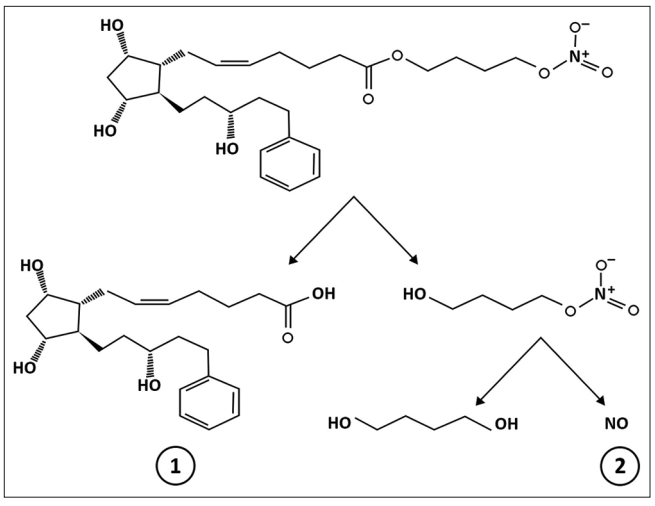

Figure 1: Latanoprost acid (1) and nitric oxide (2) – the two active metabolites of LBN

Table 1: Major drug trials on Rho kinase inhibitors in glaucoma

Author	Study type	Subjects	Sample size	Follow-up	Outcome			Conclusion
SNJ 1656 Inoue *et al.*[17]	RCT*	POAG, OHT 22≤IOP ≤31	66	7 days	Placebo SNJ 0.03% SNJ 0.05% SNJ 0.1%	Change at trough** -2.2 (1.9) -3.8 (2.7) -4.3 (2.3) -4.0 (2.5)	Change at peak*** -1.5 (2.2) -5.0 (2.4) -4.4 (2.7) -4.5 (1.9)	
AR-12286 Williams *et al.*[18]	RCT	POAG, OHT 24≤IOP ≤36	89	7 days	Vehicle AR-12286 0.05% 0.1% 0.25%	Mean diurnal IOP change QD AM -1.9-4.0-5.0-4.8	Mean diurnal IOP change BID -2.4-4.1-4.4-6.0	AR-12286 was well tolerated and provided statistically significant ocular hypotensive efficacy
Ripasudil Tanihara *et al.*[19]	RCT	POAG, OHT 21<IOP <35	210	8 weeks	Placebo Ripasudi 0.1% Ripasudil 0.25 Ripasudil 0.4%	Change at trough -2.2-3.4-3.2-3.5	Change at peak -2.5-3.7-4.2-4.5	K-115 0.4% BD selected to be the optimal dose
Ripasudil Phase 3 Tanihara *et al.*[6]	Non randomized Open label	POAG, OHT, XFG 15<IOP ≤35	388	1 year	Ripasudil 0.4% BD Ripasudil 0.4% BD + PGA Ripasudil 0.4%BD + BB Ripasudil 0.4% BD + FC PGA and BB	Change at trough -2.6-1.4-2.2-1.7	Change at peak -3.7-2.4-2.0-1.7	IOP-lowering effect and an acceptable safety profile as monotherapy or additive therapy
Ripasudil with timolol Phase 3 Tanihara *et al.*[7]	RCT	POAG, OHT IOP ≥18 on timolol	208	8 weeks	Placebo Ripasudil 0.4% BD	Change at trough -1.5-2.4	Change at peak -1.3-2.9	Additive IOP-lowering effect at trough and peak levels when combined with timolol
Ripasudil with latanoprost Tanihara *et al.*[7]	RCT	POAG, OHT IOP ≥18 on latanoprost	205	8 weeks	Placebo Ripasudil 0.4% BD	Change at trough -1.8-2.2	Change at peak -1.8-3.2	Additive IOP lowering at peak when combined with latanoprost
Netarsudil Bacharach *et al.*[10]	RCT, Double masked	POAG, OHT 24 ≤IOP ≤36	224	28 days	Netarsudil 0.01% QD Netarsudil 0.02% QD Latanoprost 0.005% QD	Change at trough -5.4-5.9-7.6	Change at peak -5.5-5.7-6.8	AR-13324 0.02% was less effective than latanoprost by approximately 1 mmHg
ROCKET 1 Netarsudil Phase 3 Serle *et al.*[11]	RCT, Double masked	POAG, OHT 20 <IOP <27 at 8 AM and 17 <IOP <27 at 10 AM and 4 PM	411	3 months	Netarsudil 0.02% QD Timolol 0.05% BD	Mean diurnal IOP 22.5 22.3	Diurnal range of change from baseline -3.3 to -5.0-3.7 to -5.1	Netarsudil 0.02% was found to be effective and well tolerated
ROCKET 2 Netarsudil Phase 3 Serle *et al.*[11]	RCT, double masked	POAG, OHT 20 <IOP <27 at 8 AM and 17<IOP <27 at 10 AM and 4 PM	756	12 months	Netarsudil 0.02% QD Netarsudil 0.02% BD Timolol 0.5% BD	Mean diurnal IOP 21.4 21.5 21.5	Diurnal range of change from baseline (maximum baseline IOP <25 mmHg) -3.3 to -4.6-4.1 to -5.4-3.7 to -5.1	Netarsudil statistically noninferior to timolol 0.05% in the subgroup of patients with IOP <25 mm of Hg

Contd...

Table 1: Contd...

Author	Study type	Subjects	Sample size	Follow-up		Outcome		Conclusion
Fixed combination netarsudil + latanoprost Phase 2 Lewis *et al.*[20]	RCT, double masked	POAG, OHT 24 ≤IOP <36 at 8 AM and IOP ≥21 at 10 AM and 4 PM	298	28 days	Latanoprost 0.005% + Netarsudil 0.01% QD Latanoprost 0.005% + Netarsudil 0.02% QD Latanoprost QD Netarsudil 0.02% QD	Mean diurnal IOP baseline 25.1 (2.3) 25.1 (2.4) 26.0 (2.8) 25.4 (2.7)	Mean diurnal IOP 17.3 (2.8) 16.5 (2.6) 18.4 (2.6) 19.1 (3.2)	FDC AR-13324 0.02% and latanoprost 0.005% provides statistically superior ocular hypotensive effect when compared to individual components
Pooled data Mercury 1-2 fixed drug combination of netarsudil and latanoprost Asrani. S *et al.*[14]	RCT	POAG, OHT	1468	3 months	Netarsudil + Latanoprost Netarsudil Latanoprost	Mean diurnal IOP at baseline 23.6 23.6 23.5	Mean diurnal IOP 3 months 15.8 18.4 17.4	Once-daily netarsudil/ latanoprost FDC**** produced statistically significant reduction in mean IOP

*RCT – randomized control trial, **Change from baseline at trough, ***Change from baseline at peak, and **** Fixed drug combination

LBN metabolizes into the prostaglandin analogue, latanoprost acid, and butanediol mononitrate; butanediol mononitrate further metabolizes into 1,4 butane diol and NO. Latanoprost acid and NOare the two active metabolites.[24] [Fig. 1]

Latanoprost acid binds to the pProstaglandin F receptor and increases the uveoscleral outflow by matrix metalloproteinases-mediated remodelling of the extracellular matrix of the ciliary muscle.

In the eye, NO synthetases are present in the Schlemm's canal, trabecular meshwork, and ciliary body. NO causes vasodilation and smooth muscle cell relaxation. It decreases cell contractility and volume, thereby increasing trabecular outflow.

LBN is thus a single molecule that provides two active metabolites that work through two different pathways for reducing intra ocular pressure.

The VOYAGER study compared different concentrations of LBN and latanoprost 0.005% and found that LBN (0.024%) caused a significantly greater reduction in mean diurnal IOP on day 28 with comparable adverse effects.[25] The CONSTELLATION study compared LBN (0.024%) to timolol 0.5% and concluded that LBN caused a statistically significant decrease in both diurnal and nocturnal IOP versus timolol, which caused a significant reduction from baseline in only the diurnal IOP.[26] Subsequently, the APOLLO and LUNAR studies found that LBN 0.024% was noninferior to timolol 0.5%.[27-29] Finally, the JUPITER study evaluated long-term safety of LBN with a follow-up period of 52 weeks.[30] Most frequently reported adverse events were conjunctival hyperemia (17%), eye lash growth (16%), eye irritation (11%), eye pain (10%), and increased iris pigmentation (10%). Major trials on LBN are summarized in Table 2.

More evidence is awaited on the role of LBN as adjunctive therapy. A recent retrospective study on patients on netarsudil and LBN as adjuvant therapy concluded that both showed similar efficacy as when used in monotherapy.[31]

LBN is currently dosed once daily at bedtime. The safety profile of the drug in pregnancy and lactation has not yet been established. Animal studies with systemic administration during embryogenesis have shown adverse effects.[32]

Newer Drug Delivery Systems

Medication noncompliance is a significant challenge for glaucoma patients who commonly complain of difficulty while instilling drops and difficulty in adhering to complex eye drop administration schedules. In an attempt to ease chronic medication use, new sustained drug delivery systems have been developed in the past two decades.

Ocusert was the first sustained pilocarpine implant introduced in 1975, but the product was soon taken off the market because of poor medication tolerability.

The bimatoprost implant (Durysta™) is a sustained release, biodegradable implant that uses the NOVADUR drug delivery system for intracameral use. The implant is administered into anterior chamber using a 28 gauge, single-use, prefilled applicator. The drug delivery system is made of biodegradable polymers that disintegrate by hydrolysis into carbon dioxide

Table 2: Major drug trials on Latanoprostene bunod in glaucoma

Author	Study type	Subjects	Sample size	Follow-up	Outcome		Conclusion
VOYAGER study Weinreb *et al*.[25]	Randomized, investigator masked, parallel group, dose ranging	POAG, OHT	413	28 days	LBN 0.006% LBN 0.012% LBN 0.024% LBN 0.040% Latanoprost 0.005%	Reduction in mean diurnal IOP -7.81-8.26-9.00 8.93-7.77	LBN 0.024% once daily was the lower of the two effective concentrations
CONSTELLATION Liu *et al*.[26]	Prospective, open-label randomized crossover trial	Early POAG, OHT	25	28 days	LBN 0.024% Timolol 0.05%	Decrease in nocturnal IOP from baseline 2.5±3.1 2.3±3.0	LBN caused more nocturnal IOP reduction and increase of ocular perfusion pressure than timolol
APOLLO study Weinreb *et al*.[27]	RCT, Double masked	POAG, OHT	420	3 months	LBN 0.024% showed greater IOP lowering than timolol 0.5% BID through the day		
LUNAR study Medeiros *et al*.[28]	RCT, Double masked	POAG, OHT	387	3 months	LBN 0.024% was noninferior to timolol 0.5% over 3 months, with significantly greater IOP lowering at all but the earliest time point evaluated		
Pooled analysis of APOLLO and LUNAR Weinreb *et al*.[29]	RCT	POAG, OHT	840	12 months	LBN 0.024% provided greater IOP-lowering compared with timolol 0.5% and maintained lowered IOP through 12 months		
JUPITER study Kawase *et al*.[30]	Single arm, open label	POAG, OHT	130		LBN 0.024% was safe and well tolerated in Japanese subjects with OAG or OHT when used for up to 1 year		

and water. Artemis 1 trial showed that both concentrations of durysta (10 and 15 mcg) were noninferior to timolol 0.5%.[33] In this trial, subjects with POAG and OHT received the implant 3 times at 16 week intervals, and after the third administration, 82.1% in the 10 mcg group and 87.8% in the 15 mcg group did not require additional IOP lowering medications for 1 year.

There were no adverse events related to eye lash growth, skin hyperpigmentation, or periorbital fat atrophy. The main concern was the drop in corneal endothelial cell density (CECD). Greater than 20% decrease in CECD was noted at 20 months in 10.2 and 20.8% of the 10 and 15 mcg group, respectively. In phase 3 trials, 3.6% of eyes in the 10 mcg group and 10.3% eyes in the 15 mcg group needed implant removal to correct corneal edema and further loss of corneal endothelial cells. Interestingly, phase 1 and 2 trials of the same drug concentrations in which the drug administration was further spaced apart and provided at unfixed intervals showed lesser corneal endothelial cell loss and did not require implant removal.[34] Ongoing trials are now evaluating new regimens of administration that will prevent significant corneal endothelial cell loss.[35]

Another sustained release application is the bimatoprost ocular ring (BIM ring) which is a silicone and polypropylene ring impregnated with bimatoprost, available in diameters ranging from 24 to 29 mm, designed for insertion between the upper and lower fornices. It continuously elutes bimatoprost for a period of 6 months, after which it needs to be replaced. The rate of drug elution decreases with time, ranging from 35 μg per day on the day of insertion to 6 μg per day at 6 months. IOP control over 6 months was found to be comparable to 0.03% bimatoprost topical drops with the main adverse effect being mucinous discharge from the eye in some patients.[36] Phase 3 trials are awaited and the device is not currently FDA approved for clinical use. Similar to the concept of the ring, contact lenses are an attractive option for drug delivery due to patient familiarity and long hours of use. The use of micelle-laden contact lenses for delivery of glaucoma medications are currently undergoing animal studies and while initial results are promising, the inherent risks of long-term contact lens use need to be considered.[37]

Travoprost punctum plugs (OTX-TP, Ocular Therapeutix, Inc.) is an investigational device undergoing phase 2 clinical trials. Travoprost impregnated in polyethelene glycol resorbable hydrogel rod is inserted into the upper or lower punctum. Within the hydrogel rod, travoprost particles are encapsulated in polyactic acid microparticles, which hydrolyze with time to provide a sustained delivery of travoprost over 90 days.[38] The rod is also impregnated with fluorescein to aid visualization. When OTX-TP was compared to twice daily administration of timolol 0.5%, both the groups showed significant IOP lowering, 4.5–5.7 mmHg for the OTX-TP group and 6.4–7.6 mmHg for the timolol group. The timolol group, interestingly, showed more IOP reduction than expected, which was attributed to the longer contact time of the drug with the ocular surface due to the presence of the placebo punctal plug. A major concern stated in the study was the retention of the plugs. The retention rates were 91, 88, and 48% at days 60, 75, and 90, respectively. The major adverse events reported were foreign body sensation (38.5%), itchiness (15.4%), and epiphora (3.8%). The tolerability of the implant improved with time.

Nanotechnology is another novel route of drug delivery that is fast evolving. Nanoparticles range from 1 to 100 nm in size and medications piggybacked on to various nanoparticles have the ability to bypass biological barriers rendering the

drug directly at the target site.[39] Subconjunctival injection of dorzolamide-loaded polymer microparticles, supraciliary injection of brimonidine-laden microspheres, and intravitreal injection of brimonidine, travoprost, and bimatoprost-laden nanosponges have completed successful animal studies.[40]

Investigational Glaucoma Medications

Cannabinoids

Cannabinoids are derived from the cannabis plant (phytocannabinoids) or are artificially produced (synthetic cannabinoids). They interact with cannabinoid receptors 1 and 2 in the human body (CB1 and CB2), which are the natural receptors for endocannabinoids which modulate pain, memory, and appetite. CB1 and CB2 are expressed in the human retina, ciliary body, iris, Schlemm's canal, trabecular meshwork, and the retinal pigment epithelium.[41,42]

The neuroprotective effect of cannabinoids is linked to the inhibition of glutamate release. Hommer *et al*.[43] reported a significant increase in the optic nerve head blood flow with 5 mg oral Dronabinol in 24 subjects, when compared to a placebo. Many animal studies also support better retinal ganglion cell survival with the use of cannabinoids.

Oral cannabinoid Delta 9 tetrahydrocannabinol (THC) was reported to demonstrate IOP reduction 30 min after administration. However, on long-term use, over 9 months, drug doses had to be increased due to development of tachyphylaxis. Most patients discontinued the study due to side effects including dizziness, confusion, sleepiness, anxiety, and depression.[44,45]

Palmitoyl ethanolamide (PEA) is a congener of the endogenous cannabinoid, anandamide (AEA) that is cosynthesized with AEA in many human cells. It prolongs the action of AEA by competing with fatty acid amide hydrolase involved in the hydrolysis of AEA. The use of PEA in glaucoma was first reported by Gagliano *et al*.[46] in a cross-over study with a reduction in IOP of 6.2% after 2 months of treatment. Oral PEA was also effective in reducing the IOP spike post yttrium aluminum garnet laser iridotomy.[47]

Inhalational cannabinoids reportedly caused a 2.1 mm of Hg drop in IOP from baseline 80 min after administration of cigarettes containing 12 mg Delta 9 THC, but the IOP lowering effect was found to be linked with tolerance.[48] Inhalational administration of Delta 9 THC led to higher IOP reduction compared to oral administration. However, the IOP reduction was noted to be short term with a significant decrease in IOP (4.1 ± 1.5 mmHg) at 30 min that peaked at 90 min (6.6 ± 1.5 mmHg). The most common side effect was a significant decrease in systolic and diastolic blood pressures resulting in postural hypotension.[49]

Topical cannabinoids have failed to demonstrate a significant effect on IOP in clinical trials. The challenge with topical administration is the lipophilic nature of cannabinoids. Mineral oil, needed as vehicle for topical formulations, leads to poor penetration of the drug, lid inflammation, and conjunctival hyperemia.[50] Topical formulations of THC with cyclodextrins, which are cyclic oligosaccharides with a central cavity that is hydrophobic to hold the drug molecule and an outer surface that is hydrophilic so as to allow water solubility, are undergoing animal studies.[51]

Albumin solubilized, intravenous Delta 9 THC caused a dose-dependent peak IOP lowering of 60%, but the effect was short lived.[52,53] Hypotension and presyncopal episodes were the most commonly reported side effects.

Despite extensive research, the role of cannabinoids in medical management of glaucoma remains equivocal. The relatively short-term effect on IOP, the risks of developing tachyphylaxis, and serious side effects impacting patients' general and neurocognitive health greatly outweigh the potential benefit at this time. Future research may provide stronger evidence for their use in neuroprotection with tolerable side effects.

Adenosine receptor agonists

Adenosine is a nucleoside that activates the G protein linked to adenosine receptors, A1, A2A, A2B, and A23. It increases the conventional outflow facility by shrinkage of cell volume and remodeling of the extracellular matrix in human trabecular meshwork cells. A1, A2A, and A3 agonists are currently undergoing Phase 1 and 2 trials. Phase 2 trials of trabodenoson, a selective A1 agonist, showed clinically and statistically significant IOP reduction with no serious adverse events.[54,55]

Prostanoid receptor agonist

Omidenepag isopropyl (OMDI) is a nonprostaglandin, selective, prostanoid EP2 receptor agonist, known to decrease IOP by increasing the conventional and uveoscleral outflow. Phase 1 trials of OMDI showed clinically significant IOP reductions and the drug was well tolerated.[56] Recently published Phase 3 trials from Japan established noninferiority of OMDI 0.002% when compared with latanoprost 0.005% in reducing IOP in POAG and OHT over 4 weeks.[57] The common adverse events reported were conjunctival hyperaemia (24.5%), increased corneal thickness (11.7%), and photophobia (4.3%). A mean increase of 15 μm (2.7%) in central corneal thickness was found in patients on OMDI, the mechanism of which is not well understood. There were no reports of corneal edema or drop in visual acuity, further research on the effect of the drug on corneal health including corneal endothelial count may be warranted. This drug is currently approved for use in Japan.

Small interference RNA

RNA interference is the cutting-edge technology of specific gene silencing, using small bits of RNA called small interference RNA (siRNA).[58] SYL040012 is a siRNA developed to specifically silence the Beta 2 adrenergic receptor (ADRB2) at the ciliary body, thereby reducing the aqueous humor production. *In vitro* and *in vivo* studies in animal models of SYL040012 have shown significant IOP reduction and good safety profile.

Neuroprotection

Neuroprotection is the holy grail of glaucoma care. Glaucoma is known to be a neurodegenerative disease which causes chronic progressive RGC death, and glaucoma treatment remains restricted to reduction in IOP at this time. Lowering IOP removes a stressor for neuropathy and arguably is a form of neuroprotection. The search for non-IOP-dependent neuroprotection is ongoing. Though a consensus on the actual cause of glaucomatous optic neuropathy is awaited, the cellular processes that cause RGC death include exposure to neurotoxic substances like NO and glutamate, deprivation of internal trophic factors, loss of cellular self-repair process, and intracellular destructive process.[59] [Fig. 2].

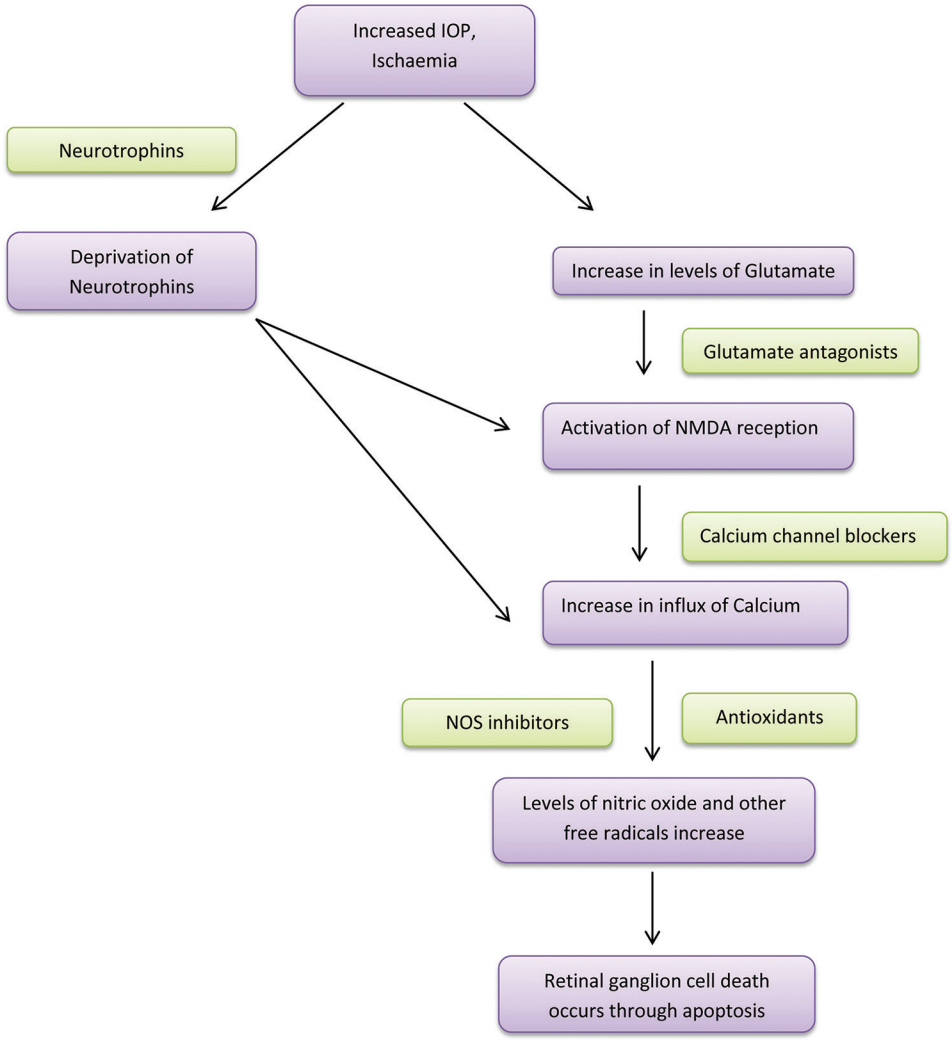

Figure 2: Neuroprotection in glaucoma

The rationale of treatment is that the intervention corrects the imbalance between the cellular death and survival signals, thus, preserving visual function.

Memantine

Elevated levels of glutamate are toxic to retinal ganglion cells and the resulting cell death is mediated by excitotoxicity of the N-methyl-D-aspartate (NMDA) receptor, by causing an excess of intracellular calcium and cell death.[60] Memantine is an NMDA receptor antagonist and can prevent cell death by calcium influx. Four-year follow-up results from two double-masked, placebo-controlled, multicenter RCTs with 2298 patients with POAG showed that memantine at the 10 and 20 mg daily doses did not prevent or decrease progression of glaucoma based on standard automated perimetry and optic disc photography findings.[61]

Brimonidine

The IOP-independent neuroprotective effect of brimonidine, an alpha-2 adrenergic agonist, has been demonstrated in animal models. The proposed mechanism involves upregulation of antiapoptotic factors, modulation of glutamate-induced excitotoxicity, inhibition of NO synthetase, and inhibition of glial activity.[62,63] Studies have demonstrated a significant reduction in retinal nerve fiber layer loss in OHT patients treated with brimonidine compared to those treated with timolol.[63,64]

Neurotrophins

Neurotrophic factors play a key role in cell survival. Brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factor, glial cell-line-derived neurotrophic factor and nerve growth factor (NGF) are potential candidates in neuroprotection undergoing preclinical studies. Valproic acid, traditionally used to treat epilepsy, has been demonstrated to induce neuroprotection by stimulating the BDNF–TrkB pathway. Animal studies demonstrated protective effect of topical application of NGF drops on RGCs in a rat model of glaucoma. Topical NGF drops have also been shown to demonstrate improvement in visual fields, contrast sensitivity, and electrofunctional tests in a few patients with advanced glaucoma.[65] Obstacles in the safe administration of these molecules at the intended site of action, poor understanding of pharmacokinetics, and lack of clarity on the long-term effects of these agents remain challenges in the translation to human trials.[66]

Gene therapy

Gene therapy for glaucoma is still in the early stages of research. The large number of chromosome loci responsible for POAG, challenges in gene transfer with final binding at the intended site, and the possibility of mutagenesis have all dampened progress of this mode of treatment.[67]

Aquaporin 1 is a protein in the ciliary body involved in aqueous production by facilitating the transmembrane transport of water. Disruption of Aquaporin 1 by gene therapy with CRISPR-Cas9 RNA has been reported to reduce IOP in animal models.[68] The treatment which targets a gene involved in a physiologic process rather than a specific gene mutation has the potential to be universally applicable.

A unique adeno-associated virus (AAV) gene therapy for glaucoma that targets the BDNF has been validated in mouse models. Intravitreal injection of AAV2 vectors increased the production of BDNF and increased duration of action of BDNF by upregulating tropomyosin-related receptor kinase B.[69]

Stem cell therapy

Traditional glaucoma treatment modalities aim to delay or arrest the progression of glaucoma. Stem cell therapy provides the captivating possibility of regenerating and repopulating RGCs and possibly restoring vision lost from glaucoma. Preclinical studies have validated that mesenchymal stem cells secrete neurotrophins which promote cell survival and can repopulate RGCs in the retina.[70]

Stem cell therapy may also play a role in cell-based functional restoration of the trabecular meshwork. Current evidence shows that there is a population of adult stem cells in the Schwalbe's ring and the anterior trabecular meshwork.[71] These adult stem cells play a crucial role in tissue repair and may also be expanded *in vitro* for tissue regeneration. Restoration of aqueous humor flow in mouse models following transplantation of iPSC-derived trabecular meshwork cells has been reported.[72] Further clinical validation of the role of stem cells in glaucoma management is awaited.

Alternative medicine

Dietary supplementation with Alpha lipoic acid has been shown to decrease oxidative stress and improve RGC survival in animal models of glaucoma.[73] The association of Vitamin C with POAG failed to reach statistical significance.[74,75] Though the current evidence is limited by the smaller sample sizes, unpredictability of visual field tests and short follow up, forskolin containing supplements have shown to decrease IOP beyond the reduction achieved by antiglaucoma medications alone.[76] Flavanoids like Gingko biloba have been demonstrated to have a positive impact on ocular blood flow though the impact on the preservation of visual fields remains unclear. Ginko biloba extracts have also demonstrated neuroprotective and antiinflammatory effects on retinal ganglion cells in animal studies.[77]

Nutritional supplementation has a good safety profile, larger, better designed RCTs with longer follow-up are required to evaluate its role in glaucoma.

There has been considerable interest in the recent past on the role of YOGA and lifestyle changes in glaucoma. Current literature provides little evidence to support the use of YOGA, relaxation techniques, or special diets for slowing/arresting progression of glaucoma.[78]

Cytidine 5'diphosphocholine or citicoline is an endogenous compound involved in the synthesis of membrane phospholipids. It is known to increase the levels

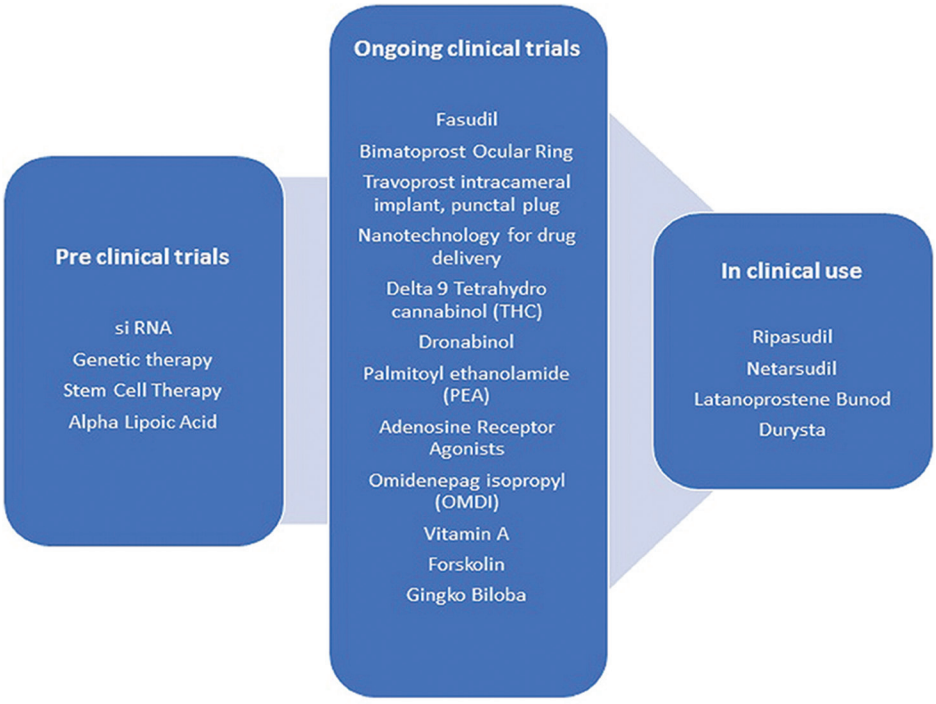

Figure 3: New glaucoma medications at various stages of development

of dopamine, serotonin, and noradrenaline in the central nervous system.[79] Pecori Giraldi *et al*.[80] first studied the effect of intramuscular (IM) injections of 1 g of citicoline for 10 consecutive days in glaucoma patients and reported an improvement in visual fields by computerized perimetry in 75% of the 34 examined eyes. Another prospective study with 23 participants, who were followed over 10 years, reported better visual field preservation in the subgroup that received 1 g citicoline IM for 15 days repeated every 6 months, in addition to the topical hypotensive medications.[81] Many studies using oral citicoline 500 mg BD over different dosing schedules ranging from 2 weeks to 60 days have demonstrated an improvement in visual function as measured by visually evoked potential and pattern electro retinogram[82,83] Ottobelli *et al*. studied the effect of the oral solution of citicoline on 41 patients with POAG who were concurrently on topical hypotensive medications and had a documented progression rate of more than -1 dB per year despite maintaining IOP less than 18 mm of Hg. Over 2 years, participants taking the oral solution of citicoline were noted to have a significant reduction in the mean rate of visual field progression.[84] A recent randomized control trial evaluated the effect of citicoline eye drops on the rate of further progression in patients on topical hypotensive medications with documented progression on visual field testing and IOP of less than 18 mm of Hg.[85] RNFL thickness measurements suggested that the citicoline eye drops may slow disease progression in these patients. The study reported 1.86 μm of RNFL loss in 3 years in citicoline group, versus 2.99 μm of RNFL loss in the placebo group ($P = 0.02$). The study, however, had a small sample size and many patients underwent a change in the treatment regimen or surgery during the follow-up period. A larger prospective trial is needed to elucidate the role of citicoline in glaucoma.

Conclusion

To conclude, the past few decades have opened up multiple new horizons in glaucoma treatment. [Fig. 3]. With the pace and scale of ongoing research, we have reason to look forward to newer medications, delivery systems, and novel therapeutic modalities being available for patient care.

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Conflicts of interest

There are no conflicts of interest.

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