Review Article

Recent Advances in the Medical Management of Glaucoma

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Abstract

Glaucoma, a pervasive cause of irreversible blindness in India, is a complex and stealthy adversary. This ocular disease is influenced by a multitude of risk factors, making its management more of an art than a rigid science. Successfully taming glaucoma demands unwavering dedication from both ophthalmologists and patients. Staunch adherence to treatment, regular follow-ups, timely investigations, and personalized therapy adjustments are critical, especially in resource-limited settings where the battle is most arduous. Despite the introduction of novel classes of glaucoma medications and the conclusion of numerous extensive clinical trials, the fundamental challenges persist. While the pharmaceutical arsenal for glaucoma has expanded, the core principles of therapy remain largely unchanged. Debates continue to swirl around concepts like the "monocular therapeutic trial," "target intraocular pressure (IOP)," and "maximal medical therapy." Diagnostic techniques for detecting and monitoring glaucoma have indeed advanced, yet they still lack the precision to reliably predict individual patient responses. This comprehensive review unravels recent medical advancements in glaucoma management, shedding light on innovative treatments such as Rho kinase inhibitors, Latanoprostene Bunod, unoprostone, NMDA receptor antagonists, and neuroprotective agents. These breakthroughs offer a glimmer of hope to those fighting this relentless foe, breathing fresh air into the ongoing battle against glaucoma, a condition that can steal sight silently and relentlessly.

Keywords: Glaucoma, Recent advances, Rho kinase inhibitors, Latanoprostene Bunod, Unoprostone, NMDA receptor antagonists

Introduction

The escalating burden of irreversible vision loss caused by glaucoma presents a growing concern. Epidemiological studies focused on adults aged 40 and above have unveiled a glaucoma prevalence ranging from 2.7 to 4.3% among the Indian population.[1-5] Alarming projections predict that by 2040, an additional 27.8 million individuals in Asia will grapple with this condition, with India and China bearing the heaviest load.[6] Glaucoma currently plagues 1.2 million individuals, contributing to 5.5% of overall blindness cases, firmly establishing it as a prime culprit of irreversible blindness in India.[7]

The multifaceted nature of glaucoma's pathogenesis underscores the challenge it presents. While several factors play a role, intraocular pressure (IOP) remains the sole modifiable risk factor in preventing glaucomatous vision loss. Medical management takes the forefront in treatment, and this realm has seen remarkable growth. The introduction of Rho kinase inhibitors, with a unique mechanism of action compared to existing anti-glaucoma medications, marks a significant milestone. Latanoprostene Bunod, a single molecule producing two active metabolites that target different pathways to reduce intraocular pressure, has emerged as a promising innovation.

Innovations like bimatoprost implants and travoprost punctum plugs aim to simplify the treatment regimen for glaucoma patients. Nanotechnology is paving the way for novel drug delivery methods. Ongoing research into latrunculin B, adenosine receptor agonists, specific gene silencing, and stem cell therapy promises to revolutionize

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glaucoma treatment. Additionally, neuroprotective agents such as memantine and neurotrophins are undergoing trials. The potential benefits of dietary supplementation with alpha lipoic acid, Forskolin, and *Ginko biloba* are also under evaluation.[8] This comprehensive review delves into the latest advancements in glaucoma medications, innovative drug delivery techniques, and the promising future of glaucoma treatment.

Unoprostone

Unoprostone Isopropylate, a recent addition to the prostaglandin analog class, distinguishes itself as a docosanoid—a structural analog of an inactive cyclic derivative of arachidonic acid.[9,10] Unlike other prostaglandin analogs, it boasts a 22-carbon chain backbone, setting it apart from the typical 20-carbon structure found in similar agents.[9,10] This innovative compound is available in a 0.15% ophthalmic formulation to be applied twice daily.[9,10] unoprostone's mechanism of action involves reducing intraocular pressure (IOP) by enhancing uveoscleral and trabecular meshwork outflow without affecting aqueous humor production.[9] When used as monotherapy, unoprostone delivers a clinically significant IOP-lowering effect comparable to betaxolol.[10] Additionally, a study found that a 0.12% unoprostone isopropyl solution, applied topically twice daily for six weeks, matched the effectiveness of 0.5% timolol in controlling IOP in individuals with chronic open-angle glaucoma or ocular hypertension.[11] In a six-month study, unoprostone isopropylate was shown to provide an additive IOP-lowering effect when used alongside topical β-blockers in patients with primary open-angle glaucoma without significant systemic side effects.[12] Furthermore, research involving healthy volunteers demonstrated unoprostone's capacity to significantly increase microcirculation in the optic nerve head, choroid, and retina.[13] However, it's essential to note that unoprostone may lead to minor side effects like iris hyperpigmentation and abnormal eyelash changes, although these occurrences are relatively rare in extended clinical studies.[13]

Rho Kinase Inhibitors

In 1993, a pivotal discovery unfolded, revealing the role of cytoskeletally active agents, such as Rho kinase, in the intricate regulation of trabecular outflow.[14] The Rho family encompasses two key effectors, the Rho kinase isoforms, ROCK 1 and ROCK 2, both central players in this ocular symphony.[14] Rho kinase inhibitors emerge as crucial elements in this narrative, enhancing aqueous outflow by reducing resistance and empowering Schlemm's canal endothelial cells to create crucial pores.[15] Another hypothesis suggests that Rho kinase inhibitors induce relaxation of smooth muscle fibers within the trabecular meshwork, thus facilitating outflow.[15] Experimental evidence even hints at changes in Schlemm's canal cytoskeleton, leading to decreased focal adhesions in the juxtacanalicular meshwork.[16] The commercially available formulations of Rho kinase inhibitors, ripasudil and netarsudil, target both ROCK1 and ROCK 2 receptors.[14] Ripasudil hydrochloride hydrate at 0.4% delivers a notable reduction in intraocular pressure (IOP), ranging from 2.6 to 3.7 mmHg in patients with primary open-angle glaucoma (POAG) and ocular hypertension (OHT).[17] Commonly reported adverse events include conjunctival hyperemia (76%), blepharitis (21%), and allergic conjunctivitis (20%).[17] When used alongside timolol maleate 0.5%, Ripasudil 0.4% showcases an additional IOP-lowering effect of 0.9 to 1.6 mmHg, while the additive effect with latanoprost 0.005% results in a reduction of 1.4 mmHg.[18] Netarsudil, a Rho kinase inhibitor and norepinephrine transporter inhibitor, effectively reduces IOP by alleviating outflow resistance.[19] Notably, Netarsudil is linked to a reduction in aqueous humor production in animal studies and a decrease in episcleral venous pressure in both animal and human research, primarily attributed to its norepinephrine transporter inhibitor activity.[19] In a double-masked randomized controlled trial (RCT), the efficacy of Netarsudil at 0.01 and 0.02%, as well as latanoprost 0.005%, dosed once daily, was explored in patients with ocular hypertension (OHT) and primary open-angle glaucoma (POAG) exhibiting IOP levels between ≥24 and <36 mmHg.[20] Impressively, both concentrations of netarsudil demonstrated IOP reductions statistically on par with latanoprost.[20] Subsequent RCTs delved into the effectiveness of netarsudil 0.02% combined with timolol maleate 0.5% in patients with a lower baseline IOP of <27 mmHg.[21] In both studies, Netarsudil exhibited statistically similar IOP-lowering effects compared to timolol 0.05% in the subgroup of patients with IOP <25 mmHg.[21] Recent case series reported a distinct reticular pattern of corneal edema in patients receiving netarsudil, affecting visual acuity, but notably resolving upon discontinuation of the medication.[22,23]

The Mercury-1 and Mercury-2 trials shed light on 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%.[24] These studies underscored the FCNL's superior IOP reduction compared to monotherapy, with conjunctival hyperemia, cornea verticillata, and subconjunctival hemorrhage emerging as the most common adverse events.[25] Finally, Fasudil, a novel Rho kinase inhibitor, has displayed promising results in the treatment of end-stage glaucoma.[26]

The significance of Rho kinase inhibitors as adjunctive therapies is noteworthy due to their distinct mechanism of action compared to currently employed medications. However, their relatively high incidence of conjunctival hyperemia and subconjunctival hemorrhages may pose challenges to long-term compliance. The safety and efficacy of Rho kinase inhibitors in specific populations, such as individuals under 18 years of age, pregnant women, and lactating women, remain subjects of further exploration.

Latanoprostene Bunod [LBN]

Latanoprostene bunod 0.024% is a unique compound that metabolizes into two active intra-ocular pressure lowering agents, namely latanoprost acid, a PGA and nitric oxide

(NO). Latanoprostene bunod metabolizes into latanoprost acid and butanediol mononitrate; butanediol mononitrate further metabolizes into 1,4 butane diol and NO.[27] Latanoprost increases the uveoscleral outflow, while 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.[28] 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 in only the diurnal IOP.[29] Finally, the JUPITER study evaluated the long-term safety of LBN with a follow-up period of 52 weeks.[30] The most frequently reported adverse events were conjunctival hyperemia (17%), eyelash growth (16%), eye irritation (11%), eye pain (10%), and increased iris pigmentation (10%).[30]

Newer Drug Delivery Systems

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

The bimatoprost implant (Durysta™) is a sustained-release drug delivery system for intracameral use. The implant is administered into the anterior chamber using a 28 gauge, single-use, prefilled applicator. Artemis 1 trial showed that both concentrations of durysta (10 and 15 mcg) were non-inferior to timolol 0.5%.[31] 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.[31] There were no adverse events related to eyelash growth, skin hyperpigmentation, or periorbital fat atrophy.[31] The main concern was the drop in corneal endothelial cell density (CECD).[31] A greater than 20% decrease in CECD was noted. 3.6% of eyes in the 10 mcg group and 10.3% of eyes in the 15 mcg group needed implant removal to correct corneal edema and prevent further loss of corneal endothelial cells. [32]

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.[33] It continuously elutes bimatoprost for a period of 6 months, after which it needs to be replaced. 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.[33] 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 is currently undergoing animal studies.[34]

Travoprost punctum plugs are an investigational device undergoing phase 2 clinical trials. Travoprost impregnated in polyethylene glycol resorbable hydrogel rod is inserted into the upper or lower punctum. Travoprost particles are encapsulated in polylactic acid microparticles, which hydrolyze with time to provide sustained delivery of travoprost over 90 days.[35] The rod is also impregnated with fluorescein to aid visualization. The major adverse events were retention of a plug, foreign body sensation (38.5%), itchiness (15.4%), and epiphora (3.8%). The tolerability of the implant improved with time.[35]

Nanotechnology is another novel route of drug delivery that is fast evolving. Nanoparticles range from 1 to 100 nm in size and medications piggybacked onto various nanoparticles have the ability to bypass biological barriers, rendering the drug directly at the target site.[36]

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 (CB1 and CB2), which are the natural receptors for endocannabinoids and are expressed in the human retina, ciliary body, iris, Schlemm's canal, trabecular meshwork, and the retinal pigment epithelium.[37,38]

The neuroprotective effect of cannabinoids is linked to the inhibition of glutamate release. Hommer *et al*. reported a significant increase in the optic nerve head blood flow with 5 mg oral Dronabinol in 24 subjects when compared to a placebo.[39] 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 a vehicle for topical formulations, leads to poor penetration of the drug, lid inflammation, and conjunctival hyperemia.[40]

Despite extensive research, the role of cannabinoids in medical management of glaucoma remains equivocal. The relatively short-term effect of IOP, the risks of developing tachyphylaxis, and the serious side effects impacting patients' general and neurocognitive health greatly outweigh the potential benefits 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.[41,42] It increases the conventional outflow facility by shrinkage of cell volume and remodeling of the extracellular matrix in human trabecular meshwork cells.[41,42] A1, A2A, and A3 agonists are currently undergoing phase 1 and 2 trials.[41,42] Phase 2 trials of trabodenoson, a selective A1 agonist, showed clinically

and statistically significant IOP reduction with no serious adverse events.[41,42]

Prostanoid Receptor Agonist

Omidenepag isopropyl (OMDI) is a non-prostaglandin, 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.[43]

Small Interference RNA

RNA interference is the cutting-edge technology of specific gene silencing, using small bits of RNA called small interference RNA (siRNA).[44] SYL040012 is a siRNA developed to specifically silence the beta 2 adrenergic receptor (ADRB2) at the ciliary body, thereby reducing the aqueous humor production. I*n-vitro* and *in-vivo* studies in animal models of SYL040012 have shown significant IOP reduction and a good safety profile.

Neuroprotection

Neuroprotection is the holy grail of glaucoma care. Glaucoma is known to be a neurodegenerative disease that causes chronic progressive RGC death, and glaucoma treatment remains restricted to a 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. 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, causing an excess of intracellular calcium and cell death.[45] 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 the progression of glaucoma based on standard automated perimetry and optic disc photography findings.[46]

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.[47] Valproic acid, traditionally used to treat epilepsy, has been demonstrated to induce neuroprotection by stimulating the BDNF–TrkB pathway.[47] Animal studies demonstrated a protective effect of topical application of NGF drops on RGCs in a rat model of glaucoma.[47] Topical NGF drops have also been shown to demonstrate improvement in visual fields, contrast sensitivity, and electro functional tests in a few patients with advanced glaucoma.[47]

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 the progress of this mode of treatment.[48]

Aquaporin 1 is a protein in the ciliary body involved in aqueous production by facilitating the transmembrane transport of water.[49] Disruption of Aquaporin 1 by gene therapy with CRISPR-Cas9 RNA has been reported to reduce IOP in animal models.[49] The treatment that targets a gene involved in a physiologic process rather than a specific gene mutation has the potential to be universally applicable.

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.[50] 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 Schwalbe's ring and the anterior trabecular meshwork.[51] These adult stem cells play a crucial role in tissue repair and may also be expanded in vitro for tissue regeneration.

Alternative Medicine

Dietary supplementation with Alpha lipoic acid has been shown to decrease oxidative stress and improve RGC survival in animal models of glaucoma.[52] 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.[53] Nutritional supplementation has a good safety profile, and larger, better-designed RCTs with longer follow-ups are required to evaluate its role in glaucoma. Cytidine 5'diphosphocholine or citicoline is an endogenous compound involved in the synthesis of membrane phospholipids. It is known to increase the levels of dopamine, serotonin, and noradrenaline in the central nervous system.[54] Pecori Giraldi *et al*. first studied the effect of intramuscular (IM) injections of 1 g of citicoline for ten consecutive days in glaucoma patients and reported an improvement in visual fields by computerized perimetry in 75% of the 34 examined eyes. A recent randomized control trial evaluated the effect of citicoline eye drops on the rate of progression in patients on topical hypotensive drugs. RNFL thickness measurements suggested that the citicoline eye drops may slow disease progression in these patients.[55]

Conclusion

In conclusion, the field of glaucoma treatment has witnessed a remarkable surge in research and innovative initiatives over the past few decades. These advancements promise to augment the ophthalmologist's armamentarium with an array of glaucoma medications boasting diverse mechanisms of action. The future of glaucoma management appears to be both promising and transformative. The emergence of novel medications, ingenious drug delivery systems, and groundbreaking therapeutic approaches heralds a new era in patient care. These innovations are poised to simplify the often complex landscape of drug dosing, thereby enhancing patient compliance and, ultimately, the prognosis for those affected by this insidious eye condition.

As we stand on the precipice of this exciting new chapter in glaucoma treatment, it is evident that the relentless pursuit of advancements in the field will not only provide patients with more effective and accessible treatment options but also improve their overall quality of life. The collaboration between researchers, clinicians, and pharmaceutical companies underscores the collective commitment to combat this leading cause of irreversible blindness. With these remarkable developments, glaucoma management is poised to become more patient-centric, ensuring better outcomes and a brighter future for all those affected by this sight-threatening condition.

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