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Review Article

Recent Pharmacological Advancement in Glaucoma Management

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Abstract

Glaucoma is a leading cause of blindness, and it is defined as a neurodegenerative disorder that ultimately effects the retinal layers resulting in blindness. Several therapeutics aim at minimizing intraocular pressure, a major hallmark of glaucoma. A comprehensive understanding of existing therapeutics and their drawbacks will help us design blueprints for effective therapeutics and management regimes for effective glaucoma management. The current review will present an insight into current and developing therapeutics existing for efficient glaucoma management.

Keywords: Glaucoma; Drugs; Clinical Studies

Introduction

Glaucoma is a neurodegenerative disease which effects the retinal ganglion cells (RGCs) leading to irreversible and progressive vision loss [1-4]. In the United States, glaucoma is currently the second leading cause of permanent blindness. In 2020, it was estimated that there were more than 50 million people with primary open angle glaucoma (POAG) and that number is expected to rise to 80 million by 2040 [5]. Acute angle closure glaucoma can lead to a sudden and very fast decline in vision while POAG typically has a slower and more insidious onset often requiring routine eye exams to diagnose, monitor and manage [6]. Glaucoma is classified as 'early onset' if prior to the age of 40 while the majority are diagnosed after the age of 40 [7]. The pathophysiology of glaucoma is complex and multifaceted as showed in pre-clinical [8-10] and clinical studies leading to the eventual degeneration of the optic nerve [11]. As far as the mechanical etiologies, are concerned, increased intraocular pressure (IOP) has been shown to be a major hallmark of glaucoma. As a result, many therapies directed against glaucoma target IOP [12]. The review discusses various drug classes and trails exploring successful management of glaucoma.

Drugs-analogs and blockers

Several classes of drugs aim at reducing the IOP as a strategy for glaucoma management. Some of the most promising drugs are discussed below.

Prostaglandin analogs

Usually, prostaglandin analogs are considered first line therapeutic agents to reduce IOP in glaucoma patients. Prostaglandins are lipophilic derivatives of arachidonic acid and were found to have significant IOP lowering effects. Out of all the prostaglandins, E2 and F2α are found in greatest number

within ocular tissues [13,14]. These class of drugs work through increasing uveoscleral, and TM mediated aqueous humor outflow [15]. Additionally, they have been proven to have relatively low side effects and help improve patient quality of life. The major side effects are conjunctival hyperemia, increased periocular skin and iris pigmentation, longer and thicker eyelashes, and change in iris color in certain cases. Systemic conditions that limit the use of prostaglandins include underlying cardiovascular conditions and/or significant liver or kidney diseases [16,17]. Currently, the most widely prescribed prostaglandin analogs are Latanoprost, Travoprost, Bimatoprost, and Tafluprost [13]. Latanoprost (0.005%) was the first topical prostaglandin analog that was developed in 1982 and approved in 1996 [18]. It has shown efficacy in lowering IOP and preserving visual field in patients with open-angle glaucoma [19,20]. It is believed that its specific mechanism of action is through prostanoid receptors (F2α) in the ciliary body and ocular muscle tissues that relax the tension and lower resistance to aqueous outflow by modulating metalloproteinase proteins [13]. Travoprost is another prostaglandin analog which is unique in that is exhibits full agonism at the F2α receptor [21]. Bimatoprost has a unique amide group which allows for slightly different metabolism of the drug compared to the other prostaglandin analogs [22,23]. Bimatoprost has been found to be more efficacious in people for whom Latanoprost was ineffective or show any serious side effects [13].

Beta blockers

In the case that prostaglandin analogs cannot be administered, beta blockers are the second line agents that are considered promising alternative. There are a few main differences when compared to prostaglandin analogs. Despite both being topical treatment options, beta blockers have to be administered frequently. Their mechanism of action is by reducing IOP via diminishing the intrinsic production of aqueous humor by blocking beta adrenergic receptors in the ciliary epithelium [24-26]. Beta 1 receptors are more prevalent within the ciliary epithelium but nonselective beta 1 and beta 2 antagonists may be more efficacious compared to beta 1 selective antagonists. The main local side effect of beta blocker use is worsening of existing dry eye condition [16]. However, beta blockers can lead to more systemic effects and therefore can have increased contraindications to its use. Because of their prominent cardiovascular effects, beta blockers are avoided as glaucoma management regime in patients with bronchial asthma, bradycardia, hypotension, atrioventricular heart block, congestive heart failure, severe allergic rhinitis, and muscle weakness [16,27]. Additionally, for diabetic patients, beta blocker usage can exacerbate hyperglycemia and is to be used with extreme caution [28,29]. Some of the most common beta blockers used are propranolol, timolol, betaxolol, levobunolol, metiapranolol, and carteolol.

Alpha agonists

Alpha agonists can also serve as second line options for glaucoma treatment. They work through decreasing the production of aqueous humor as well as facilitating enhanced uveoscleral outflow. These agents have to be applied 2 - 3 times per day [30]. There are nonselective alpha agonists as well as alpha 2 selective agonists such as Apraclonidine and Brimonidine [30]. Local ocular side effects following administration of these class of drugs include periocular contact dermatitis while broader side effects are decreased salivation, lethargy, and headache. Currently, Apraclonidine is only used for short term prophylactic increases in IOP post laser procedures due to their high rate of allergic blepharoconjunctivitis [15]. Additionally, apraclonidine has had high reported rates of tachyphylaxis leading to its discontinuation as a chronic glaucoma therapy [13]. Nonselective alpha agonists have also had higher incidences of systemic hypotensive effects therefore indicating cautioned use in cardiovascular patients. Alpha agonists have also been suggested to possibly have neuroprotective role via the alpha 2 receptors [31,32] in animal models. Additionally, patients taking brimonidine were less likely to have visual field progression compared to other treatments such as timolol [33].

Carbonic anhydrase inhibitors

Another class of drugs that can be supplemented during glaucoma management include the carbonic anhydrase inhibitors. Inhibition of carbonic anhydrase isozyme II in the ciliary epithelium results in a decrease in aqueous humor production. By reducing bicarbonate ions and reducing fluid flow, they decrease the overall production of aqueous humor thereby controlling IOP [34]. The carbonic anhydrase inhibitors are divided into 2 groups mainly divided on the mode of administration: systemic and topical [34]. Despite their success in reducing IOP, the main deterrence to the

use of systemic carbonic anhydrase inhibitors is their adverse effects that include paranesthesia, nausea, vomiting, depression, kidney stones, and metabolic acidosis [15,35]. For these reasons, topical carbonic anhydrase inhibitors are many times used as they reach the ciliary body swiftly through corneal penetration [34] and have less adverse side effects that may include ocular stinging, burning, sensation of foreign body, and possible blurring of vision [15]. The main carbonic anhydrase inhibitors that are chiefly used are dorzolamide [36] and brinzolamide [37].

Rho kinase inhibitor

The Rho protein family is a GTPase family. It is active when bound to guanosine triphosphate (GTP) and inactive when bound to guanosine triphosphate (GDP). This class of drug is considered to be the newest class of medication available and netarsudil was approved in 2017 by the FDA. Rho kinase inhibitors have two proposed mechanisms of action. First, it is reported that inhibiting rho kinase improves the permeability of TM and Schlemm's canal [38]. Rho kinase increases cell stiffness leading to mitigated aqueous humor outflow due to its role as a serine/threonine protein kinase leading to regulation of cytoskeletal activities and smooth muscle contraction with calcium. By inhibiting rho kinase, rho kinase inhibitors like Netarsudil can reduce the resistance of aqueous humor flow [39,40]. Additionally, it acts by lowering aqueous humor production thereby regulating increased IOP. Some other additional benefits of these drugs include offering enhanced antioxidation properties in the TM thereby inhibiting reactive oxygen species (ROS) production and promoting cell survival [41]. This is vital in decreasing the rate at which glaucoma progresses and help alleviate glaucoma symptoms. Some side effects of rho kinase inhibitors include conjunctival hyperemia, subconjunctival hemorrhages, blurred vision, eyelid erythema, increased lacrimation, and reduced visual acuity. This is possibly due to rho kinase inhibition leading to calcium sensitization and therefore blood vessel dilation [15]. Some of these side effects have been shown to decrease with prolonged usage. With many trials, rho kinase inhibitors have been shown to be a beneficial adjunctive therapy as it has multifaceted approach in addressing increased IOP that other drugs lack [42-44]. In 2019, the FDA approved a fixed combination of rho kinase inhibitor and the prostaglandin analog latanoprost for the treatment of POAG and ocular hypertension. These two combinations offer a synergistic effect in decreasing IOP [15].

Clinical phase studies and other treatment alternatives

Clinical studies are vital to assess the safety margin and effectiveness of novel therapeutics in humans. A study done in 2021 used *in vivo* models to demonstrate the benefit of nicotinamide in rat glaucoma models with RGCs degeneration due to increased IOP as well as optic nerve degeneration by axotomy [45]. The metabolic disruption in the study was prevented by nicotinamide which proved to be neuroprotective and hence it was clinically tested. Recently, Glaucoma Nicotinamide Trial, a prospective, randomized, placebo-controlled double masked clinical trial was conducted. In the study, POAG patients received either nicotinamide or the placebo. Results indicated substantial improvement in visual function which was short term and hence supported a need for long-term analysis [46].

Citicoline is an intermediate product in the synthesis of cell membrane phospholipids, and it exhibits neuroprotective effects including controlling glaucoma progression [47,48]. Patients on Citicoline had significantly lower retinal nerve fiber layer loss after 3 years and had improved vision [48]. Docosahexaenoic acid (DHA) is an omega-3 polyunsaturated fatty acid with antioxidant effects. Patients who were administered a combination of both Citicoline and DHA had a statistically significant decrease in mean defect of visual field and increase in visual field index after 3 months [47]. Only a synergistic effect of both these molecules exhibited a statistically significant improvement in vision as compared to when they were administered individually [47]. One major drawback of the study was the short duration of trial. Examinations and measurements occurred at 1, 2, and 3 months after initiation of the proposed therapies. Continued monitoring and follow-up may be vital in determining the true potential of this combinatorial treatment.

Another major molecular event that is reported during glaucoma progression is mitochondrial dysfunction. One of the mechanisms of action behind this is the lack of nicotinamide adenine dinucleotide (NAD) placing the RGCs at greater risk for damage during increased IOP [45,49]. It is hypothesized that the nicotinamide (amide version of Vitamin B_3) can be used to replace NAD levels thereby offering its therapeutic effect [50].

Conclusion

Decreasing IOP is critical first step to curb the detrimental effect of glaucoma. Currently, several therapeutic options mainly work towards decreasing the IOP through a variety of mechanisms. However, their side effects raise concerns and hence need for alternative therapeutics is the need of the hour. Developments like cellular transplants, implants, and nanotechnology are gaining attention due to their minimal side-effects and efficacy. Despite their promising outcomes, comprehensive studies need to be carried out to investigate their long term effects and recognizing their safety profile prior to approval in clinical environment. Future studies are focusing on nanomedicine, epigenetic modifications, gene studies etc. Glaucoma management requires a combination therapy based on its multifaceted mechanisms.

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Conflicts of Interest

The authors declare no conflict of interest.

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