Glaucoma Actual and Future Strategies of Treatment A Review of Literature

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Abstract

The objective of this study is to present a review of glaucoma therapy and the new strategies of treatment. Glaucoma the major cause of blindness worldwide,is an eye disease that lead to blindness if not treated. There are several different types of glaucoma, divided into the primary or secondary open-angle or angle-closure glaucoma. The medical treatment strategies are divided into current available glaucoma medications, that are focused on lowering intraocular pressure (IOP), new pressure lowering targets, prospective neuroprotective interventions, and finally possible neuroregenrative strategies. For patients who do not respond to antiglaucoma medications, laser trabeculoplasty and incisional surgery are further methods that can be used to lower intraocular pressure. The identification of new strategies such has been hampered by lack of understanding of the etiology of glaucoma.The present review seeks to provide an overview of the present and new treatment strategies in the management of glaucoma.

Conclusion. Glaucoma is a common eye disease that is usually associated with an elevated intraocular pressure. Treatment options for patients with glaucoma include medications, laser therapy, and incisional surgery. The risks and benefits of each type of treatment must be carefully considered to maximize the treatment's benefits while minimizing adverse effects.Recent approaches aim to rescue RGCs (retinal ganglion cell) and regenerate axons in order to restore visual function in glaucoma.

KEYWORDS: Glaucoma, Treatment strategies, intraocular pressure lowering drugs, review.

INTRODUCTION

Glaucoma refers to a group of eye conditions, which cause progressive damage to the optic nerve, retinal ganglion cell (RGC) death, and characteristic damage to the visual field.

According to The World Health Organization, glaucoma accounted for 2 % of visual impairment and 8 % of global blindness in 2010, and the number of glaucoma patients is estimated to increase due to a growing population. It can occur at any age but is more common in older adults. The most common form of glaucoma has no warning signs. The effect is so gradual that you may not notice a change in vision until the condition is at an advanced stage.Vision loss due to glaucoma can't be recovered. So it's important to have regular eye exams that include measurements of your eye pressure. If glaucoma is recognized early, vision loss can be slowed or prevented. If you have the condition, you'll generally need treatment for the rest of your life.

The classification of glaucomarelies on the appearance and obstruction of the drainagepathway. In open angle glaucoma (OAG) the drainagepathwayappearsnormal and in angle-closure glaucoma (ACG) the drainagepathwayisobstructed. Glaucoma isalsoclassifiedaccording to whetheritisprimary or associated with detectablecomorbidity, secondary glaucoma, normal-tension glaucoma, glaucoma in children and Pigmentaryglaucoma.Glaucoma can be treated with eyedrops, pills, laser surgery, traditionalsurgery or a combination of thesemethods. The goal of any treatment is to preventloss of vision, asvisionloss from glaucoma isirreversible.

The most common subtype of glaucoma is primary OAG (POAG). Despite the normal clinical appearance of the drainage pathway the aqueous outflow is restricted in most POAG and referred to as high-tension glaucoma (HTG). Glaucoma is associated with an increase in intraocular pressure (IOP), and to date IOP lowering drugs remain the only clinically validated treatment of glaucoma. Despite the significant importance of IOP in the risk of glaucoma progression, it is recognized that elevated IOP appears in the absence of the characteristic optic nerve changes (ocular hypertension (OHT)) and conversely glaucomatous optic nerve damage appears in the absence of an elevated IOP (low-tension glaucoma (LTG)). Therefore, despite the fact that IOP lowering interventions reduce the risk of progression and delay the disease onset of glaucoma, the pathogenesis is controversial and not completely understood. In this matter non-IOP-dependent risk factors appear to be responsible for approximately 30-70 percent of glaucoma cases.

The present review seeks to 1) briefly summarize the current treatment strategies for glaucoma, 2) discuss future treatment strategies for glaucoma i.e. new targets for IOP-lowering, targets for neuroprotection, targets for neuroregeneration, laser and surgical therapy.

CURRENT TREATMENT STRATEGIES FOR GLAUCOMA

Although glaucoma is a complex and poorly understood disorder, the primary goal of therapy is lowering IOP.

The first anti-glaucomatous drop was introduced in 1875 and there are currently several types of IOP-lowering eye drops used to treat glaucoma. The eye drops include β-blockers, carbonic anhydrase inhibitors, prostaglandin analogs, α2-adrenergic agonists, and parasympathomimetic drugs. the eye-drops often come as combined drops. To date fixed-combination eye-drops include prostaglandin analogs/β-blockers, carbonic anhydrase inhibitors/β-blockers, and α2-adrenergic agonists/β-blockers. Finally, a combination of carbonic anhydrase inhibitors /α2-adrenergic agonists was approved by the United States Food and Drug Administration in April 2013, and as an exception a triple fixed combination of prostaglandin analogs/α2-adrenergic agonists/β-blockers is available in Mexico.

Over all, the current available glaucoma eye-drops all seek to decrease the IOP. They can be grouped into therapeutic agents that decrease the production of aqueous humor production and/or increase the drainage through the trabecular meshwork (TM) and/or increase uveoscleral outflow.

ß-blockers (reduces the production of aqueous humor**)**
•Timolol (Optimol, TimacarDepot, Timoptol-LA, Timolol, Nyogel L.P., Timogel, Timosan, Aquanil) •Levobunolol* •Carteolol (Ocupress)* •Metipranolol (OptiPranolol)* •Betatoxol (Betoptic) •Nipradilol*
Carbon anhydraseinhibitorsCAI)s (reduce IOP by inhibiting the ciliaryepithelium and controllingaqueousformation)
•Dorzolamide (Trusopt, Arzolamid, Dorzolamid) •Brinzolamide (Azopt) •Acetazolamide (Diamox) - oralmedication •Methazolamide (Neptazane) - oralmedication*

Prostaglandinanalogs (lower IOP by accelerating the uveoscleraloutflow**)**
•Tafluprost (Taflutan, Saflutan, Zioptan*) •Latanoprost (Xalatan, Monoprost, Latanoprost) •Bimatoprost (Lumigan,) •Travoprost (Travatan) •Unoprostoneisopropyl (Rescula)*
Sympathomimeticdrugs (reduce the production of aqueous humor**)**
•Brimonidine (Alphagan, Alphagan-P*, Bimonidintartrat, Brimoratio, Glaudin) •Apraclonidine (Iopidine) •Dipivefrin (Propine)* •Epinephrine (Gluacon, Epifrin)*
Parasympathomimeticdrugs(miosiswhichincreasethe rate of fluiddrainage from the eye**)**
•Pilocarpine (Pilokarpin, Isopto Carpine*, Pilocar*, Pilopine HS*) •Echothiophate (PhospholineIodide)*

FUTURE TREATMENT STRATEGIES FOR GLAUCOMA

Many mechanisms have been proposed to address the pathogenesis of glaucoma. However, none seems to characterize the disease sufficiently, and the multifactorial etiologies of glaucoma become a fundamental challenge in the development of new treatment strategies. Nevertheless elevated IOP together with yet-to-be elucidated cellular and molecular changes result in glaucomatous neurodegeneration. In this aspect treatment strategies can be grouped into:

1. IOP Lowering Strategies
2. Neuroprotective Strategies
3. Neuroregenerative Strategies

NEW TREATMENT STRATEGIES FOR IOP LOWERING

It is clear that multiple factors give rise to glaucomatous damage, and it is recognized that the most evident risk factor is IOP. The cause of elevated IOP in POAG is thought to be due to an increased accumulation of extracellular matrix material (ECM) in the TM (trabecular meshwork). From the current approved glaucoma medications only prostaglandin analogues may have a role on modulation of the molecular changes that occur in the TM of glaucoma patients. Hence, prostaglandins may induce stimulation of matrix metalloproteinases, and in this way lead to increased spacing between the ciliary muscle bundles. Since the importance of IOP in the progression of glaucoma is evident, current new strategies target IOP lowering pathways. Among these exist two main approaches that try to increase the outflow facilities in the TM.

The first strategy seeks to modulate the contractility of TM. It has been shown that TM possesses smooth muscle cell-like properties, and that TMs contractile properties can be regulated by several enzymes.

The second therapeutic concept includes alteration in the behavior of TM, and strategies to affect the shape and loosen the cell-to-cell junction and/or cell-to-ECM adhesion within the TM have become experimental targets for lowering IOP. In addition, new therapeutic targets aim to decrease aqueous humor production or to improve the uveoscleral outflow by different subcellular pathways from those already existing.

IOP LoweringStrategies	NeuroprotectiveStrategies	NeuroregenerativeStrategies
IncreasingTrabecularMeshwork Outflow ROCK Endothelin-1 NitricOxide TGF-ß CTGF Adenosine Angiopoietin-like7 molecules Cannabinoids Cochlin Latrunculins Melatonin Ghrelin Increasing the UveoscleralOutflow Angiotensin II Ghrelin Cannabinoids Serotonin DecreasingAqueous Humor Production Forskolin Serotonin Cannabinoids Angiotensin II	Exitotoxicity NMDA antagonists (Memantine) Modulation of Müller cells Oxidative stress Antioxidants (α-tocopherol) Ginkgo Biloba MitochondrialDysfunction Mitochondrialtargetedantioxidants (Q10) Inflammation- Abnormal Immune Response - TNF-α Biologicalresponsemodifiers (Ethanrecept) AgmatineModulation of T-cellreaction (Cop-1) Modulation of PLA2-induced inflammation ProteinMisfolding Agents targetingAß Heat shock proteins Glial Cell Modulation TGF-ß, CNTF, PDGF OtherPathways Estradiol Statins Erythropoietin	Cell Repair Inflammatorystimulation (CNTF) Gene Therapy (Nogo Receptorinterference) SurgicalApproaches Lens Injury Stem Cell Therapy CNTF-secreting RPE cells MSC transplantation
Abbreviations are: Rho-associatedKinase (ROCK), TumorGrowthFactor-ß (TGF-ß), ConnectiveTissueGrowthFactor(CTGF), TumorNecrosisFactor-α (TNF-α), Phospholipase A2 (PLA2), Amyloid-ß (Aß), CiliaryNeurotrophicFactor (CNTF), Platelet-derivedGrowthFactor (PDGF), RetinalPigmentEpithelialCells (RPE), MesenchymalStemCells (MSC).		

NEUROPROTECTIVE TREATMENT STRATEGIES

In order to simplify the complexity of the proposed new neuroprotective treatment strategies, these can be grouped into targets that interfere with excitotoxicity, oxidative stress, mitochondrial dysfunction, inflammation - abnormal immune response, protein misfolding, and glial cell modulation. Obviously, such a division of treatment strategies is not definite and most targets will interfere with more pathways.

Other Pathways

A recent study has provided strong evidence that topical estrogen drops are neuroprotective in a rodent model of glaucoma. Finally, long-term use of statins, the glycoprotein, erythropoietin (EPO), has been suggested to be a potential therapeutic neuroprotectant in glaucoma.

NEUROREGENERATIVE TREATMENT STRATEGIES

Growing evidence suggests cell repair or cell-replacement therapy as a new treatment approach. Stem cells hold great promise for neurodegenerative disorders such as glaucoma.

Cell Repair

A significant number of patients will be diagnosed at a later stage by which their axons have already been injured. In these cases, the ideal therapies should encourage axon regeneration to rebuild connections from the RGCs to the brain. Knockout of NgR1 has been shown effective for enhancing axonal regeneration after optic nerve crush.

Surgical Approaches for Neuroregeneration

Penetrating injury as well as lens injury has been suggested to result in the release of low-grade inflammatory molecules, which secondly leads to axonal regeneration.

Stem Cell Therapy

Substantial evidence has correlated neurotrophic factor deprivation with RGC death and new therapies aim to supplement these. A clinical trial using bone marrow-derived MSCs on glaucoma induce axonal regeneration.The outcome of this study is expected in 2017 (Phase I, #NCT01920867).

Laser therapy

Argon Laser Trabeculoplasty (ALT) applied for open-angle glaucomaThe laser treats the trabecular meshwork of the eye, increasing the drainage outflow, thereby lowering the IOP.

Selective Laser Trabeculoplasty(SLT)—for open-angle glaucoma.SLT is a newer laser that uses very low levels of energy. It is termed "selective" since it leaves portions of the trabecular meshwork intact.

Laser Peripheral Iridotomy (LPI) applied for angle-closure glaucoma. This procedure is used to make an opening through the iris, allowing aqueous fluid to flow from behind the iris directly to the anterior chamber of the eye. This allows the fluid to bypass its normal route.

Cycloablation

Two laser procedures for open-angle glaucoma involve reducing the amount of aqueous humor in the eye by destroying part of the ciliary body, which produces the fluid.

Traditional **Surgery**

Trabeculectomy

When medications and laser therapies do not adequately lower eye pressure, doctors may recommend conventional surgery. is used in both open-angle and closed-angle glaucomas. In this procedure, the surgeon creates a passage in the sclera (the white part of the eye) for draining excess eye fluid. A small bubble of fluid called a "bleb" often forms over the opening on the surface of the eye, which is a sign that fluid is draining out into the space between the sclera and conjunctiva. Many surgeons perform trabeculectomy with an anti-fibrotic agent that is placed on the eye during surgery and reduces such scarring during the healing period. The most common anti-fibrotic agent is Mitomycin-C. Another is 5-Fluorouracil, or 5-FU.

Drainage Implant Surgery

Several different devices which consists of a small silicone tube that extends into the anterior chamber of the eye, to aid the drainage of aqueous humor out of the anterior chamber and lower IOP. This type of surgery is preferred in patients whose IOP cannot be controlled with traditional surgery or who have previous scarring. Newer nonpenetrating glaucoma surgery, which does not enter the anterior chamber of the eye, shows great promise in minimizing postoperative complications and lowering the risk for infection. However, such surgery often requires a greater surgical acument and generally does not lower IOP as much as trabeculectomy.

Some Promising Surgical Alternatives

The ExPress mini glaucoma shunt is a stainless steel device that is inserted into the anterior chamber of the eye and placed under a scleral flap. It lowers IOP by diverting aqueous humor from the anterior chamber. The ExPress offers the glaucoma surgeon an alternative to either repeating a trabeculectomy or placing a more extensive silicone tube shunt in those patients whose IOP is higher than the optic nerve can tolerate.

The Trabectome is a new probe-like device that is inserted into the anterior chamber through the cornea. The procedure uses a small probe (electrocautery) that opens the eye's drainage system through a tiny incision and delivers thermal energy to the trabecular meshwork, reducing resistance to outflow of aqueous humor and, as a result, lowering IOP.

Canaloplasty, a recent advancement in non-penetrating surgery, is designed to improve the aqueous circulation through the trabecular outflow process, thereby reducing IOP. Unlike traditional trabeculectomy, which creates a small hole in the eye to allow fluid to drain out, canaloplasty has been compared to an ocular version of angioplasty, in which the physician uses an extremely fine catheter to clear the drainage canal.

CONCLUSION

Glaucoma remains a major cause of blindness worldwide. Various new targets to treat glaucoma have been suggested, but to date the only available glaucoma medication is IOP lowering compounds, which are only decreasing the rate of progression. Hence, no cure for glaucoma exists. The identification of new therapeutic targets has been hampered by lack of understanding of the etiology of glaucoma, and the limited number of animal models available that likely represent only a small subset of human glaucoma cases. Since glaucoma may be a spectrum of different pathologies leading to the same endpoint, the outcome from clinical trials may be lost in the diversification of etiologies.

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