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REVIEW

NOVELTIES IN MEDICAL TREATMENT OF GLAUCOMA

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Abstract
The purpose of this study is to review the current medical treatment and the new and better alternatives for patients with glaucoma.
Glaucoma refers to a group of related eye disorders that have in common an optic neuropathy associated with visual function loss. It is one of the leading causes of irreversible blindness worldwide. Glaucoma can damage vision gradually so it may not be noticed until the disease is at an advanced stage.
Early diagnosis and treatment can minimize or prevent optic nerve damage and limit glaucoma-related vision loss. Nowadays, research continues for the improvement of current medical treatment.
Keywords: glaucoma, medical treatment, preservative-free, drug delivery, gene therapy

Introduction

The term glaucoma refers to a group of diseases that have in common an optic neuropathy associated with visual function loss. Although elevated intraocular pressure (IOP) is one of the primary risk factors, it does not have a role in the definition of the disease [**1**].

Glaucoma is the second most frequent cause of irreversible blindness in developing countries.

The most common form of glaucoma is primary open angle glaucoma. It accounts for over 90% of glaucoma in adults. The incidence of the disorder significantly increases beyond the age of 40, reaching a peak between the ages of 60 and 70 [**2**].

Quality of life (QoL) is closely linked with visual function; if both eyes have advanced visual function loss, the quality of life is reduced considerably.

In general, patients do not have symptoms of glaucoma until large, irreversible visual field defects have occurred.

The goal of therapy in glaucoma is to achieve a target pressure that will arrest or prevent optic nerve head damage and progression of field defects, to maintain related QoL at a sustainable cost [**3,4**].

There is no single target IOP level appropriate for every patient; it needs to be estimated for each eye of every patient separately.

There is no ideal treatment of glaucoma. For a drug to be considered close to ideal, it has to have minimal local and systemic side effects,

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to generate as few fluctuations as possible in IOP, to have a lasting effect after administration and to generate a high adherence to treatment [**5,6**].

Medical therapy has a few limitations:

- topical drugs doubles tear production to 2 μl/ min
- only 20% of a drop actually reaches the eye
- the tear film washes the entire active substance in 5 minutes
- pressure on the lacrimal points for 1-2 minutes after administration reduces side-effects and increases absorption.

The overall cost, the difficulty in compliance, and the effects warring off in time make the medical therapy a challenge.

Indications for initiating the treatment

The decision to initiate therapy in glaucoma is serious. Once started, therapy generally is continued for the rest of the patient's life. The therapy has untoward side effects, significant costs, and can diminish QoL. In addition, the public health impact of treatment is enormous; therapy is expensive and requires regular medical attention.

Determining when to start treatment is a decision that must be individualized for each patient. Any decision to initiate therapy must weigh the patient's risk factors for the development or progression of glaucoma against the risk of side effects and inconveniences of treatment [**7**].

Patients considered glaucoma suspects and patients with risk factors such as a family history of the disorder, middle myopia, glaucoma in the other eye, or differences between the optic cup in the two eyes should be monitored closely. Follow-up examinations should be performed three to four times a year, especially for patients not undergoing treatment [**2**].

It is recommended to initiate the treatment with monotherapy. If it reduces IOP to the target and is well tolerated, therapy can be left unchanged. If it does not seem effective, first it should be switched with another monotherapy from the same class of drugs or another class entirely.

If monotherapy is well tolerated but it did not succeed in achieving the target IOP, the addition of a second drug should be considered. It is recommended to combine agents with different modes of action to achieve a superior IOP lowering.

However, multiple drugs reduce the adherence to treatment so, when available, a fixed combination should be used [**4**].

Classes of topical antiglaucoma drugs

The number of available agents for the medical treatment of glaucoma has expanded greatly. At first, the choice was limited to miotics, epinephrine, or oral carbonic anhydrase inhibitors.

Topical beta-blockers were introduced as a therapy for glaucoma in the 1970s and they represented a significant advance. Topical carbonic anhydrase inhibitors, alpha-adrenergic agonists, and prostaglandin analogs have also become available; they effectively lower intraocular pressure (IOP) and have advantageous side-effect profiles for most patients [**7**].

There are 5 classes of drugs:

- prostaglandin analogs (latanoprost, tafluprost, travoprost) and prostamides (bimatoprost)
- beta-receptor antagonists: nonselective (timolol, levobunolol, metipranolol, carteolol, befunolol) and beta-1-selective (betaxolol)
- carbonic anhydrase inhibitors: topical (brinzolamide, dorzolamide) and systemic (acetazolamide, methazolamide, dichlorphenamide)
- alpha -2 selective adrenergic agonists: apraclonidine, brimonidine, clonidine
- parasympathomimetics (pilocarpine, carbachol).

For a drug to be considered effective, it has to lower the IOP with at least 20%. A 10% decrease in IOP is considered ineffective. The IOP reduction varies between classes of drugs: 25-35% with prostaglandin analogs, 20-25% with beta-receptor antagonists, 20% with carbonic anhydrase inhibitors, 25-35% with alpha-2 selective adrenergic agonists and 20-25% with parasympathomimetics [**4**].

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Side effects and contraindications of topical antiglaucoma drugs

Prostaglandin analogs

Local side effects: burning sensation, conjunctival hyperaemia, foreign body sensation, itching, periorbital fat atrophy, increased pigmentation of periocular skin, eyelash changes, increased iris pigmentation, reactivation of herpes keratitis, uveitis, cystoid macular oedema in eyes with known risk factors for macular oedema.

Systemic side effects: exacerbation of asthma, dyspnea, chest pain, muscle-back pain.

Contraindications: contact lenses, unless reinserted 15 minutes following the administration of the drug [**4**].

Beta-receptor antagonists

Local side effects of nonselective agents: dry eye, conjunctival hyperaemia, corneal anesthesia, allergic blepharoconjunctivitis.

Local side effects of selective agents: burning, stinging.

Systemic side effects of nonselective agents: bradycardia, hypotension, arrhythmia, heart failure, syncope, bronchospasm, depression, sexual dysfunction.

Systemic side effects of selective agents: respiratory and cardiac side effects less pronounced then nonselective agents, depression, sexual dysfunction.

Contraindications: asthma, history of COPD (chronic obstructive pulmonary disease), sinus bradycardia (<60 beats/ min), heart block, cardiac failure [**4**].

Carbonic anhydrase inhibitors

Local side effects: burning, stinging, superficial punctuate keratitis, bitter taste, blurred vision, tearing.

Systemic side effects: headache, urticaria, pruritus, angioedema, asthenia, dizziness, paresthesia, and transient myopia.

Contraindications: patients with low corneal endothelial count, due to increased risk of corneal oedema.

Alpha-2 selective adrenergic agonists

Local side effects: lid retraction, limited mydriasis, conjunctival blanching, periocular contact dermatitis, allergy or delayed hypersensitivity, allergic blepharoconjunctivitis.

Systemic side effects: dry mouth and nose, fatigue, sleepiness, bradycardia, hypotension.

Contraindications: oral monoamine oxidase (MAO) inhibitor users, pediatric age, very low body weight [**4**].

Parasympathomimetics

Local side effects: conjunctival hyperaemia, reduced vision due to accommodative myopia, retinal detachment, lens opacities, precipitation of angle closure, iris cysts.

Systemic side effects: intestinal cramps, headache, bronchospasm.

Contraindications: post-operative inflammation, spastic gastrointestinal disturbances, uveitis, neovascular glaucoma, patient at risk for retinal detachment, peptic ulcer, bradycardia, hypotension, recent myocardial infarction, epilepsy, Parkinsonism [**4**].

New research in prostaglandin analogs

Generalities

The prostaglandin analogs have become the preferred choice for initial therapy.

Since their development in the 1990s, prostaglandin derivates (latanoprost, travoprost, bimatoprost, and tafluprost) have progressively replaced beta-blocker as first-choice therapy because they are the most effective IOP-lowering agents, they lack relevant systemic side effects, and they require only one daily administration [**4**].

The research continues for the improvement of these agents.

Latest studies about prostaglandin analogs

It is known that cyclodextrins (CDs) can form complexes with hydrophobic drugs, influencing their stability, availability, solubility, and tolerance.

A variety of CDs were screened and the most appropriate CD for the formulation of latanoprost for an ocular topical application was selected. PropylaminoβCD was demonstrated to have the best trade-off between latanoprost stability and availability. It formed a complex

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involving the ester group of latanoprost providing protection to its ester bond, while ensuring proper latanoprost solubilization.

In vivo experiments demonstrated that the latanoprost-propylaminoβCD formulation led to lower ocular irritation than the commercial latanoprost formulation used as a reference [**8**].

Comparing bimatoprost 0.01% with bimatoprost 0.03% showed no differences in lowering IOP between the two agents. Patients who were given bimatoprost 0.01% showed a lower rate of side effects, a reduced rate of conjunctive hyperaemia with 65% and a better adherence to treatment [**14**].

Preservative free prostaglandin analogs

Recently, a number of generics, preservative-free and BAK (benzalkonium chloride) -free prostaglandin formulation have entered the glaucoma market.

Preservatives are substances that prevent contamination of the solution during usage and facilitate the diffusion of drugs through ocular surfaces. The most common preservative used in glaucoma drugs is BAK. However, its use is known to be associated with side effects on the ocular surface.

The preservatives used in antiglaucoma drugs are the following:

- quaternary ammonium salts (BAK, Poliquad)
- mercury derivatives (thimerosal)
- oxidative complexes (sodium perborate, oxychloro complex)
- amidines (chlorhexidine)
- molecular tampon ionic system (SofZia)
- alcohols (chlorobutanol, phenylethanol).

Clinical studies have now demonstrated that preservative-free formulations of antiglaucoma medications have the same efficacy as preserved formulations, achieving equivalent reductions of intraocular pressure, with fewer side effects on ocular surface [**9**].

Current substances available without preservative are the following: timolol, betaxolol, carteolol, dorzolamide, travoprost, latanoprost, tafluprost. The BAK-free fixed combination on the market is travoprost + timolol (DuoTrav).

The first $PGF_{2\alpha}$ analogue with a preservative-free formulation is tafluprost 0.0015%. Tafluprost demonstrated more potent fluoroprostaglandin (FP)-receptor binding than latanoprost and reduced IOP to a greater extent than latanoprost and was well tolerated [**10**].

Travoprost BAK-free was released. These formulations are preserved with Sofzia™, an oxidizing agent that contains borate, zinc and sorbitol, which provides an antimicrobial effect through a proprietary formulation of several buffering agents or with Polyquad, a detergent-type preservative. Compared with travoprost 0.004% with BAK, travoprost 0.004% BAK-free proved to be equivalent in both safety and efficacy [**11**].

A study comparing the status of the ocular surface, as documented by TBUT (tear break-up time), corneal staining and OSDI (ocular surface disease index), in patients switching from latanoprost with BAK to travoprost without BAK concluded that BAK, a common preservative for glaucoma drops, may increase OSDI by disrupting the tear film and increasing conjunctival inflammation. A change to a non-BAK-preserved PGA resulted in a measurable improvement of TBUT, corneal staining and OSDI and also a reduction in toxicity [**12-15**].

New research in beta-receptor antagonist agents

Generalities

Although the discovery of prostaglandin agents was an important step in the treatment of glaucoma, research for improving beta-receptor antagonists, continues.

Preservative free beta-receptor antagonists agents

Preservative-free betaxolol was studied to evaluate ocular surface changes in patients with primary open-angle glaucoma (POAG) as well as the hypotensive effect. The study proved preservative-free betaxolol to be safe and efficient in the treatment of glaucoma [**16**].

It is known that beta-blockers have the potential to be systemically absorbed, which may cause adverse cardiovascular effects. A study was conducted to determine whether the initiation of ophthalmic timolol was associated with an increased risk of hospitalization for bradycardia. The risk of bradycardia was significantly increased in the 31-180 days after timolol initiation. No increased risk was

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observed in the first 30 days or beyond 180 days of continuous exposure.

The study concluded that the use of timolol might lead to bradycardia. The patients should be closely monitored after treatment initiation with topical nonselective beta-blocker eye drops [**17**].

Fixed combinations

Generalities

When a patient does not respond to monotherapy, the use of multiple topical treatments may jeopardize adherence to treatment. Therefore, when available, a fixed combination is preferable.

Currently, all fixed combinations available in Europe contain a beta-blocker agent. Knowing the side effects of beta-blockers, patients with serious cardiopulmonary diseases must be excluded before prescribing fixed combinations [**4**].

Existing fixed combinations:

- prostaglandin analogs (PG) and beta-blockers (BB): travoprost + timolol (DuoTrav), latanoprost + timolol (Xalcom, Xaloptic Combi), bimatoprost + timolol (Ganfort)

- carbonic anhydrase inhibitor and BB: dorzolamide + timolol (Cosopt), brinzolamide + timolol (Azarga)

- parasympathomimetics + BB: pilocarpine + timolol (Fotil)

- alpha -2 selective adrenergic agonists and BB: brimonidine + timolol (Combigan).

Recently, new fixed combinations have been submitted to EMEA (European Medicines Agency): a combination containing a carbonic anhydrase inhibitor (brinzolamide 1.0%) and an alpha 2 adrenergic receptor agonist (brimonidine tartrate 0.2%) (SIMBRINZA®) and a combination of tafluprost 0.0015% and timolol 0.5% (TAPCOM®).

Latest studies about fixed combinations

The direct comparison between a fixed combination of bimatoprost-timolol and travoprost-timolol showed no significant difference in lowering IOP. Both fixed combinations had no significant effect on conjunctiva hyperaemia. Patients on travoprost-timolol fixed combination had significantly less superficial punctuate keratopathy. However, bimatoprost-timolol fixed combination produced additional IOP lowering in patients previously treated with non-fixed combination of latanoprost and timolol [**20**].

Transition to fixed-combination travoprost 0.004%/ timolol 0.5% preserved with polyquaternium-1(polyquad) in patients with insufficient response to bimatoprost 0.03%/ timolol 0.5% preserved with benzalkonium chloride proved to be effective in significantly reducing IOP [**21**].

Anti-VEGF agents in the treatment of neovascular glaucoma

Generalities

Neovascular glaucoma (NVG) is a group of secondary angle closure glaucoma which led by a variety of diseases that have anoxia or ischemia to the retina. Some studies have found that the etiology was related to the vascular endothelial growth factor (VEGF) [**22**].

The role of antivascular endothelial growth factor (anti-VEGF) agents in treating various ophthalmic diseases is currently being investigated. Many advances have been made in order to understand the way anti-VEGF agents work and when to implement them clinically for neovascular glaucoma.

Their use leads to regression of iris and angle neovascularization, intraocular pressure control when the angle remains open and prompts symptomatic improvement. In addition, research of anti-VEGF agents has revealed a dose-dependent inhibition of fibroblast proliferation.

Through future research, the antiangiogenic and anti-fibroblast properties of anti-VEGF agents might prove beneficial in patients treated for various forms of glaucoma [**23**].

Latest studies about anti-VEGF agents in neovascular glaucoma

The efficacy and safety of intravitreal bevacizumab (IVB) in the treatment of neovascular glaucoma (NVG) is a subject of current research.

Studies concluded that the use of bevacizumab might be effective in manipulating

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growth factors in the anterior chamber. It could serve as a first line treatment for NVG. Also it seemed to reduce iris neovascularization. Clinical trials are needed to confirm these results before its use is authorized [**24,25**].

Aflibercept was also considered for the treatment of neovascular glaucoma. Intravitreal aflibercept resulted in rapid regression of neovascularization of the iris and angle (NVI and NVA) and stable or reduced IOP. These results suggested that intravitreal aflibercept might be an effective treatment for stage 1 and 2 NVG, resulting in rapid and sustained regression of NVI and NVA and control of IOP [**26**].

Generic drugs

Generic drugs have been of interest lately. Per FDA requirements, generic drugs must have the same active ingredients, strength, dosage forms, labeling, indications, and routes of administration as the corresponding branded drugs. Also, the FDA mandated that generic drugs are bioequivalent to branded drugs, meaning that the amount of absorption of a generic drug must be within a certain range relative to the branded drug. Currently, there has been an economic push for generic drugs to be the preferred drug of choice given the financial relief provided by these compared to branded drugs [**18**].

Based on clinical experience, the doctor is the one who decides if a patient should be treated with generic drugs or the original molecule.

Given that cost can significantly determine adherence, switching patients to generic medications might help improve patients' drug-regimen adherence (by 28%). Lower co-pay was associated with improved adherence after generic drug's introduction [**19**].

However, the efficacy and tolerability of generics was not well studied and some clinical studies showed inconsistent results depending on the type of the generic drug.

Neuroprotection

Generalities

Visual field loss in glaucoma is due to death of retinal ganglion cells. Neuroprotection (reducing or slowing down the loss of ganglion cells in glaucoma) appears to be the only way forward.

Experimental data showed that patients are more likely to benefit from neuroprotectants in diseases in which the neurons die slowly, such as in glaucoma, than in a disease in which the death of a set of neurons is rapid.

If a neuroprotectant can be administered in such a way that it reaches the retina in appropriate amounts, with insignificant side effects, it is likely to attenuate ganglion cell death and thus the glaucoma patient will benefit from this.

Latest studies about neuroprotection

A lot of studies focused on Rho kinase inhibitors as promising therapeutics in neuroprotection and neuroregeneration. Rho-associated coiled-coil forming protein kinase (ROCK) inhibitors have the potential to become very prominent drugs for future glaucoma treatment. Their field of action in the eye is not restricted to IOP reduction by targeting the trabecular meshwork or improving filtration surgery outcome. Progress has been made in elucidating their ability to improve ocular blood flow, to prevent retinal ganglion cells (RGC) death, increase RGC survival and to slow down axonal degeneration or induce proper axonal regeneration [**27,28**].

Irbesartan, an angiotensin II blocker was studied as a possible retinal ganglion cell neuroprotector in an ex vivo retinal explant model. Irbesartan (10 μM) almost doubled ganglion cell survival after four days, contrary to angiotensin II (2 μM) reducing cell survival by 40%. The study concluded that angiotensin II blockers protect retinal ganglion cells in this model and may be worth further investigation as a neuroprotective treatment in models of eye disease [**29**].

Ghrelin was also studied for possible antioxidant and neuroprotective effects on the retina in an experimental glaucoma model. Immunohistochemistry staining of retinas for glial fibrillary acidic protein (GFAP), S-100 and vimentin expression showed that in the ghrelin group, apoptosis and expression of GFAP, S-100 and vimentin was significantly lower than in the vehicle control group.

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This study suggested that ghrelin had antioxidant and neuroprotective effects on the retina in an experimental glaucoma model. Further studies are needed to back these findings [**30**].

Another drug with potential neuroprotective effects is edaravone. Studies showed that the neuroprotective activity of edaravone was found to be more influential by administration at the start of the glaucoma process [**31**].

Other agents are still studied: memantine, calcium channel blockers, Gingko biloba derivatives.

New methods for drug delivery in glaucoma patients

Generalities

Ocular drug transport barriers pose a challenge for drug delivery: the ocular surface epithelium, the tear film and internal barriers of the blood-aqueous and blood-retina barriers. Traditional drug administration reduces the clinical efficacy especially for poor water-soluble molecules and for the posterior segment of the eye.

Durasert is a fully bioerodible, long-term, sustained release implant delivering latanoprost. The product is designed to be administered by an eye care professional into the subconjunctival space of the eye in a minimally invasive procedure. The effect lasts from 3 to 6 months. The implant solves the problems of non-compliance and the inability to administer the drops [**34**].

Nanoparticles (NPs) have been designed to overcome the ocular barriers, increase the drug penetration at the target site and prolong the drug levels by fewer drug administrations in lower doses without any toxicity compared to the conventional eye drops.

Drug delivery systems have the potential to improve patient adherence, reduce side effects, increase efficacy, and preserve sight for glaucoma patients. Mucus-penetrating particle topical administration nanotechnology could improve the effectiveness of approaches for glaucoma [**32**].

Latest studies about drug delivery methods

Hybrid polyamidoamine (PAMAM) dendrimer hydrogel/ poly (lactic-co-glycolic acid) (PLGA) nanoparticle platform (HDNP) for codelivery of two traditional antiglaucoma drugs brimonidine and timolol maleate showed no cytotoxic effect and prolonged residence time with slowly released period thus enhancing drug bioavailability in glaucoma treatments [**32,33**].

Formulation of dorzolamide hydrochloride and methazolamide-loaded solid lipid NPs (SLN) in a nanoemulsion form offers a more intensive treatment of glaucoma, a decrease in the number of applications per day and a better patient compliance compared to conventional eye drops [**32,35,36**].

A study about nanoliposome drug delivery system for the longer-term delivery of latanoprost was published to establish the safety and efficacy of a single subconjunctival injection of nanoliposomal latanoprost in subjects with a diagnosis of either ocular hypertension (OHT) or primary open-angle glaucoma (POAG).

A clinically and statistically significant IOP reduction (≥20 % IOP reduction) was observed through 3 months after injection. The nanomedicine reported in this study is the first nanocarrier formulation that has an extended duration of action in humans, beyond a couple of weeks. The findings opened up a new treatment modality, which will greatly enhance patient compliance and improve treatment outcomes [**37**].

Other means of improving drug delivery were also studied.

Recently, a study was published on the effect of the dinucleotide P(1), P(4)-Di (adenosine-5') tetraphosphate (Ap4A) in improving adrenergic anti-glaucomatous delivery by modifying the tight junction proteins of the corneal epithelium.

The study concluded that, when Ap4A was topically applied two hours before the adrenergic compounds, the concentration of brimonidine or timolol in the aqueous humour increased, producing a more profound effect on IOP. Therefore, Ap4A treatment resulted in a better entrance of adrenergic anti-glaucomatous compounds within the eye and improved

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therapeutic efficiency by increasing corneal epithelial barrier permeability [**38**].

Melatonin agonist– agomelatine

Agomelatine is an agonist of melatonin that is used in the treatment of major depressive disorders. A study addressing for the first time agomelatine effects on the IOP of patients affected by POAG was published. An ability to decrease IOP in experiment animals and in normal human subjects was shown.

Given orally, Agomelatine showed a significant hypotonising effect, stably decreasing IOP roughly by 30% of the enrolment value after 15 and 30 days of treatment [**39**].

Angiotensin and bradykinin system axes

Recently discovered, novel IOP-lowering agents that pertain to the renin-angiotensin and kallikrein-kinin axes offer new means of treating and controlling ocular hypertension (OHT).

A study presenting the properties and actions of diminazene aceturate (DIZE; a novel angiotensin-converting enzyme-2 activator) and FR-190997 (a non-peptide bradykinin receptor-2 agonist) was published in relation to their anti-OHT activities in rodent and respectively in cynomolgus monkey eyes. It is anticipated that these compounds will pave the way for future discovery, development, and marketing of novel drugs to treat glaucoma and thus help save sight for millions of people affected by this slow progressive optic neuropathy [**40**].

Gene therapy in glaucoma

Generalities

Glaucoma is a chronic progressive disease for which the ideal treatment would provide a localized long-lasting therapy with minimal side effects. A gene therapy approach in which a mutated gene is replaced or inactivated, or in which a new gene is introduced, could provide a novel and more effective way of targeting the disease.

Latest studies about gene therapy

Using viral and nonviral vector gene delivery systems to target specific tissues involved in the pathogenesis of glaucoma, possible gene therapy targets were identified: trabecular meshwork, ciliary body, ciliary epithelium, Müller cells, and retinal ganglion cells [**41**].

Three genes involved in the pathogeny of glaucoma were identified: the myocilin gene (MYOC), optineurin gene (OPTN) and WD repeat domain 36 (WDR36).

Mutations in the myocilin gene cause autosomal dominant juvenile primary open-angle glaucoma and approximately 3% of cases of adult-onset open-angle glaucomas.

A recently described causative gene for normal-tension glaucoma, optineurin (optic neuropathy-inducing protein) is another potential target and additional targets are likely to be identified.

Four basic notions should be met by any genetic therapy targeted to an ocular disease: an efficient and nontoxic gene delivery technique, sufficient knowledge of the genetic basis of the disease to select an appropriate therapeutic approach, proper control of the expression of the therapeutic gene and the availability of an animal model of the disease for preclinical testing. Glaucoma is a disease in which some of these conditions can be met [**42**].

Stem cells and ocular tissue regeneration

Stem cells, including putative resident eye stem cells, mesenchymal stem cells, embryonic stem cells, and induced pluripotent stem cells have been investigated for their potential in various eye-specific pathologies to replace the loss of retinal ganglion cells and photoreceptors in retinal degenerative diseases and toward engineering transplantable patient-specific cornea or lenses.

Studies show that different stem cell types have distinct capacities to produce eye-specific cells or even the entire retina [**43**].

Stem cells research offers great hope for treating various eye pathologies. However, there are many challenges ahead before the era of stem cell-based therapy in the eye truly arrives.

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Conclusions

Glaucoma is an optic neuropathy characterized by retinal ganglion cell death and axonal loss. It remains a major cause of blindness worldwide. All current modalities of treatment are focused on lowering the intraocular pressure. However, it is clear that a significant number of glaucoma patients show disease progression despite the pressure lowering treatments.

As the market developed, generic drugs appeared, providing corresponding efficacy (but not enough studied) as the original molecule at a lower price.

To reduce side effects on the ocular surface, preservative-free drugs entered the market. Studies proved them as effective as their predecessors in lowering the IOP.

To improve adherence to treatment, fixed combinations were developed. Current fixed combinations available contain a beta-receptor antagonist. Given the systemic side-effects of beta blockers, patients with serious cardiopulmonary diseases cannot receive such therapy.

The role of antivascular endothelial growth factor (anti-VEGF) agents in treating various ophthalmic diseases is currently being investigated. Studies concluded that intraocular injections of anti-VEGF agents reduce iris neovascularization and lowers IOP in patients with neovascular glaucoma.

Much attention has been given to the development of neuroprotective treatment strategies and gene therapy, but the identification of such has been difficult by lack of understanding of the etiology of glaucoma.

Methods to improve drug delivery have also been studied. Nanoparticles have the potential to revolutionize drug delivery, thus increasing adherence to treatment, diminishing the possibility of side-effects and prolonging actual effects.

Studies have focused on other potentially new antiglaucoma agents such as agomelatine (an agonist of melatonin), diminazene aceturate (a novel angiotensin-converting enzyme-2 activator), FR-190997 (a nonpeptide bradykinin receptor-2 agonist), and stem cells. It is anticipated that these compounds will pave the way for future discovery, development, and marketing of novel drugs to treat glaucoma and thus help save sight for millions of people afflicted with this slow progressive optic neuropathy.

References

1. American Academy of Ophthalmology. The Eye M.D. Association, Glaucoma, section 10, 2011-2012.
2. Lang Gerhard K. Ophthalmology-a short textbook, 2000, Thieme Stuttgart, New York.
3. Venkatesh Prana N. Aravind FAQs in Ophthalmology, 2013, Jaypee-Highlights Medical Publishers, INC.
4. European Glaucoma Society, Terminology and guidelines for glaucoma, 4th edition, 2014.
5. Maier P, Funk J, Schwarzer G, Antes G, Falck-Ytter Y. Treatment of ocular hypertension and open angle glaucoma: meta-analysis of randomised controlled trials. 2005.
6. World Glaucoma Congress. 2013, Vancouver.
7. Yanoff M, Duker J. Ophthalmology, fourth edition, 2014, Elsevier Saunders.
8. Rodriguez-Aller M, Guinchard S, Guillarme D, Pupier M, Jeannerat D, Rivara-Minten E, Veuthey JL, Gurny R. New prostaglandin analog formulation for glaucoma treatment containing cyclodextrins for improved stability, solubility and ocular tolerance. Eur J Pharm Biopharm. 2015 May 8.
9. Louati Y, Shaarawy T. Controversy: Is Benzalkonium Chloride Necessary in Antiglaucoma Drops?, 10.5005/jp-journals-10008-1115.
10. Hamacher T, Airaksinen J, Saarela V, Liinamaa MJ, Richter U, Ropo A. Efficacy and safety levels of preserved and preservative-free tafluprost are equivalent in patients with glaucoma or ocular hypertension: results from a pharmacodynamics analysis. Acta Ophthalmologica. September 2008; 86, 14-19.
11. Lewis RA, Katz GJ, Weiss MJ et al. Travoprost BAC-free Study Group Travoprost 0.004% with and without benzalkonium chloride: a comparison of safety and efficacy. J Glaucoma. 2007; 16:98–103.
12. Horsley M, Kahook MK. Effects of prostaglandin analog therapy on the ocular surface of glaucoma patients. Clin Ophthalmol. 2009; 3: 291–295.
13. Yee RW, Norcom EG, Zhao XC. Comparison of the relative toxicity of travoprost 0.004% without benzalkonium chloride and latanoprost 0.005% in an immortalized human cornea epithelial cell culture system. Adv Ther. 2006; 23:511–519.
14. Kahook M, Noecker R. Comparison of corneal and conjunctival changes after dosing of travoprost preserved with *Sof*Zia, latanoprost with 0.02% benzalkonium chloride, and preservative-free artificial tears. Cornea. 2008; 27:339–343.
15. Katz et al. Am J Ophthalmol. 2010; 149:661–71.
16. Onischenko AL, Dimaksyan MV, Kolbasko AV, Zilina NM. Preservative-free betaxolol for POAG patients: evaluation of hypotensive effect and ocular surface safety. Vestn Oftalmol. 2015 Mar-Apr; 131(2):76-80.

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17. Pratt NL, Ramsay EN, Kalisch Ellett LM, Nguyen TA, Roughead EE. Association between Ophthalmic Timolol and Hospitalisation for Bradycardia. J Ophthalmol. 2015; 2015:567387.
18. Zore M, Harris A, Tobe LA et al. Generic medication in ophthalmology. Br. J Ophthalmol. 2013; 97:253-257.
19. Stein JD, Shekhawat N, Talwar N, Balkrishnan R. Impact of the introduction of generic latanoprost on glaucoma medication adherence. Ophthalmology. 2015 Apr; 122(4):738-47.
20. Lee MY, Teh NC, Nur Zulekha M, Thayanithi S, Jelinar MN, Rizal AM, Arfah W. The Effects of Fixed Combination of Bimatoprost-Timolol and Travoprost-Timolol on Intraocular Pressure in Patients With Primary Open-Angle Glaucoma or Ocular Hypertension, Previously on Nonfixed Combination of Latanoprost and Timolol. Asia Pac J Ophthalmol (Phila). 2012 Jul-Aug; 1(4):208-12.
21. Schnober D, Hubatsch DA, Scherzer ML. Efficacy and safety of fixed-combination travoprost 0.004%/ timolol 0.5% in patients transitioning from bimatoprost 0.03%/ timolol 0.5% combination therapy. Clin Ophthalmol. 2015 May 7; 9:825-32.
22. Jia X, Duan X. Application of anti-VEGF agents in treatment of neovascular glaucoma and anti-scarring in filtering surgery. Zhonghua Yan Ke Za Zhi. 2015 Apr; 51(4):314-8.
23. Horsley MB, Kahook MY. Anti-VEGF therapy for glaucoma. Current Opinion in Ophthalmology. March 2010; 21, 2:112–117.
24. Martínez-Carpio PA, Bonafonte-Márquez E, Heredia-García CD, Bonafonte-Royo S. Efficacy and safety of intravitreal injection of bevacizumab in the treatment of neovascular glaucoma: systematic review. Archivos de la Sociedad Espanola de Oftalmologia. 2008; 83(10):579-588.
25. Yazdani S, Hendi K, Pakravan M, Mahdavi M, Yaseri M. Intravitreal Bevacizumab for Neovascular Glaucoma: A Randomized Controlled Trial. Journal of Glaucoma. October/ November 2009; 18, 8:632-637.
26. SooHoo JR, Seibold LK, Pantcheva MB, Kahook MY. Aflibercept for the treatment of neovascular glaucoma. Clin Experiment Ophthalmol. 2015 May 28.
27. Van de Velde S, De Groef L, Stalmans I, Moons L, Van Hove I. Towards axonal regeneration and neuroprotection in glaucoma: Rho kinase inhibitors as promising therapeutics. Prog Neurobiol. 2015 Jun 17. pii: S0301-0082(15)00060-X.
28. Tanihara H, Inoue T, Yamamoto T, Kuwayama Y, Abe H, Suganami H, Araie M. Additive Intraocular Pressure-Lowering Effects of the Rho Kinase Inhibitor Ripasudil (K-115) Combined With Timolol or Latanoprost: A Report of 2 Randomized Clinical Trials. JAMA Ophthalmol. 2015 Apr 16.
29. White AJ, Heller JP, Leung J, Tassoni A, Martin KR. Retinal ganglion cell neuroprotection by an angiotensin II blocker in an ex vivo retinal explant model. J Renin Angiotensin Aldosterone Syst. 2015 Jan 26.
30. Can N, Catak O, Turgut B, Demir T, Ilhan N, Kuloglu T, Ozercan IH. Neuroprotective and antioxidant effects of ghrelin in an experimental glaucoma model. Drug Des Devel Ther. 2015 Jun 2; 9:2819-29.
31. Aksar AT, Yuksel N, Gok M, Cekmen M, Caglar Y. Neuroprotective effect of edaravone in experimental glaucoma model in rats: a immunofluorescence and biochemical analysis. Int J Ophthalmol. 2015 Apr 18; 8(2):239-44.
32. Zhou H, Hao JL, Wang S, Zheng Y, Zhang WS. Nanoparticles in the ocular drug delivery. Int J Ophthalmol. 2013; 6(3): 390–396.
33. http://www.psivida.com/products-durasert.html.
34. Yang H, Tyagi P, Kadam RS, Holden CA, Kompella UB. Hybrid Dendrimer hydrogel/ PLGA nanoparticle platform sustains drug delivery for one week and antiglaucoma effects for four days following one-time topical administration. ACS Nano. 2012; 6(9):7595–7606.
35. Li R, Jiang S, Liu D, Bi X, Wang F, Zhang Q, Xu Q. A potential new therapeutic system for glaucoma: solid lipid nanoparticles containing methazolamide. J Microencapsul. 2011; 28(2):134–141.
36. Ammar HO, Salama HA, Ghorab M, Mahmoud AA. Nanoemulsion as a potential ophthalmic delivery system for dorzolamide hydrochloride. AAPS Pharm Sci Tech. 2009; 10(3):808–819.
37. Wong TT, Novack GD, Natarajan JV, Ho CL, Htoon HM, Venkatraman SS, Nanomedicine for glaucoma: sustained release latanoprost offers a new therapeutic option with substantial benefits over eyedrops, Drug Deliv Transl Res. 2014 Aug;4(4):303-9
38. Loma P, Guzman-Aranguez A, Perez de Lara MJ, Pintor J. Diadenosine tetraphosphate improves adrenergic anti-glaucomatous drug delivery and efficiency. Exp Eye Res. 2015 May; 134:141-7.
39. Pescosolido N, Gatto V, Stefanucci A, Rusciano D. Oral treatment with the melatonin agonist agomelatine lowers the intraocular pressure of glaucoma patients. Ophthalmic Physiol Opt. 2015 Mar; 35(2):201-5.
40. Sharif NA. Novel potential treatment modalities for ocular hypertension: focus on angiotensin and bradykinin system axes. J Ocul Pharmacol Ther. 2015 Apr; 31(3):131-45.
41. Demetriades AM. Gene therapy for glaucoma. Curr Opin Ophthalmol. 2011 Mar; 22(2):73-7.
42. Borrás T, Brandt CR, Nickells R, Ritch R. Gene Therapy for Glaucoma: Treating a Multifaceted, Chronic Disease. Invest. Ophthalmol. Vis. Sci. 2002; 43(8):2513-2518.
43. Liu Y, Wang J, Luo Y, Chen S, Lewallen M, Xie T. Stem Cells and Ocular Tissue Regeneration, Asia Pac J Ophthalmol (Phila). 2013 Mar-Apr; 2(2):111-8.

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