ARTYKUŁ PRZEGLĄDOWY REVIEW ARTICLE

DOI: 10.24292/01.OT.200323.1

Glaucoma – new possibilities, new research

Dorota Szumny[1, 2], Małgorzata Mulak[2, 3]

[1] Chair and Department of Pharmacology, Medical University of Wroclaw
Head: Prof. Adam Szeląg, MD, PhD

[2] Department of Ophthalmology, University Clinical Hospital in Wroclaw
Head: Prof. Marta Misiuk-Hojło, MD, PhD

[3] Department and Clinic of Ophthalmology, Wroclaw Medical University
Head: Prof. Marta Misiuk-Hojło, MD, PhD

HIGHLIGHTS

The paper describes new drugs for the treatment of glaucoma that have been introduced and therapies that are currently being investigated.

ABSTRACT

Research efforts to develop effective and safe antiglaucoma drugs have been ongoing for many years. The cornerstone of treatment is still baroprotection, as this is virtually the only method available to protect the optic nerve and slow glaucoma progression, which can be easily controlled by an ophthalmologist. Research is also being conducted in the direction of neuroprotection, where new compounds are being evaluated, as well as those that have been used for years as adjunctive treatments. The greatest hope lies in gene therapy, which still has many problems to be solved, but it is the only one that offers hope for the patient's complete recovery.

Key words: glaucoma, treatment, new drugs, new therapies, neuroprotection, gene therapy

INTRODUCTION

Glaucoma, a multietiologic disease of the optic nerve, has been known for a long time, and research efforts have been ongoing for many years to develop effective and safe antiglaucoma drugs. The cornerstone of treatment is still baroprotection, as this is virtually the only method available to protect the optic nerve and slow progression, which can be easily controlled by an ophthalmologist [1].

The new formulations not only reduce the production of the aqueous fluid and increase the outflow of the aqueous fluid through various pathways, but have a direct effect on the structure of the trabecular meshwork and Schlemm's canal, modeling the shape of the cells through a specific α-actin contained in the smooth muscle trabeculum. Enzymes that regulate the contraction and diastole of the trabecular meshwork include Rho (ROCK) kinase, myosin light chain kinase and phosphatase, adenosine triphosphatase and others [2, 3].

NEW DRUGS

A new, but not entirely novel, drug is **latanoprost bunod**, which is a combination of a long-known prostaglandin (0.024% latanoprost) with a new molecule, which is butanediol mononitrate. The drug (trade name Vyzulta) was approved by the US FDA (Food and Drug Administration) in 2017. The formulation has a two-pronged effect: latanoprost increases the outflow of aqueous fluid through the choroidal-retinal pathway, while butanediol mononitrate, through the release of nitric oxide, causes relaxation of the bead and Schlemm's canal, which improves outflow through the iris-retinal angle.

A relatively new hypotensive drug, albeit registered in Japan as early as 2014, is the Rho kinase inhibitor **ripasudil** (trade name Glanatec). It can be used in all types of glaucoma (primary open-angle glaucoma, angle closure glaucoma, secondary glaucoma), in monotherapy, and in combination with all antiglaucoma drops. It does not cause significant side effects, and allergic conjunctivitis and eyelid margins are rarely observed. However, it should be noted that significant damage to the beading significantly affects the effectiveness of the product, so it is better to use ripasudil in the early stages of glaucoma [4].

Drugs in this group also include **netarsudil**, registered by the FDA in 2017, which consists of two inhibitors: Rho (ROCK) kinase and norepinephrine transport (NET) (trade name Rhopressa). The drug has a dual action; inhibition of Rho kinase results in relaxation of the trabecular mucosa, which facilitates the outflow of the aqueous humor through the conventional route, and blockade of norepinephrine transport results in reduced production of the aqueous humor. Drops are used once daily; at higher doses, there is a possibility of cross-reactivity with other kinase enzymes, increasing the risk of side effects. A combination formulation of netarsudil and latanoprost is being studied.

Clinical trials are also underway on other formulations such as the bead-modulating selective adenosine A_1 receptor agonist, **trabodenoson**, which increases secretion and activates metalloproteinases (MMPs), thus altering the structure of the trabeculum and facilitating the outflow of the aqueous fluid through the angle of seepage. The clinical trial also includes work on the combination of trabodenoson with latanoprost [5].

Currently (early 2023), **in phase III clinical trials**, for glaucoma, the following are being evaluated among the compounds known to date: metformin (neuroprotection), nicotinamide, *Ginkgo biloba*, α-tocopherol, sildenafil, memantine, glatiramer acetate (neuroprotection), trabodenoson [6].

NEW DRUG DELIVERY ROUTES

Other forms of drug application are also in the spotlight, such as depot formulations, subconjunctival polymers, or subconjunctival, periocular, or intravitreal injections of drug microparticles administered to different locations, such as around the ciliary body or closer to the retina. These new methods could allow for a gradual, slow release of the drug, without the need for daily drop applications [7, 8].

NEUROPROTECTION

In addition to reduction in intraocular pressure, a trend in glaucoma therapy is neuroprotection. The problem with restoration of the optic nerve is related to its histological properties. Peripheral nerves have a myelin sheath composed of lemocytes (Schwann cells), which allow them to regenerate, while nerve II is surrounded by a myelin sheath composed of oligodendrocytes, which do not have this ability [9–11].

One preparation that may play a neuroprotective role is **citicoline** (CDP-choline), a natural component of living organisms and a precursor to phosphadiocholine (a cell membrane phospholipid). It is a compound that has long been used in neurology as an adjunct therapy for stroke or Parkinson's disease. Citicoline exhibits protective effects: inhibits the release of free fatty acids from nerve cell phospholipids, increases the concentration of the antiapoptotic protein bcl-2 in the retina, and protects against the toxic effects of glutamate. Neuroscientists take advantage of its ability to increase the concentration of neurotransmitters such as dopamine, norepinephrine, and serotonin. The neuroprotective effects of citicoline have also been demonstrated in glaucoma, in vivo, and in vitro studies [12, 13].

Rejdak et al. performed experimental studies in rats with damaged optic nerves; animals were intraperitoneally ap-

plied with citicoline and then, the status of retinal ganglion cells (RGCs) was assessed. Animals treated with citicoline showed less loss of ganglion cells compared to the control group [14].

Studies in recent years have shown the usefulness of this compound in the treatment of optic nerve diseases, including glaucoma, as beneficial effects of intramuscular and oral supplementation have been shown on the parameters of visual evoked potentials (decrease in latency and increase in amplitude) and on the parameters of visual field and electrophysiological tests (VEP). The recommended dose is 500 to 2,000 mg per day. Ganglion cells are also positively affected by citicoline in drops, as studies in experimental animals have shown that, when administered topically, it penetrates the vitreous body, with the carrier being macromolecular hyaluronic acid. The available citicoline drops (Citogla VIS) contain 0.075% hyaluronic acid and 2% citicoline in a liposomal solution (citicoline carrier) [13].

Neuroprotection – experimental therapies

Among various strategies with potential neuroprotective effects, substances such as glutamate antagonists, e.g. memantine; *Ginkgo biloba* extract; neurotrophic factors, e.g. BDNF (brain-derived neurotrophic factor) and CNTF (ciliary neurotrophic factor); calcium channel blockers, e.g. nimodipine; antioxidants, e.g., natural flavonoids, coenzyme Q10; α_2 adrenergic receptor agonists, e.g., brimonidine; nitric oxide synthase inhibitors; drugs that affect blood vascular flow used as antiglaucoma drugs; and stem cell transplantation to protect retinal ganglion cells [15].

Other points of grip are also sought for nerve protection. The HuR RNA-binding regulatory protein (the so-called "immortality protein") has been identified in ganglion cells, which is responsible for normal retinal function and determining endogenous neuroprotection. The RNA binding protein, HuR, modulates mRNA processing and gene expression of several stress response proteins. Decreased levels of this protein have been found in patients with primary open-angle glaucoma and in rats with induced glaucoma. It appears that increasing HuR protein levels can significantly slow the progression of glaucoma [16].

Researchers face various difficulties. In addition to new potentially therapeutic substances, they are working to improve research methods so that new therapies can be applied in clinical settings. Researchers from Upper Silesia have proposed a novel therapy. They evaluated the use of Schwann cells, extracted from the sciatic nerves of rats, in in vitro studies and in animal models. Specially prepared Schwann cells were injected into the vitreous body, achieving positive effects: neuroprotective effects and stimulation of ganglion cell regeneration. The new method eliminates some of the barriers to precursor cell transplantation and allows the observation of direct neuroprotective and regenerative effects in glaucoma without additional modifications to the transplanted cells [17].

EXPERIMENTAL GENE THERAPY

Gene therapies in ophthalmology are no longer a novelty. Several ocular gene therapies have already been developed in the laboratory and have been put into clinical trials for patients. In December 2017 FDA approved the first viral ocular gene therapy: voretigene neparvovec (Luxturna™, Spark Therapeutics, Inc.) for the treatment of two forms of inherited retinal dystrophies (pigmentary retinopathy and Leber congenital blindness) [18].

Gene therapy involves inserting, deleting, or altering genetic material within cells to repair or compensate for loss of gene function. By altering the genetic material, it is possible to increase the production of proteins that will fight the disease, or even produce new proteins to do so.

Gene therapy can address genetic risk factors by replacing or silencing defective genes that contribute to the development and progression of glaucoma. It can also enable cells in the eye to continuously produce drugs, thus replacing the need for daily use of eye drops with a particular therapeutic substance [19].

To achieve a therapeutic effect, genetic material, such as DNA or RNA, is injected into the eye. One common and effective way to administer this material is through the use of viral particles or vectors that transfer the genetic material to the cells of interest. Cells can also be harvested or processed from stem cells, subjected to gene therapy in a lab dish, and then injected into the eye. Among the used viral vectors there are retroviruses, adenoviruses and adeno-associated virus, while the nonviral vectors used are DNA material, such as liposomes or naked DNA, and protein vectors, such as cell therapy [19].

Gene therapy has the advantage of being able to specifically target known disease mechanisms and cells and the prospect that a single administration will result in a long-lasting therapeutic effect and possibly a cure. By injecting a gene therapy vector directly into the eye, treatment achieves the desired goal more effectively than with eye drops or oral medications. The eye organ is ideal for gene therapy because it forms a separate compartment where inflammation is relatively muted compared to other organs [18].

Potential gene therapy strategies in glaucoma

The most promising gene therapy strategies being developed for the treatment of glaucoma include lowering eye pressure by increasing the drainage of the aqueous fluid or decreasing its production. Increased drainage through the aqueous fluid outflow pathways could be achieved by injecting the gene therapy vector into the anterior chamber,

while decreased production could be achieved by injecting into the vitreous body chamber [3].

Gene therapy in glaucoma is being studied in: animals (mice, rats, rabbits, monkeys), human glaucomatous reticular cell lines and humans. Genes currently under evaluation include p27KIP1, RhoA, GFP/LacZ, CMV, WPRE, MMP-3, C3 transferase, RhoA, $P2Y_2$ receptor, β_2-adrenergic receptor [7]. In a paper published by 'Nature' in 2022, researchers evaluated a gene therapy aimed at permanently lowering intraocular pressure through de novo biosynthesis of prostaglandin F2α within the anterior chamber. This study showed a dose-dependent reduction in intraocular pressure in normotensive rats for 12 months. Importantly, therapy could be temporarily stopped, resulting in an increase in intraocular pressure. Therapy was well tolerated at low and medium doses, with no major adverse effects on the anterior chamber. Success in human trials could be an alternative to current treatment strategies, leading to a reduction in intraocular pressure without the need to follow a daily treatment regimen [20].

Matrix metalloproteinases (MMPs) contribute to maintaining the homeostasis of the aqueous outflow through their ability to remodel the extracellular matrix, which has a direct effect on the resistance of the aqueous flow and intraocular pressure. Researchers have observed reduced MMP-3 activity in the aqueous fluid of glaucoma patients. Using a recombinant adenoassociated virus, they were able to affect MMP-3, what resulting in an increase in aqueous fluid and a decrease in intraocular pressure. An in-depth study of MMPs is a direction in the search for treatment in patients who do not respond optimally to conventional pressure lowering drugs [21].

Gene therapy also responds to a neuroprotective strategy in glaucoma. In this case, the viral vector in gene therapy should be injected into the vitreous body chamber, close to the retina. Cells could be prepared in a dish in the lab to enable them to produce neuroprotective drugs and then given to the vitreous body by injection or encapsulated in a capsule implanted in the eye. The latter approach is being tested in a clinical trial for glaucoma: genetically modified cells are contained in an NT-501 capsule (Neurotech Pharmaceuticals, Inc.). Cells in the special capsule continuously release ciliary neurotrophic factor (CNTF), a protein that has been shown to have neuroprotective effects in animal models of glaucoma [8].

CONCLUSION

New treatments for glaucoma offer hope for patients who, despite ongoing treatment, do not stop the progression of lesions, and on the other hand, may become first-line drugs for newly diagnosed glaucoma. Highly specialised procedures, such as gene strategies, make it possible to break the causal chain, however, at this stage these treatments are in the experimental phase. A viable form of modern conservative therapy are the hypotensive and neuroprotective drugs discussed above, which are likely to be widely used in the near future, including in Poland.

CORRESPONDENCE
Dorota Szumny, MD, PhD
Chair and Department of Pharmacology,
Medical University of Wroclaw
50-345 Wrocław, ul. Mikulicza-Radeckiego 2
e-mail: dorota.szumny@umw.edu.pl

ORCID
Dorota Szumny – ID – http://orcid.org/0000-0002-7814-3517
Małgorzata Mulak – ID – http://orcid.org/0000-0003-3598-6693

References

1. Novack GD, Robin AL. Ocular pharmacology. J Clin Pharmacol. 2016; 56(5): 517-27.
2. Wierzbowska J. Terapie eksperymentalne w jaskrze. OphthaTherapy. 2014; 1(4): 239-45.
3. Szumny D. Nowe trendy w farmakoterapii jaskry. OphthaTherapy. 2019; 6(1): 26-9.
4. Kusuhara S, Nakamura M. Ripasudil hydrochloride hydrate in the treatment of glaucoma: safety, efficacy, and patient selection. Clin Ophthalmol. 2020;14: 1229-36.
5. Li G, Torrejon KY, Unser AM et al. Trabodenoson, an adenosine mimetic with A1 receptor selectivity lowers intraocular pressure by increasing conventional outflow facility in mice. Invest Ophthalmol Vis Sci. 2018; 59(1): 383-92.
6. Clinicaltrials.gov. Glaucoma [Available from: https://clinicaltrials.gov/ct2/results?cond=Glaucoma&age_v=&age=1&gndr=&type=&rslt=&phase=2&Search=Apply].
7. Amador C, Shah R, Ghiam S et al. Gene therapy in the anterior eye segment. Curr Gene Ther. 2022; 22(2): 104-31.
8. Miller PE, Eaton JS. Medical anti-glaucoma therapy: Beyond the drop. Vet Ophthalmol. 2021; 24(Suppl 1): 2-15.
9. Schuettauf F, Rejdak R, Thaler S et al. Citicoline and lithium rescue retinal ganglion cells following partial optic nerve crush in the rat. Exp Eye Res. 2006; 83(5): 1128-34.
10. Matteucci A, Varano M, Gaddini L et al. Neuroprotective effects of citicoline in in vitro models of retinal neurodegeneration. Int J Mol Sci. 2014; 15(4): 6286-97.
11. He S, Stankowska DL, Ellis DZ et al. Targets of Neuroprotection in Glaucoma. J Ocul Pharmacol Ther. 2018; 34(1-2): 85-106.
12. Parisi V, Oddone F, Ziccardi L et al. Citicoline and retinal ganglion cells: effects on morphology and function. Curr Neuropharmacol. 2018; 16(7): 919-32.
13. Parisi V, Oddone F, Roberti G et al. Enhancement of retinal function and of neural conduction along the visual pathway induced by treatment with citicoline eye drops in liposomal formulation in open angle glaucoma: a pilot electrofunctional study. Adv Ther. 2019; 36: 987-96.
14. Rejdak R, Toczołowski J, Kurkowski J et al. Oral citicoline treatment improves visual pathway function in glaucoma. Medical Science Monitor. Med Sci Monit. 2003; 9(3): PI24-8.
15. Doozandeh A, Yazdani S. Neuroprotection in Glaucoma. J Ophthalmic Vis Res. 2016; 11(2): 209-20.
16. Smedowski A, Liu X, Podracka L et al. Increased intraocular pressure alters the cellular distribution of HuR protein in retinal ganglion cells–a possible sign of endogenous neuroprotection failure. Biochim Biophys Acta Mol Basis Dis. 2018; 1864(1): 296-306.
17. Smedowski A, Liu X, Pietrucha-Dutczak M et al. Predegenerated Schwann cells–a novel prospect for cell therapy for glaucoma: neuroprotection, neuroregeneration and neuroplasticity. Sci Rep. 2016; 6(1): 23187.
18. Komáromy AM. Is Gene Therapy an Option for Glaucoma? [online]. https://www.brightfocus.org/glaucoma/article/gene-therapy-option-glaucoma.
19. Ross AG. Gene Therapy and Glaucoma: An Update [online]. https://www.reviewofophthalmology.com/article/gene-therapy-and-glaucoma-an-update.
20. Chern KJ, Nettesheim ER, Reid CA et al. Prostaglandin-based rAAV-mediated glaucoma gene therapy in Brown Norway rats. Commun Biol. 2022; 5(1): 1169.
21. O'Callaghan J, Crosbie DE, Cassidy PS et al. Therapeutic potential of AAV-mediated MMP-3 secretion from corneal endothelium in treating glaucoma. Hum Mol Genet. 2017; 26(7): 1230-46.

Authors' contributions:
All authors have equal contribution to the paper.

Conflict of interest:
None.

Financial support:
None.

Ethics:
The content presented in the article complies with the principles of the Helsinki Declaration, EU directives and harmonized requirements for biomedical journals.