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Current Therapeutic Approach for Glaucoma

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Abstract

Glaucoma is one of the leading causes of blindness in the world, and its incidence is on the rise. The purpose of this study is to explain current medicinal and surgical therapy trends in open-angle glaucoma care. Over the last decade, the availability of glaucoma drugs has increased, as has the use of laser trabeculoplasty, resulting in a decrease in invasive incisional surgery. Furthermore, a novel type of glaucoma surgery known as micro invasive glaucoma surgery has arisen to bridge the gap between conservative medicinal care and more invasive surgery.

Introduction

Glaucoma is a category of ocular neuropathies characterized by the loss of retinal ganglion cells (RGCs) and their axons form the optic nerve (8). This damage is often caused by abnormally high pressure in your eye. Glaucoma is one of the leading causes of blindness for people over the age of 60. treated by lowering your eye pressure (intraocular pressure). The common process for all kinds of glaucoma is the loss of RGCs and their axons, with typical atrophy and cupping of the optic nerve head, regardless of the underlying cause (ONH). (5) Depending on the situation of the patients, therapy options may include prescription eye drops, oral medications, laser treatment, surgery, or a combination of any of these (23).

Medical therapies: Nowadays, a new therapeutic approach for glaucoma have be discovered for surgeons in recent years. Several different stent implant is coming onto the market, they are consist of different kinds of materials, some are made of titanium, porcine collagen cross-linked with glutaraldehyde, or the biocompatible material SIBS, and new variations based on old techniques such as goniotomy and cyclo-photocoagulation are discovered, which should have a better effect on reduction of intraocular pressure (14). In various conferences and congresses, surgical studies are presented almost exclusively with results that are collected after 3, sometimes after 6, and very rarely after 12 months postoperatively, some of which were carried out without any control groups, some of which were mixed with different kinds of glaucoma groups. And usually, the number of patients in glaucoma mixed groups is different at the beginning and the end during the observation period, From a statistical point of view, they should not be compared with each other. Many of the studies presented do not meet the quality criteria of good scientific work and are more for local political purposes. We have reached a point of surgical activism that is not sufficiently questioned in a company-neutral manner and that simulates expectations of better glaucoma care that are often not met in everyday practice. On the other hand, it has been shown that the timing of the surgical intervention is of fundamental importance in curbing glaucomatous progression. In this case, if the target pressure is not adequately adjusted with medication, the long-term progression prognosis is all the more favorable the earlier surgical intervention is made. The associated positive effects of the surgical interventions are the better limitation of the intraocular pressure fluctuation, the improvement of the patient's drip adherence, and the associated reduction of the eye drop-associated side effects on existing general diseases, e.g. B. Beta-blockers in asthma patients (24) and alpha-2-agonists during antidepressant therapy with monoamine oxidase (MAO) inhibitors. Nevertheless, surgical interventions in ophthalmology play a subordinate role in glaucoma care. In 2019, glaucoma surgeries including laser photocoagulation and minimally invasive glaucoma surgery accounted for just 2.8% of all intraocular surgeries (1).

This indicated that drug therapy continues to be at the forefront of glaucoma treatment, and therefore critical review remains inevitable. The range of anti-glaucomatous eye drops available today is very large,

and in most cases, glaucoma patients can be adjusted to their personalized target pressure sufficiently well with these eye drops. The local and systemic spectrum of side effects of the substances used seems particularly important to me since successful glaucoma therapy is only possible if they are taken into account. For example, local beta-blockers or alpha-2-agonists lower the blood pressure, so that in the case of pre-existing arterial hypotension or much more frequently in the case of existing antihypertensive therapy, the blood pressure drops too much and the nocturnal hypotension of the blood pressure can lead to further glaucoma progression **(**2**)**. In addition, only focusing on the intraocular pressure is not a sufficiently good long-term strategy. The number needed to treat **(**NNT**)** indicates a value of 7 **(**NNT= 7**)**, which means that one has to treat 7 patients with primary open-angle glaucoma **(**POAG**)** to arrest progression in one patient **(**= 7**) (**13**)**. This is even more evident in patients with ocular hypertension. Here, the NNT is 16–20 to prevent conversion to a POAG **(**13**), (**7**)**. These numbers are quite sobering. It is therefore now essential to reconsider the current therapy concept, both from a clinical and a scientific point of view. The lowering of the intraocular pressure should not be treated as a sensible approach in complex glaucoma therapy, but the lowering of the intraocular pressure is only one option of glaucoma therapy. additionally, their systemic effects and additive effects on the eye, which can positively support the glaucoma process, must also be taken into account.

In ophthalmic practice, the use of laser in the treatment of various forms of glaucoma is an essential method. Angle-closure and open-angle glaucoma are widely treated with both Argon and Yag lasers nowadays. Furthermore, Diode lasers have lately been used in the treatment of glaucoma. In addition, lasers are being utilized to treat intractable glaucoma that is not controlled by medicine alone **(**11**)**. It is assumed to be generated by heat energy directed toward the trabecular meshwork, which produces localized scarring and so opens space in nearby structures, or by cytokine and phagocytosis inflammation, which causes structural alterations with enhanced outflow **(**22**)**.

Angelo P Tanna published the "Rho Kinase Inhibitors as a Novel Treatment for Glaucoma and Ocular Hypertension" for an extended possibility of reducing intraocular pressure. This substance is the first new drug group to be introduced since 1996 with the prostaglandin analogue latanoprost and has been available since 2014 with ripasudil in Japan and since 2017 with netarsudil in the USA. As a new drug, the Rho-kinase is inhibited, which leads to improved drainage, especially in the trabecular meshwork. However, the intraocular pressure reduction is no better than that of the beta-blocker timolol and the prostaglandin analogue latanoprost, and conjunctival hyperaemia is the most common side effect after the operation. From my point of view, the combination of netarsudil and latanoprost is currently clinically useful, since it lowers the intraocular pressure more than the individual components and achieves a target pressure range below 15mmHg in 32%. For many of the specified mechanisms of action, however, only experimental data are available so far, they first have to be confirmed clinically in humans. What is interesting about this new class of substances, however, is that no systemic contraindications have been described to date.

Several cohort studies in diverse populations have found vascular risk factors for various features of glaucoma, although the results are mixed. There is no particular treatment for the choroidal or optic nerve head vasculature at this time. Some IOP-lowering drugs work by causing ciliary body vasoconstriction **(**20**)**. Increased oral absorption of dietary NO donors decreased the prevalence of parafoveal visual field abnormalities in a large cohort study **(**6**)**, which suggests that medicines acting on the ocular vasculature may have a therapeutic effect. The contribution by Ms. and Mr. Pillunat is about "vascular therapy concepts in glaucoma patients"**(**19**)**. Although this topic has been discussed for decades and both authors tirelessly promote these important issues clinically and scientifically, the vascular risk factors in glaucoma still receive too little attention. Her important contribution is not about new therapeutic drugs, but about the realization of therapy concepts already proven in the practical handling of glaucoma patients. Treatment with statins, calcium channel blockers, Ginkgo biloba extract, increased physical activity, and fluid replacement is possibilities to improve vascular conditions, in addition to improving systemic blood pressure and decreasing an elevated central retinal venous pressure.

Citicoline is cytidine-5-di phosphocholine **(**CDP-choline**)**, which is metabolized into phosphatidylcholine **(**lecithin**)**. It is essential for the synthesis of phospholipids in cell membranes, is synthesized endogenously, and crosses the blood-brain barrier. Citicoline **(**cytidine 5'-di phosphocholine**)** is a naturally occurring endogenous chemical that has been researched as a potential new glaucoma treatment. Citicoline has been shown to have activity in a variety of central neurodegenerative diseases, and experimental evidence suggests that it acts as a neuromodulator and neuroprotector on neuronal cells, including RGCs, resulting in improved visual function, visual field extension, and other central benefits for the patient. **(**4**)** Citicoline has positive effects on memory and is already used therapeutically in vascular dementia. A slower perimetric progression was shown in glaucoma in a 2-year study, which was also confirmed in a 10-year study. In a recently published review from Codeiro's working group, the level of evidence for the neuroprotective effect of citicoline in glaucoma is classified as 1b, which almost corresponds to the highest level of evidence **(**25**)**. In this respect, an accompanying therapy with citicoline in glaucoma patients is a useful option.

Gene and cell therapy is a new approach for glaucoma therapy, Long-term IOP control via increased aqueous humour drainage, including inhibition of fibrosis following filtration surgery, RGC neuroprotection and neuro regeneration, ocular biomechanics modification for improved IOP tolerance, and inhibition of inflammation and neovascularization to prevent the development of some forms of secondary glaucoma are all possible applications of gene and cell therapies. Gene and cell therapies are rapidly evolving in the lab and have many potential advantages over many conventional drugs, including longer duration with continuous drug release and a therapeutic effect that can be tailored to specific

molecular disease pathways within a single human or animal patient. However, some anatomical and cellular obstacles make this a very difficult task to achieve. Detailed knowledge of these roadblocks is essential for the creation of successful glaucoma therapy. Researchers are making headway toward this goal, thanks to the development of sophisticated delivery methods that can navigate these hurdles and deliver therapeutic genes to RGCs. Nonviral gene delivery, such as polymer-based nanoparticles, liposomes, and dendrimers, is presently the safest option; however, more study is needed before they can be employed safely and successfully in ocular gene therapy applications. Additionally, other than close-proximity administration, there is a considerable requirement for obtaining cell-specific targeting. The following applications for better glaucoma therapy will be listed here: increased aqueous humor drainage **(**1**)**, decreased aqueous humour production **(**2**)**, and/or prevention of gonio implant bleb fibrosis **(**3**)**, neuroprotection and neuro regeneration of RGCs and their axons **(**4**)**, modification of ocular biomechanical properties for improved IOP tolerance **(**5**)**, and inhibition of inflammation and neovascularization to prevent the formation of PIFVM and secondary, neovascular glaucoma **(**9**)**.

Poor adherence is a key restriction of medical glaucoma therapy, which has been studied more fully in human patients than in veterinary patients. Because eye drops are not used as frequently as they should be, glaucomatous optic neuropathy might worsen. **(**18, 3, 17**)** Poor adherence, particularly in senior patients, can be caused by a variety of causes, such as forgetfulness or technical issues with eye drops administration. Many pharmaceutical companies are developing biodegradable intracameral medication implants that continually deliver prostaglandin mimics inside the eye as an alternative. **(**Miller & Eaton, 2021**)** Allergan plc's bimatoprost implant DurystaTM was authorized by the US Food and Drug Administration **(**FDA**)** in March 2020 to decrease IOP in patients with human open-angle glaucoma **(**OAG**)** and ocular hypertension. Other implants for long-term intraocular medication delivery are now being tested in preclinical and clinical settings. **(**16, 10**)**

Primary open-angle glaucoma is viewed as systemic neurodegeneration **(**24, 12**)** that is triggered by neuro inflammation **(**15**)**. The etiology of primary open-angle glaucoma is a primary mitochondriopathy, which drives these processes forward via the derailed oxidative stress. As ophthalmologists are required to deal with these processes and expand our pathophysiological ideas about the occurrence of glaucoma.

Ginkgo biloba extract is the most well-documented of all supplemental medical drugs at the moment, and it appears to have the most potential utility. Ginkgo biloba extract has many qualities that might make it useful in treating glaucoma with non-IOP-dependent processes. GBE's several positive effects, such as improved ocular blood flow, antioxidant activity, platelet-activating factor inhibitory activity, nitric oxide inhibition, and neuroprotective activity, suggest that it might be a potential therapeutic target for glaucoma **(**21**)**.

In summary, it is important in the future to make better use of the therapy options already known, both locally and systemically, to target the therapy goal of stable functional and structural findings in our

glaucoma patients. In addition to an individualized, effective medicinal glaucoma therapy, the timely use of surgical interventions and the consideration of the existing systemic diseases are also part of this. In addition, additional neuroprotective therapies are recommended, which are already available, such as coenzyme Q10 or the citicoline. It is hoped that more targeted and effective neuroprotective agents will become available in the future, but neuroprotective therapy is already available today.

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