ABSTRACT

Objectives: To create a review article about potential breakthroughs in the pharmacological treatment of glaucoma.

Material and Methods: Non-systematic review of literature.

Results: There are four potential breakthroughs in the pharmacological treatment of glaucoma, or acting either by reducing intraocular pressure, or by neuroprotection or modulation of vascular function, and also through new drug delivery methods.

Conclusions: In the near future, we will be faced with several new ways of approaching the pharmacological treatment of glaucoma patients

Key-words: Glaucoma, Intraocular pressure, Pharmaceutical Preparations, Equipment and Supplies, Review.
RESUMO

Objetivos: Elaborar um artigo de revisão sobre novas formas de tratamento farmacológico da neuropatia glaucomatosa.

Material e Métodos: Revisão não sistemática da literatura.

Resultados: Existem quatro vias potenciais que podem mudar o tratamento farmacológico do glaucoma, quer através da redução da pressão intraocular, como através da neuroprotecção ou modulação da função vascular, e também através de novos métodos de administração de fármacos.

Conclusões: Num futuro próximo vão surgir, na área do glaucoma, novas formas de abordar o tratamento farmacológico que mostram já resultados promissores

Palavras-Chave: Glaucoma, Pressão intraocular, Fármacos, Dispositivos médicos, Revisão.

Glaucoma, an optic neuropathy, is one of the major causes of visual impairment worldwide and is accountable for around 12% of global blindness. Lack of early diagnosis and frequent need for life-long treatment make it a public health issue. For several years, no significant advances have been made regarding pharmacological therapeutics. However, several authors recently presented compelling evidence of potential breakthroughs, either by the enhancement of intraocular pressure (IOP) lowering, the mainstay of treatment, or through other treatment routes, such as vascular function improvement, neuroprotection or new drug delivery methods.

1. NEW TARGETS FOR IOP LOWERING

Currently there are six classes of drugs approved for clinical use: miotics, beta-blockers, alpha-agonists, epinephrine derivatives, carbonic anhydrase inhibitors, and prostaglandin analogues. Their mechanism of action is either by improving aqueous humor (HA) outflow or by decreasing HA production.

New potential drug therapies undergoing research include: Rho kinase, endothelin-1, transforming growth factor-β, connective tissue growth factor, nitric oxide, angiopoietin-like molecules, adenosine, latrunculins, cochinl, cannabinoids, melatonin, ghrelin, angiotensin II, serotonin and forskolin.

In this review we will focus on the ones that are potentially reaching the broad clinical market soon, which are Rho kinase (ROCK) inhibitors, adenosine agonists, and nitric oxide (NO) donors. Interestingly their mechanism of action lies mainly in the trabecular meshwork (TM), which is probably the IOP lowering target that has not been fully used so far (Figure 1).
Regarding ROCK inhibitors, some have already reached phase 3 clinical trials. AR-13324 (Rhopressa®, Aerie Pharmaceuticals, California) is able to lower IOP not only by increasing outflow through the conventional (trabecular meshwork) pathway, but also by reducing episcleral venous pressure\(^5\) and inhibiting the norepinephrine transporter (NET; which reduces the amount of aqueous produced)\(^6\). In a 3-arm phase 3 trial, Rocket 2 (held in the United States), Rhopressa® (0.02% qd or 0.02% bid) was compared to timolol (0.5% bid) in subjects with baseline IOP between 20 and 25 mmHg, with similar baseline demographic characteristics between groups. Patients were followed for 3 months and the primary endpoint of non-inferiority was achieved in all evaluations. The most common side effect was conjunctival hyperemia, deemed mild, present in 83% of patients\(^5\). New results of this molecule are expected in mid-2016, when Rocket 4 trial results are presented and submission to the United States Food and Drug Administration (FDA) is planned. Along side Rhopressa®, research is also being done with Roclatan® (Aerie Pharmaceuticals), a fixed combination of Rhopressa® and latanoprost, drugs that lower IOP through different mechanisms. A phase 2 trial, held in the United States, with 297 patients showed superiority of Roclatan® in lowering IOP when compared to latanoprost alone (from 25.1mmHg at baseline to 16.5 mmHg at day 29; about 2mmHg greater reduction comparing to latanoprost alone), at every time point in the study\(^6\). Phase 3 studies of Roclatan® have already started in the United States but results are still to be reported. No systemic side effects were reported both for Rhopressa® and Roclatan®, and conjunctival hyperemia seems to be the greatest limitation found so far. Another ROCK inhibitor showing promising results is K-115 or Ripasudil (Glanatec®, approved for glaucoma treatment in Japan). A 52-week prospective, multicenter trial with 388 patients [mixed primary open angle glaucoma (POAG), ocular hypertension (OHT) and exfoliation glaucoma] conducted in Japan, showed that 0.4% Ripasudil bid has an IOP-lowering effect as monotherapy, but also as additive therapy (to prostaglandin analogues or \(\beta\)-blockers). As monotherapy Ripasudil lowered IOP by 3.7 mmHg (baseline IOP 19.3+2.7mmHg; 19.2% reduction), and a subgroup analysis, dividing patients according to IOP \(\geq\) or \(<\) 21, showed an IOP-lowering effect in both groups (-3.3mmHg (17.1%) if IOP<21mmHg and -4.8 mmHg (24.9%) if IOP\(\geq\)21mmHg). Also, Ripasudil showed a similar additive IOP-lowering effect when compared with commonly used second-line antiglaucoma medications (carbonic anhydrase inhibitors and brimonidine). Since all study cohorts had patients with different diagnosis, future studies should aim for more homogeneous cohorts. Conjunctival hyperemia (74.6% of patients vs 1.9% with placebo) was the most common side effect (like with Rhopressa®), and most cases were mild, transient and had spontaneous resolution\(^7\). Despite these results, a combination with latanoprost or timolol might not be possible, since Ripasudil needs to be administered twice daily and it reduces the bioavailability of timolol\(^8\).

Apart from ROCK inhibitors, also NO donors are showing promising results in recent published literature. NO donors, like ROCK inhibitors, increase aqueous outflow through the TM. Latanoprostene bunod 0.024% (Vesneo®, Bausch + Lomb and Nicox), a NO-donating prostaglandin F2\(\alpha\) receptor agonist, combines latanoprost acid with butanediol mononitrate, which is a NO-donating molecule. In a phase 3 clinical trial it has proven to be more effective than timolol in lowering IOP, with qd dosing regimen\(^9\), and was also able to increase ocular perfusion pressure\(^10\). It is not commercially available as yet, but is pending approval by the USA FDA (set for July 2016).

Adenosine agonists are another apparently successful drug class. Human’s TM has 4 adenosine receptors, 3 of which are able to lower IOP (A1, A2a, A3; the latter can also increase IOP), and several drugs are already being used in clinical trials targeting these receptors. Trabodenoson (Inotek Pharmaceuticals), an A1 agonist, proved its ability to lower IOP in a phase 2 clinical trial with 144 patients, by decreasing IOP 7 mmHg by day 28 with qd dosing\(^11\). No systemic side effects were reported and patients had less hyperemia than what is known to happen with prostaglandin analogues. A phase 3 clinical trial is being conducted, but no results have been provided so far. There are also other drugs (targeting A2a receptor, OPA-6566, Acuera and Otsuka Pharmaceuticals and ATL313, Santen Pharmaceuticals) that have shown ability to lower IOP, but couldn’t reach the results of trabodenoson.

These three new drug classes (ROCK inhibitors, NO donors and adenosine agonists) have shown promising results and have several drugs in advanced stage human trials. They all lower IOP by increasing TM outflow, which might be the key to enhance our pharmacological arsenal for glaucoma patients.
2. Improving vascular function - blood flow and ocular perfusion pressure

“The excavation of the disc in glaucoma is not a purely mechanical result of exalted pressure: it is, in part at least, an atrophic condition which, though primarily due to pressure, includes vascular changes and impaired nutrition in the substance of the optic disc... which may probably progress even though all excessive pressure be removed” by Priestly Smith, 1885

More than 100 years ago several theories were introduced regarding the pathophysiology of primary open angle glaucoma (POAG). The mechanical theory was during several decades the only one ophthalmologists thought about (high IOP is the main risk factor and the only one with proven treatment) when seeing glaucoma patients, however in view of current knowledge one must take into account ocular blood flow (OBF; as well as neuroprotection as seen below in the next section) as being related to glaucomatous damage\textsuperscript{12}. This field of research is especially relevant when we think of normal-tension glaucoma (NTG), where the mechanical component of the equation has less weight and yet patients still develop axonal loss with time.

Ocular blood flow is dependent on ocular perfusion pressure (OPP), which is the difference between the arterial and the venous blood pressures. Since the venous blood pressure is equal or slightly higher than IOP\textsuperscript{13} we can estimate OPP as the difference between 2/3*arterial pressure and IOP (2/3 accounts for the difference in hydrostatic pressure between the arm and the eye)\textsuperscript{14}.

In view of this knowledge, we can say there is a blood flow reduction if the IOP is high or arterial blood pressure is low. However, as many other mechanisms in the eye, also OBF has a complex relationship with OPP, since vascular tone (resistance) is another factor in play. Changes in OBF can result only from changes in vascular resistance (vasoconstriction or vasodilation) independently of changes in OPP. Optic nerve blood vessels have autoregulation (change their tone to maintain a constant blood flow according to IOP and blood pressure, and also according to metabolic demand\textsuperscript{15}), but this also depends on levels of vasoactive agents (especially NO and endothelin) and the way the endothelium responds to these factors\textsuperscript{13, 16}.

Several studies have shown low OPP to be a risk factor for the prevalence, incidence and progression of glaucoma\textsuperscript{17-20}, reinforcing the importance of the ischemic damage to the optic nerve head (ONH).

Since we are looking into the amount of blood and perfusion of the ONH, we must consider systemic vascular diseases that may enhance ischemic damage. The ones already associated with glaucoma progression include migraine\textsuperscript{21, 22}, systemic hypotension\textsuperscript{22-25}, nocturnal dipping pattern of blood pressure (being a non-dipper or extreme dipper were related to glaucoma progression)\textsuperscript{26, 27}, Alzheimer’s disease\textsuperscript{28-32}, primary vascular dysregulation (PVD) and Flammer syndrome (includes PVD and a cluster of signs and symptoms; it is prevalent and benign in the healthy population, but may contribute to the progression of certain diseases, like glaucoma)\textsuperscript{33, 34}

2.1. Clinical evaluation of OBF

There are several methods used for the evaluation of ocular blood flow [colour doppler imaging (evaluates retrobulbar vascular circulation)\textsuperscript{35}, laser doppler velocimetry, laser doppler flowmetry\textsuperscript{36}, angiographic techniques (invasive with fluorescein or non-invasive with angio-optical coherence tomography), optical doppler tomography]\textsuperscript{30, 37}, but a detailed description is beyond the scope of this review.

2.2. Potential treatments

First of all, there is still no drug able to increase ONH blood flow. However we must always bare in mind the “do no harm” oath, since increasing blood flow or selectively recruiting blood for the ONH might have important side effects.

Some studies suggested a beneficial influence of long-term beta-blockers carteolol and betaxolol on ONH circulation\textsuperscript{38, 39}. OBF regulation can be improved by magnesium, calcium channel blockers\textsuperscript{40} as well as with carbonic anhydrase inhibitors\textsuperscript{16}. However, the incidence of glaucoma was increased in patients on calcium channel blockers in the Rotterdam Eye Study\textsuperscript{41}.

Ocular blood flow and perfusion of the optic nerve seem to be important to every glaucoma patient and not only to NTG patients. We just need to better understand the weight the different risk factors play in this complicated equation that leads to ganglion cell death.
3. Neuroprotection

Current treatments for glaucoma are focused generally on lowering IOP, since it is the main risk factor. However, retinal ganglion cells (RGCs) loss can occur even with normal IOP levels. In recent years, there has been substantial concern in the development of neuroprotective therapies that could save RGCs from glaucomatous injury or repair neurons that have been damaged, in order to preserve and potentially restore visual function. Neuroprotection shows potential as a complementary therapy to IOP-lowering medications/procedures for those patients in whom lowering IOP is not enough to prevent progression. A number of mechanisms have been proposed to explain RGC death in glaucoma, including excitotoxicity, oxidative stress, protein misfolding, neurotrophin deprivation, and immune-mediated inflammation. Potential therapeutic approaches will be covered here, however there is still no proof of a clinically relevant effect for any neuroprotective agent in glaucoma.

**Excitotoxicity** is a proposed contributor to glaucomatous damage. In glaucoma patients there is an increased level of the excitatory neurotransmitter glutamate, which can be toxic to RGCs. Glutamate is a main excitatory neurotransmitter in the vertebrate retina and its interactions with specific membrane receptors play essential roles in retinal visual transduction. However it can also stimulate N-methyl-d-aspartic acid receptors (NMDARs) leading to extensive levels of calcium entering cells, thus activating phospholipases, endonucleases and proteases, which ultimately leads to RGC death. Since they inhibit glutamate excitotoxicity, NMDAR antagonists, glutamate release inhibitors, and calcium channel blockers, have been proposed as potential neuroprotectors. In vivo and in vitro studies have suggested that blocking NMDARs exerts a neuroprotective effect. The most studied NMDARs antagonists are MK801 and memantine. MK801 has been found to protect RGCs in glaucoma rat models, showing a reduction in the number of apoptotic RGCs in comparison to controls. However, there is also evidence that MK801 is neurotoxic, as so it has not reached advanced stages of clinical research. Memantine is the best known antagonist of NMDARs and is approved by the FDA for the treatment of Alzheimer’s disease. It is the only neuroprotective agent that has completed phase III clinical trials in patients with open-angle glaucoma (OAG). However, Allergan® announced that low-dose oral memantine in OAG failed to show a statistically significant reduction in disease progression, despite having showed a reduction in a previous trial. Although the clinical trials did not demonstrate any significant efficacy, further studies are ongoing. Alpha2-adrenergic agonists, such as brimonidine, seem to inhibit glutamate release. Other potential mechanisms for brimonidine’s neuroprotective effect include BDNF (a neurotrophic factor) increase, and activation of anti-apoptotic genes. Brimonidine has showed significant protection against RGC death, preventing further cell death when applied after the IOP was increased in a chronic ocular hypertensive rat model. Furthermore it seems to increase RGC survival after optic nerve and retinal injury in various animal models. In humans, a multicenter clinical trial (The Low-pressure Glaucoma Treatment Study study), evaluated visual field stability in 190 normal tension glaucoma patients, randomized to receive topical monotherapy with brimonidine or timolol. Brimonidine treated patients showed less visual field progression than timolol treated patients. This effect was attributed to an IOP–independent protective effect of brimonidine, which could act as a neuroprotective agent, although other possible explanations have been made, such as a harmful effect of timolol. Calcium channel blockers (such as nifedipine, iganidine, lomerizine and flunarizine) have been shown to improve glutamate metabolism and increase blood flow to RGCs, providing substantial neuroprotection against RGC loss. Further preclinical studies are still required to prove their safety and efficacy.

**Oxidative stress** results from the build up of reactive oxygen species (ROS) generated during normal metabolism. It is hypothesized that oxidative stress plays a role in RGC death in POAG, by causing damage in the TM, the ONH and the retina. Multiple anti-oxidants have risen as potential neuroprotective agents, such as melatonin, aminoguanidine, vitamin E, Ginkgo Biloba and coenzyme Q10 (CoQ10). Melatonin has demonstrated a neuroprotective effect on RGCs in vitro and in vivo. Aminoguanidine is believed to reduce ROS production, by inhibiting NO synthetase 2 (NOS-2), and showed significant prevention of RGC loss in rat glaucoma models. However, to date, it is not yet clear whether NOS-2 is expressed by cells within the ONH of glaucoma patients. Vitamin E as a daily supplementation in glaucoma patients was found to be associated with a reduction in the rate of glaucomatous progression. Ginkgo Biloba has been proved to be...
neuroprotective thanks to its antioxidative, rheological, antithrombotic and anti-inflammatory effects, as well as vasorelaxative and antivasospastic properties. In a retrospective study that evaluated the long-term effect of Ginkgo biloba extract (80 mg, 2 times daily) on progression of visual field defects in patients with normal tension glaucoma, it was showed that the regression coefficients of MD, PSD, and VFI improved significantly after 12.3 years. Another important antioxidant is CoQ10. The intravitreal administration of CoQ10 in rat glaucoma models seems to minimize glutamate release and protect RGCs against ischemia-induced injury. A study compared pattern evoked retinal and cortical responses in patients who underwent treatment with coenzyme Q10 and vitamin E in addition to b-blocker, with patients who were only treated with b-blockers. Topical application of the association of CoQ10 with vitamin E showed a beneficial effect on the inner retinal function with consequent enhancement of the visual cortical responses in patients with OAG.

With regards to protein misfolding, amyloid deposition has been implicated in the pathogenesis of glaucoma, as it happens with other neurodegenerative diseases, such as Alzheimer’s and Parkinson’s disease. Guo et al has showed that targeting the amyloid formation and aggregation pathways, with drugs such as b-secretase inhibitors, can effectively reduce glaucomatous RGC apoptosis in vivo. Another point of interest are Heat Shock Proteins (HSP). Under normal conditions, they have multiple functions, one of which is the regulation of protein degradation. Their expression seems to be increased in eyes of glaucoma patients and animals with chronic hypertension. Geranylgeranylacetone (GGA), an anti-ulcer drug used clinically for the treatment of gastric disorders, has been shown to induce HSP72 synthesis in multiple tissues. The systemic administration of GGA was proved, in a rat model, to protect RGCs from glaucomatous damage and suggests a novel pathway for neuroprotection in glaucoma.

Neurotrophin deprivation is another mechanism being targeted as a potential source of neuroprotective drugs. Neurotrophic factors (NTFs) are growth factors involved in the maintenance and enhancement of neuronal cell survival. In theory, pharmacological agents that could directly supply exogenous neurotrophins or up regulate endogenous neurotrophins could represent a therapeutic approach. Topical nerve growth factor (NGF), an endogenous neurotrophin, showed in a study that evaluated 3 patients, with progressive and advanced glaucoma despite control of IOP, improvement after 3 consecutive months of treatment. Visual field mean defects showed improvral up to 5% [from (-32.90, -33.90, -34.27) to (-31.50, -32.10, -34.30)] by the end of NGF treatment and a further 1 to 15.8% (-27.70, -29.20, -33.90) 3 months after NGF discontinuation. As for visual evoked potentials, authors found a reduction of latency and increase in amplitude after NGF treatment. This study supports the evidence that topical NGF treatment may be an effective adjunct therapy for glaucoma. Others NTFs, as BDNF, GDNF and CNTF, have shown potential to enhance survival of RGCs after optic nerve injury. With regard to CNTF, a Phase I clinical trial for an CNTF implant in patients with POAG (NCT01408472) was completed in October 2014 and the results are yet to be published. Some limitations regarding neurotrophin supply have been identified, including potential instability of eyedrops, the necessity of repeated intravitreal administration and the short lasting effect.

Immune system-mediated events are emerging as a major contributor in glaucomatous damage. An inflammatory neurodegenerative process seems to occur in glaucoma due to prolonged glial activation and sustained release of pro-inflammatory mediators, such as tumor necrosis factor-alpha (TNF-α). Agmatine, an anti-inflammatory agent, was shown in vitro and in chronic ocular hypertensive rat models to inhibit TNF-α production in RGCs under hypoxic conditions. Also, etanercept, a TNF-α blocker, was able to inhibit microglial response, preventing axonal degeneration and subsequent RGC loss in a rat glaucoma model. Although the present evidence supports the immune system activation in glaucoma, its causative importance remains poorly understood.

Another substance that has proved neuroprotective activity is citicoline. It showed a neuroprotective effect on RGCs over the long term and a neuroenhancing effect on RGC function in the short term. Effects on glaucoma have been studied since 1989 in humans and animal models. More recently, a multicentric study on the effect of citicoline oral solution in patients with progressive glaucoma showed a reduction in the mean visual field progression rates in 2 years. Citicoline was also recently made available as eye solution, and an experimental study showed an improvement of RGC function, as shown by PERG parameters. Additional results of a prospective randomized study with topical citicoline in OAG patients, showed an enhancement in PERG amplitude. Citicoline has rarely shown adverse effects, as gastrointestinal
discomfort, uneasiness, and irritability, confirming that this molecule is safe and can be used for long-term treatment. \textsuperscript{69, 72}

The results provided above may open new therapeutic approaches for glaucoma, introducing neuroprotection as a complementary treatment modality.

\textbf{4. New drug delivery methods}

Non-surgical glaucoma therapy, so far, consists almost exclusively in eyedrops, the mainstay of glaucoma drug delivery. Poor patient compliance, particularly when more than one IOP reducing drug is required (approximately 40\% of patients at five years), is one of the problems we face with glaucoma patients. \textsuperscript{73} Also, low drug bioavailability and the potential for local and systemic side effects are some of the disadvantages of conventional delivery methods. In this context, there is a growing need for new delivery platforms, with enhanced patient convenience and sustained drug release.

**Contact lenses (CLs)** were first explored for glaucoma therapy in the 1970’s. \textsuperscript{74} This approach was shown to be effective, but it did not reach the clinical stage mainly because lenses released the drugs in a burst, which could increase the potential for toxicity and require insertion of multiple lenses per day. New forms of achieving sustained drug release were explored since then. The mechanism of action resides in drug diffusion into the post-lens tear film followed by absorption by the cornea, resulting in an increased retention of drug on the corneal surface. Drug molecules released from CLs into the post lens tear film have a longer residence time (of at least 30 min), compared to eye drops (2-5 min), and a greater bioavailability (up to 50\% or more). \textsuperscript{75-78} Despite numerous advantages, most ophthalmic drugs have shown low affinity for conventional contact lenses. Therefore several improvements have been attempted: modified medicated contact lenses; imprinted medicated contact lenses; medicated contact lenses with nanoparticles. Regarding modified CLs, Cheng-Chun Peng et al. carried out an animal study with timolol delivered via extended wear contact lenses ACUVUE TruEye® compared to eye drops. They found a comparable reduction in IOP between methods, but with only 20\% drug dose with CLs, which shows how CLs have higher drug bioavailability. \textsuperscript{79} Also Chauhan et al. have recently designed a silicone-hydrogel CL incorporating vitamin E, which can significantly increase drug release duration. As an example, release durations of timolol and dorzolamide increased from a few hours to 50-hours when 20\% vitamin E was incorporated into the lenses. \textsuperscript{80} Imprinted medicated CLs are a recent method of controlled drug release. Molecular imprinting is able to embed functional monomers within the CL, created during the CL polymerization process. \textsuperscript{81} These molecularly imprinted pockets increase drug loading ability, while providing an adequate release rate. \textsuperscript{82} However, stability of imprinted cavities is dependent on a high crosslinking degree, which means that transparency, flexibility and optical performance of these CL can be threatened. Finally, nanoparticles are another way for drug incorporation within the CL matrix. Hyun Jung Jung et al. published a study of extended release of timolol from nanoparticle loaded silicone-hydrogel CLs. They found that 5\% particle loading can deliver timolol at therapeutic levels for about a month at room temperature. \textsuperscript{84} Jung and Chauhan found that sustained release of timolol in therapeutic levels occurs for 2 to 4 weeks and stated that the drug was released only at body temperature, which is an important feature, so that during storage the drug does not suffer premature release. \textsuperscript{85}

In a recent in vitro study, acetazolamide in CLs was used to lower IOP with a prolonged release over several weeks. \textsuperscript{86} This is promising since acetazolamide is only available as an oral treatment with several systemic side effects. Despite all these promising results, the amount of clinical studies regarding these nanosystems is still scarce.

**Ocular drug-eluting inserts** are solid or semisolid devices meant to be placed in the conjunctival sac. The reduced frequency of administration due to the constant rate of drug release achieved for a prolonged time has the potential to improve patient compliance while minimizing systemic absorption through the nasal mucosa. Juçara Ribeiro Franca et al. studied a bimatoprost-loaded ocular insert in animal glaucoma models. They found an enhanced preconeral drug residence time compared to conventional eye drops and effectiveness in lowering IOP for up to 4 weeks after one application, while with eyedrops, once treatment was interrupted at 2 weeks, IOP increased in the following week. \textsuperscript{87} Recently, Ivan Goldberg et al. developed a sustained-release bimatoprost ocular insert that provided six months of clinically significant IOP reduction from a single insert, with a mean diurnal IPO reduction of 4.7 to 6.5 mmHg from baseline. \textsuperscript{88} So, results are promising.
demonstrating feasibility of this new sustained drug delivery method.

**Surgically implanted reservoirs** are able to ensure a sustained drug concentration over an extended period of time (up to several weeks or even months)\(^9\). Subconjunctival administration is safe and well tolerated by patients, and is already used routinely for the treatment of several ocular diseases. Natu et al reported a sustained drug release of dorzolamide-loaded subconjunctival implants in rabbit eyes for up to 4 weeks\(^9\). Similarly, IOP lowering beyond 50 days was demonstrated in rabbit eyes after a single injection of latanoprost-loaded liposomes\(^9\). Surgically implanted reservoirs in the vitreous have the potential to provide the most extended drug release. These implants are available for drug delivery for other ocular diseases and have been studied for use in glaucoma as well. A multicenter randomized clinical trial (NCT00693485) studied the safety and effects on visual function of a brimonidine intravitreal implant in patients with glaucoma, however, without results published so far. A prospective phase 1/2 clinical trial with 75 POAG patients is evaluating the IOP lowering ability and safety of a biodegradable bimatoprost sustained-release implant (BimSR). BimSR was administered intracamerally in the study eye, while the fellow eye began topical bimatoprost 0.03% qd. In a 6-month interim report regarding efficacy and safety, BImSR was well tolerated and results were comparable to topical bimatoprost in overall IOP reduction. Also, a single dose of BimSR controlled IOP for up to 6 months in most patients\(^9\).

The main disadvantages of these new approaches are the cost and the invasiveness of the implanted devices. This is especially the case for surgically implanted reservoirs, as there are inherent procedure risks and potential complications. Other factors to consider include patient tolerability and the potential for allergy or immune response. Also drug stability, the risk of dose dumping, and toxicity are other factors that require further careful investigation\(^9\).

Overall, new delivery methods might be able to tackle one of the main problems responsible for glaucoma progression, which is patient compliance, by potentially reducing side effects and need for constant instillation.

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Não existe nenhum conflito de interesse (nomeadamente comercial no produto, equipamento ou processo).

O trabalho não foi publicado previamente.
Os autores cedem os direitos de autor à SPO.