Chapter 6

Managing Intraocular Pressure: Innovation in Glaucoma Management

Anne-Marie Bleau, Beatriz Vargas,
Ana Isabel Jiménez and Covadonga Pañeda

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Abstract

Primary open-angle glaucoma is a progressive ocular neuropathy that if left untreated may lead to blindness. The main risk factor for developing glaucoma is increased intraocular pressure. Intraocular pressure is regulated by the balance of aqueous humour synthesis and secretion into the eye and outflow from the eye; therefore, most therapies for glaucoma seek lowering intraocular pressure to avoid disease progression. There are several types of drugs in the market for the treatment of glaucoma, but there are still unmet needs to be overcome; therefore, significant effort has been put in the last few years to develop new medicines with innovative mechanisms of action as well as devices to improve quality of life in glaucoma patients. The present review offers a thorough revision of the latest advances in the glaucoma therapy field, focusing on innovative approaches, new targets and new mechanisms of action.

Keywords: glaucoma, innovation, therapy, oligonucleotides, devices, stem cells, gene therapy

1. Introduction

Primary open-angle glaucoma (POAG) is a multi-factorial optic neuropathy characterized by retinal ganglion cell degeneration and progressive visual field loss [1]. The underlying molecular changes leading to ocular tissue damage in glaucoma are largely unknown, but it has been shown that reduction in intraocular pressure (IOP) correlates with a decrease in disease progression. As such, treatment in glaucoma is mainly oriented towards reducing IOP to reach a target reduction of approximately 25–30% from the patient's baseline [2]. Pressure in the eye is maintained by balancing the amount of fluid contained within the anterior and

posterior chambers; thus, reduction in IOP is achieved either by reducing the amount of aqueous humour (AH) secreted into the eye or by increasing its outflow [1]. AH is produced by the epithelial cells of the ciliary processes through a complex mechanism that involves ultrafiltration, active transport and diffusion; AH is thereafter secreted into the posterior chamber. AH circulates from the posterior chamber around the lens and through the pupil into the anterior chamber and exits the eye trough one of two pathways: the conventional pathway or the uveoscleral route. AH exiting the anterior chamber through the conventional route crosses the trabecular meshwork (TM) to reach the Schlemm's canal (SC) located at the limbus. Contraction of the ciliary muscle causes the TM to expand and SC to open resulting in increased outflow through this route. The main source of outflow resistance through this route is the extracellular matrix of the TM and the inner wall endothelium of the SC. Through the unconventional or uveoscleral route, AH flows from the iris angle through the anterior face of ciliary muscle into the connective tissue located between the muscle bundles to finally reach the suprachoroidal space. The fluid is thereafter drained through the sclera or the perivascular spaces into the episcleral tissue where it enters the venous circulation. In contrast to the conventional route, the main source of AH outflow resistance is the ciliary body [3].

The eye is a contained organ that is partially isolated from the rest of the body; this isolation provides a certain immune privilege and limits the amount of compound needed to perform proof-of concept studies. In addition, the eye has a sophisticated structure with many different cell types and specialized barriers making it an ideal organ for studying delivery of larger compounds. As such, the eye has often been used to study new mechanisms of action and to obtain initial data for new compounds in development. Therefore, it is not surprising that most innovative new classes of drugs have, at some point, been tested in the eye, among these new classes of drugs are aptamers, antisense oligonucleotides (ASO), short interfering RNAs (siRNA), antibodies, stem cells, gene therapy and different types of delivery approaches and devices.

Here, we will review innovative programs developing drugs for the treatment of glaucoma focusing on the latest advances oriented towards lowering IOP, paying particular attention to the mechanisms used by these drugs and devices.

2. Pharmacological innovation

Progressive and irreversible loss of vision is the most feared complication for glaucoma. While current treatments focus on lowering IOP, up to date no therapies have been approved to address the critical issue of visual field deterioration. For this reason, high unmet needs remain for the development of innovative approaches to treat such aspect of the disease. Fortunately, beyond classic eye drop medicines, various exciting therapies are emerging in the field. Overall, these techniques aim to provide either a novel alternative to reduce IOP or a protection and regeneration of retinal ganglion cells (RGCs) to ultimately reverse vision loss. In this section, we will describe novel techniques for the treatment of glaucoma. Interestingly, these complex strategies have been combined in order to achieve broader efficacy.

Traditionally, drug discovery has been based on screening large libraries of compounds to select products with specific activities. However, in the last decades, advances in the molecular

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biology field have allowed the search for active candidates to become more rational. As a result, new pharmaceuticals with innovative mechanisms of action, target specific design and improved pharmaceutical properties have emerged. Some of the advantages of these new compounds include increased specificity, reduced toxicity and the ability to address targets that cannot be engaged by traditional small molecules. Among these new pharmaceuticals are biologicals, stem cells, gene therapy and therapies based on oligonucleotides.

Developing innovative compounds for the treatment of glaucoma entails thus targeting the function of cells and tissues related to IOP control; these tissues include the ciliary muscle, the TM, the SC, collector channels and aqueous veins. The latest discoveries in molecular biology allow the identification of key molecules that control AH dynamics in these tissues, and these molecules can be used as starting point for new therapeutic strategies and discovery of new targets. In order to fully take advantage of these approaches, the characteristics of these specific tissues have to be taken into account when designing the therapeutic strategy. The following characteristics are particularly interesting when developing innovative glaucoma therapies:

1. The TM is composed of phagocytotically active cells; this facilitates the entrance of compounds that exert their action inside the cell. Phagocytosis may be enhanced by some surgical procedures.
2. Many of the cells of the TM are non-proliferative, terminally differentiated cells; this prolongs the action of certain therapies that can exert their action inside cells such as genetic therapies, antibodies and oligonucleotide-based therapies.
3. The TM and the SC are structures with the ability to present antigens and induce tolerance; this may work in favour of some therapies that usually induce an immune response.
4. Tissues responsible for IOP control are located in the anterior chamber and are more accessible than tissues of the back of the eye; therefore, invasive procedures are not usually required.

2.1. New drug targets

As mentioned above, current approaches to develop new drugs for the treatment of glaucoma are aimed towards decreasing IOP to avoid further damage to the glaucomatous eye. Five drug-types are currently approved to treat glaucoma: alpha agonists, beta-blockers, carbonic anhydrase inhibitors, prostaglandin analogues and cholinergic drugs. Given the information available from the field of genetics, it is surprising that no new targets have reached the clinic since prostaglandin analogues, but this may change in the near future. Here, we review the information and mechanistic data existing for three new targets against which several compounds are currently under clinical development.

2.1.1. Rho-associated protein kinase (ROCK) inhibitors

2.1.1.1. Description and biological function

The Rho family consists of three guanosine triphosphate (GTP)-binding proteins named RhoA, RhoB and RhoC, which belong to the Ras-superfamily of GTPases [4]. Rho proteins

bound to guanosine diphosphate (GDP) remain inactive in the cytoplasm of the cell; upon binding of GTP, these proteins become active and translocate to the cellular membrane where they exert their function [5]. The Rho activation and inactivation cycle is regulated by GTP-ase activating proteins (GAP) and guanine nucleotide-exchange factors (GEFs) that catalyse GTP and GDP exchange [6]. Rho proteins are ubiquitously expressed and participate in the regulation of cytoskeletal dynamics, thus playing a central role in cell morphology, adhesion and migration, as well as in numerous signalling pathways [7]. Increased levels of RhoA expression have been detected in optic nerve head of glaucomatous eyes [8].

One of the most comprehensively studied effectors of Rho proteins is the Rho-associated coiled-coil containing protein kinases (ROCK), which are serine-threonine kinases composed of a catalytic domain, a coiled-coin Rho-binding site and an auto-inhibitory domain [9]. In humans, ROCKs exist as two isoforms, ROCK1 and ROCK2, expressed in a wide variety of tissues including the TM and the ciliary muscle cells [10]. Multiple studies indicate that ROCK regulate the contractile properties of the TM, synthesis of extra-cellular matrix (ECM) and outflow of AH through the TM; factors known to be involved in AH dynamics [11]. In addition, ROCK1 and ROCK2 knock-out mice exhibit lower values of IOP when compared to those of their wild-type littermates [12].

2.1.1.2. Mechanism of action

Upon activation, ROCK phosphorylates a large number of substrates inducing their activation or inhibition; many of these substrates, such as the myosin light chain (MLC), the myosin phosphatase (MLP) and actin-binding LIM kinase (LIMK), actively participate in cytoskeletal dynamics and cell motility of the TM, SC and ciliary muscle [13, 14]. The contraction/relaxation status of these structures influences the resistance to AH outflow and as a result modulate IOP homeostasis. In consequence, the results of multiple studies have proposed a role of ROCK inhibitors in enhancing AH drainage through the TM by altering the cytoskeleton [15]. NF-κβ is another downstream effector of the ROCK pathway; its activation controls the translation of pro-inflammatory mediators such as interleukins or TNF-α.

The anti-fibrotic activity of ROCK inhibitors seems also to be relevant to the therapeutic role of these agents in glaucoma. Post-operative scaring is one of the main causes of filtration surgery failure; scaring tissue formed at the TM leads to poor IOP control and allows silent disease progression. The differentiation of fibroblasts to myofibroblasts during wound healing and scar formation is mediated by TGF-β that facilitates the contractile response of fibroblasts. ROCK inhibitors such as Y-27632 and AMA0526 have demonstrated to improve surgical outcome in animal models of glaucoma filtration surgery [16, 17]. Additionally, ROCK inhibitors such as Y-39983 and fasudil have been found to improve blood flow to the optic nerve head, seemingly due to their action on MLC that regulates the contraction of smooth muscle cells in the blood vessels irrigating this area [18, 19]. Finally, it has been shown that ROCK may also have an effect on central nervous system (CNS) targets involved in neuronal survival and axonal regeneration thus giving ROCK inhibitors an added-on value to their role on AH dynamics [20].

2.1.1.3. Drugs in development

Y-27632 was the first identified ROCK specific inhibitor, and **SNJ-1656** (also known as Y-39983/RKI983; Senju and Novartis Pharmaceuticals) was the first ROCK inhibitor to demonstrate an IOP-lowering effect in human subjects [21]. Despite its effect in humans, the clinical development of this compound was halted in Phase II due to insufficient efficacy and a poor tolerability profile [22]. ROCK inhibitors currently undergoing clinical trials in glaucoma include ripasudil (KowaCompany, Ltd; Japan), netarsudil (Aerie Pharmaceuticals, Inc; USA), PG324 (Aerie Pharmaceuticals, Inc; USA) and AMA0076 (Amakem; Belgium).

Ripasudil hydrochloride hydrate, formerly known as K-115 (Glanatec® ophthalmic solution 0.4%), was approved in Japan in September 2014 for the treatment of glaucoma and ocular hypertension when other therapeutic drugs are not effective or cannot be administered, at the dosage of one drop per eye, twice daily (b.i.d) [23, 24]. Compiled data from Phase II and III clinical trials indicated that this drug achieved a 15% IOP reduction (3.5 mmHg), being conjunctival hyperaemia the most frequently reported adverse event with incidence rates ranging from 55 to 74% [25, 26]. Non-clinical studies proved that ripasudil inhibited both ROCK1 and ROCK2 (IC50 0.051 and 0.019 μmol/L, respectively) and mechanistic studies performed in rabbits demonstrated that its ocular hypotensive effect is due to increased drainage of AH through the TM and SC [27]. Ripasudil induces cytoskeletal changes secondary to ROCK inhibition that lead to the retraction and rounding of the TM cells decreasing the compaction of the TM allowing aqueous outflow. Additionally, *in vitro* studies demonstrated that ripasudil reduced outflow resistance and increased SC endothelial cell permeability [28].

Netarsudil (Rhopressa™ ophthalmic solution, 0.02%), formerly known as AR-13324, is a ROCK and a norepinephrine transporter (NET) inhibitor currently in Phase III clinical trials [29]. In a Phase II study, this product achieved a 22% reduction in mean diurnal IOP after 28 treatment days when administered in eye drops once daily (*q.d)*. However, non-inferiority versus latanoprost was not met [30]. IOP reduction is thought to be achieved by three different mechanisms of action: increasing AH outflow through the TM, reducing the pressure in the episcleral vein and reducing AH synthesis. Real-time effect of netarsudil on AH dynamics was evaluated *in vivo* both in albino and pigmented mice using a custom-made optical coherence tomography system [31]. This technique confirmed that the IOP-lowering effect of netarsudil is related to its action both in proximal and distal steps of the outflow pathway. It was noted that the observed cytoskeletal changes induced by netarsudil caused the expansion of the conventional outflow tissues such as the TM and the SC avoiding its collapse at elevated IOP. As a NET inhibitor, netarsudil is thought to decrease AH secretion since elevated norepinephrine levels activate α2 adrenergic receptors responsible for AH production at the ciliary processes [32]. Finally, netarsudil is also thought to have vasodilator properties as it reduces episcleral venous pressure in rabbits facilitating AH drainage to the bloodstream [32]. Similarly to ripasudil, ocular hyperaemia was the most frequently reported AE during clinical development with incidence rates of 57% which improved during the course of the study decreasing to 24% after 28 treatment days.

Roclatan™, formerly known as PG323, is a fixed dose combination (FDC) of netarsudil 0.02% and latanoprost 0.005%, which combines the previously described mechanisms of action with

the capacity of the prostaglandins of increasing AH outflow through the uveoscleral pathway [33, 34]. This fixed combination currently in Phase III clinical trials achieved clinically and statistically superiority in terms of ocular hypotensive efficacy when compared to its individual active components at the same concentrations. However, incidence rates of ocular hyperaemia were superior in the FDC than those observed in the latanoprost group (40 vs. 60%).

AMA0076 is a locally acting ROCK inhibitor currently in Phase II clinical trials specifically designed to reduce IOP while minimizing side effects such as hyperemia. *In vivo* studies conducted in an acute hypertensive rabbit model showed that AMA0076 prevented IOP elevation more efficiently than latanoprost and bimatoprost. *In vitro* studies conducted in rabbit ocular tissues demonstrated that AMA0076 was able to induce reversible changes in cell shape and decreased the number of actin filaments and focal adhesions that may facilitate AH outflow [35].

2.1.2. Adenosine receptor ligands

2.1.2.1. Description and biological function

Adenosine is an endogenous nucleoside modulator of both intracellular and extracellular origin. Adenosine half-life is very limited (~1.5 seconds) as it is rapidly metabolized to inosine and hipoxantine; this is why extracellular levels of adenosine, which usually range from 20 to 200 nM, are considered a good indicator of cellular homeostasis. Adenosine levels increase, even up to the micromolar range, in response to cellular stress conditions such as tissue hypoxia or ischemia. In fact, adenosine levels in AH are significantly elevated in ocular hypertensive individuals when compared to normotensive individuals [36, 37].

Adenosine receptors (ARs) belong to the family of G protein-coupled receptors (GPCR) [37]. Four subtypes of AR have been identified (A1, A2A, A2B and A3), and all of them are involved in regulation of cAMP production through different pathways: A1 and A3 down-regulate cAMP levels inhibiting adenylyl cyclase, whereas A2A and A2B receptors activate adenylyl cyclase, increasing cAMP production. ARs are expressed in numerous ocular tissues such as ciliary body, TM, SC and retina. Activation/inactivation of ARs impacts AH formation, outflow and consequently IOP homeostasis. Additionally, ARs are also involved in retinal function, impacting blood flow and neuronal survival [36].

2.1.2.2. Mechanism of action

Activation of A3 receptors results in activation of Cl^-channels in the non-pigmented ciliary epithelial (NPE) cells of the ciliary epithelium where AH is produced [38]. Studies conducted in A3AR knockout mice and in mice treated with A3AR antagonists showed that absence or inhibition of this receptor significantly decreases IOP when compared to native or untreated animals [39]. On the contrary, mice treated with A3AR agonists show enhanced chloride release resulting in increased AH production and rise in IOP. AR can also affect AH outflow; there are two pathways by which AR agonists increase conventional outflow through the TM and SC: cell volume modification mediated by ion transport and ECM remodelling [36]. A1, A2A and A3 AR agonists have shown to increase Ca^{2+} in the cells of the SC and to diminish

TM cell volume [40]. Outflow resistance in the TM is dependent on the composition of the ECM; activation of A1 ARs triggers signalling cascades that lead to the expression of high levels of metalloproteases such a MMP-2 and MMP-9, enzymes participating in ECM remodelling enhancing AH outflow and decreasing IOP. On the contrary, A2A and A2B AR activation increase ECM deposition and therefore difficult AH outflow increasing IOP [41].

In view of the previously exposed mechanisms, it can be concluded that AR ligands play a key role in IOP control. In general terms, adenosine binding to A1AR in the TM reduces outflow resistance. However, A2A AR stimulation may result in IOP increase or decrease depending on the alterations to the resistance in the SC. Finally, activation of A3 AR mediates activation of Cl^-channels in the NPE cells inducing AH production, while A3 AR antagonists prevent adenosine-induced activation of Cl^- channels decreasing IOP.

2.1.2.3. Drugs in development

Numerous AR ligands (both agonists and antagonists) are being developed with the purpose of exploiting their potential for modulation of IOP. The adenosine analogues that are currently in glaucoma clinical trials include trabodenoson (Inotek Pharmaceuticals, US), OPA-6566 (Acucela, US and Otsuka Pharmaceutical, Japan), ATL-313 (Santen Pharmaceutical) and CF-101 (Can-Fite Bio Pharma, US).

Trabodenoson, formerly known as INO-8875/PJ-875, is a highly selective A1 AR agonist administered in eye drops currently in Phase III clinical trials. The IOP-lowering effect of four different doses of trabodenoson ranging from 50 to 500 μg was evaluated when administered b.i.d during 28 consecutive days in a Phase II clinical trial [42]. Administration of trabodenoson resulted in a dose-related IOP reduction; the highest dose tested achieved a statistically significant IOP reduction in 25% (6.5 mmHg) when compared to placebo. All the doses tested showed a good tolerability profile. The proposed mechanism of action for trabodenoson involves activation of the A1 adenosine receptor that promotes phosphorylation of the extracellular signal-regulated kinases ERK1 and ERK2, resulting in increased secretion of MMP-2 and changes in the ECM that decrease TM resistance to the AH outflow.

OPA-6566 and **ATL-313** are two A2A agonists currently in Phase I clinical trials; at this point of development, little information on their clinical development is available. Both drugs are anticipated to increase AH outflow via the conventional pathway of the TM and SC rather than the uveoscleral pathway.

CF-101 is an A3 AR agonist orally administered presently in Phase II clinical trials. Recently, CF-1001 failed to meet its primary endpoint as no statistically significant differences in IOP were found between the CF101 group and the placebo group after 16 treatment weeks.

2.1.3. Nitric oxide donors

2.1.3.1. Description and biological function

Nitric oxide (NO) is a gaseous endogenous signalling molecule synthesized by nitric oxide synthases (NOS) that catalyse the oxidation of the amino acid L-arginine to form NO and

L-citrulline. There are three NOS isoforms: the neuronal NOS (nNOS or NOS-1), the endothelial NOS (eNOS or NOS-3) and the inducible NOS (iNOS or NOS-2). NOS-1 and NOS-3 are activated by the calcium/calmodulin complex in response to an increase in calcium and produce NO in the pico- or nanomolar scale. On the contrary, NOS-2 activation is calcium independent and produces NO in a micro- to millimolar scale [43].

NOS-3 is expressed in TM, SC, ciliary body and uveal vascular endothelium. NOS-1 is located in nerve fibres in the cornea and lens epithelium and iNOS is detected after directed stimulation in the TM and in the ciliary body and vessels. This expression pattern of NOS enzymes in the anterior segment of the eye suggests that NO plays a key role in the regulation of AH dynamics. In fact, levels of NO and NOS expression are diminished in glaucomatous human eyes. In addition, NOS-3 knock-out mice exhibit elevated IOP levels due to a reduction in the conventional outflow, whereas the opposite effect is observed in NOS-3 over expressing transgenic mice [43, 44].

2.1.3.2. Mechanism of action

NO stimulates soluble guanylatecyclase (sGC) leading to the elevation of intracellular cyclic guanosine monophosphate (cGMP levels), a secondary messenger that interacts with protein kinases and phosphodiesterases. Multiple studies indicate that the NO-cGMP pathway regulates IOP levels increasing AH outflow through the conventional route and by reducing AH secretion [43].

Cytoskeletal changes at the TM seem to be the underlying mechanism mediating the increase in AH outflow induced by NO. NO induces vascular smooth muscle cells (VSMC) relaxation by stimulation of cGMP synthesis that subsequently activates protein kinase G (PKG). This results in inhibition of the Rho-kinase cascade and leads to inhibition of the MLC-2 phosphorylation. Analogously to VSMCs, TM cells also exhibit contractile properties and modulation of these properties by NO is thought to mediate changes that result in a reduction in outflow resistance. Additionally, it has been demonstrated that inhibition of multi-drug resistance-associated protein-4 also induces TM cellular relaxation mediated by cGMP-PKG pathway [45]. NO could also mediate its IOP-lowering effects by targeting cells of the SC. In fact, Rho-kinase inhibition mediated by NO-cGMP regulates actin dynamics and cell contractility in cultured SC cells [46].

2.1.3.3. Drugs in development

Latanoprostene bunod (LBN; BOL-303259-X; Bausch & Lomb) is a novel nitric oxide-donating prostaglandin F2a analogue currently in Phase III clinical trials [47]. In the eye, LBN is metabolized to two moieties. The first, latanoprost acid, is an F2alpha prostaglandin analogue, while the second, butanediol mononitrate, releases nitric oxide, which activates the soluble cGMP signalling pathway. LBN achieves IOP control simultaneously enhancing AH outflow through the conventional and the uveoscleral routes. Doses ranging from 0.006 to 0.040% of LBN solution were administered once a day to patients with OAG or OHT for 28 consecutive days. LBN at 0.024 and 0.040% achieved statistically significant reductions in mean IOP when compared to latanoprost. During the Phase III clinical trial LBN 0.024% (QD) was not only

non-inferior to timolol maleate 0.5% dosed twice daily (b.i.d) after 3 months of treatment but also provided significantly greater IOP reduction. LBN exhibited a similar safety profile than prostaglandins being conjunctival hyperaemia the most frequently reported AE.

2.2. New mechanisms of action

New drug targets are certainly playing an important part in modernising the way glaucoma will be treated in the future. But innovation in glaucoma is not only focused in the discovery of new drug targets, but it is also taking advantage of new and exciting mechanisms of action that seek to solve unmet needs that current treatments cannot solve. In the following section, we will give an overview of drugs using innovative mechanisms of action, focusing on those that have in the past few years entered in clinical development for glaucoma. It should be noted that although antibodies fall into this category of drugs using new mechanisms of action, they have not been included in this section since, up to the authors' knowledge, there are no clinical programmes currently developing antibodies for the treatment of glaucoma. A section on neuroprotective drugs has been included at the end of this section to highlight the importance these drugs are acquiring in the glaucoma pipeline.

2.2.1. Oligonucleotide-based compounds

Oligonucleotides have in the past decades turned out to be an interesting therapeutic approach, particularly due to their ability to address intracellular targets. Oligonucleotides can be designed to target specific genes or RNAs with the aim of altering gene expression or even exert a direct interaction by binding to molecules. The main classes of oligonucleotides that are currently being developed as therapeutic tools are aptamers, ASOs, siRNAs and microRNAs (miRNAs) [48].

2.2.1.1. Aptamers

Aptamers are RNA or DNA oligonucleotides that form a 3D structure designed to interact with large or small molecules. Aptamers typically bind to proteins but can be designed to act upon other types of molecules [49]. Aptamers, contrary to antibodies, are chemically synthetized products that do not require biological steps in their production processes; this results in products that are very well controlled without significant variability among batches. Aptamers have not been widely tested in the context of glaucoma. Pegaptanib, a first-in-class FDA-approved aptamer for the treatment of age-associated macular degeneration (AMD), has been briefly studied for the treatment of neovascular glaucoma [50]. This compound binds to a subtype vascular endothelial growth factor (VEGF), $VEGF_{165}$, hampering its ability to bind to its cell surface receptor thus impairing neovascularization [51]. In addition, ARC81, an anti-transforming growth factor-β (TGF-β) aptamer, has been studied for the reduction in corneal scaring, a common complication of glaucoma filtration surgery [52].

2.2.1.2. Antisense oligonucleotides (ASOs)

ASOs are single-strand RNA or DNA oligonucleotides, of approximately 15–25 bp, that mediate mRNA degradation by an RNaseH-mediated mechanism [53]. These compounds have

been widely used to study cell function and lately applied to therapeutics. There are two FDA approved ASOs; vitravene, an intravireally administered ASO for the treatment of cytomegalovirus retinitis in AIDS patients and mipomersen, an intravenously administered ASO for the treatment of familiar hypercholesterolemia [54, 55]. The main advantage of this class of compounds is that they modulate gene expression without altering the genetic code, and that their action upon their target gene can be rapidly modified. In addition, as other oligonucleotides, ASOs are chemically synthetized, with all the advantages this entails. On the other hand, ASOs are labile products that require chemical modifications to increase their stability; these modifications can potentially increase their toxicity [48, 56].

There are two ASOs under development for treatment of different types of glaucoma; Aganirsen (GS-101) and ISTH0036. Aganirsen is a 25-bp ASO targeting insulin receptor substrate-1 (IRS-1) administered in eye drops; this compound is being developed for the treatment of corneal neovascularization and has also been tested in neovascular glaucoma [57]. ISTH0036 is a fully modified phosphorothioate 14-bp oligodeoxynucleotide with a 3 + 3 LNA-gapmer pattern targeting TGF-β2. TGF-β2 is an anti-proliferative and anti-inflammatory factor that is upregulated in the AH of POAG patients. Increases in TGF-β2 correlate with deposition of fibrillar extracellular matrix in the TM, one of the hallmarks of POAG [58]. These extracellular depositions in the TM hamper AH outflow and consequently result in IOP increase. ISTH0036 is currently being tested in a Phase I dose-finding clinical study in patients with advanced glaucoma undergoing filtration surgery due to uncontrollable elevated IOP. The compound is administered intravitreally (IVT) at the end of trabeculectomy; the outcomes of the study are safety, tolerability and effect on IOP.

2.2.1.3. Short interfering RNAs (siRNAs)

siRNAs are double-stranded RNA molecules of approximately 19–25 bp that mediate gene silencing by blocking translation of specific mRNAs into their corresponding protein [59]. These molecules, although usually larger than ASOs, are in general more potent and stable than ASOs. Depending on the target tissue and the level of expression of the target gene, these compounds can be administered in eye drops avoiding invasive administration methods, if deeper regions need to be accessed IVT administration may be required [60]. In addition, once the siRNA has entered the RISC complex its action lasts for quite some time, this means that a single molecule would be able to mediate the degradation of several mRNAs thus amplifying the effect of the compound. This prolonged action is particularly interesting in the case of glaucoma as it could avoid sudden increases in IOP due to skipped doses.

Bamosiran (SYL040012) is a 21-bp unmodified siRNA targeting adrenergic receptor β2 (ADRB2) for the treatment of glaucoma. This compound is administered in eye drops and penetrates the eye to reduce synthesis of AH by blocking the ADRB2 at the ciliary body and possibly also at the TM [61, 62]. In contrast to traditional beta-blockers, bamosiran acts only locally in the eye; this is because the molecule is rapidly degraded when it reaches systemic circulation, thus reducing the likelihood of systemic side effects. This characteristic makes bamosiran a safe compound for the treatment of individuals with risk of heart disease or other alterations in which beta-blockers are contraindicated.

QPI-1007 is a 19-bp siRNA targeting Caspase-2. This product, administered by IVT injection, is under development for the treatment of several optic neuropathies, including glaucoma [63]. Caspase-2 is specifically activated during ganglion cell death leading to irreversible loss of vision, thus reducing its expression could potentially protect retinal ganglion cells from apoptosis.

2.2.2. Gene therapy

Gene therapy is a technique that uses genetic material to modify the disease state, usually using a vector to transfer the genetic material. For ophthalmic affectations, distinct viral vectors can be used for the delivery of such genetic material. Most-studied vectors include adenovirus (AdV), adeno-associated virus (AAV), herpes simplex virus (HSV) and lentivirus; all of them offering distinct pros and cons [64]. While large advancement has been achieved in different eye diseases, gene therapy for glaucoma has faced substantial limitation due to the lack of obvious genetic alterations. Indeed, causative and risk factor genes such as myocilin (MYOC), optineurin (OPTN), Cytochrome P450 1B1 (CYP1B1), caveolin (CAV1/CAV2) and TANK-binding kinase 1 (TBK1), among others, represent less than 10% of glaucoma cases worldwide [65]. Up to date, only one gene therapy trial for glaucoma has been listed (Trial ID: US-0589). This Phase I study proposes to evaluate the safety of SCH-412499 (rAd-p21) after a single injection into the sub-conjunctival space of the eye in glaucoma subjects prior to trabeculectomy. The treatment uses an AdV vector for the expression of p21 WAF-1/Cip1, a potent cyclin-dependent kinase inhibitor to reduce wound healing process and fibroproliferation after filtering surgery [66]. No results have been disclosed yet; however, pre-clinical studies demonstrated a safe profile with strong anti-proliferative effect after filtration surgery in animal models [67, 68].

In collaboration with Mayo Clinic (Rochester, USA), Oxford BioMedica plc (Oxford, UK) is developing a novel gene therapy approach for the treatment of chronic glaucoma. Pre-clinical studies have been undertaken to determine the feasibility of the LentiVector® platform for the delivery and expression of cyclooxygenase (COX-2) and prostaglandin F2α (PGF-2α) genes to reduce IOP in glaucomatous patients. According to the company's announcement, pre-clinical studies demonstrated a good tolerance for the LentiVector® when used at high doses, with the ability to transduce proper target cells following transcorneal injection into the anterior chamber. Moreover, data showed a long-term gene expression for up to 5 months. Although pre-clinical efficacy studies on IOP have been planned, no additional results have been published.

Besides these two emerging gene therapy treatments for glaucoma, most investigational developments are still in pre-clinical phases, showing relative effect on IOP. For example, the COX-2 and PGF-2α gene therapy models previously described demonstrated a prolonged decrease in IOP in large animal models [69]. Similarly, using lentiviral-based dual expression vector to deliver prostaglandin F synthase, significant reduction in IOP has been achieved [70]. However, the overall reduction in IOP produced by these vectors was not as extensive as that observed for topical PG eye drops. Likewise, different gene therapy strategies to modulate the RhoA or Rho-kinase pathways showed an efficient but moderate IOP-lowering effect [71, 72]. In an elegant way, gene therapy has also been adapted to steroid-induced glaucoma.

In these patients, topical instillation of glucocorticoids is known to produce ocular hypertension by producing a downregulation of the matrix metalloproteinase 1 (MMP1) gene in the TM. Because the patients are under an on and off treatment schedule with glucocorticoids, a new self-complementary AAV has been generated for the expression of MMP1 under the control of a glucocorticoid response element. This allows for the induction of MMP1 expression only after the administration of glucocorticoids, a strategy that presents great advantages. Using this novel system, a reduction in IOP was detected in large animal model and would be highly beneficial in clinic [73].

In addition to cell transduction and adequate gene expression modulation, the route of administration is a critical factor for effective gene therapy. Interestingly, optimum delivery and transduction of AdV have been found through the TM and the SC, structures from where the AH flows [74]. However, the complexity of the whole outflow tract, which includes various cell-types harbouring different transduction properties, may impair the overall efficacy of gene therapy. Moreover, the possible systemic exposure with unwanted side effects is an important downside of direct release of viral vectors that can drain into the retinal venous circulation. Although we are still a long way from the instauration of gene therapy in glaucoma treatment, the advancement achieved in the field is encouraging and sustains the feasibility of such technique in human.

2.2.3. Stem cell therapy

Once glaucoma has reached advanced stages with irreversible vision loss, the nearly unique alternative is to replace the retinal ganglion cells of the optic nerve to restore functional vision. Hence, future objectives aim at regenerating the optic nerve in blind eyes using stem cell therapy. While the majority of clinical trials using stem cells have been conducted in neuroretinal degenerative diseases, trials in glaucoma are only starting to emerge. This is because the replacement of RGCs is a most tricky task and will depend on (1) cell engraftment, differentiation and migration to the ganglion cell layer, (2) the growth of axons into the optic disc and (3) the establishment of effective synapse connection [75]. To do so, cells can be implanted into different compartments of the eye, although most commonly tested sites are intravitreal or sub-retinal. The stem cells used can be of various sources and are often engineered *in vitro* through gene therapy [76]. Autologous transplantation of genetically modified cells that originate from the same patient has been favoured due to larger safety window, reducing host-defense mechanism and immune reaction such as those produced by AdV viral vectors. Because of the novelty of these methodologies, the primary goals of current registered clinical trials are towered first on safety outcomes (monitoring of adverse and serious adverse reaction), and secondary outcomes on efficacy (visual acuity, eye fundus and visual field improvement). In general, patients with advanced stages of glaucoma are recruited because of the lack of previous safety studies involving humans.

A novel Phase II trial aims to test the efficacy and safety of adipose-derived regenerative cells for the treatment of glaucomatous neurodegeration (NCT02144103). After liposuction, cells are harvested and isolated from fat tissues and injected into the same patient by subtenon administration. The rationale behind the use of adipose-derived mesenchymal stem cells is based on

their capacity to differentiate into retinal pigment epithelium cells. Another promising treatment uses autologous bone marrow-derived stem cells (BMSC): after prior isolation and culture, these cells are injected intravitreally into the worst eye of the patient (NCT02330978). Safety parameters are the first objective of this Phase I trial, although an improvement in visual acuity and visual field are expected in secondary outcomes. Mechanisms for such potential effects remain uncertain. Surprisingly, in animal models, BMSCs have been shown to survive after intravitreal injection, although without showing any apparent differentiation ability. There are actual evidences that BMSC cannot pass the vitreoretinal interface, suggesting that BMSCs may act in a paracrine manner, most likely by providing neuroprotection, rather than by differentiating into RGCs [77]. A larger clinical trial is currently running to evaluate the efficacy of such BMSC therapy, comparing distinct injection sites for various ophthalmic diseases, including glaucoma (NCT01920867). Routes of injection include retrobulbar, subtenon, intravenous, intravitreal and intraocular, which may provide valuable information on the ability of BMSCs to improve visual acuity depending on the delivery site. Overall, big hopes are expected from these trials and their success would definitively represent important breakthrough.

Aside from clinical trials, numerous pre-clinical studies are underway to explore the capacity of different stem cell populations to provide neuroprotection or regeneration of optic nerves. For example, a novel stem cell therapy has been explored to prevent the loss of TM function and cell number observed in glaucoma. The TM and SC operate to drain out the AH and play pivotal role in sensing IOP fluctuation. In conjunction with the modulation of the extra-cellular matrix and enzymes activity, these two structures adapt to adjust the resistance to fluid flow. The aim of this new stem cell therapy, although still at pre-clinical stages, is to obtain new functional TM-like cells to restore functional outflow tract. Recently, in a mouse model of glaucoma, transplantation of induced pluripotent stem cells (iPSC) differentiated into TM cells was shown to reduce neuronal loss and IOP [78]. Surprisingly, the cell transplant led to increased proliferation of pre-existing TM cells. Obviously, further investigation will be needed to confirm the feasibility of these innovative therapies and to efficiently apply them to regular clinical practice.

2.2.4. Neuroprotective drugs

Transport of neurotrophic factors (NTFs) along RGCs axons is critical for cell survival, and unfortunately, this process is found altered in glaucoma. Indeed, the mechanical compression of the optic nerve hinders retrograde travelling of NFTs, leading to induction of the apoptotic cascade. Neuroprotective therapy thus aims to prevent RGCs cell death and damage of the optic nerve. Neuroprotective drugs have been initially developed for the treatment of various neuropathic diseases and their success raised the possible application for the prevention of vision loss in glaucoma. Pre-clinical studies have clearly demonstrated the efficacy of neuroprotective therapy for glaucoma; however, it has not yet been translated into clinic. When looking retrospectively, the development of such therapies has been hampered by the failure of Memantine to meet its primary outcome in Phase II trials, and consequently the drop from clinical development. This drug belongs to a new class of Alzheimer's disease medications that inhibits NMDA receptors to counteract the toxic effect of L-glutamate accumulation into the nervous system. It has been shown to strongly reduce RGCs loss in various animal species [79]. Unfortunately, Memantine

failed to demonstrate any protective properties in glaucoma patients [80]. Consequently, companies became skeptical over undertaking such risky clinical trials. Up to date, the main difficulty relies on the fact that long-term efficacy for neuroprotection is extremely hard to prove. Nonetheless, the rationale behind this therapy remains valid and is still currently explored, mostly that a myriad of signalling pathways can be modulated to protect RGCs. The fact that many of these targets act through an IOP independent manner provides an appealing approach to treat patients with normal tension glaucoma. This chapter will explore some of these avenues, focusing on survival factors, apoptotic mechanisms and oxidative stress.

One of the best strategies to achieve neuroprotection focuses on the delivery of NTFs to RGCs using cell therapy. A Phase I clinical trial has been completed to evaluate the safety and efficacy of the NT-501 CNTF Implant after intravitreal injection into one selected eye (Neurotech Pharmaceuticals, Inc; NCT01408472). The implant contains human cells (designated NTC-201) that originate from a retinal pigment epithelial cell line genetically engineered to produce human ciliary neurotrophic factor (CNTF). A role for CNTF in neuroprotection of the retina has been established in a wide number of pre-clinical studies, which was shown to promote cell survival of RGCs in most animal models [81]. In human, such implant has been previously proved to release CNTF consistently over a 2-year period without producing systemic exposure, hence avoiding the need for multiple injections [82]. Outcomes have not been reported yet but studies suggest favourable pharmacokinetic of the implant with possible treatment of chronic retinal degenerative diseases. Overall, MSCs and BMDS transplant represent a valuable tool for long-term delivery of various NTFs as well as anti-inflammatory cytokines that may prevent apoptosis of RGCs.

Activation of apoptosis is a key mechanism in RGCs cell death and increasing amount of anti-apoptotic agents are currently being investigated for the treatment of glaucoma. Since apoptosis often occurs in early stages of the disease, its detection is of prime importance to prevent irreversible damage lost. A new Phase I study is evaluating the ability of ANX776 to identify RGC apoptosis as part of a new detection of apoptosing retinal cells (DARC) technique (NCT02394613). The primary purpose of the study is to develop a new diagnosis tool for glaucoma in healthy patients. As previously described, QPI-1007 is a promising candidate to achieve neuroprotection by reducing the expression of Caspase-2 (NCT01965106 and NCT01064505). Interestingly, brimonidine, a selective alpha2-adrenergic agonist, has been shown to protect against optic nerve damage independently of its IOP-lowering effect, most likely by inducing the production of the anti-apoptotic proteins Bcl-2 and Bcl-XL [83]. Effectively, in a clinical trial, normal tension glaucoma patients treated with brimonidine displayed preserved field function as compared to those that were given timolol [84]. Curiously, other classic IOP reducing agents have been proved to yield neuroprotective effect because of a dual mechanism of action. A different example is the beta adrenergic blocker Betaxolol. This drug interacts with other channels such as the sodium and L-type calcium channels, an affinity that was proposed to contribute to the protection of the visual field observed in treated patients [85]. Interestingly, a Phase III trial named 'Stop Retinal Ganglion Cell Dysfunction Study' is currently running to compare the protective effect of numerous hypotensive medications routinely used in clinic (NCT02390284). The trial recruits patients with normal vision and eyes are evaluated for changes in the pattern electroretinogram (PERG) and retinal nerve fibre layer (RNFL) thickness.

Therapy	Description	Phase/stage	Outcome	Trial ID
ASO	Intra-vitreal injection of ISTH0036 as an addition to filtration surgery	Phase I/recruiting	Safety and tolerability	NCT02406833
siRNA	Bamosiran eye drops for POAG	Phase II/completed	Safety, dose finding, IOP-lowering effect	NCT02250612
siRNA	QPI-1007 injection in primary angle closure glaucoma	Phase II completed	Safety and tolerability and pharmacokinetics	NCT01965106
Gene therapy	Intraocular delivery of p21 WAF-1/Cip1 gene before glaucoma surgery	PhaseI/unknown	Safety and tolerability, fibroproliferation and wound healing	US-0589
Gene therapy	LentiVector® platform for the delivery of COX-2 and PGF-2α to reduce IOP	Pre-clinical	Safety, IOP-lowering effect	
Stem cell therapy	Subtenon injection of adipose-derived regenerative cells	Phase II/recruiting	Safety, change in visual acuity, eye fundus, visual field	NCT02144103
Stem cell therapy	Intra-vitrial injection of BMSCs	Phase I/recruiting	Safety, change in visual acuity and visual field, optical coherence tomography, RGC function	NCT02330978
Stem cell therapy	Retro-bulbar, subtenon, intra-venous, intra-vitreal and intraocular injection of BMSCs	Phase II/recruiting	Change in visual acuity and visual field	NCT01920867
Stem cell therapy, neuroprotection	Delivery of NT-501 CNTF Implant	Phase I/completed	Safety, vision, visual field, nerve fibre layer, optic nerve topography	NCT01408472
Neuroprotection	RGCs protection by hypotensive eye drops	Phase III/recruiting	Change in PERG, RNFL	NCT02390284
Neuroprotection	Single intra-venous injection of ANX776 as new detection of apoptosing retinal cells (DARC) technique	Phase I/active	Safety and DARC count	NCT02394613

Table 1. Current clinical trials for new mechanisms of action for glaucoma.

Anti-oxidants also represent an attractive alternative to prevent long-term RGC damage. Due to high metabolic activity during visual transduction, retinal cells are particularly sensitive to oxidative stress, mainly in elderly. Increased levels of reactive oxygen species (ROS) and associated DNA damage have been reported in glaucoma patients [86]. Numerous pre-clinical studies in glaucoma animal models have shown a neuroprotective benefit for a large variety of anti-oxidant such as Vitamin E, Coenzyme Q10, Ginkgo biloba extract and other Chinese medicines [79]. One clinical trial previously addressed the impact of oral versatile anti-oxidants on glaucoma progression, comparing Ginkgo biloba and α-tocopherol for 3

months (NCT01544192), however no clear benefits have been reported, and other similar studies failed to find differences among treatments (**Table 1**) [87].

3. Innovation in medical devices and surgical procedures

There are two types of surgical procedures aimed at lowering IOP, trabeculoplasty and trabeculectomy. The former is aimed towards treating the TM with LASER to diminish AH resistance and increase drainage into collecting channels or into the outside of the eye. In the latter, a part of the TM is removed to reduce resistance to outflow. These approaches usually reduce IOP for a period of up to 5 years, but additional medical or surgical interventions are commonly required after this period due to scaring or secondary complications. Improvements in surgery thus seek using artificial channels that enlarge drainage routes or shunts that bypass the TM draining the AH directly to the SC or to the suprachoroidal space [88]. In the last decade, minimally invasive glaucoma surgery (MIGS) has gained popularity due to its minimal tissue destruction, short surgery time and fast post-operative recovery. Here, we present an overview of glaucoma draining devices that are in development for these procedures.

3.1. Drainage devices to the SC or to the sub-conjunctival space

The SC is an endothelium-lined channel derived from the TM located at the joining point of the sclera and cornea. The TM is composed of three layers: the innermost uveal meshwork, the middle layer section composed of connective tissue called the corneoscleral meshwork and the third layer, also known as juxtacanalicular tissue. The juxtacanicular tissue is a non-fenenstrated endothelial layer immersed in fibres and a rich extra-cellular matrix that lines the inner wall of the SC. In humans, 75% of the resistance to AH outflow is exerted by the TM, mainly by the juxtacanalicular portion and the deposition of glycosaminoglycans in the TM ECM [89]. As such, bypassing the TM draining the liquid to the SC has been widely used as an approach to alleviate elevated IOP. Several devices are currently under development with the aim of improving the outflow through the TM.

3.1.1. Devices in development

The Glaukos iStent (Glaukos Corporation, Laguna Hills, CA, USA) is a heparin-coated micro stent that bypasses the TM by creating a pathway from the anterior chamber to the SC [90]. Implantation of this device in patients undergoing cataract surgery resulted in a sustained decrease in IOP (IOP ≤ 21 mmHg) in 72% of patients 12 months after implantation compared to 50% in the control group. Twenty-four months after surgery 61% still had IOP levels below 21 mmHg whereas in the control group 50% of patients maintained the targeted IOP. Other outcomes included in the study, such as decrease in IOP ≥ 20% and medications reduction, were also positive for the device-implanted patient group. Further studies have shown that sustained elevated IOP may affect the shape of the SC and therefore implanting one iStent may not be sufficient to achieve a sustained decrease in IOP. To solve this issue studies implanting several iStents have been performed showing promising data [91].

The Hydrus microstent (Ivantis Inc., Irvine, CA, USA) is an intra-canalicular scaffold made of nitinol that is surgically implanted into the SC during cataract surgery. This device is manufactured to follow the curve of the SC and widens the opening of the canal avoiding its collapse. The efficacy of this device has been studied in patients undergoing cataract surgery and the results of these studies show that reduction in washed out diurnal IOP ≥ 20% was higher in the implanted group compared to the cataract surgery alone group 24 months after surgery (80 vs. 46%). Implantation of the device was also able to reduce the use of hypotensive medications [92].

InnFocus Microsunt, previously known as the MIDI Arrow (InnFocus Inc., Miami, FL, USA), is made of poly(styrene-block-isobutylene-block-styrene) SIBS, a synthetic thermoplastic elastomeric biomaterial that does not cause inflammation. The implant is used in conjunction with Mitomycin C to modulate would healing post-surgery. This device is placed in the anterior chamber and drains into the scleral surface [93]. The device was implanted in 23 eyes that had failed maximum tolerated glaucoma medication. The patients were followed for a period of 3 years; 14 patients received the implant alone whereas the rest were implanted concomitantly to cataract surgery. Years 1, 2 and 3 after the procedure 100, 91 and 95% of the patients fulfilled the success criteria of the study (IOP ≤ 14 mm Hg and IOP reduction ≥20%), and the mean number of glaucoma medications was reduced from 2.4 ± 0.9 to 0.3 ± 0.8, 0.4 ± 1.0 and 0.7 ± 1.1, respectively. Adverse events of the procedure included transient hypotony (13%) and transient choroidal effusion (8.7%); both adverse events resolved spontaneously [94].

The XEN45 Gel Stent (Allergan, Dublin, Ireland) is a soft flexible implant initially developed by AqueSys but later acquired by Allergan. The device is manufactured in collagen-derived gelatine cross-linked with glutaraldehyde and is injected through the anterior chamber into the sub-conjunctival space. The device swells upon hydration creating the channel. The XEN45 is approved in Europe, Turkey, Canada and Switzerland for reduction in IOP in patients with POAG where previous medical treatments have failed and is in late stage development in the USA. In Europe, the device can be used in conjunction with cataract surgery or as a standalone procedure. The data obtained from clinical trials show a mean drop of 47% from preoperative IOP in the standalone procedure and a 40% decrease when combined with cataract surgery. The main adverse events of this procedure include intra-operative sub-conjunctival or anterior chamber bleeding (1.2%), cataract-related complications (0.8%), post-operative hyphema (2.6%), self-limiting choroidal effusion (1%) shallow anterior chamber (0.8%), viscoelastic injection into the anterior chamber (0.6%) and anterior chamber tap to release retained viscoelastic (0.4%).

3.2. Drainage devices to the suprachoroidal space

There are several devices designed to drain AH from the anterior chamber to the suprachoroidal space, where the fluid is reabsorbed by the scleral channels of the choriocapillaries. These devices are based on the existence of a difference in hydrostatic pressure between the supra-choroidal space and the anterior chamber; this difference favours unidirectional flow from the anterior chamber to the suprachoroidal space reducing IOP. The materials used to manufacture these devices vary from gold to non-biodegradable polymers; materials that are inert, non-biodegradable and biocompatible to ensure proper function of the device.

3.2.1. Devices in development

The CyPass (Transcend Medical, Menlo Park, CA, USA) is a fenestrated polyamide supraciliary device that connects the anterior chamber with the suprachoroidal space. The device is implanted during cataract surgery and its efficacy has been tested in a multi-centre, prospective study enrolling 136 subjects with two cohorts. Cohort 1 was composed of subjects with OAG requiring cataract surgery that had uncontrolled IOP (IOP; ≥21 mmHg, $n = 51$), whereas cohort 2 was composed of subjects with OAG requiring cataract surgery with controlled IOP (<21 mmHg, $n = 85$). Glaucoma medications were stopped post-surgery but could be restarted if needed. The results of the study indicate that there was a reduction of 37% in mean IOP 24 months after surgery. There was a statistically significant decrease in the need for glaucoma medications in both cohorts [95]. Further development of this device includes a randomized controlled trial that is currently underway (**Table 2**).

	Device	Manufacturer	Material	Status	Trial ID
Devices draining to the SC or to the sub-conjunctival space	iSTENT	Glaukos Corporation	Non-ferromagnetic titanium	FDA approved in patients undergoing cataract surgery. Phase IV	NCT00326066
	Hydrus microstent	Ivantis	Nitinol (alloy of nickel and titanium)	Phase III	NCT01539239
	InnFocus Microshunt	InnFocus	Poly(styrene-block-isobutylene-block-styrene) SIBS	Phase IV	NCT02177123
	XEN45	Allergan (AqueSys)	Collagen-derived gelatine	Phase IV	NTC02006693
Devices draining to the suprachoroidal space	CyPass	Transcend Medical	Non-biodegradable polyimide	Safety and Efficacy	NCT01085357
	SOLX gold shunt	SOLX	Gold	Phase III	NCT01282346
	Aquashunt	OPKO health	Polypropylene	Safety and Efficacy	NCT00834223
	STARflo	iSTAR Medicals	Silicone microporus material	Safety and Efficacy	NCT02272569

Table 2. Devices in development for glaucoma.

The SOLX gold shunt (SOLX Inc., Waltham, MA, USA) communicates the anterior chamber with the suprachoroidal space via 19 channels formed between the two 24-karat medical-grade gold plates that form the shunt. The device is approved in Europe but still investigational in the USA. Several clinical trials have been conducted for this device with different outcomes. Success for this device was defined as a target IOP between 5 and 22 mmHg and an IOP decrease ≤20%. Most clinical studies for this device have yielded a success rate around 80%. In contrast, in a study performed by Hueber and co-workers enrolling 31 patients implanted with the device and followed up for a period of 4 years most patients (97%) failed

the established success criteria. This difference outcome may be due to a fibrotic reaction to the device in this particular trial [96].

The Aquashunt (OPKO Health Inc., Miami, FL, USA) is a device made of polypropylene curved to accommodate the eye's shape. The results from a clinical study enrolling 15 patients with uncontrolled IOP indicate that eight of the patients achieved an IOP reduction of 31%, four of which needed concurrent medical therapy to reach satisfactory IOP after a period of 12 months. Further clinical studies have not been initiated [96].

The STARflo glaucoma implant (iSTAR Medical SA, Wavre, Belgium) is made of a microporous silicon elastomer and implanted intrascleraly into the suprachoroidal space. Clinical data are available from a limited number of cases, and it shows a reduction in the pre-operative IOP of 37.0 mmHg to a post-operative IOP of 14.3 mmHg 12 months after implantation. The reduction in glaucoma medication intake went from 3.25 medications/day to 1.5 intake/day.

4. Conclusions

Current medical therapy for glaucoma is insufficient to avoid the deleterious effects of this progressive ophthalmic neuropathy. In the last decade, significant efforts have been made in order to develop new products that use novel approaches to address the unmet needs of a disease that is still the second cause of blindness. This review gives an overview of these approaches, focusing on new targets that regulate AH balance in the eye or that are involved in fibrosis and scaring; processes that complicate the long-term success of glaucoma filtration surgery.

New mechanism of actions such as therapies based on oligonucleotides, gene therapy and stem cells is also reviewed. Products based on these mechanisms of action are already showing promising results in the clinical setting and may represent new options for patients that have uncontrolled IOP and that do not respond to current therapy.

A brief overview of neuroprotective approaches is also given; products based on this approach represent an excellent complementary option for IOP reduction strategies.

Finally, improvements in medical devices used to increase AH outflow are also reviewed. New devices achieve significant reduction in IOP and many can be used as stand-alone procedures offering an option to patients and settings where glaucoma medications are not a medically viable option.

Innovation in glaucoma may eventually change current disease treatment paradigms in order to offer solutions to a wider number of patients for whom current treatment options cannot stall disease progression. Achieving a sustained IOP reduction that warrants optic nerve protection over time is the main goal to be achieved, and some of these products may contribute towards that goal. As it has been the case for current glaucoma therapy, significant advances in quality of life of glaucoma patients may come from combining different approaches together to treat glaucoma in a comprehensive way.

Author details

Bleau Anne-Marie, Vargas Beatriz, Jiménez Ana Isabel and Pañeda Covadonga*

*Address all correspondence to: cpaneda@sylentis.com

Sylentis c/Santiago Grisolía, Tres Cantos, Madrid, Spain

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