Abstract: Introduction: Personalised medicine is the future goal across all specialities. Accurate prediction of optimal treatment beneficial and adverse effects could transform patient management. This is of particular importance in chronic conditions, where a 'trial and error' approach over months and years can contribute to significant morbidity. Glaucoma is a chronic irreversible progressive optic neuropathy, a leading cause of blindness worldwide. An ideal personalised approach in glaucoma clinic would be to answer the inevitable question in a patient's first visit: 'Which treatment option will work best for me so that I won't go blind?'
Areas covered: This review will give an overview of the knowledge we have acquired to achieve this goal, particularly discussing using patient's individual risk factors, their genetic profile and different treatment modalities, including therapy compliance, to personalise care.
Expert opinion: Pharmacogenomics and genetic profiling are the most tangible ways in which glaucoma management can be personalised. Future challenges will include developing realistic animal models to reflect the underlying genetic patterns in glaucoma that to investigate their interaction with different treatments.

Key words: glaucoma, neuroprotection, pharamacogenetics, pharmacogenomics, vascular risk factors, compliance, adherence, personalisation

1. Introduction

Glaucoma is a group of chronic, progressive optic neuropathies characterized by the degeneration of retinal ganglion cells (RGCs) and their axons, leading to irreversible loss of visual field, and ultimately to blindness [1,2]. Glaucoma is the second cause of blindness after cataract worldwide but is the most common irreversible cause.[3] Worldwide it is estimated that 64.3 million people suffer from glaucoma [4]. Early detection of glaucomatous change is important, in order to start treatment immediately to delay the progression of the disease and vision loss.

Although normal tension glaucoma (NTG) exists, where the intraocular pressure (IOP) remains within a normal range of below 21 mmHg, raised intraocular pressure (IOP) is a recognised significant risk factor for glaucoma. Elevated IOP is however neither necessary nor sufficient for diagnosis or manifestation of the disease. Raised IOP may result from either an excessive production of aqueous humour by the ciliary body, or more commonly, from decreased outflow through the trabecular meshwork, located at the iridocorneal angle. The angle characteristics form one of the main aspects used for glaucoma classification. Glaucoma may be classified into open- or closed-angle according to the position of iris-lens complex with respect to the TM. Further differentiation involves primary or secondary forms depending on the presence of an apparent biological cause. Glaucoma may be divided into acute or chronic depending on disease course and also juvenile or adult according to age of onset [5].

Increased RGC apoptosis and axonal loss within the inner retina are the earliest neurodegenerative changes in glaucoma, and directly correlate with the clinical and functional

severity of the disease. However, the pathogenesis of glaucoma involves a complex relationship between a number of factors and the sequence of events leading to apoptotic cell death is not yet fully elucidated. Elevated intraocular pressure (IOP), oxidative stress, glial cell activation, glutamate excitotoxicity, neurotrophic factor disruption, dysregulation of the immune system and mitochondrial dysfunction all contribute to this final disease pathway. As the damaged optic nerve is the main element in the pathophysiology of the disease, the obvious therapeutic strategy would be to directly target the optic nerve and retinal ganglion cells. However, only one agent, brimonidine, has been tested in clinical trials to be used as a potentially valuable neuroprotective agent. The only currently available therapeutic strategy therefore aims at targeting the only known modifiable risk factor for glaucoma, raised IOP. Given our limited potential for therapeutic strategies, an important consideration concerning glaucoma therapy is its personalization according to key patient characteristics. In this review, we will discuss personalization of therapy based on systemic disease factors, pharmacogenetics of glaucoma and patient factors, including adherence, to guide the choice of treatment modality.

2. Normotensive Glaucoma and Vascular Risk Factors

Normal tension glaucoma (NTG) contributes to up to one half of primary open angle glaucoma (POAG), in which there is no measured elevation of the intraocular pressure (IOP) [6]. NTG is a diagnosis of exclusion with diurnal IOPs commonly required to confirm the diagnosis. OCT scanning of the optic nerve head to aid classification of optic cupping into glaucomatous or non-glaucomatous is also valuable in these patients [7–9]. The clinical characteristics of NTG have many similarities to those in POAG, with a few notable distinctions. Disc haemorrhages, peripapillary atrophy and a narrower neuroretinal rim for a given amount of visual field loss, particularly inferiorly and temporally, are more common findings in NTG. [10,11] Focal areas of cupping, known as acquired pits of the optic nerve (APON), are associated with paracentral scotomas, which are close to fixation, deep and focal. Furthermore, NTG is commonly associated with comorbidities and vascular risk factors, giving the potential for personalisation of treatment for this subgroup of glaucoma.

IOP reduction remains a key focus in NTG management, however, this alone may be inadequate. The landmark glaucoma trials: the Ocular Hypertension Treatment Study (OHTS), the Early Manifest Glaucoma Trial (EMGT), the Advanced Glaucoma Intervention Study (AGIS) and the Collaborative Normal Tension Glaucoma Study (CNTGS), have each demonstrated that lowering IOP in glaucoma is advantageous [12–17]. But, the IOP level is not proportional to disease progression and disease progression can still occur in patients with a 20-30% reduction in IOP and in patients with an IOP less than 21 mmHg [12,13]. There is therefore an urgent need to target glaucoma risk factors and causes which are independent of IOP.

It was first suggested in 1959 that circulatory compromise may lead to visual loss in NTG [18]. Vasospasm, small vessel disease and dysfunctional autoregulation, causing ocular blood flow compromise, are now established to be key factors in the pathogenesis of NTG [19]. Vasospasm predicts progression of visual fields particularly in females and in those of Japanese ethnicity [20]. NTG may also be associated with central or peripheral vascular disease, namely

migraine and Raynaud's disease, and low blood pressure. Impaired blood flow velocities are demonstrated in NTG and POAG with visual field progression despite normal IOP [21,22]. A thorough history when assessing a patient with presumed NTG therefore necessitates pertinent questions regarding associated systemic comorbidities to help personalise treatment. Systemic vascular diseases associated with progression of NTG include migraine, low blood pressure, Alzheimer's disease, primary vascular dysregulation (PVD) and Flammer syndrome. Vascular risk factors have also been demonstrated to be significant in other forms of glaucoma.

2.1 Migraine

Studies have extensively reported the association between NTG and migraine [23]. In the Collaborative Normal Tension Glaucoma Study, migraine was a risk factor for development and progression of NTG [24]. Migraine was also shown to be a predictor of disc haemorrhages in NTG in the Low-Pressure Glaucoma Treatment Study [25]. Cursiefen's study identified that migraine occurs in 28% of NTG sufferers, whereas only 12% of healthy controls and 10% of high intraocular pressure glaucoma [26]. This suggests an underlying vascular mechanism possibly via migraine-related ischaemia linking some forms of NTG and migraine.

Migraine is associated with transient cerebral vasospastic episodes, which cause impairment in the mechanisms of autoregulation of blood flow in the central nervous system [27]. Sufferers have a higher frequency of silent cerebral infarcts, which may be further evidence to a pathophysiological mechanism of hypoperfusion or embolism in NTG. Dysfunctional autoregulation in patients with glaucomatous optic neuropathy may result in optic nerve ischemia, disc haemorrhages and microinfarction [11,28].

Migraine has been shown to not only be a significant risk factor in NTG, but also in those with hypertensive POAG [29,30]. Few studies have looked at the significance of vascular risk factors in PACG, however, migraine has not to date been implicated. Nevertheless, symptoms of angle-closure may be similar to migrainous features, so migraine may be under-diagnosed in this cohort of patients [29].

2.2 Systemic Hypotension

Systemic hypotension and vasospasm are known risk factors for glaucomatous optic neuropathy, and their relationship has been established [31]. Low systolic blood pressure is a risk factor for the presence of disc haemorrhages in NTG [25]. Studies have demonstrated that patients with rapid progression of NTG had low systemic blood pressure and over two-thirds of them also suffered from vasospasm [31]. Several reports have demonstrated an association between hypotension, particularly nocturnal arterial hypotension and progression of NTG, which may be due to optic nerve hypoperfusion [32]. Greater than a 10% dip in systolic blood pressure at night is associated with both disc haemorrhages and a higher risk of field deterioration. Therefore ambulatory blood pressure monitoring is advisable for patients on antihypertensives with suspected NTG to enable optimisation of their medication to stabilise their blood pressure [32–34]. Other studies have demonstrated that nocturnal hypotension is also significant in patients with POAG, although this has not been shown as a risk factor in PACG [35].

2.3 Alzheimer's Disease

Retinal vessel abnormalities have been identified in both NTG and Alzheimer's Disease. Retinal vascular changes may reflect the vascular dysregulation in the retina and cerebral microvasculature, leading to low perfusion pressure in patients with glaucoma and AD [36]. Sugiyama's study compared single photon emission computed tomography (SPECT) scans in NTG patients compared to healthy controls and it was demonstrated that NTG patients had AD-like perfusion patterns, suggesting a similar underlying pathology [37]. Helicobacter Pylori is also postulated to be a common risk factor between NTG and Alzheimer's Disease, by promoting platelet and leucocyte aggregation and promoting release of pro-inflammatory substances and acute phase proteins [38]. Eradication of Helicobacter Pylori has been shown to lead to a beneficial effect on glaucoma progression, further adding to its contribution as a risk factor in the disease [39]. POAG patients, not just of the NTG subtype, have also been demonstrated to share vasculature abnormalities with Alzheimer's Disease [40,41]. Zabel et al used OCT-A to confirm there were abnormalities of the entire retinal circulation in both AD and POAG patients; however the deeper circulation was more affected in AD compared to the superficial circulation in POAG [41].

2.4 Primary Vascular Dysregulation and Flammer Syndrome

Vascular dysregulation can lead to over and under perfusion of a particular supply territory and may be either primary or secondary to another disease process [42]. Primary vascular dysregulation (PVD) has been a recognised association in NTG patients, particularly in females, and sufferers of PVD syndrome also had a higher rate of migraines [43–45]. Splinter haemorrhages are known to be linked to PVD syndrome, so may explain why haemorrhages often occur in patients with NTG [46]. Ocular blood flow has been shown to be correlated with peripheral circulation in PVD patients [47]. Changes in ocular blood flow due to disturbed autoregulation can lead to unstable oxygen supply and oxidative stress, which is a recognised mechanism of glaucomatous optic neuropathy [42].

Flammer Syndrome is a term given to patients with primary vascular dysregulation with a phenotype of typical symptoms and signs, characterised by an altered reaction of blood vessels to various stimuli, including cold, emotional stress and hypoxia [48]. Most patients with Flammer Syndrome are healthy and the disease is in fact a protective risk factor for cardiovascular disease. However, the condition is strongly associated with NTG, as well as other ocular diseases including retinitis pigmentosa, Leber's hereditary optic neuropathy and central serous retinopathy.

2.5 Effects of improving ocular blood flow in glaucoma patients

The evidence of compromised ocular blood flow in particularly normotensive glaucoma or progressive POAG with treated IOP raises the importance of treatments targeting optic nerve head blood flow. B-adrenergic antagonists, including carteolol and betaxolol, have been shown to lead to improvements in optic nerve head circulation after 3 weeks of topical treatment in healthy volunteers [49,50]. Similar effects have been identified with topical tafluprost in glaucoma patients with myopic discs and with topical latanoprost in healthy eyes, leading to

increased tissue blood velocity in the optic nerve head at least temporarily even after single drop instillation [50–52]. This effect was independent of the associated IOP reduction and may be related to local production of prostaglandins [53]. These effects were replicated in NTG patients treated with latanoprost-cartelol combination drops, who were shown to have improved optic nerve head blood flow by 10% after 3 months of treatment [54]. Furthermore, brimonidine 0.2% drops have been shown to increase ocular blood flow in POAG patients, although this has not been replicated in other types of glaucoma or larger studies [55,56].

Recognition of patient risk factors indicating compromised ocular blood flow therefore allows for personalisation of treatment to target the underlying pathogenesis.

3. Pharmocogenetics in glaucoma

Early forms of glaucoma are typically inherited as Mendelian traits while those with adult onset are more complex genetically and their development depends on the presence of multiple gene variants which are independently commonly found in the population.[57] Genome-wide association studies (GWAS) on different ethnic groups are steadily increasing the number of gene loci possibly implicated in glaucoma onset. Nevertheless, the precise role of those genes in health and disease is often unknown, and a deeper insight of the pathophysiological molecular mechanisms underlying glaucoma could lead to a new set of therapies, including gene-therapy. An increasingly developing field of research is the one of pharmacogenomics, the aim of which is to personalize treatment according to a given genetic profile. Many ongoing studies aim to identify genes associated with the disease to aid the following aspects of glaucoma:

- Diagnosis, risk scoring, prognosis and counselling
- Understanding of pathogenic mechanism
- Development of mouse models for drug discovery and testing
- Responsiveness to therapy and avoidance of drug side effects

The aim of pharmacogenetics studies is to analyse the interpersonal variation in response to glaucoma therapy and implementation of predictive strategies to avoid side effects of drugs. Among the available classes we find alpha-agonists, beta blockers, carbonic anhydrase inhibitors, miotics and prostaglandins (Table 1) [58]. The first three groups of drugs act primarily on the reduction of aqueous production at the level of the ciliary body, while the latter increases the drainage of aqueous through the uveoscleral pathway. Miotics work by disengaging the iridocorneal angle and thus are mainly used in closed-angle forms.

It is well known from clinical practice that some patients are non-responders or partial responders to given therapies. The current approach to insufficient responders is shifting patients to a different medication or combination of more than one drug. This approach is time consuming because it necessitates strict patient monitoring and incurs a period of potential suboptimal pressure control. Despite being now far from clinical practice, we know that single nucleotide polymorphisms (SNPs) of particular genes can influence the pharmacokinetics and dynamics of a drug, and in this way alter its efficacy. We report here an update of the

knowledge reached so far on glaucoma pharmacogenetics which is important in the personalization of treatment and also review the genetics of glaucoma, the understanding of which has the potential for specific gene targeting, and the possible future directions of personalized glaucoma management according to patients' genetic profile.

3.1 Beta-blockers

Beta blockers are among the most commonly used drugs available to control IOP. They have the advantage of being cheap but the IOP control can be suboptimal and subject to fluctuations. They act at the level of the ciliary body and are implicated in reduction of IOP through reduction of aqueous humor production.

Analyzing the problem of response from the pharmacokinetic point of view, timolol, a non-specific beta blocker, has been reported to have reduced IOP lowering effect in dark eyes. Generally it is less effective in black people than in those with fair skin. This may be explained by melanin binding timolol and thereby lowering its bioavailability [59]. Timolol is metabolized mainly in the liver by CYP2D6 and to a lesser extent by CYP2C19. CYP2D6 is expressed in negligible amounts in the ocular tissues [59]. It has been shown that polymorphisms of the CYP2D6 are able to alter the rate of metabolism of timolol. It has been estimated that roughly 80% of topical timolol goes into systemic circulation, poor metabolizers of timolol may be subjected to the risk of cardiological and respiratory adverse events. Polymorphisms in CYP2C19 are associated with different drug responses [60].

Pharmacodynamics are also involved in the variable response that is often seen with these drugs. It has been shown that homozygous variations in the beta-2 adrenergic receptor (ADRB2) are able to influence 20% of the IOP response [61]. Beta-2 receptor polymorphisms are not linked with glaucoma pathogenesis but rather with earlier disease onset when POAG is present. Conversely some SNPs on beta-1 adrenergic receptors seem to be susceptibility factors for POAG [61,62].

3.2 Prostaglandins

Prostaglandin analogues are the most commonly used first-line treatments for glaucoma. They are able to lower IOP by enhancing the drainage of aqueous humor through the uveo-scleral pathway. It has been shown that the ciliary body strongly expresses prostaglandin receptors. The signal transmitted is able to upregulate the production of an array of matrix metallo-proteinases (MMP) decreasing in this way the resistance to fluid passage.

Among this class of drugs latanoprost, a prostaglandin F2-alpha analogue, is one of the most commonly used in first line. Some polymorphisms localized on prostaglandin F2-alpha receptor, MMP-1, SLCO2A1 and GMDS genes have been related to different responses to latanoprost. SLCO2A1 gene codes for a latanoprost transporter which is important for the delivery of the active molecule in the target tissue. GMDS gene instead codes for GDP-mannose 4,6 dehydratase which is involved in the synthesis of fucose. Fucose is important in many different signalling mechanisms [63–65].

3.3 Steroids, ocular hypertension and steroid induced glaucoma

The maintenance of normal IOP is dependent on strong trabecular meshwork (TM) matrix remodelling. Physiological increase in IOP induces the production of matrix metalloproteinases (MMPs). Defects of MMPs production or activation result in ocular hypertension [66].

Numerous *in vitro* studies on TM cells suggest that steroids are able to upregulate the production of extracellular matrix proteins, inhibit MMPs synthesis/activation and increase the cross links between the actin cytoskeleton filaments. Altogether these mechanisms could theoretically decrease the *in vivo* drainage of aqueous humor. One of the most important genes involved in the deposition of extracellular matrix proteins at the level of the TM is the one coding for myocilin (MYOC), also known as trabecular meshwork-induced glucocorticoid response (TIGR) gene. MYOC is upregulated in times of stress and following pharmacological treatment with glucocorticoids, therefore, even if TIGR is wild-type in these conditions it may cause reduced aqueous outflow [67]. Some studies focused on gene polymorphism involved in steroid-induced ocular hypertension and glaucoma. The genes so far linked are GPR158, a G-protein-coupled receptor, and HCG22, a mucin protein [66]. These findings have the potential to predict predisposition to IOP increase in certain individuals before starting long term steroid therapies [66].

3.4 Glaucoma Genetics and pharmacogenomics

A number of genes have been involved in different types of glaucoma (Table 2).

3.4.1 Early-onset POAG: Juvenile Open Angle Glaucoma and Familial Normal Tension Glaucoma

Early onset forms typically occur before the age of 40 years old and are subject to Mendelian inheritance patterns. In this category there are types due to developmental abnormalities and others occurring in developmentally normal eyes. Among the ones occurring in normally formed eyes we find juvenile open angle glaucomas and familial normal tension glaucoma.

Juvenile open angle glaucoma (JOAG) is characterized by onset before 40 years of age and despite some variability there can be severe phenotypes with very high IOP refractory to treatment. One of the most common mutations occurs on the myocilin gene (MYOC). There are many possible mutations but notably some of them give rise to autosomal dominant inheritance [68]. These are missense mutations which are linked to the most severe forms of JOAG. Other MYOC abnormalities are seen also in adult-onset POAG. Overall MYOC mutations are present roughly in 8-36% of JOAG [69].

The underlying pathogenic mechanism in MYOC-related JOAG is a dominant negative or gain of function mutation which result in protein misfolding and accumulation with endoplasmic reticulum (ER) stress. This results in unfolding protein response (UPR) and, if long lasting, in cell death. The end point of the process, which involves the cells of the TM is the accumulation of extracellular matrix, decreased aqueous humor outflow and increased IOP [70].

In familial normal tension glaucoma the IOP of patients is normal and therefore the underlying pathogenetic mechanism of RGC loss differs from other forms. There are some rare mutations in optineurin (OPTN) and Tank-binding protein 1 (TBK1) genes which are able to cause aggressive early onset forms inherited with an autosomal dominant pattern [71,72]. These genes are linked with autophagy and apoptosis. An interesting aspect of this type of glaucoma is that it shares some mutations with amyotrophic lateral sclerosis (ALS), in which OPTN and TBK1 mutations have also been found. Conversely ATXN2 mutation, has been identified in ALS and POAG [73]. These mutations probably are responsible of early degeneration and death of RGC. The genetics here shows the presence of susceptibility to optic nerve cell damage.

3.4.2 Adult onset glaucoma: POAG, PACG and Pseudoexfoliation

Primary open angle glaucoma (POAG) is the most common type of glaucoma. IOP elevation here is important only in two-thirds of cases since the other third is represented by the subgroup of normal tension glaucoma (NTG). This type of glaucoma is most commonly inherited as complex traits, which are related to complex combinations of single gene polymorphisms (SNPs) which alone give only a relatively small contribution to disease risk. The involved loci have been found through large GWAS and are involved in several biological processes including cytokine signalling, lipid metabolism (some studies suggest a protective role against glaucoma of statins for this carriers [74]), fructose and mannose metabolism; cell membrane biology, cell division, ocular development, extracellular matrix and ROS scavenging [75,76].

Primary Angle Closure Glaucoma (PACG) is particularly common in Asia. The course of the disease can be acute, sub-acute and chronic. Angle closure is the mechanical cause of hampered aqueous outflow and this results in elevated IOP. Familial forms of this disease can be inherited in autosomal dominant or recessive forms according to the gene involved. Mutated genes not only cause PACG but are accompanied either by pathology of the nanophthalmos spectrum (MFRP and TMEM98 genes)[77] or by Best retinal degeneration (BEST1 gene) [78]. GWAS has found also here many associated genes which are mostly related to anterior chamber depth (ACD) and choroidal tissue thickness [79]. In fact variants of these genes relates to short ACD and to increased thickness of choroidal tissue. Choroidal tissue thickness depends mostly on cell-cell adhesion proteins. Patients with mutations of these proteins are at risk of angle closure if exposed to anticholinergics.

Pseudoexfoliation syndrome (PXFS) is a disease related generally to ocular aging. It is characterized by the deposition of fibrillary material on the lens and TM. This material clogs the TM causing an increase in IOP and degeneration of the optic nerve. The origin of this fibrillary material has not yet been identified but it is likely to come from unstable surrounding connective tissue. One of the genes identified by GWAS is LOXL1 which is significant in elastin and collagen metabolism and mediating extracellular matrix stability. Interestingly, one of its SNP variants (rs3825942) is associated with a 20-fold increased risk of PXFS [80]. Carriers are also more susceptible to vascular problems and pelvic organ prolapse. Nevertheless this LOXL1 variant has been shown to be necessary but not sufficient to develop PXFS and related glaucoma. There is not only a genetic component in this syndrome but also an environmental

one. In fact UV light exposure, low folate and high coffee intake are likely to contributors to pathogenesis [80].

3.5 Pharmacogenetics and possible therapeutic targets

Genetic studies in glaucoma are bringing to light many possible therapeutic targets which may be exploited by drugs and gene-based therapies to tackle both Mendelian and polygenic forms of glaucoma. A deeper and thorough understanding of the molecular underlying mechanism involved in the pathogenesis is a fundamental step in order to plan and test tailored pharmacological strategies. Our aim now is to highlight the most understood pathogenic models and the relative ongoing pre-clinical and clinical studies.

3.5.1 Neuroprotection: Neurotrophins, Inhibiting Apoptosis and ER Stress

The aim of this strategy is to slow down RGC death in order to decrease the speed of progression of the disease. There are different possible approaches which can followed.

Neurotrophins are substances endogenously produced which play a key role in neuronal survival. Physiologically RGCs receive neurotrophins from Muller cells and through retrograde axonal transport from the brain. Lack of neurotrophins has been suggested as a possible contributing cause of RNFL thinning. Studies in rats confirm that high IOP is able to inhibit their retrograde transport from the superior colliculus to the RGC body. Some important neurotrophins are brain derived neurotrophic factor (BDNF), ciliary neurotrophic factor (CNTF), glial cell-line derived neurotrophic factor (GDNF). These molecules have been shown to be important for neuronal growth and survival and their supplementation can be therefore a possible approach to delay optic nerve cell degeneration. Among the aforementioned molecules the most tested one is BDNF. BDNF receptor is called TrkB, some molecules able to stimulate it are 29D7 monoclonal antibody, 7,8-DHF and deoxygeduin. These molecules have been shown to potentially being able of enhancing RGC survival *in vitro* and *in vivo*, however further studies are ongoing. Short term benefits have been extensively proved but long term ones probably require sustained treatment. Possible strategies include gene therapy although hurdles here concern the design of vectors with long term expression modulation [81].

Apoptosis is a physiological process of programmed cell death. It is however implicated in RGC death in glaucoma. Some anti-apoptotic molecules which have been tested are Etanercept (TNF-alpha inhibitor), minocycline (second generation tetracycline), FK506 (calcineurin inhibitor), Baclofen (GABA receptor antagonist) and brimonidine (alpha-2 adrenergic agonist). They have shown some ability to inhibit different pro-apoptotic molecules and prolong RGC survival *in vitro* and *in vivo*. There are also some *in vitro* studies on lentiviral mediated overexpression of CtBP2 able to show decreased cell death of RGCs [81].

Upregulation or supplementation with chaperones to alleviate the stress on endoplasmic reticulum (ER) is a potentially therapeutic avenue. Some molecules have shown promising results *in vitro* and *in vivo* in mouse models. An example is sodium 4-phenylbutyrate which has shown to alleviate the phenotype of transgenic MYOC mutated mice [82]. Since no associated

pathology occurs with loss of function of MYOC, knock out of this gene can be a potentially feasible approach with CRISPR-Cas9 technology.

3.6 Trabecular meshwork and uveoscleral pathway

The extracellular matrix of the TM is made up by a thick meshwork of matrix protein such as laminin, fibronectin, proteoglycans and glycosaminoglycans. An important role is than played by the endothelial cells lining the TM and the Schlemm's canal which have strong actin cytoskeletal network implicated in increasing aqueous outflow resistance. Aqueous passes from the anterior chamber to the Schlemm's canal by passing para-cellularly and trans-cellularly through this monolayer of cell.

It has been shown that molecules such as TGF-beta2 have higher concentrations in glaucomatous eyes. This specific factor is implicated in matrix deposition at TM level. Resistance is related also to the level of tension of the matrix proteins. In fact NO is able to decrease IOP through the relaxation of TM. Another possible target is Rho Kinase which is involved in the process of contraction of actin cytoskeleton [83]. Up to now different molecules are targeting TM processes involved in increase IOP. In this group we find inhibitors of Rho kinase, nitric oxide donors and adenosine agonists. In this context we find the only ongoing gene therapy trial for glaucoma. It concerns the use of TGF-beta2 antisense RNA to block the overexpression of this molecule which is a common feature of glaucomatous eyes [83].

4. Personalization of Treatment Modalities

Many therapeutic options for glaucoma exist, including topical medical treatment, laser and surgery. Lowering intraocular pressure (IOP) has always been the main focus of glaucoma management, although more recently a considerable amount of resources have been invested in research for IOP-independent mechanisms. The type and the level of treatment depend on several factors, both condition-and patient-related, such as glaucoma subtype, stage of disease, visual prognosis and comorbidities, which could be used to personalize treatment and choose a specific treatment modality for each patient [84].

4.1 Topical therapy

Topical medical treatment is usually the first line therapy for glaucoma, because eye drops are effective, non-invasive and, at least theoretically, easy to use. Five different classes are available, with different mechanisms of action and effects, but all with the same aim to reduce IOP: they are prostaglandins analogues, carbonic anhydrase inhibitors, beta-blockers, alpha-agonists, cholinergic agents or a combination of them. They are usually prescribed from one to four times a day and adherence to their recommended regimen is necessary in order to achieve maximal hypotensive effect.

4.2 Personalisation of topical treatment

On a practical level, personalisation of topical therapy is a frequent exercise in glaucoma clinics. Whilst a stepwise approach is the overall treatment plan, patients' individual factors are taken into consideration.Frailty level, comorbidities and adherence are considered to choose a drug based on the dosing frequency required. The initial IOP and the reduction needed drive the choice of combination drops or multiple drops. The 'target IOP' is chosen dependent on the initial IOP and the level of progression of glaucoma and may be altered over the disease course [85]. Importantly, the presence of ocular surface disease, allergy or comorbidities to avoid side effects or intolerances such as drop toxicity, beta-blocker induced breathlessness or dizziness is also a key component of a glaucoma assessment. These general considerations personalise glaucoma treatment, yet still a significant time delay occurs in the disease course of patients in order to reach the optimal treatment for patients, raising the need for further personalisation.

It is established that intraocular pressure follows a circadian rhythm; generally the IOP reaches the highest values in the morning and the lowest at night [86–90]. Several studies tried to assess whether specific classes of hypotonic drops would be more effective than others at reducing IOP when administered at specific times of the day or night [86,90,91]. More specifically Orzalesi *et al.* showed that the effects of latanoprost (prostaglandin analogue), brimonidine (α_2 agonist) and a fixed combination of timolol and dorzolamide (β-adrenergic antagonist and carbonic anhydrase inhibitor respectively) varied significantly throughout the various phases of the circadian IOP curve [86]. These results could be useful when deciding what type of hypotonic drug should be prescribed to patients, provided that a 24-hour measurement of IOP variations is performed. This would allow each patient to have the most suitable treatment option.

Ethnicity is also an important patient factor that helps guide personalized treatment. As mentioned above, some studies have suggested that African American individuals responded less than White individuals to topical β-adrenergic antagonists. However, inconsistencies were identified with others finding they responded more to prostaglandin analogues, while others found no difference [92–95]. The Ocular Hypertension Treatment Study (OHTS) [26] provided a great opportunity to answer to this question, due to the larger sample size compared to previous studies. However, the results demonstrated similar response rates to β-adrenergic antagonists and prostaglandin analogues in both African American and White individuals, thus excluding ethnicity as a possible criterion in decision making [96]. Further research is therefore necessary to find robust evidence to tailor therapy according to ethnicity.

4.2.1 Variations in drug response

Although all eye drop classes act by lowering the IOP and the pharmacology of these drugs has been studied comprehensively, the mechanisms responsible for variations in drug response are not still fully understood. The most likely explanation is that the efficacy of treatment is probably given by a combination of factors, not only related to the pharmacokinetics and pharmacodynamics of the drugs, but also to factors intrinsic and extrinsic to the single patient. We consider as intrinsic factors age, gender, weight, disease state, genetics, ocular and systemic conditions; on the other hand, extrinsic factors are environmental factors such as diet,

alcohol, tobacco, chemicals, other drugs, and also patient adherence to treatment, access to healthcare and drugs costs and availability [62].

The more we understand about the factors involved in drug response, the more we would be able to direct each single patient towards the therapy that is the most appropriate for him. Personalised medicine for glaucoma is the aim that we reach for: on one hand, it would help to offer patients options customized to their genetic profile and their characteristics, and on the other hand, it would help doctors to provide prognosis with more confidence and prescribe targeted drugs, without depending on the current trial-and-error approach and without continuously changing the therapeutic regimen, which may negatively affect patient's conditions, because the delay in finding the right therapeutic regimen could contribute to progressive vision loss.

4.3 Newer and potential therapeutic agents

Although being the cornerstone of glaucoma medical therapy for the last decades, there are limitations including, firstly, the need of multiple different classes of drops to achieve good IOP control and secondly, the presence of several side effects at both local and systemic level, which may undermine patient adherence. This is why in recent years many studies focused on finding novel targets for therapy, as current classes have become quite old-fashioned [97]. Recently, new interesting experimental approaches have been researched, although not yet brought into the clinic: new targets could be potentially exploited, such as the Rho kinase family [97–101], melatonin receptors [97,98,102]), adenosine receptors [97,98,103]) endocannabinoids [97,98,104], fatty acid amide hydrolase (FAAH) [97,98] and nitric oxide, alone or combined with other agents [98].

Rho-kinase inhibitors (ROCK) (Ripasudil, Netarsudil) are the newest class for management of glaucoma in the clinic [97,98]. Although the exact mechanism of action is unclear, they are known to exert their effect by inhibiting some Rho kinase isoforms in the trabecular meshwork (TM) and thereby modulating the TM cytoskeleton to reduce its stiffness, increasing aqueous humor outflow and thus contributing to lowering the IOP [97]. A phase III clinical trial [99] showed that Ripadusil 0.4% achieved an IOP reduction ranging from –2.6 to –3.7 mmHg. ROCKs are also believed to have a direct protective effect on neurons by limiting retinal ganglion cells apoptosis [97,99]. Some studies [97,100] reported conjunctival hyperemia as a common (40-70%) side effect, though transient and mild, together with a few cases of blepharitis and allergic conjunctivitis, which may limit their use in the clinical practice; thus it should be known which patients are more prone to develop these conditions before prescribing them these classes of drugs. Very recently, fixed dose combinations (FDC) of Rho-kinase inhibitors and prostaglandin analogues (Netardusil 0.02% + latanoprost 0.005%) have been approved by the FDA and proved to be significantly superior in lowering the IOP than the two classes of drugs alone in phase II trials (-8.6 mmHg for the FDC vs –7.6 mmHg of latanoprost and –6.3 mmHg of Rho kinase inhibitor); phase III trials are being carried out, but are not yet available [99,101].

Melatonin is a neurohormone derived from tryptophan, produced mainly in the pineal gland and, to a lesser extent, also in the retina. Its great therapeutic potential derives from the fact that the

retina and intraocular tissues are endowed with melatonin receptors (MT1-MT3) which could be exploited by agents to modulate the IOP. Melatonin receptor (MT) agonists have been investigated as IOP lowering agents and they also proved to work as antioxidants with a radical scavenger activity, suggesting that their supplementation to pharmacological and surgical measures could be a promising treatment strategy in the management of intraocular pressure [97,102]. A few analogues exist: agomelatine (N-[2-(7-methoxynaphthalen- 1-yl)ethyl]acetamide) and Tasimelteon (N-(((1R,2R)-2-(2,3-dihydro-1-benzofuran-4-yl)cyclopropyl)methyl)propanamide), but their efficacy should be correlated to the clinical profile of patients, their medical conditions and glaucoma subtype [97]. *In vivo* administration of agomelatine in experiments performed on rabbits showed a 21% reduction after 180 minutes from administration in normotensive conditions and 69% reduction in hypertensive conditions [97,105].

Adenosine receptors are expressed in intraocular tissues and contribute to regulate aqueous humor secretion and absorption. Since they are distributed differently in various tissues, their precise modulation in each tissue could be exploited to control IOP levels. This is why agonists and antagonists of such receptors are new emerging agents for the management of glaucoma: some of them act on the trabecular meshwork and the ciliary body to reduce outflow resistance, others increase blood flow across the retina and optic disc, thus reducing vascular resistance and preventing retinal ganglion cell damage, working as neuroprotectants. Trabodenoson for instance, is a selective adenosine-based compound that targets receptor A1 by increasing humor aqueous outflow through the trabecular meshwork and thus lowering IOP: it was demonstrated a mean reduction of -4mmHg (range –3.5 to -5.0 mmHg) [97,103,106].

The endocannabinoid system also takes part in aqueous humour flow and can be therefore exploited in the modulation of IOP levels. Endocannabinoids exert their functions by acting on receptors (CB1 and CB2) widely distributed within the eyes at the level of the ciliary body, trabecular meshwork, Schlemm's canal and the retina. It has been postulated that an increase in their levels could have a neuroprotective effect, while a reduction could be implicated in the pathogenesis of glaucoma. Since endocannabinoids are degraded mainly by fatty acid amide hydrolase (FAAH) in the ciliary body and some retinal cells, agents that inhibit this enzyme and that may have a beneficial effect on the reduction of IOP have been researched. Two FAAH inhibitors, Δ9-tetrahydrocannabinol (Δ9-THC) and WIN 55,212-2, have proved to be effective: in particular, Δ9-THC was found to decrease IOP by 30% up to 8-hour treatment [97,104].

Nitric oxide (NO) is a ubiquitous signaling molecule synthesized starting from L-arginine by NO synthase (NOS). In eyes it exerts several functions, such as regulating the vascular tone, processing the visual stimuli and modulating the IOP by regulating the outflow resistance of the trabecular meshwork. Based on this mechanism, newly designed NO-donating drugs have been proposed, which combine the trabecular meshwork outflow-increasing effect of NO, which is however time-limited, with the IOP-lowering ability of known topical agents, which are metabolized within the eye and release NO locally, bypassing the issue of NO short half-life. One of these agents, latanoprostene bunod, has been created from a prostaglandin analogue backbone (latanoprost, which increases uveoscleral outflow) with a terminal butyl nitrate ester functional group (a NO-donating moiety which increases trabecular meshwork outflow by

relaxation of TM cells). This synergistic effect gave promising results and got approved by the US FDA [98,107].

4.3 Laser

Laser treatment has been traditionally performed when topical eye drops are no longer effective at lowering the IOP, or as an intermediate step between drugs and traditional surgery. However, it was proved that it can also be used as first line therapy. Patients with uncontrolled glaucoma despite maximal therapy, those who cannot benefit from drops because of the adverse effects of their preservatives, or due to lack of adherence to the prescribed treatment or, again, for patients who cannot afford multiple hospital visits for monitoring and treatment adjustments, are those most likely to take advantage from laser treatment as a first-line therapy [108–110]. Several studies show that the use of laser managed to reduce IOP more than medical therapy in more than 75% of previously unoperated eyes, with similar efficacy: -9 mmHg vs –7 mmHg respectively over 5.5 years of follow-up according to the Glaucoma Laser Trial (GLT) [110,111]; an even greater IOP reduction (-1.2 mmHg) from laser therapy with respect to topical therapy over a longer follow-up time was showed in The Glaucoma Laser Trial Follow-up Study [110,111] and The Early Manifest Glaucoma Trial [13] performed a randomized clinical study to compare the effects on IOP of laser trabeculoplasty vs no treatment or later treatment and found an average reduction of IOP of 5.1 mmHg (25%) in the former group.

Several types of laser treatment are available. Argon laser trabeculoplasty (ALT) was previously commonly used, especially for open-angle glaucoma. The two most accepted theories about its mechanisms of action are the mechanical and cellular theories. According to the mechanical theory, ALT uses thermal energy to induce scarring to some areas of the trabecular meshwork and thereby open the adjacent, untreated trabecular spaces, thus improving aqueous outflow. The cellular theory instead proposes that the laser induces coagulative necrosis in the trabecular meshwork and macrophages are thus recalled to the site of necrosis to phagocytose debris and clear the meshwork. [112] It is likely to improve outflow from a combination of the two mechanisms.

With the advent of selective laser trabeculoplasty (SLT) the number of laser procedures has dramatically increased since the early 2000s[108,113]: SLT achieves similar results to ALT but, with a shorter duration and lower power, it has less traumatic effects on the trabecular meshwork, because it selectively targets the pigmented cells while sparing adjacent cells [112]. It is effective at lowering the IOP and can be used in early treatment for patients not compliant to glaucoma medications, either as primary treatment or in addition to medical therapy [113]. The LiGHT trial is a multicentre randomised controlled trial aimed at comparing the benefits of using either SLT (followed by medical therapy when necessary) or standard medications as first-line treatment for open-angle glaucoma and ocular hypertension and demonstrated the cost-effectiveness of SLT and the slightly better clinical outcomes, suggesting it as an alternative to topical drops. They found: 1) Better control of IOP, due to its continuous effect on the trabecular meshwork throughout the day, compared to the episodic administration of topical drops; 2) Lower rates of disease progression at the end of the follow-up period; 3) Lower risk of side effects, which are partly responsible for patients interrupting treatment and for lack of

adherence; 4) a drop-free control of IOP after laser trabeculoplasty for at least 36 months in the majority of cases (74.2%), which is a major achievement, given that one of patients major concern regards the everyday instillation of topical drops [109]. Although the effect of the laser is not permanent, it can be repeated and, if it is successful, patients no longer need complex treatment regimens and the risk of nonadherence is thus eliminated [109]. The study also demonstrated that using SLT as first-line treatment significantly reduced the costs of surgery and medications for ocular hypertension and open-angle glaucoma, by saving to the NHS 451 £ per patient [109].

Micropulse laser trabeculoplasty (MLT) is one of the newer types of laser developed, that delivers repetitive microsecond pulses of energy followed by intermittent periods of rest, so that it prevents accumulation of thermal energy [108,110,112,113]. MLT does not cause mechanical damage and scarring to the trabecular meshwork, but it induces a cascade of cytokines and interleukins that reduces tissue damage and increases aqueous outflow. A prospective study showed that MLT managed to reduce IOP by 20% at 12 months in 75% of patients [108]. Several studies have demonstrated comparable results between ALT, SLT and MLT [108,110,112,113].

Titanium-sapphire laser trabeculoplasty (TSLT) is a subtype of laser trabeculoplasty emitting near-infrared energy in pulses of 5-10 ms, which allows deeper penetration into the juxtacanalicular meshwork and selective absorption by phagocytic cells, in order to prevent damage to the rest of the trabecular meshwork. Although it is a quite recent technology and limited evidence exists, a pilot study compared the IOP reduction of 8 mmHg (32%) in the TSLT group with respect to a decrease of 6.5 mmHg (25%) in the ALT group. If confirmed by future studies, TSLT could be possibly used as an alternative to ALT in patients with POAG [108,114,115].

Pattern scanning trabeculoplasty (PLT) is a recent computer-guided approach that applies a sequence of pattern laser spots onto the trabecular meshwork, using shorter pulse duration than ALT, thus reducing the thermal injury diffusion distance and achieving a good cellular response without causing excessive coagulative damage and tissue scarring. Two studies on PLT found a mean IOP reduction of 24% and 27.1% respectively, with no statistically significant difference with respect to ALT [108,115–117].

Cyclophotocoagulation is another technique particularly useful in refractory glaucoma or patients with limited visual potential. It exploits a semiconductor diode laser to destroy part of the ciliary body and thus reduce humour aqueous production. It demonstrated a potential reduction of IOP by 45%, however it is limited by the risk of persistent hypotony in 10% of cases and possibly total vision loss, therefore it should be used with caution [118]. Two types of photocoagulation exist: transscleral diode cyclophotocoagulation (TCP), which is usually reserved for cases of refractory glaucoma or when surgery is not recommended due to some features of the eyes themselves and endoscopic diode cyclophotocoagulation (ECP), especially used in combination with cataract surgery to further decrease IOP [108]. They have very similar outcomes, but one can be chosen over the other according to the needs of the patient.

Finally, Laser Peripheral Iridotomy (LPI) is used to create a hole in the iris and allow fluid to drain directly into the anterior chamber, bypassing its normal pathway. LPI is the traditionally preferred initial method for managing anatomically narrow angles and to prevent angle-closure glaucoma attacks. The Zhongshan Angle Closure Prevention Trial (ZAP) conducted in China was a prospective trial, in which 889 patients with narrow angles had an LPI performed in one eye only. After 72 months of follow-up, 19 of the treated eyes compared to 36 of untreated eyes developed acute angle closure [119]. Given the low incidence of primary angle closure (PAC), the researchers recommended that LPI is not a widespread practice for all cases with narrow angles. LPI can be personalised to patients by perhaps offering to those at higher risk, such as those requiring frequent pupillary dilation for other ocular conditions, or if access to emergency eye services may be limited.

4.4 Surgery

Management of glaucoma is usually considered in a step-wise approach, from topical eye drops, to laser, to surgery, due to the increased risk and invasiveness. However, studies have highlighted the benefit of early laser, described above, or early surgery to reduce the risk of visual impairment during patients' lifetimes. The Collaborative Initial Glaucoma Treatment Study (CIGTS) compared medical treatment to trabeculectomy as early management in glaucoma [120,121]. Long-term follow up demonstrated that early surgery may be beneficial for patients presenting with more advanced glaucomatous disease, excluding diabetics or Afro-Caribbean patients, who appear to have increased visual field progression compared to those medically treated only.

4.4.1 Trabeculectomy

The most common type of surgery is trabeculectomy, which is used in both open and closed-angle glaucoma and consists of creating an opening in the sclera, a flap that allows fluid outflow into the subconjunctival space. It has been considered the gold standard in surgical intervention since its development in 1968 [118], being able to achieve IOP reduction in 86-96% of cases [118,122]. An alternative to trabeculectomy is trabeculotomy, whereby a part of the trabecular meshwork is removed using an electrical current, however it is reserved mainly for children [123].

The main reason for glaucoma filtering surgery failure is fibrosis: the scleral flap may close spontaneously as an attempt to heal, causing the IOP to rise again. Antifibrotic agents such as mitomycin-C (MMC) or 5-fluorouracil (5-FU) added to trabeculectomy have been increasingly used since their introduction in the early 1980s [124–126], due to their ability to combat tissue fibrosis after surgery [124].

Mitomycin C is an alkaloid that exhibits direct cytotoxic effects by inhibition of DNA-dependent RNA-synthesis [124,127] and thus induction of apoptosis in fibroblasts in Tenon's capsule, which are the main players in the inflammatory response, wound healing and scar formation after trabeculectomy [124,128]; moreover, it has also been shown to have potent antiangiogenic properties [124,129]. Patients most likely to benefit from MMC augmentation after trabeculectomy are mostly those with POAG, where it showed to be more effective, compared

to normal tension glaucoma (NTG). Several studies demonstrated that these patients achieved a greater IOP reduction than those treated with balanced salt solution (BSS), they didn't show visual field progression nor did they require further glaucoma surgery [124]. Now in modern trabeculectomy surgery, mitomycin C is almost always used and higher doses are used in those with increased scarring risk, commonly due to uveitic or neovascular glaucoma, previous intraocular surgery or Afrocarribean ethnicity or young age [130] .

Congenital glaucoma unresponsive to conventional surgical treatment may benefit from antifibrotic augmentation: patients demonstrated an adequate IOP control with no disk cupping progression, nor enlargement of corneal diameter and no deterioration of visual acuity [124]. Trabeculectomy with MMC may be a good option for patients with poorly controlled neovascular glaucoma (NVG): in fact, the obstruction of the outflow pathways of the trabecular meshwork by the proliferating fibrovascular tissue may lead to permanent synechiae with a consequent increase in IOP difficult to control [124].

Bleb needle revision after failed trabeculectomy has reported higher success rates when augmented with MMC and 5-FU and similarly, nonpenetrating glaucoma surgery (NPGS) showed higher success rates without higher risks of complications than trabeculectomy alone [124,131]. On the other hand, trabeculectomy augmented with MMC has been associated with higher failure rates in patients with previous vitrectomy and no consensus exists yet about its use in conjunction with glaucoma drainage devices [124,132,133]. On the contrary, categories of patients that were found not to benefit from MMC augmentation were: patients with normal tension glaucoma (NTG), due to the high rate of sight-threatening complications i.e. bleb-leak and late hypotony and secondary glaucoma, except for inactive uveitic glaucoma without prior intraocular surgery [124,134,135].

5-fluorouracil is a pyrimidine analogue that interferes with RNA synthesis by inhibiting incorporation of thymidine into DNA.[124] Similarly to (although to a lesser extent than) mitomycin C, 5FU induces apoptosis of fibroblasts in Tenon's capsule, but differently from it, it has no demonstrated anti-VEGF properties. The Fluorouracil Filtering Surgery Study Group demonstrated that 5FU may be useful in patients at high risk of bleb failure, such as those with previous surgery or failed filtration surgery. However, for patients with NVG, although the initial results were promising, the probability of later failure is high. As far as patients at low risk, the results are controversial [124].

Whether one antifibrotic agent is better than the other remains controversial and none of them comes without risks and adverse effects, including late-onset leaks, prolonged hypotony, corneal epithelial toxicity and bleb-related endophthalmitis.

4.4.2 Glaucoma Drainage Implants (GDIs)

In recent years, Glaucoma Drainage Implants (GDIs) have been increasingly used. They are tubes that divert aqueous humour from the anterior chamber into an external reservoir where a fibrous capsular bleb forms subconjunctivally [136]. Although trabeculectomy has been traditionally preferred except for refractory glaucoma, the high risk of complications, including endophthalmitis, hypotony, long-term ocular surface irritation, cataract progression and filtration

failure, contributed to shunts popularity also for nonrefractory glaucoma [108,136,137]. The Tube versus Trabeculectomy (TVT) study demonstrated that patients undergoing shunt surgery had a higher success rate than trabeculectomy in a 5 year-follow up. However, as far as IOP reduction, both procedures were similarly effective (41.1% reduction in tube shunt surgery vs 49.5% in the trabeculectomy group after a 5 years follow-up) [136]. Tubes are mainly reserved for patients with failed previous trabeculectomy, or high risk of failure of trabeculectomy, including uveitic or neovascular glaucoma.

4.4.3 Microinvasive glaucoma surgery (MIGS)

Nonpenetrating Glaucoma Surgery includes other less frequent procedures, such as viscocanalostomy, in which a window in the sclera is done to allow fluid outflow and deep sclerectomy, which aims at widening the drainage meshwork, sometimes also implanting a device inside. A meta-analysis compared trabeculectomy with non-penetrating surgeries and demonstrated that non-penetrating surgeries cannot achieve IOP reduction as high as trabeculectomy, they cost more and if they fail, they may compromise the success of future filtering procedures, therefore their use is quite limited. This is where the need of minimally invasive glaucoma surgery came from [138].

Microinvasive glaucoma surgery (MIGS) is considered an intermediate step between pharmacological therapy and invasive surgery that manages to lower the IOP with an *ab interno* approach, causing minimal trauma while guaranteeing high safety and rapid recovery [108,137,139,140]. MIGS is suitable for patients with mild to moderate glaucoma, exfoliation and pigmentary glaucoma and ocular hypertension [137]. The iStent (Glaukos Corporation, Laguna Hills, California) is one of the most used: it is a microbypass stent made from heparin-coated titanium that is inserted *ab interno* into the Schlemm's canal through a corneal incision with a preloaded injector, in order to create a channel that allows the aqueous humour to drain directly from the anterior channel into collector channels, bypassing the juxtacanalicular trabecular meshwork, which is considered the site with the highest resistance to aqueous outflow [137,140]. It has been demonstrated that multiple iStents could be used simultaneously to further decrease the IOP [137,139,140]. Second-generation models called iStent inject (Glaukos Corporation) were also redesigned to offer several advantages: less invasive surgical procedures with a more direct implantation in the Schlemm's canal, no sideways movements during the injection manoeuvre and the possibility to preload two stents on the injector simultaneously [137]. Contraindications to iStents include angle closure glaucoma, neovascularization and conditions that increase the episcleral venous pressure (Sturge-Weber disease, retrobulbar tumours, thyroid eye disease) [137]. The Hydrus microstent (Ivantis Inc, Irvine, California) is a nickel-titanium intracanalicular scaffold inserted through a corneal incision with a preloaded injector that dilates the Schlemm's canal to allow aqueous drainage into multiple collectors. Although it is not commercially available yet, it has shown promising results [108,139]. The Trabectome (Neomedix Inc, Tustin, California) exploits microelectrocautery to ablate a strip of tissue from the trabecular meshwork and the inner wall of the Schlemm's canal, while leaving a channel for drainage of the humour [108,140]. It destroys tissue selectively, leaving adjacent untreated tissues unaffected.

Other MIGS devices exploit other pathways to reduce the IOP without targeting the Schlemm's canal: for instance, the CyPass Micro-Stent (Alcon Laboratories, Inc, Ft. Worth, TX) is a suprachoroidal shunt that can be inserted *ab interno* via a corneal incision, into the suprachoroidal space; it delivers aqueous humor from the anterior chamber to the supraciliary space through microholes. Despite being approved by the US FDA in 2016 for use during cataract surgery in eyes with coexisting cataract and glaucoma, the pivotal Study of an Implantable Device for Lowering Intraocular Pressure in Glaucoma Patients Undergoing Cataract Surgery (COMPASS trial) was conducted to assess the effectiveness of this device, randomizing patients in two groups: phacoemulsification alone or with Micro-Stent implantation. The initial two-year data demonstrated the superiority of the combined procedure with respect to phacoemulsification alone in reducing IOP by more than 20%. However, a 3-years extension of the trial was carried on to evaluate the safety profile. The Study to Assess Long-Term Safety of the CyPass Micro-Stent in Patients Completing the COMPASS Trial (the COMPASS-XT study) revealed few sight-threatening side effects in the group under study during the 5 years of follow-up. The key finding was the difference between the two groups in mean corneal endothelial cell loss after 24 months, for which reason the Micro-Stent has been voluntarily withdrawn from the market two years later by Alcon Laboratories [141].

A third pathway to decrease IOP is the subconjunctival space. The XEN Gel Stent (Allergan) is a soft cross-linked porcine collagen implant inserted *ab interno* into the subconjunctival space via a preloaded injector, thus avoiding the potential risks related to conjunctival incisions given by traditional filtering surgery [108,140]. A pilot study in 2015 on the combination of XEN gel with phacoemulsification demonstrated a mean IOP reduction from 22.4 to 15.4 mmHg after 12 months, although latest versions of the implant have been developed and now they are usually associated with subconjunctival MMC during surgical insertion. Nonetheless, there is growing interest in XEN Gel Implant due to its greater potential of IOP reduction compared with the other pathways [138].

The suprachoroidal and subconjunctival pathways may be more suitable for patients with more advanced stages of the disease, however at the moment MIGS devices are targeting patients with mild or moderate stages. A metanalysis conducted by Lavia et al. [142] compared the effects of MIGS in lowering IOP to medical therapy, cataract surgery, and other different MIGS devices: in before-after series MIGS seemed effective in lowering IOP from 1.60 to 11.8 mmHg [143,144]. There is currently no evidence to identify what patients are most likely to benefit from each type of MIGS device, therefore further research will be needed on the topic [118].

A study conducted by Musch *et al.* [145] aimed at evaluating factors associated with IOP during a nine year follow-up period in patients treated either medically or surgically. The results showed that surgery as an initial approach reduced IOP more than medications by 2.2 mmHg and therefore some categories of patients with elevated IOP could benefit from surgery as a first-line therapy. For instance, patients with pseudoexfoliative OAG presented with significantly higher IOP than those with primary or pigmentary forms; glaucomatous patients with afferent defects in pupillary response, which is usually due to optic nerve damage and thus indicative of a severe stage of disease, had higher IOP. These patients could benefit from surgery as initial treatment. The authors also investigated demographic variables to find other categories of patients who could benefit from the surgical approach: parameters such as age, gender and

race were not predictive of IOP, but inconsistent findings have been found throughout literature [145–148]. Patient education level was inversely related to mean IOP and the authors hypothesized that this outcome was probably affected by unmeasured variables, such as patient adherence to treatment, socioeconomic factors or dietary influences [145]. Therefore, these patients may benefit from an initial medical therapy and switch to surgery only if the medication were no longer effective in lowering the IOP or if adherence to topical treatment is a concern.

Even if surgery may be the first choice in some categories of patients, the first step in treatment is usually eye drops, which require patient acknowledgement and adherence in order to be effective; it is therefore fundamental that doctors explain thoroughly to their patients the importance of therapy and most of all, their full adherence. A significant issue particularly initially after detection, is poor adherence due to a variety of factors, including lack of understanding of treatment requirement and ocular side-effects.

4.5 adherence to therapy

Patients' failure in following physicians' instructions has always been described in every field of medicine and it has been universally known as a limiting factor in the achievement of therapeutic goals [149].

Several research studies throughout literature reported that approximately fifty per cent of patients do not adhere to medical therapy, by either not taking their medications at all, or by taking them incorrectly. Moreover, 80% of patients fail dietary restrictions and prescribed exercise, or continue 'bad habits' such as smoking and alcohol consumption, despite being advised against them.

Nonadherence has been reported to be higher in chronic diseases than acute conditions, probably because acute illnesses may be self-limiting and require a lower level of adherence by the patient in the long-term care. Moreover, nonadherence has been proved to be higher in adults with respect to children, either because of the additional care of their parents, or because usually adults have various comorbidities or long-standing poor health habits that make it more difficult to stick to the regimen prescribed.

4.5.1 Adherence in glaucoma

Glaucoma is no exception: patients' adherence to treatment is a real issue in this condition. In fact, this condition has all of the aforementioned features: it is a chronic disease that affects primarily elderly people, who usually have many comorbidities and a complex therapeutic regimen. Despite the introduction of many classes of drugs and the greater awareness of patients about the importance of following the prescribed treatment regimen, patient non-adherence to therapy remains a significant problem [150].

Glaucomatous patients have to deal with many constraints: lifelong treatments, difficulties in the self-administration of drops, often several instillations per day, possibly difficult access to the pharmacy and struggling with the costs of the medications. All these factors contribute to make glaucoma medical therapy very difficult to cope with.

Given the fervent debate about this topic, several studies have been carried out to assess patient adherence to medical therapy, but different rates have been reported throughout literature, ranging from 5 to 80% [151]. The reason for such a wide range is probably due to both the different definitions given to the terms "compliance" and "adherence" and the various devices used to measure it.

Very often the terms compliance and adherence are used interchangeably, but they actually have a slightly different meaning. Compliance has been defined as "the extent to which patients' behaviours correspond to the physician's recommendations". Since this definition seems to connote a certain degree of passivity by the patient, who simply has to follow a daily treatment imposed by the clinician, many physicians rather prefer the term adherence, which instead implies an active participation of the patient in the medical decision [152].

As far as adherence assessment, both direct and indirect methods exist to measure it. Direct methods include observation of the patient while taking the drops, or measurement of the amount of drug in body fluids. Indirect methods instead consist of patient self-reported adherence, questionnaires and diaries, pharmacy refill rates, electronic devices, each with their pros and cons [153].

Direct observation of patients while taking the medications is not feasible for glaucoma, because often treatments require several administrations per day and the clinician cannot be physically present every time. Measurement of drug levels in body fluids (blood, saliva, urine) could be helpful in assessing patients adherence, but there are two drawbacks: one is that drug levels measurement is not always routinely available for most medications in particular for topical eye drops; second, patients may take the drugs just before the clinical appointment, and thus results can be misleading [154].

As far as indirect methods, asking patients themselves would be the most straightforward way to do it. However, when asked about adherence to treatment, usually patients substantially overestimate their actual adherence, either because they can't remember the details about the timing and dosage of their medications, or in an attempt to please the clinician. Therefore, even if asking directly to patients to self-report adherence to treatment proved to be able to detect more than 50% of those with low adherence, this may not be the most reliable method.

Pharmacy records could be a precise tool for estimation of patient adherence to therapy, provided that patients refer only to the pharmacy where the measurements are taken and that they do not throw away or give to others the drugs. Several studies tried to estimate adherence by looking at pharmacy records and prescription refills. A useful parameter is the medication possession ratio (MPR), which refers to the amount of medication that a patient has in a certain time period divided by the number of days between two subsequent prescription refills. If the MPR is lower than 1, it means that the patient has insufficient medication over that time period [153].

Finally, electronic dosing aids of different types now exist, that are able to measure timing and dosage of drug consumption and thus give an estimate of adherence to topical medication. These devices are embedded with an electronic chip that records each time and date that the container is opened and closed [153]. Unfortunately, also these new adherence measures have

their limitations: they are expensive, can be used for short periods of time and are usually available only for monotherapy, and patients prescribed with just one medication have been shown to be more compliant than patients under several medications [155]. One of the most used is Travalert, a computerized bottle holder that reminds patients when they have to instill their drops and records the dosing time. However it can be used only for travoprost-containing medications (Travatan), or for travoprost/timolol fixed combinations (Duotrav) and it is therefore quite limited in its applications [156]. Other measuring tools are the so-called Medication Event Monitoring Systems (MEMS), caps applied to standard medicine bottles which record the time and date everytime the bottle is opened and closed by the patient. Unfortunately, these devices can only give information about the act of opening and closing the bottle, but won't assess whether the patient actually instills the drops. Moreover, all these electronic tools are quite new and very expensive, and therefore are not yet clinically applicable for routine practice [157].

Since no consensus exists on which is the best way to measure patient adherence, research is very active in trying to find new, feasible and reliable methods to improve patient adherence.

4.5.2 Reasons for nonadherence

Several authors tried to investigate the reasons for patients nonadherence and the answers given are more or less always the same throughout literature [158,159]. When patients are asked why they don't take medications as prescribed by their physicians, the majority blames it on forgetfulness (30%), or they claim to have other priorities (11%), lack of information (9%), emotional factors (7%) or sometimes they are not able to provide any specific reasons. In addition, among other factors that may adversely affect adherence, patients also reported difficulty in instilling the drops, especially those affected by either dementia or chronic neurologic and systemic diseases that make them weak and physically unable to press the drop container and pour them in their eyes. Moreover, some medications frequently show side effects, such as stinging, burning and hyperemia, which are very often unbearable after some time and they become responsible for discontinuation of therapy.

A few patients complain about the costs of the drugs, the poor availability and the difficult access to the pharmacy. Furthermore, patient's education and doctor-patient relationship are two other factors that may negatively affect patients' behavior: they are less likely to be compliant to treatment if they are not fully aware of its importance, either because nobody properly explained them, or because they can't understand what they are being told.

Very often patients blamed the poor adherence to the amount of drops and drugs prescribed: the more complex the therapeutical regimen, the lower the adherence. Patients who have to use medications once or twice daily show higher rates of adherence than patients prescribed three or four times a day. Furthermore, patients sometimes report that it is easier to forget about the doses during the day rather than those in the morning or evening.

Knowing the main reasons for patients nonadherence could be very useful for physicians, in order to help to solve their patients' problems and to try to increase their adherence to the treatments prescribed. Three aspects which doctors could and should focus on are: 1) simplification of therapeutic regimens; 2) making sure that patients acknowledge to have

glaucoma and understand the importance of adherence to treatment; 3) ensuring that patients fully comprehend their instructions and follow them.

4.5.3 The Glaucoma Adherence and Persistency Study (GAPS)

The Glaucoma Adherence and Persistency Study (GAPS) was designed to assess patient adherence, by analysing data from databases that collected medical charts and phone interviews [160]. The authors identified eight factors that can be considered barriers to adherence: (1) all the glaucoma knowledge being provided by the doctor. (2) not believing that reduced vision is a consequence of not taking the medications as recommended; (3) having problems paying for medications; (4) difficulties in taking medications while traveling or when away from home; (5) not acknowledging stinging and burning as side effects; (6) being non-white; (7) receiving samples; and (8) not receiving a phone call visit reminder. Among them, only two issues are not liable to the clinician i.e. having problems paying for medications and patient ethnicity. As far as the other six, doctors should put effort in building a relationship with their patients, discuss their issues with therapy and help solve them. Physicians should make sure all patients understand their disease, the importance of treatment, and the risks encountered if therapy is not followed. Doctor-patient communication plays a fundamental role in glaucoma treatment: in fact, as the results of the GAPS study demonstrate, patients with lower adherence are those who claim to receive less information from their doctors, have fewer questions answered, and to not receive instructions about drop instillations or side effects. It would be important that physicians built a strong patient relationship, in order to understand the needs of each one of them and work together, to make sure that they overcome the obstacles that prevent them from being fully compliant to therapy. This would be the first step towards a more personalised treatment for glaucoma and to stop poor adherence from undermining the effectiveness of care.

5. Conclusion

Personalised approaches to treatment of any medical condition are most effective when there is multifactorial pathogenesis, perfectly exemplified in glaucoma. The exact pathophysiology of glaucoma remains to be identified, particularly in normotensive glaucoma or early-onset glaucoma without a family history of the condition. In tailoring therapy to each patient, by a thorough history and assessment of the patient's cardiovascular status and peripheral vascular disease, we can target and treat specific risk factors for the disease, such as the vascular risk factors described above. Pharmacogenomics allows clinicians to predict the drug response based on patients' genetic predisposition, which can overcome many of the issues currently faced in clinical practice, including non-response and tachyphylaxis, in order to more efficiently reach patients' optimal treatment. Genetic analysis can help predict susceptibility to glaucoma and the type in order to diagnose the silent condition early and with accuracy.

Whilst this review is not attended to be a meta-analysis, review of the literature and studies relevant to this work, have demonstrated the considerable work that requires to be done to use genetic profiling to 'intelligently' treat patients. Genes are clearly inadequate to predict disease alone, especially in glaucoma, which is highly influenced by environmental risk factors also. The

next decade of research into pharmacogenetics and pharmacogenomics should lead to exciting advances to help us depend less on our 'one protocol fits all' trial and error approach and aim to provide optimal care to ultimately reduce glaucomatous decline in visual function.

6. Expert Opinion

Glaucoma genetic studies can inform on three key areas: (i) Disease aetiology; (ii) Disease progression; (iii) Optimal treatment strategies. It may therefore be useful for identifying those likely to develop disease, predicting speed of disease progression over time, deciding optimal therapeutic strategies, and in the future developing new therapeutic targets.

Genetic testing in hereditary glaucoma, could help to identify underlying genetic causes and predict inheritance patterns and disease progression, which would help decide screening and follow-up guidelines. This could enable some patients with a strong family history of glaucoma to be discharged from secondary care to regular optometrist screening if key genetic markers are absent. Equally those with certain genetic markers could have their follow-up frequency increased to identify disease onset early and a better prognosis and prediction for disease morbidity could be achieved to help patients better plan their lifestyles and even career choice.

Current clinics are inundated by patients who suffer from treatment side effects, or who are inadequately treated. Significant clinic capacity and time in the patient's disease course are wasted through a trial and error approach to treatment management. Genetic profiling could potentially reduce this by predicting treatment side effects, intolerance and optimal treatment. Pharmacogenomic studies will need to be replicated with larger sample sizes to provide more robust data to implement this in clinical practice.

Other promising areas of research involve being able to accurately forecast glaucoma progression, in order to achieve an adequate IOP target early in the disease course. This would take into consideration various risk factors of disease, including starting pressure, comorbidities, disc morphology, family history, corneal thickness and genetic status, to create a likely trajectory for field loss over time, based on differing pressure levels. An engineering technique commonly used in aeronautics, Kalman filtering, has been used to predict disease progression in diabetes and prostate cancer, and has recently been shown to be useful in glaucoma also [161]. Using perimetric and tonometric measurements from AGIS and CIGTS, Kalman filter models were developed to show slow, fast and non-progressors of open angle glaucoma. This highlights the potential for choice of target pressure based on models of disease progression.

Increasingly personalised healthcare will be the future of management of a range of conditions and will be most helpful in those for which standard treatments are not always beneficial. We currently do our best to categorise patients into the type of glaucoma on initial assessment, which can help predict effectiveness of therapeutic approach. However, in the future, an ideal management approach would be to use their lifestyle and cardiovascular risk factors and their genetic profile to accurately predict which treatment modalities would be most efficacious or most toxic and the rate and severity of visual loss over time.

These advances would allow for more cost-effective glaucoma management by reducing wastage of non-efficacious treatments and could also reduce glaucoma-associated morbidity by treating the condition in a more targeted way. Introducing routine genetic profiling into the clinical practice is unlikely however unlikely to occur even in the next couple of decades. More likely, genetic profiling could be used where patients are refractory to treatment or in complex glaucoma cases. Even if genetic profiling were to be used, it will not hold all the answers; environmental and other interaction affecting genetic expression will need to be elucidated first. Considerable basic science research will continue in the next few years to decades to establish further pharmacogenomics in glaucoma. Appropriate genetic animal models would help to test *in vivo* the effect of differing treatments, as they interact with recognised genetic characteristics in glaucoma. Future clinical trials would translate these findings by testing drugs in patients with underlying genetic characteristics.

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