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CHAPTER 13

Primary open angle glaucoma: an overview on medical therapy

Michele Vetrugno*, Francesco Cantatore, Giuseppe Ruggeri, Paolo Ferreri, Alfonso Montepara, Alessandra Quinto and Carlo Sborgia

Glaucoma Center, Department of Ophthalmology, University of Bari, Bari, Italy

Abstract: The purpose of this review is to discuss the topics relevant to the use of intraocular pressure-lowering strategies, which remains the first line in the management of glaucoma. Estimates of blindness from glaucoma and identification of risk factors remain of interest for all ophthalmologists. New functional tests offer promise for better detection and more accurate diagnosis of glaucoma. We finally discuss the impact of various glaucoma therapies, the principles of monotherapy and fixed combinations, which offer benefits of convenience, cost, and safety.

Keywords: glaucoma; medical therapy; prostaglandins; risk factors

Introduction

Glaucoma is nowadays defined as a progressive optic neuropathy (Gupta and Weinreb, 1997) with a typical associated visual field loss, and it is one of the leading causes of preventable blindness in developed countries.

It is estimated that glaucoma approximately causes the 10% of all blindness (Quigley, 1996).

Since life expectancy is increasing, all the efforts need to be focused on maintaining the quality of patient's life, and alleviating the social and economic burden of glaucoma.

Glaucoma treatment has been available for more than a century. Nevertheless, due to the unproven efficacy of glaucoma therapy and also to the additional treatment modalities, which have expanded the available options, there is a considerable controversy within the glaucoma researchers community concerning how the open angle glaucoma should be treated, and, particularly, which weapons should be employed.

Glaucoma prevention consists in identifying the risk factors associated with the optic neuropathy and attempting to treat those factors for which a therapy exists. For decades intraocular pressure (IOP) has been considered the only risk factor associated with glaucoma and for this reason the goal of many therapeutic options is to treat it. Having the researchers recognized the existence of other treatable risk factors, new therapeutic options should include blood flow, neuroprotection, and genetically based agents.

This work aims to provide an overview on the medical treatment, especially referring to three matters:

- When to treat
- Whom to treat
- How to treat

*Corresponding author. Tel.: +39805592525;
Fax: +39805478918; E-mail: m.vetrugno@oftalmo.uniba.it

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When to treat

This is the first step in glaucoma treatment, and this item is directly linked to the current opinions about the early glaucoma diagnosis or high-risk ocular hypertension.

Affirmed that, since glaucoma is a slowly progressing disease, someone believes that an early diagnosis and a consequently early treatment may not be essential.

A definition of early glaucoma is needed, in order to guide physicians in their diagnostic and therapeutical decisions. Early glaucoma is a silent condition, without symptoms, as many patients do not even know they are suffering from this disease until it has further progressed. Thus, all the efforts should be dedicated in the population screening, in order to identify affected people.

Current findings suggest that glaucoma may remain undetected in approximately 50% of the population, until some loss of vision has occurred; moreover, even nowadays, a delay in diagnosis is possible for a great proportion of patients (Caprioli and Garway-Heath, 2007).

Early detection, together with an appropriate treatment, can actually improve patients' outcomes.

Referring to the impact of an early treatment on its outcome, first it has to be clarified if the intended outcome is the field loss or the disability prevention: the former refers to the visual function, whereas the latter is related to the quality of life.

The existence of a tolerated IOP range without optic nerve damage, and, on the other side, of IOP levels commonly considered as normal characterized instead by a glaucoma rate of progression, is to correlate with an individual optic nerve damage sensibility.

It is still up for discussion whether a treatment should start as soon as possible, since there are findings showing that considerable retinal ganglion cells (RGCs) death may go undetected.

Schwarzt and Budenz, early treatment supporters, believe that prolonged elevation of the IOP triggers a series of events that results in the ganglion cells progressive loss, even after the IOP is adequately controlled (Schwarzt and Budenz, 2004). This hypothesis may explain why some patients continue to progress despite an adequate control of the IOP. It has been generally agreed that an early detection does not automatically imply an early treatment: the early detection and the early treatment should be considered separately.

If the early treatment loses importance, then an alternative strategy in the ocular hypertension management is waiting for signs of manifest glaucoma (optic nerve changes or visual field abnormalities).

Although a decision of an early treatment may not be made, other appropriate measures, such as close monitoring, may be considered (Caprioli and Garway-Heath, 2007).

Early detection may benefit the physician–patient relationship. It is important that the physician educates and counsels the patient about his condition to ensure that he becomes engaged in the disease management.

The patient surveillance should match the risk level. For example, a patient who is highly suspected for glaucoma may be asked to come back for follow-up in 6 months, instead of 1–5 years check-up for patients with a lower risk of disease.

Although the ultimate impact of delaying the treatment is currently unknown, there is evidence showing that early treatment can prevent or at least delay progression to glaucoma.

The Ocular Hypertension Treatment Study (OHTS) first findings, showed that lowering the IOP with topical hypotensive medications, can prevent or delay progression to glaucoma in OHT patients without definite evidences of glaucomatous damage (Kass et al., 2002).

In this study, at 5 years follow-up, the cumulative probability of progression to glaucoma in the treated group was less than a half, comparing with the untreated group.

Early IOP-lowering intervention was also found to reduce the rate of conversion from OHT to glaucoma in the European Glaucoma Prevention Study (EGPS, 2005). Although findings suggest that the rate of conversion to glaucoma from OHT is relatively low, it is essential that those in whom the disease progresses receive appropriate care.

It was suggested that follow-up study to the Early Manifest Glaucoma Trial (EMGT) should be conducted to investigate progression rates of patients who received early treatment, compared with those who received later treatment.

In the 6-year EMGT, early intervention delayed disease progression in the treatment group with early glaucoma compared with untreated patients (Heijil et al., 2002).

In other words, the matter is to determine if early treatment is beneficial for the long-term visual outcome or whether it is acceptable to observe progression behavior and then treat the patient on the basis of observed progression behavior.

For social and economic reasons, the glaucoma screening is a useful and necessary task, with possible benefits for individuals and the health care system, thanks to the early diagnosis and early therapy of patients suffering from glaucoma. Knowledge from literature shows that an early treatment of patients with glaucoma decreases blindness risk and lowers the direct and indirect costs for patients with glaucoma.

Whom to treat

In prescribing initial medical therapy for glaucoma or ocular hypertension, a number of factors have to be considered. It was thought that treatment should begin if it is deemed necessary to preserve the quality of life, but that initiation should be considered on an individual base. According to this, discovering and treating people at risk of visual function's loss with an individualized management is preferable.

As recommended in the OHTS (Caprioli and Garway-Heath, 2007), not all hypertensive patients should be treated, but several parameters should be taken into account, among which

- social-economic impact of a long-term treatment
- likelihoods that the treatment is useful for the patient
- patient's health status
- life expectancy
- patient's relative risk of developing glaucoma.

Considering more specifically the medical therapy, the following parameters have to be considered:

- efficacy
- side effects
- costs
- convenience of dosing
- diurnal fluctuation.

For these reasons, glaucoma therapy can vary according to the single patient but its principle aim is to preserve visual function at the lowest risks, costs, and side effects for the patient.

As for the chance of beginning the medical treatment, some risk factors have to be considered: the presence of glaucomatous damage in the fellow eye, a family history in the first degree relatives, a pre-treatment tonometry readings, the age, and the race.

Genetics

Much research has been focused on the gene expression, protein processing, and mutations of MYOC/TIGR, which is associated with both juvenile- and adult-onset primary open angle glaucoma (POAG). Investigations of other glaucoma related genes such as PITX2, FOXC1, and CYP1B1, are enabling a better understanding of anterior segment development and its relation to glaucoma (WuDunn, 2002).

Age

Glaucoma is age-related, and its prevalence increases up to 0.2% per year in patients aged from 50 to 54; up to 2% in an elder population aged above 70 years and its incidence is estimated to be 0.11% per year in people between 55 and 74. Perhaps the increased prevalence in advanced ages indicates a longer exposure to higher pressure levels or a major optic nerve susceptibility (EGS, 2003). The burden of a visual impairment is not uniformly distributed throughout the world; the least developed regions support the largest share. Visual impairment is also unequally distributed across age

groups, being largely confined to adults aged 50 and over (Caprioli and Garway-Heath, 2007).

Race

The Baltimore Eye Survey indicates that POAG prevalence is four times higher in Afro-Americans than in other races (Tielsh et al., 1991). Moreover Afro-Americans glaucomatous blindness probability is four to eight times higher than in Caucasian-Americans. The role of race in glaucoma rate of progression has not been cleared up but basically a hereditary mechanism occurs.

Ocular and systemic abnormalities

Other possible but controversial risk factors are myopia >4 diopters, pseudoexfoliation, thin cornea, and vascular diseases like systemic pressure, vasospasm (Raynaud syndrome), migraine, prinzmetal angina, and diabetes (EGS, 2003).

IOP fluctuations

Unless the IOP is so high to be danger for patient visual function, a medical treatment should not be started at the first visit. The IOP should be measured more than once and preferably more times a day, in order to quantify the diurnal fluctuation. The IOP is characterized by diurnal fluctuations in a large proportion of healthy people. Its variations are generally less than 4 mmHg, with higher levels in the morning. Differential IOP suggests the efficacy of the drug used, above all when it is not affected by diurnal fluctuation. A recent study (Schwarzt and Budenz, 2004) suggests that high IOP diurnal fluctuation, even in treated patients, can result in more progression, compared with patients who do not show high diurnal fluctuations. The range of the initial daily IOP variation was more predictive of the risk of visual field loss, progression than was the mean or the peak IOP.

This concept that a greater range of diurnal IOP variation is more damaging to the eye has suggested a different approach to glaucoma therapy, namely that the treatment should be aimed at trying to minimize the diurnal fluctuation in the IOP as well as to eliminate pressure peaks. The duration of many antiglaucoma drugs action is fairly short, so that some of the drug's effect is already wearing off before the next dose is administered (Wilensky, 2004).

Tonometry and pachymetry

Glaucoma screening usually uses only one parameter (IOP) to detect and to discriminate glaucoma patients but glaucoma actually requires a variety of diagnoses, therefore a single test would not be sensible and specific enough to detect glaucoma. With the use of a single device such as tonometry, there is a high probability of a false-positive. The diagnosis should be confirmed by the disc damage assessment and by the trends in visual field.

Based on this rationale, the rate of progression then determines how treatment's targets should be set. Corneal thickness can influence IOP assessment, as well as its curvature and hydration. Central corneal thickness (CCT) evaluation by pachymetry is intended as an aid to correct the IOP measurements, above all when it is necessary to cast doubts about starting glaucoma treatment.

Optic nerve condition and visual field stage

The presence of risk factors is important in order to establish treatment guidelines in preventing optic nerve rate of decay. The most important indications about the relative glaucoma damage risk are the current damage and the rate of progression (EGS, 2003).

Another screening parameter should be the optic nerve head morphology, since the diagnosis of glaucoma is very closely associated with a morphologic change in the optic nerve head. Damage stage can be evaluated by optic nerve and visual field assessment.

Optic nerve stereoscopic evaluation is based on glaucoma damage signs such as neuroretinal rim thinning (at superior and inferior poles), notching, splinter optic disc hemorrhages, cup

asymmetry, parapapillary atrophy, bared circumlinear vessels.

- Neuroretinal rim thinness can affect all disc sectors, but generally it is often remarkable at inferior and superior poles, so that inferotemporal edge is not characteristically the thickest.
- Disc hemorrhages represent a sign of local vascular damage and their presence is likely to be pathological.
- A parapapillary atrophy can be present in no glaucomatous eyes, so it is intended as a clue.
- An early sign of acquired rim thinning is a bared circumlinear vessel at the edge of the disc.
- In early glaucoma stages slit-like, grove-like, and spindle shaped defects are more evident, coexisting a generalized thinning of nerve fiber layer (NFL).

An initial alteration is generally characterized by both diffuse thinning and one or more localized defects. Since those NFL defects are present up to 3% in no glaucomatous eyes, they are likely to be pathological. An optic nerve or visual field damage rate of progression is typical of glaucoma, but it is very difficult to evidence it during the first patient assessment. Rate of progression can be determined by a continuous follow-up.

An advanced optic nerve damage, clinically evident, rapidly progressing, affected by risk factors, requires an aggressive treatment by lowering the IOP. Although the IOP lowering by medical therapy has been shown to be beneficial in delaying or preventing the glaucoma onset in ocular hypertensive and delaying or preventing visual field loss in people with glaucoma, there is a potential therapy downside it (Schwarzt and Budenz, 2004).

If the medical treatment is not effective in obtaining stated IOP target or in preventing the decrease in clinical data, other therapeutical options, such as laser therapy or surgery, can be considered on the individual needs.

According to Schwarzt and Budenz (2004) in a 90-year-old ocular hypertensive patient with no visual field loss, for example, observation might be a better strategy than lowering the IOP by 20%, especially if the therapy introduces the risk of ocular or systemic side effects or high medication costs.

At the other end of the spectrum, the authors consider a 60-year-old patient with severe, progressive glaucoma who has IOP in the mid-20s on maximal medical therapy and has already received laser trabeculoplasty. The risk of permanent disability is high without IOP lowering, and the benefits of trabeculectomy are high. In this case, it is probably worth to accept the small complications risk from trabeculectomy surgery.

How to treat

A medical treatment is considered effective when the mean effect produced by that drug is similar to published average effect on general population and this effect should be higher than the ones found by tonometry, that are affected by errors and variations (EGS, 2003).

IOP lowering is the most effective therapeutical approach to avoid function loss, because a high IOP is the main risk factor for glaucomatous damage onset. Normal IOP level is a statistical outcome, based on population measurements, so it cannot be applied to all patients arbitrarily.

Although the disease progression is usually slow, it may be faster in individuals whose optic nerve is more susceptible to IOP-related damage. There is substantial evidence which confirms that lowering IOP is effective in reducing glaucoma rate of progression in some or in the majority of the patients. Before setting medical treatment, baseline IOP levels should be measured and compared with the ones found during the follow-up. Moreover, the relative risk of developing optic nerve damage depends on the mean IOP, the maximum IOP, and the IOP fluctuations.

Generally, the more advanced is the damage, the lower is the target IOP: the goal of glaucoma therapy in ocular hypertension is lowering IOP by at least a 20% in patients with moderate to high risk of progression. In patients with perimetry-proven glaucoma, IOP should be lowered by at least a 30% in early to moderate glaucoma, and perhaps a 40 to 50% in severe glaucoma (Schwarzt and Budenz, 2004).

Target IOP can vary during glaucoma natural history, and this is the reason for a continuous re-evaluation of treatment efficacy. Several trials have been carried out comparing drugs safety and efficacy in lowering the IOP, but they are not very reliable, due to the diversity of population's samples studied.

According to EGS guidelines (EGS, 2003) topical treatment should be started in one eye at a time.

It is preferable to start with monotherapy and in the last few years there has been a gradual change in medical treatment choice.

If the first drug used is not effective in decreasing the IOP or is not well tolerated, it is preferable to change agent category.

Moreover, if the topical agent used in monotherapy does not produce side effects but it is not sufficient in decreasing the IOP, another topical agent can be added.

The antiglaucoma topical agents can also be associated to achieve the target pressure.

Drugs having the same action cannot be combined with each other (for example, two different beta-blockers or two prostaglandin analogs).

It is also recommended to use no more than two combined drugs where the second one should be added only if it is useful to achieve the target IOP.

An increase in the required drug dosage does not produce further therapeutical effects but only side effects.

When evaluating any class of medications, we must consider the therapeutic index (Robin, 1997). This is a measure of the relative potency, considering both the efficacy and the safety of a medication. The therapeutic index is a ratio of the toxic dose, typically at the 50% of the response level. The greater is the therapeutic index, the greater is the difference between the amount of medication that causes a beneficial effect and that dosage that commonly induces life-threatening side effects. The smaller is the therapeutic index, the smaller is the difference between a therapeutically desirable effect and a potentially serious side effect.

The medications now available fall into five classes:

- beta-blockers
- prostaglandin analogs
- alpha-agonists
- carbonic anhydrase inhibitors (CAIs)
- myotics.

All drugs work by lowering IOP, either by improving the aqueous humor outflow or reducing its production (Schwarzt and Budenz, 2004); they have been shown to be effective in lowering IOP and in preventing glaucoma progression, so the decision of which class of drug should be preferred, is never really based on efficacy only.

Ocular and systemic tolerability, dosing regimen, and cost must be considered as well.

If the starting IOP is higher, then the lowering percentage may be more than if the starting IOP is lower. Also these approximations only apply if the medicine is used at the frequency recommended by the drug leaflet.

As already mentioned, the duration of action of many antiglaucoma drugs is so short that some of the drug effect is already wearing off before the next dose is administered. This is clearly the case with pilocarpine, topical CAIs and alpha-adrenergics (Talluto et al., 1997), while the prostaglandin analogs such as latanoprost, travoprost, and bimatoprost have a much longer duration of action.

Beta-blockers

Beta-blockers have been introduced for glaucoma treatment in 1979 and they have been the first-line therapy until recently.

Although beta-blockers have proven to be very effective and safe when used as eye drops, there are several long-term side effects.

Side effects are generally associated more with non-selective beta-blockers, such as timolol and levobunolol; thus, on the other side, a beta1-selective beta-blocker, like betaxolol, is not as effective as a non-selective beta-blocker (Caprioli and Garway-Heath, 2007) or as the ones with intrinsic sympathomimetic activity (ISA) such as carteolol and pindolol.

All the beta-blockers are less effective in dark colored eyes (Soltau and Zimmerman, 2002).

They all decrease IOP by the reduction of the aqueous humor production (Hayreh et al., 1999) and their peak effect occurs in 2 h (EGS, 2003).

At the starting time, the dose regimen should be at the lowest concentration and the administrations should be once or twice a day, but if the clinical response is not adequate, the dosage may be increased to higher concentrations.

Dosing more than twice daily will not give any further pressure-lowering effect. The washout time needed for beta-blockers is 2–5 weeks.

No dose–response curves for the different beta-blockers treatment have been established (EGS, 2003).

Non-selective beta-blockers are usually well tolerated, but may cause an exacerbation of respiratory symptoms in patients with reactive airway disease (such as asthma) and bradycardia (Schwarzt and Budenz, 2004).

It may be worthwhile to avoid beta-blockers in smoking patients and in those with a history of bronchospastic disorders. They should be used with caution in diabetics because they may mask the symptoms of hypoglycemia. These agents should be used with caution in any patient with heart disease, heart block, or cardiac failure.

Recently, reports (Hayreh et al., 1999) suggest that beta-blockers are associated with nocturnal hypotension, which may be a risk factor in glaucomatous progression.

After a prolonged use, depression, mood alterations, memory loss, hallucinations, decreased libido, impotence, and decreased exercise tolerance have also been reported with beta-blockers.

An easy and effective way to reduce systemic side effects is to perform a nasolacrimal occlusion after the topical application, reducing plasma levels by up to 70% (EGS, 2003).

Uncommon ocular side effects are epithelial keratopathy and a slight reduction in corneal sensitivity. Caution should be used in the co-administration of beta-adrenergic blocking agents with oral and intravenous calcium antagonists, digitalis, and catecholamine-depleting drugs.

Prostaglandins

This group of medications has had the biggest impact in the last 10 years of glaucoma treatment. For a long time it has been a skepticism on using these drugs, because of the inflammation they cause. After years of dedicated researches, it was found that by slightly modifying the prostaglandin molecule, it is possible to achieve an IOP lowering and reducing the inflammation at the same time.

Prostaglandins lower the IOP by increasing the aqueous outflow through an alternative pathway.

The first drug of this class has been latanoprost, followed by travoprost and bimatoprost. These agents have been approved for both first-line and adjunctive therapy, depending on the country (Hylton and Robin, 2003).

All the above once-daily prostaglandin analogs are at least as effective, if not even more, in lowering the IOP than timolol maleate. Regarding the efficacy within prostaglandin derivatives' class, the only conclusive study (Hylton and Robin, 2003) shows that latanoprost, bimatoprost, and travoprost appear to have a similar efficacy in reducing IOP of a 20–35% from baseline.

The reduction of the IOP starts approximately 2–4 h after the administration, with a peak effect reached approximately at 8–12 h. This intraocular-lowering effect persists, but is less evident at 48 h after the administration (EGS, 2003).

The maximum IOP lowering is often achieved at 3–5 weeks from the beginning of the treatment.

The most attractive feature of the prostaglandin analogs is their ability to significantly reduce the IOP with only once-daily administration in patients with glaucoma or ocular hypertension, preferably in the evening. In fact, their IOP-lowering ability is decreased if used more than once daily.

This once-daily usage, together with the favorable local and systemic side effect profile has increased rates of compliance and reduced rates of discontinuation of therapy. The relatively lower incidence of adverse systemic effects seen with topical prostaglandins compared with more traditional glaucoma therapies has promoted their usage as the ophthalmic market sales leader.

Prostaglandin analogs are similar to each other, with regard to their overall favorable safety profile. Some non-specific associations of adverse systemic effects, including upper respiratory tract infections, headache, flu-like syndrome, and musculoskeletal pain have been reported with all the three agents.

As topical side effects have been reported: redness in the treated eye for the first weeks of use, burning, tearing, recurrent erythema, itching, hyperemia, hypertrichosis, and increased iris and periocular skin pigmentation. Conjunctival hyperemia and eyelash growth are other side effects shared by all the three compounds. In a longer term we could find a change in the iris color to brown; the change is permanent but it is not intended as pathological. However, the highest incidence of hyperemia is seen in patients on bimatoprost therapy.

A treatment with prostaglandin analogs in pseudophakic and aphakic patients has reported to be associated with cystoid macular edema (CME). The incidence of CME in patients on prostaglandin therapy appears to be higher in those patients with a compromised blood–aqueous barrier. Pseudophakic or aphakic patients who have had complicated cataract surgery or vitrectomy are at a higher risk of developing CME, even without the addition of prostaglandin agents. It has been suggested that prostaglandins can accelerate the disruption of the blood–aqueous barrier after cataract surgery (Hylton and Robin, 2003).

Alpha-agonists

This new class of drugs is vaguely related to an older drug called dipivefrin that fell from favor (Robin, 1997). There are selective and non-selective alpha-agonists. The non-selective alpha-agonists are dipivefrin and epinephrine, which can be deleterious for occludable angles and aphakic patients because of the macular edema that can occur.

Clonidine was the first relatively selective alpha2-agonist identified for clinical application.

The concern over the topical clonidine's systemic side effects, such as lowering systemic blood pressure and decreasing blood flow to the optic nerve, may have led to the clinical development of other selective alpha2-agonists, including apraclonidine and brimonidine. None of the three is purely alpha1 or alpha2-selective.

Apraclonidine causes no systemic hypotension, and brimonidine causes less frequent systemic hypotension than other agents. They primarily lower the IOP by suppressing the aqueous humor production, but also by altering the ocular blood flow to the ciliar body and by decreasing the episcleral venous pressure. They can be used twice a day in combination with other drugs, or sometimes three times a day if used alone.

Brimonidine tartrate, in contrast to apraclonidine, is a lipophilic drug and its primary route is the cornea. It is administered at a twice-daily dosing regimen. The effect seems to markedly diminish at 6 h after dosing, till a maximum of 12 h; the maximum IOP's decrease range is between 20 and 30% (EGS, 2003).

The washed-out time needed for these compounds to completely lose their action is 1–3 weeks.

Brimonidine 0.2% is the most effective dose because it is not only at the top of the dose–response curve, but it has also showed the fewest systemic and local side effects (Robin, 1997).

The most frequent side effects reported with brimonidine are dry mouth, conjunctival blanching, systemic hypotension, fatigue, and drowsiness, especially in children.

There is a tendency for a number of patients to develop allergy to the drops after several months: this propensity does not mean that the drugs should not be used, but merely that if allergy develops they should be stopped and changed to an alternative treatment.

Its selectivity for alpha2 vs. alpha1 receptors results in no mydriasis and in the absence of vasoconstriction.

Brimonidine has been associated with respiratory and cardiac depression in infants and is controindicated under the age of 2; caution is actually indicated in all the pediatric patients and the nursing mothers.

There is some hopeful research suggesting that brimonidine may have a "direct neuroprotective" effect and may prevent the retinal nerve cells degeneration (Robin, 1997).

Neuroprotection is intended as a preservation from an early ganglion cells loss, caused by toxins and ischemia. A neuroprotective treatment should be aimed at recovering dysfunctioning RGCs subsequent to glaucoma related damage. It is likely that these cells do not die immediately when

they are damaged, and the period of agony therefore represents a therapeutic window. Progress has been achieved in the study of neuroprotection, allowing a further understanding of the mechanisms involved in optic nerve degeneration, and an advance in therapeutic research. The use of other biomarkers for identifying and assessing the neuroprotective or neuroregenerative effects of a therapeutic method may be useful in the future, but their clinical relevance is currently unproven.

Carbonic anhydrase inhibitors (CAIs)

The two drugs in this class are dorzolamide and brinzolamide, and they are related to the systemic drug acetazolamide, used for many years to treat acute glaucoma.

They lower IOP by decreasing the aqueous production in the ciliary body, like the beta-blockers do. When the beta-blockers are contraindicated, dorzolamide may be a reasonable choice for the first-line therapy (Talluto et al., 1997).

The oral CAIs effectively lower the IOP but they are associated with many systemic side effects, including malaise, fatigue, paresthesia, weight loss, depression, gastrointestinal distress, and nephrolithiasis.

Dorzolamide, administered three times daily, has a peak effect approximately at 2 h after topical instillation (EGS, 2003). Initial trials showed a 16 to 26% reduction from the baseline IOP. When used alone, dorzolamide should be given three times a day, on the contrary, while used in conjunction with other ocular hypotensive agents a twice-daily dosing may be sufficient.

CAIs are generally believed to increase CO_2 in the tissues: CO_2 then, can act on blood vessels to produce vasodilatation. Additional benefits from potential improvement of ocular blood flow still need to be shown.

Several randomized trials have confirmed the blood perfusion role in glaucoma, regardless of the IOP, even though no current evidence is able to assess the required value of blood flow in glaucoma management.

Several studies (Caprioli and Garway-Heath, 2007) suggest that ischemia-promoting vascular factors may contribute to glaucomatous damage, including vasospasm, impaired ocular perfusion pressure and general vascular disorders such as low blood pressure, especially the dips at night. Visual hemifield defects could be linked to corresponding peripapillary focal vessel narrowing. Furthermore, patients with progressing glaucoma showed a lower end-diastolic velocity in the central retinal artery than do healthy persons.

Dorzolamide has an excellent additivity with other topical ocular hypotensive medications, including beta-blockers and pilocarpine.

Brinzolamide is more lipophilic than dorzolamide at a physiologic pH, thus brinzolamide can better cross the lipidic membranes. The maximal effect for brinzolamide is reached at a concentration of 1%, while higher concentrations result in more adverse events.

Systemic side effects are minimal, particularly if compared with those of the oral CAIs. They can be associated with dorzolamide treatment, nephrolithiasis, idiosyncratic agranulocytosis, and thrombocytopenia: topical ocular doses are systemically absorbed.

Stinging and discomfort, immediately after drops instillation, are the major side effects, sometimes with a slightly bitter taste if the drops are allowed to run into the tear ducts (patients practicing the punctual occlusion could avoid this). Allergic conjunctivitis and decreased visual acuity have been seen in 6% patients and often require the discontinuation of the drop.

In patients with borderline endothelial function, have been reported superficial punctuate keratitis and corneal edema, due to inhibition of Na/K-ATPase and the bicarbonate dependent Mg-ATPase which use CA-II and CA-IV, together with cases of reversible and irreversible corneal decompensation (Talluto et al., 1997).

Myotics

The cholinergic agents, such as pilocarpine 0.5%, aceclidine 2%, carbachol 0.75–3%, and acetylcholine1%, have excellent efficacy and costs, but they have been largely abandoned because of the severity of their ocular side effects compared with the newer agents available (Schwarzt and Budenz, 2004).

Pilocarpine has been the mainstay of glaucoma treatment for many years, especially before the introduction of timolol. It is a very effective drug in lowering IOP by increasing aqueous drainage through the trabecular meshwork and by a direct action on the longitudinal ciliary muscle. It lowers IOP in 1 h and its effect lasts for 6–7 h. It is used less frequently nowadays because it requires a four times a day dosage, so reducing patient's compliance.

Acetylcholine has its indication for intracameral use during surgery. Aceclidine induces less accommodative spasm, a smaller increase in lens thickness and a lower reduction of the chamber's depth compared to pilocarpine (EGS, 2003).

These agents are indicated in aphakia/pseudophakia POAG where surgery is refused or not feasible and other less potent agents are uneffective. The washout time needed to completely lose their activity is several weeks and sometimes irreversible.

Major systemic side effects are intestinal cramps, bronchospasm, and cardiac irregularities.

Moreover, there are a number of local side effects, such as stinging, lacrimation, pseudomyopia, and a small pupil, which can be a problem for focusing and for adapting to changes in the light level from a bright day outside into a darkened room. Other ocular troublesome side effects are conjunctival thickening, iris cystis, cataract, and retinal detachment.

These agents are contraindicated in patients aged <40 years, with cataract, uveitis, and neovascular glaucoma. A competitive interaction with prostaglandins is assumed, since contraction of the ciliary muscle reduces the uveoscleral space.

Fixed combinations

In glaucoma therapy, we know that both doctors and patients overestimate the adherence and that doctors are poor judges of who is and who is not compliant.

When adding a second drug, a physicians need to consider the possible impact on the patient's adherence to the first drug. The treatment's adherence seems to be of a 75% maximum in most of the studies. With the addition of another therapy, irrespective of the size, frequency of administration, and type of adjunctive therapy medication, the adherence often decreases.

Dosing regimen is an important factor in patient's compliance. Although there is a good evidence in the ophthalmic literature suggesting that the compliance is worse with a four times a day compared with a twice a day dosing regimens, an evidence for differences in the compliance between twice daily and every day dosing is lacking. A large review on compliance has found a 70% of compliance with a twice a day or an every day dosing, compared with a 52% for a three times a day dosing and a 42% with four times a day dosing (Schwarzt and Budenz, 2004).

Good reasons for limiting the maximal medical therapy are:

- increasing chances of ocular irritation and hypersensitivity
- induction of subsensitivity and receptor down regulation
- worsening of the surgical prognosis.

There are classes of topical glaucoma medications, and medications within the classes where they differ, on the basis of the frequency and severity of ocular side effects.

For example, some agents should be avoided in the following conditions:

- beta-blockers — asthma, bradyarhythmia, low blood pressure
- epinephrine — chronic conjunctivitis, tachyarrhythmia, high blood pressure
- pilocarpine — age below 40
- alpha2-agonists — severe hypotony, orthostatic dysregulation
- CAIs — allergy to sulfonamide, nephrolithiasis.

It is well known from clinical trials (OHTS, EMGT) that the initial monotherapy has failed in the IOP control within the first 2 years of treatment at least in the 50% of glaucoma patients. In the United States, the initial glaucoma therapy typically consists of topical medications and

frequently more than one agent is required to achieve adequate control of IOP.

The OHTS (Caprioli and Garway-Heath, 2007) randomized patients to the observation or to a treatment arm in which the therapeutic goal was a modest 20% IOP reduction; in that study, the 40% of patients randomized to a treatment required more than one medication to achieve the 20% of reduction goal.

Why combine glaucoma medications? For patients who require multidrug regimens to control the IOP adequately, fixed combinations offer convenience, efficacy, and safety.

If "fixed drug combinations" are considered, the advantages are:

- better compliance
- less toxicity by preservatives
- lower price than separate preparations.

Fixed combinations of glaucoma medications offer a reduction in the number of bottles of medication the patients must purchase, which can represent a cost saving for patients whose drug plan requires a per-bottle co-payment. Fixed combinations also represent a reduction in the number of drops per day required. An established washout effect resulting from rapid sequence instillation of multiple medications requires that patients wait approximately 5 min between each eye drop (Fechtner and Realini, 2004).

Fixed combinations offer a reduced time commitment for drop instillation and the potential for greater efficacy by eliminating the washout effect. The cost and time saving may enhance the compliance. Additionally, instilling two medications within one drop reduces the amount of preservative applied to the eye, which may improve the tolerability and may also favorably improve a potential surgical intervention outcome in patients who ultimately require filtering procedures.

The major limitation of fixed combination therapy is that dosing of the combined medications cannot be altered within the combination product. In some cases, for instance, a twice-daily dosing schedule of a combination product might represent too little or too much of one constituent for a given patient. In these cases, forgoing the fixed combination in favor of concomitant therapy permits individualized adjustment of the constituent doses.

Several combination products have been developed including pilocarpine, epinephrine, and beta-blockers. Largely, these are no longer widely used and are mostly of historical interest.

Modern fixed combinations use two drugs from these classes (Fechtner and Realini, 2004).

Beta-blockers–CAIs

Timolol–dorzolamide (Cosopt®)

The timolol–dorzolamide fixed combination was launched in 1998, and its development also provided a convenience for the glaucoma patients at that time. Because of its safety, efficacy, and convenience of dosing, dorzolamide quickly became a popular second-line choice. Thus, as with the older combination products, the development of the timolol–dorzolamide fixed combination product reflected the common clinical use. Starting dose is one drop twice a day. Dosing more than twice daily will not give any further pressure-lowering effect.

Beta-blockers–prostaglandins

Latanoprost–timolol (Xalacom®)

The fixed combination of latanoprost and timolol soon mirrored the common clinical use. Both can be given once per day, both are well tolerated, and they act by a different mechanism of actions, respectively, increasing the uveoscleral outflow and reducing the aqueous production.

Travoprost–timolol (Duotrav®)

Multicenter, double-masked studies have been demonstrated the efficacy and safety of this fixed combination (Barnebey et al., 2005; Schuman et al., 2005).

Travoprost–timolol fixed combination produces significant and clinically relevant reductions of the

IOP in a once-daily dosing regimen. The safety and the tolerability of the fixed combination were also equivalent to the concomitant therapy, with potential benefits that include convenience, cost savings, and elimination of potential washout effects (Hughes et al., 2005).

Bimatoprost–timolol (Ganfort®)

A double-masked, randomized study of a fixed combination bimatoprost–timolol once a day compared to a non-fixed combination bimatoprost once a day and timolol twice a day has demonstrated a comparable effect in the ocular hypotensive efficacy. The lower propensity of the fixed combination to elicit conjunctival hyperemia suggests a superior comparative benefit/risk assessment of the fixed combination in the treatment of elevated IOP (Hommer, 2007).

Beta-blockers–alpha-agonists

Brimonidine–timolol (Combigan®)

A 12-week randomized, double-masked study involving patients treated with fixed combination brimonidine 0.2%–timolol 0.5% ophthalmic solution with concomitant use of individual components, demonstrated that Combigan is safe and effective as the concomitant treatment with the individual components. Its simplified dosing regimen has the potential to improve the compliance (Goni, 2005).

In conclusion, the relative IOP reduction expected from the medical therapy is approximately 25% with a monotherapy, 35% with a combination therapy, and 40% with a maximum medical therapy (multiple drug combinations) (Fechtner and Realini, 2004). Although a number of options have been studied, for the initial IOP management in glaucoma and ocular hypertension, the medical therapy still appears to be the most widely used treatment. Within the medical management, prostaglandins make the most sense for the initial therapy. Fixed combinations appear convincing, and should be preferred to the old concepts of maximum medical therapy including different medications.

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