Managing Primary Open-angle Glaucoma – Ocular Tolerability, Compliance, Persistence and Patient Outcomes

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Abstract

Primary open-angle glaucoma (POAG) is a progressive optic neuropathy that, left untreated, can lead to irreversible damage to the optic nerve and permanent vision loss. To date, intraocular pressure (IOP) is the only modifiable risk factor for disease progression, and topical eye-drops are currently used as the leading non-surgical glaucoma therapy. Despite the efficacy of pharmacotherapy in lowering IOP, success is ultimately defined by patient compliance and patient persistence. Ocular tolerability is a crucial factor in patient compliance and persistence; non-adherence owing to adverse effects can lead to poor control of IOP and treatment failure. Prostaglandin analogues are currently the first-line antiglaucoma agents, with a good tolerability profile and a better IOP-lowering effect compared with β-blockers. Combination therapies have also shown greater efficacy in lowering IOP compared with the individual constituents, with fewer adverse effects. Treatment should be tailored to the individual patient, with a focus on ocular tolerability and its role in adherence, compliance and vision preservation.

Keywords

Primary open-angle glaucoma (POAG), intraocular pressure (IOP), β-blockers, prostaglandin analogues, combination therapy, ocular tolerability

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The optic neuropathy glaucoma affects more than 70 million people globally and is a leading cause of blindness in Europe.[1,2] The most common form is chronic or primary open-angle glaucoma (POAG), which accounts for approximately 90–95% of all glaucoma cases.[3] This slowly progressive disease is associated with several key risk factors, including an increase in intraocular pressure (IOP), age, vertical cup/disc ratio, central corneal thickness and Humphrey visual field pattern standard.[4–6] Elevated IOP is a significant risk factor for disease progression even after adjusting for age, race and visual field damage.[7] Elevated IOP can lead to optic nerve damage, and as the optic nerve is incapable of regenerating, any deterioration leads to permanent vision loss.

Currently, IOP is the only demonstrated modifiable risk factor for disease progression, and the benefits of IOP lowering have been well documented in several clinical trials; these include improved perfusion pressure, less loss of visual field and reduced disease development or progression.[8–14] While not guaranteed to ensure success in every patient with glaucoma, IOP lowering is nevertheless the only therapeutic option available that has this wealth of evidence; other options have little to no evidence-based support. Although a complete analysis of results has yet to be published, the second phase III clinical trial examining oral memantine as a neuroprotective agent in glaucoma found no significant benefit for memantine over placebo in disease progression.[4,15] Thus far, any neuroprotective benefits offered to patients with glaucoma occur as an indirect effect of lowering IOP where deterioration of the optic nerve is prevented.

Although some physicians prefer to lower IOP by a certain percentage from baseline, this approach is not always ideal: some patients will need more IOP lowering, while others will require less. Neither can an absolute target be used, because therapy in glaucoma patients should be individualised based on a number of variables. The European Glaucoma Society suggests that factors such as IOP level prior to treatment, stage of disease, rate of progression, age and life expectancy and the presence of other risk factors should all be considered in order to determine target pressure.[4] However, target pressures are not static: in clinical practice it may be necessary to continually revise the target pressure according to the individual's needs and the disease progression of the patient.

As mentioned previously, any visual damage that occurs as a result of POAG is irreversible. However, effective treatment and adequate control of IOP can arrest disease progression. Pharmacotherapies applied as topical eye-drops form the mainstay of non-surgical glaucoma therapy. Unfortunately, success in preventing visual field loss is only as successful as the degree to which patients adhere to medical therapy in terms of how and when they take their medication (compliance) and for how long (persistence). The ocular tolerability of a medication and its impact on a patient's compliance and

persistence are significant factors that can affect patient outcome. It is important for physicians to consider these factors when selecting a medical therapy, while also stressing the importance of treatment adherence to their glaucoma patients. Non-adherence due to poor ocular tolerability can lead to treatment failure because of inadequate IOP control. Glaucoma treatment should therefore be determined with regard not only to IOP lowering, but also to minimisation of systemic and ocular adverse events, while taking into account compliance as part of individualisation of patient care.

From β-blockers to Prostaglandin Analogues and Beyond

Generally, initial treatment for lowering IOP is topical medical therapy with monotherapy as first choice. Several classes of antiglaucoma medication are currently available, including β-blockers, prostaglandin analogues, alpha-2 adrenergic agonists, topical carbonic anhydrase inhibitors (CAIs) and parasympathomimetic agonists. The latest European Glaucoma Society guidelines recommend that the choice of initial monotherapy be based on physician preference.[4] In recent years prostaglandin analogues have emerged as first-line agents. Current data show that 40–75% of glaucoma patients fail monotherapy after more than two years of treatment.[10,16] In these patients, combination therapy and/or further adjunctive therapy is often considered.

In the hypothetical situation where two different drugs are available with similar intraocular pressure lowering but different degrees of side effects, it would make sense to use the drug with fewer side effects.

β-blockers

β-adrenergic antagonists block the β-receptors in the ciliary body, thereby decreasing aqueous humour production. With over 30 years of clinical experience, the strengths of β-blockers, as well as their weaknesses, are well-established. Although able to lower IOP effectively, these drugs have systemic effects on the circulation, respiration and metabolism. Notably, owing to their systemic absorption, β-blockers present concerns for patients with cardiopulmonary disease. They have been associated with congestive heart failure, bradycardia, arrhythmias, syncope, heart block and systemic hypotension.[17–22] β-blockade has also been shown to exacerbate asthma, reactive airway disease, chronic obstructive pulmonary disease and bronchitis.[20,23–25] Worsening of dry-eye syndrome, confusion and decreased libido have also been observed.[25] Because a lot of patients with glaucoma are elderly, and many of them have cardiovascular, pulmonary or respiratory problems, β-blockers have become less popular in recent years, making way for the current most commonly used first-line agents: prostaglandin analogues.

Prostaglandin Analogues

Prostaglandin analogues lower IOP by increasing uveoscleral and conventional outflow. A meta-analysis of randomised clinical trials up to 2003 showed that, compared with any other class of topical antiglaucoma agent, prostaglandins were the most potent topical agents for IOP lowering, with the highest peak mean difference from baseline IOP.[26] In addition to an enhanced IOP-lowering profile, the systemic side effects common with β-blockers are largely absent in therapy with prostaglandins. Furthermore, unlike β-blockers, prostaglandins need only a single daily dose instead of twice-daily dosing. These factors – increased IOP potency, lack of systemic side effects and convenient dosing schedule – represent the main advantages of using prostaglandins in lieu of topical β-blockers in glaucoma therapy. Prostaglandins are generally well-tolerated, although there are some local side effects that are largely of only cosmetic significance. Hyperpigmentation of the iris and periocular skin occurs quite commonly, in addition to lengthening of the eyelashes. The most common side effect of prostaglandins relates to ocular tolerability – namely conjunctival hyperaemia,[27] which is tolerable if mild, but less so if moderate to severe.

Alpha-2 Adrenergic Agonists and Carbonic Anhydrase Inhibitors

Alpha-2 adrenergic agonists decrease IOP levels by reducing aqueous humour production while increasing uveoscleral outflow,[28] while CAIs function by decreasing aqueous production.[29] Although these drug classes are also indicated as first-line glaucoma treatments, they are limited by the number of associated adverse effects. Possible side effects for alpha-2 adrenergic agonists include allergic reaction, blurring, headache, fatigue, hypotension, insomnia, depression, syncope, dizziness and anxiety. Topical CAIs are associated with blurred vision, irritation, dermatitis and bitter taste.

Combination Therapy

Although the prostaglandin analogues have a strong IOP-lowering profile, many patients still require a multimodal approach with multiple topical medications in order to achieve target pressure control;[10,16] patients are commonly treated primarily with a prostaglandin plus an additional drug in combination.[22,30–32] In some cases where target IOP is still not achieved, the addition of a third drug may be considered. However, the use of multiple topical treatments increases the risk of adverse effects and non-adherence. The convenience of dosing in these multiple drug regimens can be improved via fixed drug combinations, the most recent addition to the armamentarium of antiglaucoma drugs. The simplicity of a single as opposed to multiple administration has been shown to improve patient adherence.[33] Fixed combinations also prevent medication washout, which occurs when patients on multiple drugs apply their medications with too short an interval between drops, leading to a significant washout effect.[34] Moreover, in the event of needing to add a β-blocker to a prostaglandin-containing regimen, a once-daily fixed-dose combination product would administer less β-blocker than a twice-daily regimen, thereby reducing the rate or severity of adverse effects, as well as the daily topical preservative load, without sacrificing efficacy.[35] Several fixed-combination formulations are now available and all contain a β-blocker as one component.

Fixed-combination therapies are now widely used in glaucoma therapy, particularly the combination of the prostaglandin analogue latanoprost and the β-blocker timolol, and that of the CAI dorzolamide and timolol. The fixed combination of latanoprost/timolol has been extensively studied, and has been shown to be

equal or superior in efficacy to either component as monotherapy,[31,36–40] It has also been shown to be more efficacious than the unfixed combination.[41] In addition, latanoprost/timolol has demonstrated superiority over other combinations, including fixed combination dorzolamide and timolol[42–44] and the unfixed combination of brimonidine and timolol,[45,46] albeit with a few exceptions where dosing schedules varied or the study population was very small.[47–49]

In general, fixed combinations of antiglaucoma agents have shown superior efficacy over their individual counterparts in terms of IOP lowering,[50,51] as well as a trend towards fewer adverse effects.[42,52–56] As well as benefits, there are also limitations associated with fixed combinations of antiglaucoma agents, the most obvious of which is the inability to alter the dosing frequency of the components in the combination product. This can potentially hinder the ability to tailor therapy towards the individual, and can interfere with the optimal dosing schedule.

The Importance of Long-term Patient Compliance, Medication Persistence and Ocular Tolerability

Although the impact of non-adherence to medical therapy on clinical outcome has yet to be established, the issue is an important consideration in glaucoma management. As a chronic and progressive disease, glaucoma is a lifelong condition that will continually worsen without medical intervention. In most cases, POAG is asymptomatic until the disease has progressed enough to significantly damage the peripheral visual field; symptoms therefore present only at the advanced stage. Left untreated, loss of the visual field can extend from the peripheral to central vision. However, lack of symptoms in the early stages of POAG means that many patients do not feel compelled to follow a therapeutic regimen. This is further compounded by medications that are associated with side effects, some of which can potentially reduce a patient's quality of life; if a patient feels no immediate therapeutic benefit from taking a drug but experiences irritating or debilitating side effects, the likelihood of that patient remaining compliant is low. The frequency of doses is also an issue, as a once-daily medication is generally better than a regimen that needs to be administered twice or thrice daily.[33,57] In order to maintain long-term patient adherence in terms of both compliance and mediation persistence, tolerability should also be optimised to minimise ocular and systemic side effects. In order to convince patients to adhere to their medication, it is not sufficient only to preserve the visual field and prevent further damage; it is also necessary to offer a satisfactory level of quality of life with minimal adverse effects. Furthermore, patient adherence needs to be continuously addressed by the physician.

Ocular Tolerability

Control of IOP is of course a very important variable to consider with respect to impact on patient outcome. For the most part, a lower IOP is generally better, but again it should be noted that the best practice is to individualise treatment. Nevertheless, the importance of ocular tolerability cannot be underestimated; poor tolerability negatively affects adherence to medication usage, and reduced compliance is the main reason for treatment failure. For glaucoma patients who require lifelong treatment and follow-up care to prevent disease progression and preserve vision, long-term patient compliance and persistence with medication is imperative. One of the most important factors influencing compliance and persistence is the side effect profile, both local and systemic.[58] Indeed, patients are most often more aware of side effects than benefits. Efficacy in IOP lowering is an important factor to consider, but the balance with tolerability has to be carefully established on an individual basis, with an emphasis on maximising compliance. Clearly, patient compliance, medication persistence and ocular tolerability are inter-related variables and must all be considered when selecting a treatment. In a progressive disease such as glaucoma, efficacy is of little consequence if a patient chooses not to take his or her medicine because of the side effects.

Nearly all topical antiglaucoma medications, and in particular the prostaglandin analogues, have been associated with the development of conjunctival hyperaemia.[59] Moreover, there is the concern that this side effect may have a negative impact on adherence. Studies comparing the persistence of individual prostaglandin analogues suggest latanoprost may be associated with greater persistence than travoprost and bimatoprost.[60,61] This may be related to the lower incidence of conjunctival hyperaemia seen with latanoprost, which in turn may improve tolerability.[62,63] Latanoprost has also been associated with better persistence compared with other classes of antiglaucoma medication.[64,65] Fixed-combination latanoprost/timolol has also been associated with good tolerability and persistence of use.[35,66] In a prospective, observational, non-interventional study, patients were switched from a fixed/unfixed combination therapy or monotherapy to fixed-combination latanoprost/timolol. Of the 1,052 patients analysed, 97% remained on therapy throughout the six-month follow-up period.[35]

Summary

In the hypothetical situation where two different drugs are available with similar IOP lowering but different degrees of side effects, it would make sense to use the drug with fewer side effects. Conversely, for two drugs with reduced side effects but different efficacies, one would want to choose the drug with greater IOP-lowering potential. With the introduction of fixed-combination drugs in glaucoma treatment, physicians have been offered many more options from which to choose when selecting a therapy for their patients, further increasing the difficulty of selecting a drug that is appropriate for each patient's needs. However, the fixed-combination medications have demonstrated both improvements in IOP lowering and reductions in adverse effects, while offering a simple and convenient dosing schedule. With so many choices available to the physician and patient, the greatest challenge ahead will be to maintain patient compliance while keeping therapy reasonable and manageable for the patient. ■

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