Medical Treatment of Open-angle Glaucoma in 2011

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Abstract

Treatment possibilities for open-angle glaucoma have improved considerably in recent years. Fixed-dose combination eye drops and preservative-free preparations are used increasingly in routine clinical practice, and may reduce the frequency and severity of the medication-related ocular surface problems. Despite this progress, our knowledge of several aspects of the use of combined medication is suboptimal and in many cases treatment intensification or surgery is not introduced in time. To improve the quality of glaucoma care it is useful to review the problematic aspects of treatment.

Keywords

Open-angle glaucoma, glaucoma progression, glaucoma medical therapy, glaucoma combination therapy, benzalkonium chloride, ophthalmic preservatives, generic glaucoma medications

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Why Treat Open-angle Glaucoma?

The goal of glaucoma treatment is to prevent any further, glaucoma-related decline of visual functions (e.g., deterioration of the visual field) and not to keep intraocular pressure (IOP) under a certain artificial value (e.g., 21 mmHg).[1–4] Thus, both an understanding of the basics of the pathophysiology of glaucoma and the application of evidence-based clinical knowledge on glaucoma treatment are essential to set an appropriate individual treatment and to modify (strengthen) it when early, but established, disease progression (functional, structural or both) occurs. Therefore, no simple instruction on the treatment of the total glaucoma spectrum can be given. In this brief review, the most important new aspects of glaucoma treatment are summarised. However, they cannot be applied usefully without an appropriate basic science, diagnostic and pharmacology background, which is not included in the current review.

Diagnosis of Open-angle Glaucoma

Although details of glaucoma diagnostics are not a part of this article, this is the first important step on the way to long-term treatment success.[3,4] In those parts of the world where angle-closure glaucoma is not particularly common, ophthalmologists frequently miss the appropriate classification of the anterior chamber angle. As a consequence, many chronic, painless angle-closure glaucoma cases are misclassified as open-angle glaucoma eyes and are treated accordingly (ineffectively). Eyes with appositional angle closure or a high risk for angle closure need to be identified with van Herick's technique and then gonioscopy. In such cases, preventive neodymium-doped yttrium–aluminium–garnet laser iridotomy should be made, and then the anatomical condition should be re-investigated. Only when occlusion of the anterior chamber angle is excluded can the case be considered as open-angle glaucoma and treated accordingly. Although the various types of open-angle glaucoma (e.g., primary, pseudoexfoliative and pigment) show considerably different clinical characteristics and IOP reduction under the same treatment, the general treatment principles are the same for all open-angle glaucomas.[4]

General Principles of Treatment

Currently, treatment of open-angle glaucoma is based on a sufficiently powerful decrease of IOP.[1,4] Although several laboratory results and some clinical studies are published on the potential benefits of increased ocular perfusion or neuroprotection in open-angle glaucoma, the number of evidence-based clinical trials on these is minimal in this field[5] and no glaucoma medication is approved for an effect not related to IOP. Several herbal supplements have been tried as supportive therapy, but no benefits of these agents have been proved scientifically for glaucoma.[1]

Central cornea thickness (CCT) should not be used for mathematical correction of the measured tonometric IOP value, but the eyes should be divided into three groups:[6]

- low CCT (true IOP is probably higher than the measured IOP and the risk for progression is increased);
- average CCT (the measured IOP represents the true IOP); and
- high CCT (true IOP is probably lower than the measured IOP value).

In ocular hypertension, when no structural and functional damage can be detected but IOP is clinically elevated significantly based on several repeated measurements, the goal of treatment is to reduce the increased IOP-related risk to the average risk level (i.e., the typical normal IOP range).[4] When functional and/or structural glaucomatous damage is verified, risk factors for open-angle glaucoma (verified glaucoma in closest blood relatives, race, age, myopia) need to be investigated.[4] The IOP-related risk should be assessed by diurnal

Table 1: Mechanism of Action, Number of Daily Instillations and Main Side Effects of Medications Commonly Used to Lower Intraocular Pressure[4]

	Mechanism of Action	Number of Daily Administrations	Main Side Effects
Beta-receptor blockers Timolol 0.1 %; 0.25 %; 0.5 % Levobunolol 0.25 %; 0.5 % Carteolol 1 %; 2 % Betaxolol 0.25 %; 0.5 %	Suppression of aqueous humour production	Once or twice daily	Manifestation/worsening of bronchial asthma, bradycardia, heart failure, sexual dysfunction, depression
Prostaglandin F2 alpha analogues Latanoprost 0.005 % Travoprost 0.004 % Bimatoprost 0.03 % Tafluprost 0.0015 % Unoprostone 0.15 %	Increase of uveoscleral aqueous humour outflow	Once daily (twice daily for unoprostone)	Increased periocular pigmentation, eyelash changes, conjunctival hyperaemia, irreversible darkening of the iris, exacerbation of herpetic uveitis, cystoid macula oedema when other risk factors of cystoid macula oedema are present
Carbonic anhydrase inhibitors Dorzolamide 2% Brinzolamide 1% Acetazolamide 250 mg tablet, 500 mg intravenous injection	Suppression of aqueous humour production	2–3 times daily Twice daily 1–2 tablets or injections per day	Systemic administration: acute agranulocytosis, anaemia, thrombocytopenia; paraesthesia, gastrointestinal complaints, fatigue, depression Topical administration: bitter-taste feeling
Selective alpha 2-receptor agonist Brimonidine 0.15 %; 0.2 %	Mainly suppression of aqueous humour production	2 to 3 times daily	Fatigue, lethargy or transient coma in newborns and young children
Parasympathomimetics Pilocarpine 1 %; 2 %	Increase of trabecular outflow	3 to 5 times daily	Miosis, myopic shift of vision formation of posterior synechia

Table 2: Efficacy of Various Drugs Frequently Used to Lower Intraocular Pressure to Treat Open-angle Glaucoma (Monotherapy Data)[4]

IOP-lowering Ingredient	IOP Reduction (%) Compared to the Untreated Baseline IOP	
	Peak Effect	Trough Effect
Bimatoprost 0.03 %	33	28
Latanoprost 0.005 %	31	29
Travoprost 0.004 %	31	28
Tafluprost 0.0015 %	31	28
Timolol 0.5 %	27	26
Betaxolol 0.5 %	25	18
Brimonidine 0.2 %	23	20
Dorzolamide 2 %	20	17
Brinzolamide 1 %	20	17

IOP = intraocular pressure.

or at least daytime IOP phasing to identify IOP spikes, mean diurnal IOP and diurnal IOP fluctuation. If previous visual field test results are available, it is very useful to calculate the progression rate for mean defect (MD) in dB/year on no treatment or on the previous and current treatments.[4] If the progression rate is not controlled, treatment intensification is needed. For example, for an eye with an MD of -5.5 dB (relatively early damage level) that shows a 1 dB/year MD progression rate, only one decade is necessary to deteriorate to -16 dB MD (severe damage level), and thus early and effective intervention is needed to reduce the progression rate.

Which Features of Intraocular Pressure are Important?

It is not easy to use IOP information. The measurement frequency (IOP sampling) is necessarily small compared to the true IOP continuum even if a 24-hour IOP curve is obtained. Clinical studies strongly suggest that in eyes with elevated IOP, the mean IOP (the mathematical average of the individual time-point IOP values) is a good measure of the clinically important features of IOP.[7,8] The role of diurnal IOP fluctuation may represent a separate risk for glaucoma progression in such eyes. However, when a clinically significant medical or surgical IOP reduction is achieved, the mean IOP value is well controlled and in the low teens, the significance of long-term (between visits) IOP fluctuation increases considerably.[8–11] Thus, the general principle is to intervene early, reduce both mean IOP and IOP fluctuation and continuously monitor the visual field, the optic nerve head and the retinal nerve fibre layer for progression or stability (which is not equal to missed progression).

How to reach this goal? There are six key issues to the success:

- selection of appropriate monotherapy;
- selection of appropriate combination therapy when monotherapy is not enough;
- use of fixed-combination drugs when available and the usefulness of the individual components is verified;
- if available, the use of drops not preserved by benzalkonium chloride (non-BAK) for long-term treatment;
- evaluation and support of the patient's compliance (adherence) to the prescribed therapy; and
- introduction of laser or filtering surgery when the IOP reduction achieved with medical therapy is insufficient.

Selection of Monotherapy

Except for cases with very high IOP and advanced structural and functional damage at the time of diagnosis (when rapid and functionally significant progression may occur), the recommendation is to start IOP-lowering medication monotherapy.[4] The advantage of this approach is that many patients are well-controlled on monotherapy and combined therapy increases the risk for side effects and frequently reduces the adherence of the patient. A classification of the various

Table 3: Summary of the Fixed Combination Drugs Commonly Used to Lower Intraocular Pressure[4]

Ingredient 1	Ingredient 2 (Beta-receptor Blocker Component)	First Commercial Name in Europe	First Launching Company
Bimatoprost 0.03 %	Timolol 0.5 %	Ganfort	Allergan
Latanoprost 0.005 %	Timolol 0.5 %	Xalacom	Pfizer
Travoprost 0.004 %	Timolol 0.5 %	Duotrav	Alcon
Dorzolamide 2.0 %	Timolol 0.5 %	Cosopt	MSD
Brinzolamide 1.0 %	Timolol 0.5 %	Azarga	Alcon
Brimonidine 0.2 %	Timolol 0.5 %	Combigan	Allergan
Pilocarpine 2.0 %	Timolol 0.5 %	Fotil	Santen
Pilocarpine 4.0 %	Timolol 0.5 %	Fotil forte	Santen

IOP-lowering medications according to their mechanism of action, administration frequency and main side effects is given in *Table 1*. The IOP-lowering efficacies of the different drugs based on monotherapy data are presented in *Table 2*. When monotherapy (usually a prostaglandin analogue therapy or timolol) provides the expected IOP-lowering effect based on daytime phasing or a 24-hour diurnal IOP curve[4,12] and the individual target IOP range is reached, the treatment should be continued. If the IOP reduction does not exceed 15 % (and the patient is compliant to the therapy), a new monotherapy should be introduced (switching). No adjunctive medication is recommended in such cases because the eye is a non-responder to the first therapy.[4]

Setting a Combination Therapy

When a patient responds well to the initial monotherapy, but the target IOP is not reached with one medication, additional IOP reduction is necessary.[4] There are two ways to increase the drug-induced IOP reduction:

- add a second drug concomitantly (unfixed combination); or
- switch from the monotherapy to a fixed combination that contains the monotherapy drug plus one more ingredient (this option is limited in those countries where fixed-combination glaucoma drugs are not easily available).

Both approaches provide information on the additional IOP reduction provided by the adjunctive IOP-lowering drug. If the additional IOP reduction decreases IOP to the target range, the combination can be used long term. When available, a fixed combination of the two ingredients is preferred in the long run over the concomitant administration, since this reduces the number of daily instillations and total BAK exposure.[4,13–15] If a third IOP-lowering drug is necessary, the combination is unfixed (i.e., a combined medication that comprises a fixed combination and a different third drug).[15] It is very important to know that members of the same drug class must not be combined (thus two fixed combinations cannot be combined because all fixed combinations contain a beta-receptor blocker). This means that each ophthalmologist must know the ingredients in the medication prescribed. Another important issue is that the maximal daily dosage of a fixed combination is equal to the maximal daily dosage of the least frequently administered component of the fixed combination. The most commonly used fixed-combination glaucoma drugs are given in *Table 3*.

Intraocular Pressure Lowering Drops Preserved by Benzalkonium versus Those Not Preserved by Benzalkonium

For several decades, BAK chloride has been used widely to preserve ophthalmic products. However, it has also been known for decades that BAK worsens the signs and symptoms of dry eye or ocular surface disease (OSD) and increases the frequency of OSD.[13,14] BAK is a detergent that destroys the lipid layer of the tear film, a process that increases evaporation of the aqueous layer. In addition, BAK has a dose-dependent toxic effect on the corneal, conjunctival and trabecular meshwork cells. This toxicity varies in different ophthalmic products according to the concentration.[13,14] Such an apoptotic effect gains importance during long-term exposure (glaucoma is a life-long disease) and worsens when multiple instillations are applied (unfixed combination therapy, unnecessary adjunctive medication). The subclinical inflammation caused by long-term use of BAK decreases the probability of successful filtering surgery because it stimulates the post-operative scarring process of the filtering bleb. Previously, it was thought that some toxic effects of BAK on the corneal epithelium (damaged integrity of the intercellular barrier) were beneficial for ocular drug penetration. Now it is clear that the IOP-lowering effect of timolol, certain prostaglandin analogues, timolol/dorzolamide fixed combination and certain prostaglandin/timolol fixed combinations is independent of the presence of BAK.[16–19] In conclusion, when a BAK-free or a non-BAK preserved alternative of an IOP-lowering drug is available, use of this formulation is recommended.

Compliance to the Prescribed Medication

Several studies from all geographical regions are published on the poor compliance (adherence, persistence) of glaucoma patients.[20–23] In routine clinical practice, compliance needs to be monitored closely and supported with training and personal interactions with the patients. A decrease in the number of daily drug administration (i.e., the use of fixed combinations) is also beneficial. Fewer and less severe side effects are associated with better compliance. Thus, when a new therapy is set, the different types of side effects (individual molecule related, formulation related, drug-class related or BAK related) should be considered, based on the patient's previous experience. The patient should always be involved as a partner in the evaluation of the treatment and his/her complaints (e.g., technical problems of opening the bottle or technical problems of the instillation) should be considered seriously when a long-term therapy is set. Each patient should be carefully instructed on the correct instillation technique, including avoidance of eye–bottle contact and blinking after instillation, use of punctual compression and the separation of different instillations by a five minute interval at least.

Laser and Surgical Treatment

Although the details of laser and surgical treatment of glaucoma are not subjects of the current review, it is important to understand that when a patient progresses despite an adequate IOP-lowering treatment, further intervention should not be postponed. The later the intervention is made, the more retinal ganglion cells that are lost and thus less visual function can be preserved. The longer the BAK

exposure, the higher is the probability for increased bleb scarring after trabeculectomy. Thus, when surgery is indicated it is better to offer it early or to propose a consultation with a glaucoma specialist than to continue an unsuccessful topical medication until the clinically significant and irreversible damage develops.[24]

Original Drug or Generic Medication?

The role of generics in the treatment of glaucoma has been gaining special importance, because increasingly, latanoprost has become available in generic forms in several countries. Generics are cheaper than the original product (no need to cover the cost of the drug development) and theoretically equal in terms of efficacy and safety. However, for ophthalmic products for which no pharmacokinetic studies are possible (we cannot sample the eye to measure comparative intraocular drug concentrations between the original product and each of the many generics), equal efficacy and safety can be shown only by head-to-head evidence-based clinical studies. Such studies are seldom conducted, and in large regions of the world, simple expert summaries are sufficient to receive a waiver from comparative studies during the registration process. Certain physical characteristics of the bottle (e.g., transparency, ease of opening, size of the droplet) are not regulated sufficiently. This may result in surprisingly large between-generics differences regarding the total daily dosage of the active ingredient. Thus, the use of generics may comprise some problems and the risk–benefit relationship needs to be investigated separately for each individual generic product.

Summary

Medical treatment of open-angle glaucoma has developed considerably in recent years. Several fixed-combination drops and non-BAK preserved preparations have become widely available. However, compliance remains low among glaucoma patients, treatment selection is still frequently suboptimal and in many cases surgery is postponed until severe functional damage has developed. To improve this situation the use of regional and/or national glaucoma diagnostic and treatment guidelines[2–4] is recommended for everyday routine practice. ■

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