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Management of primary open-angle glaucoma

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Introduction

The treatment of primary open-angle glaucoma (POAG) aims at maintaining patient visual function and quality of life at a reasonable cost. This cost is defined in terms of disadvantages and side effects for the patient but also in terms of individual and collective financial costs[1]. This treatment should therefore be individualized not only to the needs but also to the rate of progression of each patient.

The goal of the treatment of POAG is to slow down as much as possible the progressive loss of optic nerve fibers that characterizes the disease and ultimately threatens the patient of blindness.

To date, the only treatment that has proved its efficacy in slowing down POAG progression, regardless of the stage, is the one that lowers the intraocular pressure (IOP), as clearly shown in several multicentric studies. This treatment also reduces the risk of conversion from ocular hypertonia to glaucoma.[1] Its goal is to achieve a target IOP which is expected to stabilize damages. While the IOP should be lowered by at least 20%, the target IOP will be determined individually because it will be lower in patients with bilateral, advanced POAG and when the initial IOP is low, life expectancy is long and glaucoma progresses.[1] The quality of life will be further impaired if both eyes have very advanced glaucoma, which also changes the target IOP. It should therefore be re-assessed at each follow-up consultation.

Several types of treatment may be used to lower the IOP in POAG: medical, laser or surgical treatments.

Most often, a medical treatment which can lower the IOP by 15-40% is used first.

Laser therapy is used if there is a lack of efficacy, contraindication to or side effects of the medical treatment or non-adherence to the medical treatment, provided that the IOP is not too high and the neuropathy is not too severe, because the expected lowering in IOP still ranges between 15 and 25%.

Surgery is indicated in case of failure, inadequacy or intolerance of the medical and/or laser treatment, non-compliance with the treatment, high ocular hypertonia (OHT) or progressive POAG, without waiting for glaucoma to be too advanced to intervene. It allows lowering IOP by up to 50%.

The management of POAG also includes the control of non-pressure risk factors involved in the progression of glaucoma, including vascular factors.

Medical treatments

Eye drops lower the IOP either by reducing aqueous humor production or by increasing its elimination or by acting on both mechanisms.

It is recommended to start treatment with a monotherapy. The latter is considered effective when it allows achieving an IOP lowering similar to the average observed in the publications in the same type of population. Based on meta-analyzes of randomized controlled studies, the most significant lowering in IOP is thus achieved with prostaglandins, then non-selective beta blockers, alpha-agonists, selective beta blockers, and finally carbonic anhydrase inhibitors (Table 1).[2] The lowering in IOP is generally greater when the initial IOP is elevated. The individual response of a patient to an eye drop may differ from that mentioned in the table and should therefore be verified on a case-by-case basis.

Eye drops	Mode of action	Peak (%)	Trough (%)
Prostaglandins/ prostamides	Increased uveoscleral elimination	31-33	28-29
Beta blockers non-selective selective	Decreased aqueous humor production	27 23	26 20
Alpha-agonists	Decreased aqueous humor production and increased uveoscleral elimination with brimonidine	25	18
Topical carbonic anhydrase inhibitors	Decreased aqueous humor production	17-22	17

Table 1: IOP lowering achieved with anti-glaucoma eye drops.

The individual response of a patient to an eye drop may differ from that mentioned in the table and should therefore be verified on a case-by-case basis.

If this initial treatment lowers the IOP to the desired target, the treatment is continued and the patient should be monitored on a regular basis, every 6 months if the deficits are stabilized, more frequently otherwise.

If this treatment is ineffective or poorly tolerated, it is recommended to change the monotherapy before adding another treatment or proposing laser therapy.

In these cases, the monotherapy is changed for another therapeutic class except for prostaglandin monotherapy where changing the active ingredient may be effective since there are non-responders to some active ingredients.

If the treatment is well tolerated, but insufficient (target IOP not achieved), a dual therapy should be considered. It is then recommended to add molecules with different modes of action and use – when possible – fixed combinations to improve compliance.

Using a dual or triple therapy as a first-line treatment is not recommended. It may however be discussed in severe glaucoma and/or when the rise in IOP is very elevated, when the required IOP lowering exceeds the expected efficacy of a monotherapy. In these particular cases, the time before introducing a second or third molecule may be reduced or even eliminated.

Finally, if combining two molecules is insufficient to achieve the target IOP, it is possible to change the last added molecule, and therefore change of dual therapy or switch to triple therapy by adding another molecule. In case of triple therapy, it is recommended to encourage the use of fixed combinations to improve compliance.

The alternatives to local triple therapy include laser or surgical treatments, or the systemic use of a carbonic anhydrase inhibitor, which is often overall poorly tolerated.

The contraindications such as the systemic side effects of anti-glaucoma eye drops should be known, including those of beta blockers that are found in all the combinations currently available.

The long-term use of anti-glaucoma eye drops may cause or exacerbate ocular surface disorders. It should therefore be assessed and taken into account in the management of glaucoma patients. When ocular surface disorders are present, preservative-free eye drops should be preferred.

The medical treatment of POAG may only be effective if it is actually instilled by the patient. Therefore, patient compliance and cooperation in the management of glaucoma proposed by the ophthalmologist are essential to achieve an effective lowering in IOP and prevent glaucoma progression. They should be verified at each consultation. The optimal treatment should include the minimum amount of eye drops to achieve the target IOP since the treatment may be different in both eyes.

Laser treatments

Laser treatments of POAG include two categories: trabeculoplasty and cyclodestruction. Both types of procedures are performed on separate anatomical sites with very different indications because one is intended for early and moderate glaucoma (trabeculoplasty) and the other (cyclodestruction) for advanced glaucoma or glaucoma refractory to medical and surgical treatments.

Laser trabeculoplasty[1]

Trabeculoplasty (TL) consists in applying laser impacts on the trabecular meshwork to increase the trabecular elimination of aqueous humor.

TL is performed under topical anesthesia using a lens suitable for angle visualization.

Two lasers may be used: the Argon laser (green or blue-green) (TRLA) or the selective Q-switched, dual-frequency YAG system laser (532 nm) (SLT):

The SLT is as effective as the TRLA in patients with POAG with 80-85% of responding eyes and an IOP lowering between 15 and 25%.

Unlike the TRLA, it is possible to safely repeat a treatment with STL, after a loss of efficacy over time of an initial LT (with TRLA or SLT).

The higher the preoperative IOP is, the greater the IOP lowering achieved post TL will be.

The efficacy of the TRLA increases with the surgeon's experience, because its use requires a good recognition of angular structures. Its efficacy will be better if the trabecular meshwork is pigmented, unlike the SLT whose results are less dependent. The response of young patients (<40 years) to the TRLA is generally poorer.

The efficacy of TL is generally assessed after 4 and 6 weeks. The complications described post-TL include an early and transient rise in IOP, moderate intraocular inflammation, peripheral anterior synechiae (for the TRLA). There is also a loss of efficacy over time on IOP lowering.

Cyclophotocoagulation [1,3]

Cyclophotocoagulation consists in destroying the ciliary processes responsible for aqueous humor production. This technique is indicated when filtration surgery has failed or exposes to significant risks of complications or failure. It is a therapeutic alternative to drainage valves.

Different lasers are used for cyclophotocoagulation:

- Transcleral or endoscopic diode laser (810 nm). The transcleral procedure is the most widespread because it is easy to perform and minimally invasive, but as it is carried out without direct visualization, it is also less accurate.
- Nd:YAG laser (1064 nm).
    - Transpupillary argon laser. This technique is used if at least 25% of the ciliary processes are accessible.

Transcleral diode laser cyclophotocoagulation requires a locoregional anesthesia and it is essential to identify the ciliary processes by transillumination to position the laser probe next to the ciliary processes. The efficacy is generally assessed after one month. The most commonly reported complications are persistent intraocular inflammation, hyphema, corneal decompensation, decrease in visual acuity, chronic hypotonia or ocular phthisis.

Surgical treatment [1,4]

Several surgical techniques are available to variably lower the IOP, by facilitating the aqueous humor (AH) drainage or reducing its production. They will be chosen depending on the evolutive stage of POAG, target IOP to be achieved, surgical history and ocular tissue condition, visual and lenticular status, and depending on the surgeon's experience.

Ab externo filtration surgeries with anterior filtration bleb: trabeculectomy (TL) and non-penetrating deep sclerectomy (NPDS)

Indicated as a first-line therapy, these surgeries protected by a scleral flap facilitate AH drainage toward the subconjunctival spaces through resection at this level of the entire trabecular filter (TL, penetrating surgery) or only of its outer part (NPDS, non-penetrating surgery). Their functional prognosis largely depends on the development of a filtration bleb which requires:

- a virgin limbic conjunctivo-tenon area covered by the upper eyelid.
- the intraoperative use of antimitotic agents (5-fluorocuracil (5-FU) or mitomycin C (MMC)) in the presence of predictable risk factors for failure due to fibrosis (long-term topical treatments, young subjects, black subjects, history of eye surgery, inflammation, scarring conjunctiva), or systematic use if NPDS is performed, which increases the success rate.
- a close monitoring of the filtration bleb healing following surgery to adjust if needed the postoperative treatment (*needling*, laser sectioning of suture, change in postoperative treatment…).

These filtration surgeries lead to IOP lowering that may exceed 50% with IOP <21 mmHg in 90% of cases at 10 years with or without adjunctive treatment.

Table 2. Pros and cons of trabeculectomy and deep sclerectomy

	Pros	**Cons**
TL	. possible regardless of the degree of ICA opening . greater lowering in IOP[2]	. opening of the eyeball (risk of hypotonia, hemorrhage) . cataractogenic . late complications related to the filtration bleb (hypotonia, infection of the filtration bleb, endophthalmitis)
NPDS	. no opening of the eyeball . fewer complications such as hypotonia, hemorrhage . little cataractogenic . more diffuse filtration bleb therefore at lower risk of complications	. difficult technique (learning curve) . only possible if the ICA is open . goniopuncture necessary in more than 60% of cases with risk of secondary iris incarceration

Small-gauge sclerokeratectomy is a variant of trabeculectomy maintained open by a drain (Express). It causes fewer complications but its cost is high and it is less effective in the long term.
Different devices designed to maintain open the NPDS decompression chamber are available, with no evidence that one is more effective than the other.

Ab externo filtration surgery with posterior filtration bleb using drainage implants (Baerveldt, Molteno and Ahmed's valve)

These drainage systems consist of a tube connected to a large plate positioned on the sclera behind the equator and around which a filtration bleb will form. They drain the HA toward the posterior subconjunctival spaces where the risk of fibrosis is less. The devices vary depending on their size, material, plate diffusion surface, presence or absence of a flow regulator system (Ahmed's valve).

They are indicated in case of failure of one or several TL or NPDS, and/or when the limbic conjunctivo-tenon tissues are too scarred. The IOP may be lowered by up to 50%, the success rates are comparable to those of TL and the risks of fibrosis or encapsulation are frequent. The most common early complication is ocular hypotonia. Late complications include corneal decompensation, ocular motility disorders, visual loss, IOP rise or externalization of a part of the device.

Ab externo filtration surgery techniques without filtration bleb

Their goal is to restore a physiological drainage of the AH to overcome filtration bled-related issues. However, they are less effective than the reference techniques (TL or NPDS) on IOP lowering.

Viscocanalostomy: the principle is that of NPDS combined with the injection of a viscoelastic agent into the Schlemm's canal (SC) and its efferents to reopen them. A filtration bleb is however found in 30% of cases. This technique is indicated for the treatment of moderate POAG because it is less effective than TL.

Canaloplasty: this is a viscocanaloplasty combined with circumferential dilation of the SC with a viscoelastic agent and its catheterization with a prolene thread which is stretched so as to maintain open the SC lumen.

Drains implanted ab externo into the supraciliary space and returning in the AC: there are several different but they are still being under validation.

Alternative techniques called MIGS (Micro Invasive Glaucoma surgery)

They include several procedures aimed at improving the safety profile of filtration surgery by limiting tissue handling.

They are performed *ab interno* or *ab externo*.

Depending on the techniques, the drainage of the aqueous humor is facilitated:

- by subconjunctival route (drains implanted transclerally)
- by trabecular route (*ab interno*: drains implanted in the SC, trabeculotomy with electrothermal ablation, *ab externo*: canaloplasty with microcatheter)

As no comparative studies with TL are available, these techniques are currently reserved for early or moderate POAG, readily in combination with cataract surgery.

Technique of ultrasound cyclodestruction of ciliary bodies.

Ultrasound (US) cyclodestruction of ciliary bodies is an alternative to laser cyclophotocoagulation of ciliary bodies. It consists in focusing high-intensity US on the ciliary processes through transducers in a miniaturized system. The place of this cyclodestruction technique in the therapeutic strategy of POAG nevertheless remains to be defined.

Combined cataract-glaucoma surgery

A combined surgery is indicated:

. if POAG requires surgery and a cataract is present.

. if cataract surgery is contraindicated and POAG is advanced and/or controlled with a heavy treatment.

Lens phakoemulsification with micro-incision is readily combined with TL, NPDS or MIGS.

The control of the IOP remains however less than after isolated filtration surgery even with the use of antimitotic agents which are recommended in case of combined surgery.

Isolated lens surgery may lower the IOP, but this IOP lowering is usually transient, variable from one patient to another and greater when the iridocorneal angle is narrow before phakoexeresis.

Management of non-pressure risk factors[5]

Some non-pressure risk factors could be involved in POAG progression, including lower ocular perfusion pressures (OPP) and sleep apnea syndrome. A lower OPP may be explained by a chronic low blood pressure, including nocturnal diastolic, an increased vascular resistance related to arteriosclerosis (HBP, diabetes, smoking, cholesterolemia) or a vasospasm. These risk factors deserve to be investigated and managed in collaboration with the attending physician especially when glaucoma worsens despite standardized ocular pressures, although the sole proven treatment to date is an additional IOP lowering.

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