

REVIEW ARTICLE

How latanoprost changed glaucoma management

Maria Francesca Cordeiro^{1,2,3}  | Stefano Gandolfi⁴ | Konstantin Gugleta⁵ |
Eduardo M. Normando³ | Francesco Oddone⁶

¹Imperial College Healthcare NHS Trust, Western Eye Hospital, London, UK

²UCL Institute of Ophthalmology, London, UK

³Department of Surgery & Cancer, Irish Clinical Oncology Research Group, Imperial College London, London, UK

⁴Ophthalmology Unit, University Hospital of Parma, Parma, Italy

⁵University Hospital and University of Basel, Basel, Switzerland

⁶Glaucoma Unit, IRCCS-Fondazione Bietti, Rome, Italy

Correspondence

Maria Francesca Cordeiro, Western Eye Hospital, Imperial College Healthcare NHS Trust, London, UK.
Email: m.cordeiro@ucl.ac.uk

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Abstract

Glaucoma is currently considered one of the leading causes of severe visual impairment and blindness worldwide. Topical medical therapy represents the treatment of choice for many glaucoma patients. Introduction of latanoprost, 25 years ago, with an entirely new mechanism of action from that of the antiglaucoma drugs used up to that time was a very important milestone. Since then, due mainly to their efficacy, limited systemic side effects and once daily dosing, prostaglandin analogues (PGAs) have become as the first-choice treatment for primary open-angle glaucoma. PGAs are in general terms well tolerated, although they are associated with several mild to moderate ocular and periocular adverse events. Among them, conjunctival hyperemia, eyelash changes, eyelid pigmentation, iris pigmentation and hypertrichosis around the eyes are the most prevalent. The objective of this paper is to review the role of PGAs in the treatment of glaucoma over the 25 years since the launch of Latanoprost and their impact on clinical practice outcomes.

KEY WORDS

glaucoma, Latanoprost, medical treatment, open-angle glaucoma, progression, prostaglandin analogues

1 | INTRODUCTION

Life expectancy has been increasing in recent decades and all countries. Western countries are experiencing growth in both the size and the proportion of older persons in the population (World Health Organization, 2021). According to a report by the World Health Organization, between 2015 and 2050, the proportion of the world's population over 60 years will nearly double from 12% to 22% (World Health Organization, 2021). The aging population is paralleled by an increase in the prevalence of sight-threatening diseases, including glaucoma, age-related macular degeneration, diabetes and diabetic retinopathy, and cataract (Tham et al., 2014; GBD 2019 Blindness and Vision Impairment Collaborators & Vision Loss Expert Group of the Global Burden of Disease Study, 2021).

Under the umbrella of the term glaucoma coexist a series of chronic and progressive optic neuropathies characterized by retinal ganglion cell death and subsequent visual field defects (Weinreb et al., 2014). Glaucoma is currently considered one of the leading causes of severe

visual impairment and blindness worldwide, affecting more than 70 million people (Prum et al., 2016; Quigley & Broman, 2006). Among the different types of glaucoma, primary open-angle glaucoma (POAG) is the most common form of glaucoma and accounts for approximately 70% of the total glaucoma cases worldwide (Tham et al., 2014).

Pathogenesis of POAG is multifactorial and largely unknown. Several risk factors have been identified, including elevated intraocular pressure (IOP), family history, age and race (Jonas et al., 2017; McMonnies, 2017; Tham et al., 2014; Weinreb et al., 2014). Among them, elevated IOP has been identified as a primary and independent risk factor, not only for the onset but also for the progression of glaucomatous damage (Leske et al., 2003, 2007; Nouri-Mahdavi et al., 2004; The Advanced Glaucoma Intervention Study (AGIS): 7, 2000). Therefore, lowering elevated IOP (enough to achieve a therapeutic goal in the 'target IOP range') is still the main approach for preserving visual function in patients with glaucoma (Boland et al., 2013; Damji et al., 2003). In most patients, medical treatment represents the first therapeutic step

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for glaucoma (American Academy of Ophthalmology Preferred Practice Pattern Glaucoma Committee, 2020).

IOP levels are determined by the balance between the production of aqueous humour by the ciliary body and its drainage by two independent pathways (namely, the trabecular meshwork and uveoscleral outflow pathway) (Weinreb et al., 2014).

Currently, we have different classes of drugs to lower IOP through different mechanisms. For example, beta-blockers and carbonic anhydrase inhibitors (CAIs) suppress aqueous formation; while prostaglandin analogues (PGAs) lower IOP by increasing aqueous humour flow through the uveoscleral pathway (Cvenkel & Kolko, 2020; Gaton et al., 2001).

PGAs are currently considered as first choice treatment for POAG, because of their efficacy, limited systemic side effects and once daily dosing (EGS Guidelines 2020; Li et al., 2016; Li et al., 2018; Weinreb et al., 2014).

Latanoprost 0.005% (Xalatan®) was the first topical PGA for treating glaucoma available on the market. Its launch, 25 years ago, meant a profound change in the paradigm of medical treatment of glaucoma (Alm et al., 1997; Alm & Stjernschantz, 1995; Camras, 1996; Camras et al., 1996).

2 | THE BURDEN OF GLAUCOMA

Glaucoma is a leading cause of irreversible blindness worldwide. It has been estimated in 2020 that glaucoma represents the cause of moderate or severe visual impairment in 4.1 million people and blindness in 3.6 million (Flaxman et al., 2017; GBD 2019 Blindness and Vision Impairment Collaborators & Vision Loss Expert Group of the Global Burden of Disease Study, 2021; Prum et al., 2016; Quigley & Broman, 2006; Sun et al., 2022; Tham et al., 2014).

POAG accounts for approximately two-thirds of cases, with primary angle-closure glaucoma (PACG) the next most common form of the condition (Tham et al., 2014).

The prevalence of glaucoma varies among different nations and regions. It has been reported to be greater among persons of African descent (ranging from 6.5% to 7.3%) (Ashaye et al., 2013; Budenz et al., 2013), followed by East Asian populations (ranging from 2.59% to 3.54%) (Song et al., 2017; Sun et al., 2022; Tham et al., 2014). The prevalence in European-derived populations seems to be slightly lower, with figures around 2% (Höhn et al., 2018; Keel et al., 2019).

Glaucoma is also largely a disease of an aging population, therefore, an increase in its prevalence is expected as the population ages (Ashaye et al., 2013; GBD 2019 Blindness and Vision Impairment Collaborators & Vision Loss Expert Group of the Global Burden of Disease Study, 2021; Jonas et al., 2017; Slettedal et al., 2020; Song et al., 2017).

The burden of visual impairment from glaucoma may generally be expected to follow the rising prevalence. The global prevalence of blindness and vision loss due to glaucoma was 75.6 (95% confidence interval [CI]: 65.0–88.1) per 100 000 in 2017. However, the prevalence

of blindness due to glaucoma varies greatly between regions with figures ranging from the 171.5 (95% CI: 146.9–200.2) subjects/100 000 in African region to the 61.1 (95% CI: 52.6–70.7) subjects/100 000 in North American region (Sun et al., 2022).

The aim of glaucoma treatment is to slow the rate of progression, so that it has no significant impact on patients' quality of life (Terminology and Guidelines for Glaucoma, 2020). Treatment options include medical, laser or surgical therapies. In many cases, medical treatment represents the first therapeutic step for glaucoma (American Academy of Ophthalmology Preferred Practice Pattern Glaucoma Committee, 2020).

In glaucoma, the introduction of latanoprost ophthalmic solution (Xalatan®), 25 years ago, has resulted in a paradigm shift in medical treatment and in significant therapeutic benefits for patients.

3 | OBJECTIVES OF THIS REVIEW

It has been 25 years since the launch of Latanoprost, the first topical prostaglandin analogue marketed for the treatment of glaucoma (Alm, 2014; Alm et al., 1997; Alm & Stjernschantz, 1995; Camras, 1996; Camras et al., 1996). Its introduction represented an important change in the therapeutic management of glaucoma. In these 25 years, PGAs have become mainly the first-line medical treatment for POAG, due to their good efficacy/safety profile and their convenient dosage (once daily dosing) (Terminology and Guidelines for Glaucoma, 2020; Li et al., 2016, 2018; Weinreb et al., 2014).

The objective of this paper is to review the role of PGAs in the treatment of glaucoma during these 25 years and their impact on clinical practice outcomes.

4 | CURRENT MEDICAL TREATMENT OPTIONS IN GLAUCOMA

IOP is recognized as the main known and modifiable risk factor, both for the development and progression of glaucoma (AGIS 2000; Leske et al., 2003, 2007; Nouri-Mahdavi et al., 2004). Hence, lowering IOP has been a cornerstone of glaucoma treatment and achieving an IOP lowering by 20%–40% has been shown to be effective for significantly reducing disease progression (Boland et al., 2013; Damji et al., 2003; EGS Guidelines 2020).

Different types of ocular hypotensive medications are currently available in Europe. They include PGAs; β -Blockers; CAIs (systemic and topical); α -2 adrenergic agonists; and parasympathomimetic drugs. They have different mechanisms of action and different IOP-lowering profiles. Table 1 summarizes their main efficacy and safety outcomes, as well as their mechanism of action.

Several landmark studies have shown the efficacy of lowering IOP using ocular hypotensive medications in preventing the development of glaucoma and slowing

TABLE 1 Overview of the ocular hypotensive medications: efficacy, safety and mechanism of action.

Medication class	Active principle	IOP reduction (%)	Mechanism of action				Decreases aqueous production	Decreases episcleral venous pressure	Local adverse effects	Systemic adverse effects
			Increases uveoscleral outflow	Increases trabecular outflow	Increases aqueous production	Decreases episcleral venous pressure				
Prostaglandin analogues	Bimatoprost, latanoprost, tafluprost, travoprost	25–35	Yes	No	No	No	No	Conjunctival hyperemia, lengthening and darkening of eyelashes, brown discoloration of the iris, uveitis, macular oedema	Minimal systemic adverse effects; may be related to headaches	
β-Blockers										
(i) Nonselective	Timolol, levobunolol, carteolol, metipranolol	20–25	No	No	Yes	No	No	Ocular irritation and dry eyes	Contraindicated in patients with asthma, chronic pulmonary obstructive disease, and bradycardia	
(ii) β1-Selective	Betaxolol	20	No	No	Yes	No	No			
Carbonic anhydrase inhibitors										
(i) Topical	Dorzolamide, brinzolamide	20	No	No	Yes	No	No	Ocular irritation, dry eyes, burning sensation with topical agents	Topical form has minimal systemic adverse effects	
(ii) Systemic	Acetazolamide, methazolamide, dichlorphenamide	30–40	No	No	Yes	No	No	None	Paresthesias, nausea, diarrhoea, loss of appetite and taste, lassitude, or renal stones	
Adrenergic agonists										
(i) α-2 Selective	Brimonidine, apraclonidine	20–25	Yes	No	Yes	No	No	Ocular irritation, dry eyes, allergic reaction is relatively common	Central nervous system effects and respiratory arrest in young children; caution in patients with cerebral or coronary insufficiency, postural hypotension, and renal or hepatic failure	
(ii) Nonselective	Dipivefrin, epinephrine	15–20	Yes	No	Yes	No	No			
Parasympathomimetics	Pilocarpine, echothiophate	20–25	No	Yes	No	No	No	Ocular irritation, induced myopia and decreased vision due to ciliary spasm	Ciliary spasm leading to headaches in young patients	

Note: Adapted from Cvenkel & Kolko, 2020; and Weinreb et al., 2014.

disease progression (Heijl et al., 2002; Kass et al., 2002; Lichter et al., 2001).

- The Ocular Hypertension Treatment Study assessed the efficacy of medical treatment in delaying or preventing the onset of POAG in patients with ocular hypertension. After 5 years of follow-up, the probability of developing glaucoma was significantly lower in the treated group than in the control group (hazard ratio (HR): 0.40; 95% CI: 0.27–0.59; $p < 0.0001$) (Kass et al., 2002).
- The Early Manifest Glaucoma Trial compared the effect of early treatment (argon laser trabeculoplasty and topical betaxolol twice daily) versus no treatment/late treatment on the progression of newly diagnosed open-angle glaucoma patients. After a median follow-up of 6 years, progression rate was significantly lower in the treatment group (45%) than in the control group (62%) ($p = 0.007$) (Heijl et al., 2002).
- Additionally, the Collaborative Initial Glaucoma Treatment Study compared the effect of medical treatment versus trabeculectomy on the disease-progression of newly diagnosed open-angle glaucoma patients. After 5-years of follow-up, visual field loss did not differ significantly by initial treatment (Lichter et al., 2001).
- The United Kingdom Glaucoma Treatment Study assessed the effect of intraocular-lowering treatment with latanoprost on vision preservation in patients with newly diagnosed open-angle glaucoma. This was the first specific study of the effect of PGAs. At Month 24, mean IOP lowering was 3.8 ± 4.0 mmHg and 0.9 ± 3.8 mmHg in the latanoprost and placebo groups, respectively. Moreover, with respect to visual function, the time to first deterioration was significantly longer in the latanoprost group than in the placebo group (adjusted HR 0.44; 95% CI: 0.28–0.69; $p = 0.0003$) (Garway-Heath et al., 2015), showing a strong effect of PGA treatment on visual field preservation.

5 | THE ROLE OF PROSTAGLANDIN ANALOGUES

5.1 | Historical aspects of prostaglandin analogues

Prostaglandins were initially isolated from prostate tissue in 1935 (Von Euler, 1935). They are a family of lipids derived from essential fatty acids and have a wide range of effects throughout the body, including constriction and relaxation of smooth muscles and regulation of the immune response (Hata & Breyer, 2004; The LipidWebb, 2022; Winkler & Fautsch, 2014). PGF_{2α}, a prostaglandin released following trauma to the eye, produces a powerful IOP lowering (Perkins, 1975). Camras et al. (1977) reported that the administration of prostaglandin F_{2α} (PGF_{2α}) and E₂ (PGE₂) to uncannulated rabbit eyes lowered IOP in a dose-dependent manner following an early ocular hypertensive effect. In an

experimental study conducted in cynomolgus monkey, the IOP lowering effect of PGF_{2α} was demonstrated to be due largely if not exclusively to an increase in uveoscleral outflow pathway (Gabelt & Kaufman, 1989).

In healthy human eyes, the prostaglandin analogue PhXA34 lowered IOP 12 h post dose. This IOP lowering effect might be explained by increased aqueous humour outflow facility (Alm & Villumsen, 1991).

Latanoprost 0.005%, the first commercially available topical PGA, latanoprost ophthalmic solution (Xalatan®) prostaglandin analogue for treating glaucoma, was launched in 1996 (Alm et al., 1997; Alm & Stjernschantz, 1995; Camras, 1996; Camras et al., 1996). These papers showed that latanoprost 0.005% effectively and safely reduced IOP in patients with glaucoma and provided evidence for its usefulness in chronic glaucoma therapy (Alm et al., 1997; Alm & Stjernschantz, 1995; Camras, 1996; Camras et al., 1996).

5.2 | Mechanism of action

Studies of aqueous humour dynamics in humans and nonhuman primates have demonstrated that the IOP lowering is mainly due to an enhanced uveoscleral outflow, with minor effects on trabecular outflow and aqueous flow (Toris et al., 1997, 2008; Weinreb et al., 2002).

In order to achieve their effect, PGAs must bind to specific receptors, located in the cell membrane and nuclear envelope (Schlötzer-Schrehardt et al., 2002). So far 9 prostaglandin receptors have been identified and their designation is primarily based on the prostaglandin for which binding is most specific (Hata & Breyer, 2004; Sharif et al., 2003; Swymer & Neville, 2012). PGF_{2α} binds the FP, EP1 and EP3 receptors with significant affinity, while travoprost binds the FP receptor (Abramovitz et al., 2000; Sharif et al., 2003).

As aforementioned, IOP is regulated by the balance between the production of aqueous humour by the ciliary body and its removal through the trabecular and the uveoscleral pathways (Weinreb et al., 2014).

PGAs and PGF_{2α} bind to EP and FP receptors in the ciliary muscle, which cause its relaxation and increased aqueous humour outflow (Alm & Nilsson, 2009; Winkler & Fautsch, 2014). Binding of prostaglandins and PGAs to ciliary muscle FP receptors also disrupts extracellular matrix turnover (Lindsey et al., 1997; Weinreb et al., 2020). Matrix metalloproteinases degrade and remodel the extracellular matrix in the ciliary muscle, iris root, and sclera, reducing outflow resistance to fluid flow (Lindsey et al., 1997; Weinreb & Lindsey, 2002). In general terms, it seems that PGF_{2α} and PGAs increases the amount of matrix metalloproteinases, while maintaining tissue inhibitor of metalloproteinase expression. This causes further degradation and remodelling of the extracellular matrix, which enhances outflow facility (Lindsey et al., 1997; Weinreb

et al., 2020; Weinreb & Lindsey, 2002; Winkler & Fautsch, 2014).

5.3 | IOP lowering effect of prostaglandin analogues

5.3.1 | Prostaglandin analogues in monotherapy

IOP lowering effect

Topical ocular hypotensive therapy remains the most common initial method of lowering IOP (American Academy of Ophthalmology Preferred Practice Pattern Glaucoma Committee, 2020). PGAs represent, due to their good efficacy and safety profile and their convenient posology (once daily), the first-choice therapy for treating glaucoma in many patients (EGS Guidelines 2020; Li et al., 2016; Li et al., 2018; Weinreb et al., 2014).

Latanoprost has been very well studied, with numerous publications of clinical trials, meta-analyses, and reviews (Alm, 2014; Digiuni et al., 2012). A review of three masked multicenter Phase III studies in 829 patients with elevated IOP in Scandinavia, the USA, and the UK showed that 6 months treatment with latanoprost reduced IOP by 35%, if given in the evening, and by 31%, if given in the morning (Alm et al., 1997). Additionally, in a randomized, double-masked, placebo-controlled crossover study, once daily latanoprost 0.005% lowered significantly the IOP (21.3%; $p < 0.001$) in normal tension glaucoma patients (Rulo et al., 1996).

Currently available PGAs include latanoprost 0.005%, travoprost 0.004%, bimatoprost (available in two doses, 0.03% and 0.01%) and tafluprost 0.0015%.

PGAs have demonstrated better IOP-lowering effect than β -blockers with fewer systemic adverse events (Eyawo et al., 2009; Garway-Heath et al., 2015; Quaranta et al., 2015). The IOP lowering starts 2–4 h after first administration, with the therapeutic effect reaching a peak at 8–12 h. These agents also minimize IOP fluctuations during a 24-h period, with a maximum effect achieved 3–5 weeks after initiation of therapy (Cvenkel & Kolko, 2020; Eyawo et al., 2009). Topical administration of PGAs leads to a mean IOP reduction from 25% to 32%, which is sustained throughout the 24-h cycle (Alm, 2014; Eyawo et al., 2009; Garway-Heath et al., 2015; Huang et al., 2011; Quaranta et al., 2015; Riva et al., 2014).

In a meta-analysis of randomized clinical trials, van der Valk et al. (2005) reported that the PGAs bimatoprost, travoprost and latanoprost were all effective in lowering IOP. These agents achieved a mean IOP reduction that ranged between 6.5–8.4 mmHg of reduction at trough and peak time points, respectively, corresponding to a mean IOP percentage reduction ranging from 28% to 31% from trough to peak time points, respectively (van der Valk et al., 2005).

Current evidence strongly suggests that the clinical profile of the PGAs is similar (Islam & Spry, 2020). Parrish et al. (2003), in a 12-week randomized clinical trial, reported that the overall mean IOP-lowering achieved by the respective agents was similar throughout the diurnal period (8.6 ± 0.3 mmHg, 8.7 ± 0.3 mmHg, 8.0 ± 0.3 mmHg

lowering for patients treated with latanoprost, bimatoprost and travoprost, respectively; $p = 0.128$).

Conversely, some studies have reported greater IOP-lowering efficacy with bimatoprost compared with latanoprost (Cheng & Wei, 2008; DuBiner et al., 2001; Gandolfi et al., 2001; Noecker et al., 2003). However, there are some methodological issues that may limit their findings, including the post hoc nature of analysis and differences in baseline IOPs among treatment groups (DuBiner et al., 2001; Gandolfi et al., 2001).

Regarding tafluprost 0.0015%, it has shown comparable IOP lowering profile to latanoprost for open-angle glaucoma and ocular hypertension (Uusitalo et al., 2010; Yang et al., 2020).

Although glaucoma treatment has to follow a patient-tailored approach, PGAs can be considered the first-choice in many different situations, such as ocular hypertension; POAG; and pseudoexfoliative glaucoma among others (American Academy of Ophthalmology Preferred Practice Pattern Glaucoma Committee, 2020; EGS Guidelines 2020). Additionally, due to their mechanism of action, PGAs may be indicated in cases of angle recession glaucoma (If possible, not during active phase) (Clement & Goldberg, 2011). On the negative side, PGAs would be considered the last choice in patients with elevated IOP secondary to trauma, inflammatory glaucoma, active macular oedema and so forth. (American Academy of Ophthalmology Preferred Practice Pattern Glaucoma Committee, 2020; EGS Guidelines 2020) (Table 2).

Safety

Although PGAs are in general terms well tolerated, they are associated with several mild to moderate ocular and periocular adverse events (AEs). Ocular and periocular AEs associated with the use of PGAs include conjunctival hyperemia, eyelash changes, eyelid pigmentation, iris pigmentation, hypertrichosis around the eyes, corneal epithelium disorder, appearance of iritis, cystoid

TABLE 2 Overview of the main indications and contraindications of prostaglandin analogues.

First choice	Last choice
<ul style="list-style-type: none"> Ocular hypertension Primary open-angle glaucoma Pseudoexfoliative glaucoma Pigmentary glaucoma Angle recession glaucoma^a 	<ul style="list-style-type: none"> Elevated IOP secondary to trauma Inflammatory glaucoma Glaucomatocyclitic iritis (aka Possner-Schlossman) Fuch's Heterochromic iridocyclitis IOP increases due to herpetic disease Active macular oedema Diabetic with macular oedema, epiretinal membrane Steroid induced glaucoma Post-surgical IOP spike Neovascular glaucoma Unilateral treatment^b

Note: Adapted from American Academy of Ophthalmology Preferred Practice Pattern Glaucoma Committee (2020) and European Glaucoma Society (EGS) Guidelines (2020).

Abbreviation: IOP, Intraocular pressure.

^aIf possible, not during active phase (Clement & Goldberg, 2011).

^bFor aesthetic reasons.

maculae oedema and deepening of the upper eyelid sulcus (Alm, 2014; Alm et al., 1997; Honrubia et al., 2009; Inoue et al., 2012; Li et al., 2018; Wang et al., 2021; Weinreb et al., 2014).

Tafluprost has been found to have higher rates of hyperemia than latanoprost and most other commonly used PGAs, which is likely related to its higher pro-inflammatory effects (Inoue et al. 2012; Inoue et al. 2020). Additionally, the results of a meta-analysis found that latanoprost 0.005% caused a lower incidence of conjunctival hyperemia than travoprost 0.004% (OR=0.51; 95% CI 0.39–0.67, $p < 0.00001$) and bimatoprost 0.003% (OR=0.32; 95% CI 0.24–0.42, $p < 0.00001$) (Honrubia et al., 2009).

Regarding eyelid pigmentation, its incidence with the use of PGAs ranged from 0% (Elgin et al., 2006) to 5.9% (Inoue et al. 2006) with latanoprost 0.005%; from 2.9% (Parrish et al., 2003) to 15.4% (Birt et al., 2010) with travoprost; and from 1.6% (Kampik et al., 2002) to 25.9% (Birt et al., 2010) with bimatoprost.

The incidence of eyelash changes in patients treated with PGAs ranged from 0% (Parrish et al., 2003) to 77% (Demitsu et al., 2001) with latanoprost; from 0.7% (Parrish et al., 2003) to 57.1% (Netland et al., 2001) with travoprost; from 2.9% (Parrish et al., 2003) to 53.8% (Inoue et al., 2012) with bimatoprost and from 4% (Oddone et al., 2022) to 34% (Inoue et al., 2012) with tafluprost.

Both eyelid pigmentation and eyelash changes were associated with duration of treatment. The incidence of eyelid pigmentation ranged between 1.5%–2.9% in subjects with <3 months of medication use and from 0%–25.9% in patients with >3 months of medication use (Inoue et al., 2012). Similarly, the incidence of eyelash growth ranged from 0% to 33.8% in patients with <3 months of use and from 0.7% to 77% in patients with >3 months of use (Inoue et al., 2012).

There is evidence suggesting that PGA therapy might decrease central corneal thickness (Hatanaka et al., 2009; Park et al., 2021; Schlote et al., 2009). Corneal and scleral thickness reduction after using PGAs might be related with the increased uveoscleral outflow (Park et al., 2021).

Iris pigmentation associated with the use of PGAs often occurs in Europeans and Americans, in whom iris pigments are green-brown, yellow-brown, blue-brown and/or of mixed colour (Camras et al., 1996). After 2 years of latanoprost use, Watson (1998) reported that increased iris pigmentation occurred in 18.8% of the patients. In Japanese people, iris pigment changes occurred in 31.7% of latanoprost patients, 37.9% of travoprost patients, 34.5% of tafluprost patients and 50.0% of bimatoprost patients (Inoue et al., 2006).

Another adverse effect to consider, mainly due to its potential impact on surgery outcomes, is deepening of the upper eyelid sulcus. The first report associating the occurrence of deepening of the upper eyelid sulcus in patients treated with a PGAs (bimatoprost) was published in 2004 (Peplinski & Albani Smith, 2004). The incidence of deepening of the upper eyelid sulcus differs among PGAs and seems to be related to the ability of PGF_{2α} to inhibit fat production (Park et al., 2011). The condition occurred in 60%, 50%, 24%, and 18% of patients using bimatoprost, travoprost, latanoprost and tafluprost, respectively (Inoue et al., 2013).

Further ocular adnexal changes associated with the use of PGAs have been described, including upper lid ptosis, loss of the inferior orbital fat pads, and enophthalmos (Filippopoulos et al., 2008; Peplinski & Albani Smith, 2004). Prostaglandin-associated periorbitopathy was more frequent in patients receiving bimatoprost or travoprost than in those treated with latanoprost or tafluprost (Shah et al., 2013).

One of the most controversial points related to the use of PGAs has been its relationship with the appearance of macular oedema or the reactivation of uveitis. A retrospective analysis of 94 patients found that 6.4% and 2.1% of patients developed anterior uveitis and cystoid macular oedema, respectively, while being treated with latanoprost (Warwar et al., 1998). It has been proposed to avoid the use of PGAs in patients at risk of developing cystoid macular oedema (such as those with diabetic retinopathy, retinal vein occlusion, history of epiretinal membrane, surgery complicated with posterior capsule rupture and vitreous humour loss, etc.) (Holló et al., 2020). Nevertheless, a systematic review of uveitis and cystoid macular oedema associated with topical PGAs use refutes the commonly believed association between prostaglandin analogue treatment and these conditions (Hu et al., 2020).

5.3.2 | Prostaglandin analogues in combination with other agents

According to the Terminology and Guidelines for Glaucoma (2020), if monotherapy treatment is well tolerated, but does not achieve target IOP, adding a second drug may be considered (Figure 1).

More than 50% of patients who fill prescriptions for glaucoma medications take more than one drug (Kass et al., 2002; Lichter et al., 2001). The different side effects associated with the use of different medical therapies are shown in Table 3.

When selecting a combination therapy, it is essential to take into account its mechanisms of action. The best option is to combine drugs with different mechanisms of action (EGS Guidelines 2020). As previously mentioned, the IOP reduction mechanism of PGAs is through an increase in aqueous humour outflow (uveoscleral/trabecular). Therefore, the best combination option would be to associate PGAs with drugs that inhibit aqueous production, such as β -Blockers, CAIs (systemic and topics) and α -2 adrenergic agonists.

Prostaglandin analogues in combination with β -Blocker

PGAs/timolol fixed combination is currently one of the most widely used topical anti-glaucoma fixed-combination eye drops (Wang et al., 2021). Latanoprost/timolol fixed combination (LTFC) provided better IOP lowering than either latanoprost or timolol monotherapy (Higginbotham et al., 2010). Additionally, Zhao et al. (2011) found no differences in IOP lowering between LTFC and non-fixed combination of latanoprost and timolol.

Different papers have evaluated the IOP lowering effect of travoprost/timolol (TTFC) and bimatoprost/

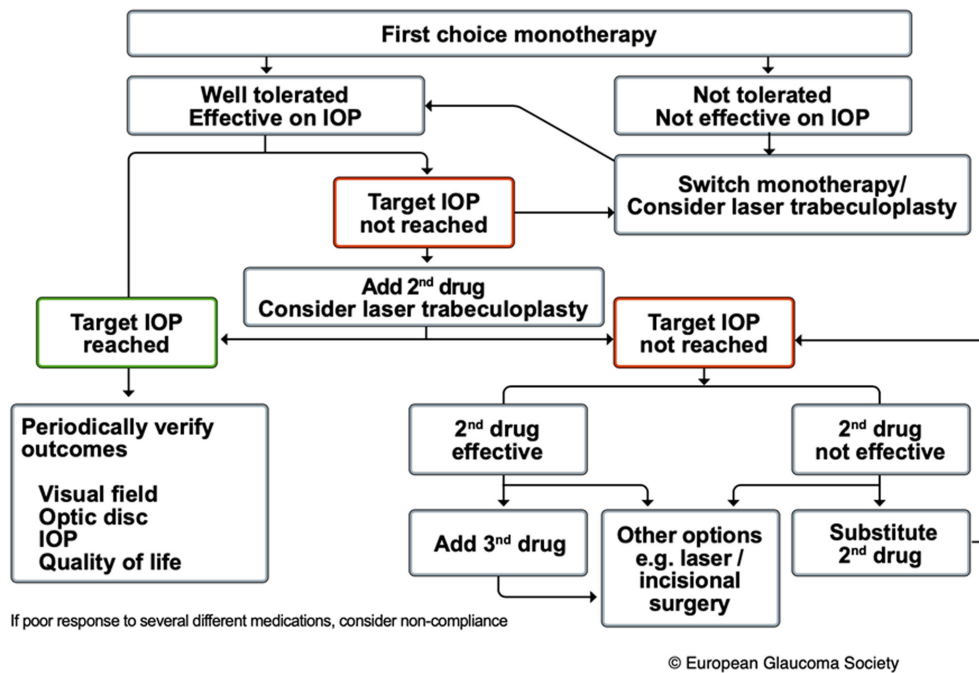


FIGURE 1 Therapeutic algorithm in glaucoma medical therapy. Reproduced from EGS Guidelines (2020).

timolol (BTFC) fixed combinations. The results of these studies point in the same general direction, indicating that both provided a good IOP lowering effect (Konstas et al., 2012, 2013; Lewis et al., 2010; Martínez & Sánchez, 2007, 2008, 2009; Nakano et al., 2015).

Tafluprost/timolol fixed combination has a superior IOP lowering effect compared with agents used as monotherapy (Kaarniranta et al., 2016; Konstas et al., 2018; Pfeiffer et al., 2014).

Fixed combination and non-fixed combination of PGAs and β -blockers result in a similar IOP lowering effect, and both are superior to monotherapy. Overall, PGAs/ β -Blocker fixed or unfixed combinations provided a percentage IOP lowering ranging between 32% and 38% (Wang et al., 2021).

In addition to the adverse effects of PGAs, the adverse effects of β -Blockers must be taken into account.

Ocular adverse reactions to β -blockers include conjunctival hyperemia, ocular surface discomfort, reduction in tear flow and worsening of the dryness in the eye, while the systemic AEs include bradycardia, heart block and arrhythmia, bronchospasm and worsening of underlying asthma or chronic obstructive pulmonary disease (Dikopf et al., 2017). Although topical β -blockers were not associated with greater cardiovascular mortality (Pinnock et al., 2016), their use is not recommended in patients with asthma, chronic obstructive pulmonary disease, bradycardia, heart block or uncontrolled heart failure (Marshall et al., 2018).

An association between the use of topical β -blockers and the development of impotence has been suggested (Stewart & Castelli, 1996). However, there seems to be an association between erectile dysfunction and glaucoma that cannot be only attributed to topical β -blockers use (Nathoo et al., 2015). Hence, young patients should be warned about the possibility of erectile dysfunction

since they may not associate the use of eye drops with this problem.

Prostaglandin analogues in combination with α -2 agonists

Combination of brimonidine tartrate (0.1%, 0.15%, 0.2%) twice daily and latanoprost (0.005%) once daily can be considered an effective therapy for lowering IOP (Stewart et al., 2004). When added to latanoprost, adjunctive therapy with brimonidine purite 0.15% lead to an additional IOP lowering of 5.8 and 3.3 mmHg at peak and trough drug effect, respectively (Mundorf et al., 2007). Additionally, in patients with pigmentary and pseudoexfoliative glaucoma, the combined therapy with latanoprost 0.005% / brimonidine 0.20% was significantly more effective than dorzolamide/timolol fixed combination in lowering IOP (9 vs. 6.5 mmHg, respectively, $p=0.044$) (Zabriskie et al., 2003).

However, when added to travoprost, timolol seemed to be more effective than brimonidine for lowering IOP (3.9 vs. 2.3 mmHg, respectively; $p=0.01$) (Reis et al., 2006).

Regarding safety, ocular AEs associated with long-term α 2-agonist use included conjunctival hyperemia, pupil dilation, and allergic conjunctivitis (Butler et al., 1995). Systemic adverse reactions associated with long-term α 2-agonists use include decreases in blood pressure and pulse, drowsiness, dizziness and dry mouth (Abrams et al., 1987).

Prostaglandin analogues in combination with carbonic anhydrase inhibitors

Several randomized clinical trials reported that the non-fixed combination of latanoprost 0.005% and brinzolamide 1% exerts a better IOP reducing effect than latanoprost monotherapy (Nakamoto & Yasuda, 2007; Nakano et al., 2016; Shoji et al., 2005).

TABLE 3 Main ocular and systemic adverse reactions of glaucoma medical therapy.

Class	Ocular AEs	Systemic AEs
PGAs	<ul style="list-style-type: none"> • Eyelash growth • Iris/eyelid pigment • Deepening of upper eyelid sulcus • Recurrence of herpes • Macular oedema post cataract surgery 	<ul style="list-style-type: none"> • Rarely, upper respiratory infection • Rarely, myalgia
β -blockers	<ul style="list-style-type: none"> • Conjunctival allergy • Hyperemia • Corneal epithelial disorders • Reduced corneal sensitivity • Blurry vision 	<ul style="list-style-type: none"> • Decrease blood pressure/pulse • Bradycardia • Worsen asthma/COPD • Depression • Impotence • Lethargy
CAIs	<ul style="list-style-type: none"> • Ocular irritation • Foreign body sensation • Itching • Stinging • Blurred vision • Corneal epithelial disorders 	<p>Topical use:</p> <ul style="list-style-type: none"> • Bitter taste • Fatigue • Diuresis • Gastrointestinal upset <p>Oral use:</p> <ul style="list-style-type: none"> • Nausea • Unpleasant taste • Dysesthesia of fingers/lips • Anorexia • Metabolic acidosis
α 2-adrenergic agonists	<ul style="list-style-type: none"> • Allergic conjunctivitis • Hyperemia • Mydriasis • Dry eye 	<ul style="list-style-type: none"> • Affects blood pressure/pulse • Drowsiness • Dizziness • Dry mouth • Dysarthria
Parasympathomimetic/ Cholinergic- agonist	<ul style="list-style-type: none"> • Miosis • Visual field constriction • Night vision loss • Myopia • Red eye • Brow ache • Retinal detachment • Cataract 	<p>Direct-acting:</p> <ul style="list-style-type: none"> • Rare systemic reactions <p>Indirect-acting:</p> <ul style="list-style-type: none"> • Sweating • Tearing • Nausea/vomiting • Diarrhoea • Bradycardia • Stomach ache

Note: Adapted from Bucolo et al., 2015 and Inoue, 2014.

Abbreviations: AEs, adverse events; CAIs, carbonic anhydrase inhibitors; COPD, chronic obstructive pulmonary disease; PGAs, prostaglandin analogues.

Additionally, latanoprost/brinzolamide non-fixed combination reduces both daytime and night-time IOP, whereas latanoprost/timolol non-fixed combination only reduced IOP during daytime, with little effect on the night-time value (Liu et al., 2009).

Non-fixed combination of 0.03% bimatoprost once in the morning and 2% dorzolamide twice daily in patients with POAG exerts an additional hypotensive effect and reduces vascular resistance in the ophthalmic artery compared to bimatoprost monotherapy (Stankiewicz et al., 2010, 2011).

Ocular adverse reactions associated with carbonic anhydrase inhibitors include conjunctival allergy, conjunctival hyperemia, corneal epithelial disorders, blepharitis, Stevens–Johnson syndrome and toxic epidermal necrosis (Silver, 2000; Strahlman et al., 1995). Because carbonic anhydrase naturally exists in the corneal endothelium, caution is needed in patients with corneal endothelial disorders (Konowal et al., 1999).

Different systemic adverse reactions have been associated with topical carbonic anhydrase inhibitor use, including headache, urticaria, angioedema, pruritus, asthenia, dizziness, paresthesia and transient myopia (EGS Guidelines 2020).

5.3.3 | Benzalkonium chloride (BAK)-free prostaglandin analogues formulations

Because many PGAs ophthalmic solutions were marketed as multi-dose, there were a need for using antimicrobial agents. In the vast majority of preserved products, Benzalkonium chloride (BAK) is used as the antimicrobial agent. Reports suggest that about 70% of eye drops are preserved with this substance (Freeman & Kahook, 2009; Steven et al., 2018). Additionally, there is evidence suggesting that preservative intolerance impacts significantly on treatment adherence, particularly in chronic disease like glaucoma (Holló et al., 2018; Tang et al., 2019).

In terms of IOP lowering, BAK-free PGAs formulations are not inferior to those containing BAK but better tolerated (Holló et al., 2018). Regarding latanoprost, according to the results of a post-hoc pooled analysis, BAK-free formulation of latanoprost significantly reduced IOP, with no significant difference versus BAK-containing formulations (Harasymowycz et al., 2021). Moreover, the results of the RELIEF study found that preservative-free latanoprost provided similar IOP lowering effect that benzalkonium chloride-latanoprost

but with a better tolerability profile (Misiuk-Hojlo et al., 2019).

With regards BAK-free Travoprost, it has shown a comparable safety, efficacy and duration of IOP-lowering effect to travoprost preserved with BAK (Gandolfi et al., 2012).

Preservative free 0.03% bimatoprost was non-inferior and equivalent to bimatoprost 0.03% ophthalmic solution in terms of lowering IOP with a safety profile similar to bimatoprost (Day et al., 2013). Finally, Bimatoprost 0.1 mg/mL preservative-free eye drops provided a similar IOP lowering profile compared to preservative-free bimatoprost 0.03% and preserved bimatoprost 0.03%, although showed a better tolerability profile (Filippelli et al., 2022).

6 | THE IMPACT OF PROSTAGLANDIN ANALOGUES ON GLAUCOMA SURGERY

The arrival to the market of new therapeutic agents has expanded the treatment options, as well as the possible combinations of medical therapies. Clinicians mainly prescribe from one of five classes of IOP-lowering medications: PGAs, β -blockers, CAIs, α 2-adrenergic agonists and parasympathomimetic-/cholinergic-agonist (Bucolo et al., 2015; Inoue, 2014).

Each class may cause local and systemic adverse events, and clinicians must take all of them into consideration when choosing the right therapy for each patient (Table 3).

Before the introduction of latanoprost in 1996, the glaucoma treatment algorithm was quite simple and the concept of maximal medical therapy encompassed two topical ocular hypotensive drugs (usually β -blockers+Parasympathomimetic/Cholinergic-agonist) and systemic carbonic anhydrase inhibitors. This algorithm became more complex as medical treatment options expanded (Figure 1).

Although topical hypotensive medication is usually the first treatment approach, many patients do not achieve adequate glaucoma control attributed to different reasons, including poor adherence, side effects or lack of maintained efficacy (Lichter et al., 2001; Newman-Casey et al., 2015).

When topical antiglaucoma treatment does not adequately control the disease, laser therapy and/or surgery is considered next (Burr et al., 2012; Musch et al., 2009; Ting et al., 2014). Trabeculectomy is regarded as the gold standard in glaucoma surgery, due mainly to its well-established efficacy at lowering IOP (Landers et al., 2012). Additionally, in difficult and/or refractory cases, where trabeculectomy is expected to provide worse clinical outcomes, drainage devices (Molteno and Baerveldt implants, and Ahmed valve) may represent a viable option (Bar-David & Blumenthal, 2018; Freedman & Rubin, 1991; Huang et al., 1999).

The introduction of PGAs had a significant impact on the number of trabeculectomies. According to a population-based analysis based on Medicare beneficiaries between 1995 and 2004, the number of

trabeculectomies decreased from 59 645 in 1996 to 24 178 in 2004 (Ramulu et al., 2007).

Moreover, from 1996 to 2001 the number of argon (photocoagulative) laser-trabeculoplasty procedures decreased from 148 816 to 75 647, respectively (Ramulu et al., 2007). This reduction may have been as a consequence of an increased utilization of newly available medical therapy, obviating the need for glaucoma procedures.

Similar results have been reported by Walland (2004), who found rates of argon (photocoagulative) laser trabeculoplasty and trabeculectomy surgery fell by 60% and 58%, respectively, between 1993 and 2003 in Australia. Moreover, the results of a retrospective analysis of the Scottish Morbidity Record revealed that, between 1994 and 1999, the number of trabeculectomies decreased from 1714 to 951, respectively (Bateman et al., 2001).

The number of US Medicare patients with a diagnosis of glaucoma remained constant from 1994 through 1999, while the total number of glaucoma procedures markedly decreased by 42.7% from 1994 (147 740 procedures) to 1999 (84 680 procedures) (Strutton & Walt, 2004). These findings seem to indicate that the introduction of PGAs reduced, or at least delayed, the need for surgical treatment in patients with glaucoma.

Interestingly, in Australia, there was a very significant increase in PGAs prescriptions between 1997 and 2003, while the number of prescriptions for other ocular hypotensive medications did not decrease to the same extent (Walland, 2004), suggesting that PGAs were rapidly and widely accepted by ophthalmologists, mainly due to their good efficacy/safety profile and convenient dosage.

Similar to what happened with the advent of PGAs, the approval of selective laser trabeculoplasty (SLT) by the United States Food and Drug Administration (FDA) represented a paradigm shift in the treatment of glaucoma (National Institute for Health and Care Excellence (NICE), 2022). Current evidence suggests that SLT is an effective and safe treatment for patients with open-angle glaucoma, providing good long-term IOP control and reduced need for incisional glaucoma and cataract. The increasingly frequent fact that SLT is being proposed as first-line therapy has led to a reduction in the number of prescriptions for ocular hypotensive drugs (Gazzard et al., 2019a; Gazzard et al., 2019b; Gazzard et al., 2023; National Institute for Health and Care Excellence (NICE), 2022).

However, a very important point to take into consideration is whether the increase in the complexity of glaucoma medical therapeutic regimen would not negatively influence surgery outcomes. In a paper published by Lavin et al. (1990), the success rate of trabeculectomy was found to be significantly higher in eyes that underwent primary trabeculectomy as compared with those who had received at least 1 year of topical glaucoma therapy before undergoing trabeculectomy ($p=0.001$).

Nevertheless, it has been reported that, in patients who have undergone trabeculectomy, 6 months of additive preoperative treatment with latanoprost did not have any significant effect on either success rate or post-operative IOP (Berthold & Pfeiffer, 2006).

In a retrospective study conducted on POAG patients with medically uncontrolled IOP who underwent primary trabeculectomy, the use of bimatoprost was identified as an independent factor for surgery failure (Miki et al., 2017). In fact, the proportion of patients with no recurrence of IOP elevation was significantly lower in the eyes without deepening of the upper eyelid sulcus (34.7%) than in those with (74.3%), $p < 0.0001$ (Miki et al., 2017).

7 | WHAT DO WE NOT KNOW AND WANT TO KNOW ABOUT PROSTAGLANDIN ANALOGUES?

As previously mentioned, the pathogenesis of glaucoma is multifactorial. Although several risk factors have been associated with the onset of glaucoma and its progression (Jonas et al., 2017; McMonnies, 2017; Tham et al., 2014; Weinreb et al., 2014), the exact mechanism by which ganglion-cell death occurs remains unknown.

The translaminal pressure (TLP) may be defined as the difference between the IOP and the cerebral spinal fluid pressure (CSFP) [$TLP = IOP - CSFP$] (Jonas et al., 2003). Several studies have shown a reduced CSFP in open-angle glaucoma patients (Berdahl et al., 2008; Jonas et al., 2013; Ren et al., 2010; Siaudvytyte et al., 2014). However, direct determination of CSFP is complex and not free of complications (Siaudvytyte et al., 2015).

Retinal vessel pulsation may be used as a surrogate of CSFP (Georgevsky et al., 2019). Current evidence suggests that the assessment of spontaneous retinal venous pulsations (SVP) may be a proxy approach to TLP difference evaluation (Golzan et al., 2011, 2012a, 2012b; Levine & Bebie, 2016; Morgan et al., 2022). Additionally, it has been reported that elevated IOP did not induce retinal vein collapse. Moreover, IOP and retinal vein diameters seem to be in phase, which may suggest the IOP is not the major driving force of retinal vein pulsations (Bollinger et al., 2020).

A literature search in PubMed performed in July 14, 2022, using the search terms “prostaglandin analogues, “ophthalmic” and “cerebral spinal fluid pressure” has shown no publications (PubMed, 2022a). Similar results were obtained with the search terms “Prostaglandin analogues (ophthalmic)” AND “Retinal vein/Venous pressure” (PubMed, 2022b).

Vascular factors are involved in the pathogenesis of POAG (Flammer et al., 2002; Grzybowski et al., 2020; Leske et al., 2003; Marjanovic et al., 2012; Martínez & Sánchez, 2005; Martínez & Sánchez-Salorio, 2010).

Different studies have evaluated the impact of PGAs on ocular hemodynamic parameters. According to published evidence, PGAs appear to have some effect on blood vessels. Experimental studies have suggested that PGAs may have, *in vitro*, some vasoactive properties in porcine ciliary arteries (Allemann et al., 2003a; Brogiolo et al., 2001; Vysniauskiene et al., 2006), although not all the studies have confirmed these findings (Allemann et al., 2003b).

In healthy subjects, latanoprost had a small effect on corneal temperature, which suggested that latanoprost

did not have any impact on the blood flow to the anterior segment of the patient's eye (Konieczka et al., 2019).

Assessment of ocular perfusion pressure (OPP) showed latanoprost was associated with a significant increase of OPP in glaucoma patients. In patients with normal-tension glaucoma, latanoprost significantly increased mean 24-h OPP (Costagliola et al., 2008; Drance et al., 1998; Greve et al., 1997; Liu et al., 2002). Similarly, Quaranta et al. (2008) found that in POAG patients, latanoprost, and dorzolamide/timolol fixed combination equally enhanced 24-h diastolic OPP. However, Ishibashi et al. (2006) did not find any significant effect of latanoprost on OPP, despite significantly lowering IOP.

Investigations of ocular blood flow revealed that latanoprost had mostly neutral effects on ocular circulation in healthy subjects and glaucoma patients (Arkasu et al. 2004; Harris et al., 2009; Inan et al., 2003; Nicoleta et al., 1996; Zeitz et al., 2005). Koz et al. (2007) reported that PGAs significantly lowered IOP and increased OPP in patients with POAG or ocular hypertension. In addition, latanoprost and travoprost were able to significantly reduce the resistivity index in the ophthalmic and central retinal arteries, respectively (Koz et al., 2007). Similarly, travoprost and bimatoprost increased significantly end-diastolic velocity of central retinal artery in newly diagnosed open-angle glaucoma patients (Alagoz et al., 2008). In previously untreated POAG patients, Gherghel et al. (2008) observed an increase in mean OPP and improvement in ocular perfusion at the optic nerve head and retina levels when treated with Latanoprost 0.005%.

Analysis of the new PGAs in healthy subjects showed that latanoprostene bunod 0.024% was associated with a significant increase in optic nerve head blood volume and oxygen saturation (Samaha et al., 2022). Additionally, latanoprostene bunod caused relaxation in previously contracted human trabecular meshwork cells by endothelin-1 (Cavet et al., 2015).

8 | CONCLUSIONS

PGAs, particularly latanoprost, have formed part of the glaucoma armamentarium for 25 years. During that time, a large number of scientific publications have been generated. They have highlighted its good efficacy and safety profile. PGAs are currently considered as the first-choice in many cases.

Regarding their safety, PGAs have been associated with different ocular AEs, most of them of an aesthetic nature, such as hyperemia, change in eyelid and iris pigmentation, hypertrichosis around the eyes, or eyelash growth. Their relationship with the appearance of post-operative macular oedema has not been fully elucidated and seems to depend on other risk factors. However, it has been suggested to avoid the use of PGAs in patients at risk of developing cystoid macular oedema.

Another adverse event that deserves special attention, mainly due to its potential impact on surgery outcomes, are the ocular adnexal changes associated with the use of PGAs. In fact, deepening of the upper eyelid sulcus was an independent factor for surgery failure.

Because of their efficacy, limited systemic side effects and once daily dosing, PGAs have changed the paradigm of glaucoma treatment, as evidenced by the large reduction in the number of laser procedures and trabeculectomies since their launch.

Beyond the deepening of the upper eyelid sulcus, the use of PGAs has not been associated with worsening surgical outcomes.

The pathogenesis of glaucoma is known to be multifactorial. Beyond their IOP-lowering effect, the role of PGAs on other factors related to the onset of glaucoma and its progression has been evaluated. Despite promising evidence, more ocular hemodynamic data and on the prevention of glaucomatous damage progression are needed.

Overall, PGAs are an effective and well-tolerated treatment for lowering IOP.

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ORCID

Maria Francesca Cordeiro  <https://orcid.org/0000-0001-8663-6525>

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