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REVIEW

Clinical utility and differential effects of prostaglandin analogs in the management of raised intraocular pressure and ocular hypertension

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Abstract: Prostaglandin analogs (PGA) are powerful topical ocular hypotensive agents available for the treatment of elevated intraocular pressure (IOP). Latanoprost 0.005% and travoprost 0.004% are prodrugs and analogs of prostaglandin F2α. Bimatoprost 0.03% is regarded as a prostamide, and debate continues as to whether it is a prodrug. The free acids of all 3 PGAs reduce IOP by enhancing uveoscleral and trabecular outflow via direct effects on ciliary muscle relaxation and remodeling of extracellular matrix. The vast majority of clinical trials demonstrate IOP-lowering superiority of latanoprost, bimatoprost and travoprost compared with timolol 0.5%, brimonidine 0.2%, or dorzolamide 2% monotherapy. Bimatoprost appears to be more efficacious in IOP-lowering compared with latanoprost, with weighted mean difference in IOP reduction documented in one meta-analysis of 2.59% to 5.60% from 1- to 6-months study duration. PGAs reduce IOP further when used as adjunctive therapy. Fixed combinations of latanoprost, bimatoprost or travoprost formulated with timolol 0.5% and administered once daily are superior to monotherapy of its constituent parts. PGA have near absence of systemic side effects, although do have other commonly encountered ocular adverse effects. The adverse effects of PGA, and also those found more frequently with bimatoprost use include ocular hyperemia, eyelash growth, and peri-ocular pigmentary changes. Iris pigmentary change is unique to PGA treatment. Once daily administration and near absence of systemic side effects enhances tolerance and compliance. PGAs are often prescribed as first-line treatment for ocular hypertension and open-angle glaucoma.

Keywords: prostaglandin analog, glaucoma, ocular hypertension, latanoprost, bimatoprost, travoprost

Introduction

Glaucoma is a common and potentially blinding ocular disease of multifactorial etiology. It is characterized by progressive acquired loss of retinal ganglion cells leading to optic nerve atrophy and visual field deficits. An estimated 60.5 million people will have open-angle and angle-closure glaucoma by 2010, increasing to 79.6 million by 2020.[1] Elevated intraocular pressure (IOP) is an important and modifiable risk factor for the development and progression of glaucoma.[2] For each mmHg reduction in IOP estimated progression risk decreased by approximately 10%. A 30% IOP reduction has been shown to slow the rate of visual field progression among normal tension glaucoma (NTG) subjects.[3] The Ocular Hypertension Treatment Study (OHTS) confirmed that a reduction of 20% is an acceptable response to treatment in ocular hypertension (OH), and the risk of developing optic disc cupping and/or visual field loss in such cases decreased from 9.5% to 4.4%.[4] However, the magnitude of IOP reduction required for

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an individual is dependent on a number of factors including IOP level at which optic nerve damage occurs, the rate and extent of glaucomatous damage, patient life expectancy, and presence of other risk factors for glaucoma.[5,6] With disease progression, the target IOP may change and is thus not static.

As newer agents with increased efficacy and tolerability are introduced into the armamentarium of topical ocular hypotensive medications, a new era of glaucoma management and declining glaucoma surgery rates is evolving.[7] Topical β-adrenergic antagonists (both selective and non-selective derivatives) were initially introduced in 1978,[7] followed by selective α_2-adrenergic receptor agonists in 1988 and topical carbonic anhydrase inhibitors in 1995.[7] Isopropyl unoprostone (Rescula®; CIBA Vision Ophthalmics, Bulach, Switzerland) was the first topical prostaglandin F2α analog (PGA) commercially available, initially in Japan in 1994.[7] Of the more currently used prostaglandin analogues (PGAs), latanoprost 0.005% (Xalatan®; Pfizer Inc., New York, NY) was launched in 1996, followed by bimatoprost 0.03% (Lumigan®; Allergan Inc., Irvine, CA) and travoprost 0.004% (Travatan®; Alcon Inc., Ft Worth, TX) in 2001.[7] Latanoprost and travoprost are both ester prodrugs of prostaglandin F2α (PGF2α). Bimatoprost is the amide prodrug of 17-phenyl-PGF2α and has been described as a prostamide,[5,8–11] although controversial.[12–15] This review will focus on the three most commonly used PGAs (latanoprost, travoprost and bimatoprost) for OH and open-angle glaucoma (OAG).

Pharmacodynamic properties of prostaglandin analogs

Latanoprost and travoprost are potent prodrug derivatives of naturally occurring PGF2α and highly selective FP prostaglandin receptor agonists. The chemical structure of travoprost differs from latanoprost (13,14-dihydro-17-phenyl-18, 19, 20-trinor-PGF2α isopropyl ester) by having a phenoxy group at carbon-16 and a trifluoromethyl group at the meta position on the phenoxy ring.[7,16] Travoprost is the isopropyl ester of a single enantiomer of fluprostenol.[17] Hydrolysis of the isopropyl ester to a biologically free and active carboxylic acid enables corneal penetration and agonism of the G-protein coupled FP receptor.

Bimatoprost is a PGF2α analog where a neutral ethyl-amide substituent replaces the carboxylic acid. It appears to mimic the activity of prostamides, a newly discovered class of naturally occurring substances with inherent IOP lowering properties biosynthesized from endocannabinoid anandamide by the enzyme COX-2.[5,8–11,18,19] Bimatoprost increases outflow facility by 40% in human organ-cultured anterior segments within 48 hours of treatment and is blocked by AGN211334 a prostamide selective antagonist.[20] Although bimatoprost is not regarded as a prodrug by some researchers,[8,11] some human studies have detected bimatoprost free acid at levels high enough to activate the FP receptor.[12–15] Lack of detection of the free acid at the site of action in other studies[8,11] could be attributed to corneal esterase deficiency in some individuals, thus inability to convert the prodrug to the active free acid form.[21]

The free acids of latanoprost, bimatoprost and travoprost all fully and selectively activate the FP receptor relative to the naturally occurring agonist PGF2α, although receptor affinity is variable. Free acids of travoprost[14,16] and bimatoprost[14,15] are, respectively, approximately 10 and 3 to 10 times more potent in activating the FP receptor than latanoprost free acid. Travoprost concentration of 0.004% is slightly lower than latanoprost at 0.005%, but probably represents a much higher dose on the dose-response curve.[22] Bimatoprost concentration of 0.03% is 6 times that of latanoprost to allow sufficient conversion to its free acid to activate the FP receptor. Subsensitivity at the FP receptor level from either desensitization or down-regulation of the FP receptor[23,24] could account for the observed reduced efficacy or even IOP increase with combination PGA therapy or increased frequency of PGA administration.

The exact mechanisms of action of PGAs are not entirely clear. Primate studies have shown that PGAs reduce IOP by enhancing uveoscleral[25–28] and trabecular outflow with little or no effect on aqueous humor formation or episcleral venous pressure.[7,10,20,21,26,29–31] Initial IOP reduction with PGAs may also be attributed to ciliary muscle relaxation via FP receptors, thus facilitating uveoscleral outflow.[32] The presence of prostaglandins in trabecular meshwork cells[31] and anterior segment organ cultures[33] support a role in aqueous outflow regulation. Latanoprost acid infused human organ-cultured anterior segments significantly increased outflow facility at 24 hours (67% vs 6% controls).[29] Proposed superior effects on trabecular outflow compared to uveoscleral outflow with bimatoprost[26] or travoprost[28] could be accounted for by measurement technique.[34]

PGAs appear to regulate matrix metalloproteinases (MMP) and tissue inhibitors of matrix metalloproteinases (TIMP) to modulate trabecular outflow resistance. MMPs are neutral zinc-dependent endoproteinases involved with normal and pathologic remodeling of extracellular matrix. Increased expression of MMP-1, -3, -17, and -24 and TIMP-2, -3, -4[35]

in human trabecular meshwork cell cultures treated with latanoprost acid for 24 hours, and MMP-1, -2, -3[36] in iris root, ciliary muscle, and adjacent sclera in monkeys may lead to hydrolysis of collagen types I and III (MMP-1), collagen IV and fibronectin (MMP-2), and collagen types III, IV, fibronectin and laminin (MMP-3), resulting in widening of the connective tissue-filled spaces among the ciliary muscle bundles[37] and loss of trabecular meshwork (TM) extracellular matrix, hence increased outflow.[29,36] Similar anterior segment morphologic changes among the different prostaglandins,[38] suggest similar mechanisms of action on uveoscleral or trabecular outflow.[31] Studies to elucidate cellular mechanisms associated with PG-induced MMP secretion and alterations in calcium signaling pathways in the trabecular meshwork are ongoing.

A small (10% to 15%) nocturnal increase in aqueous flow and uveoscleral outflow has been found from PGA use.[25,39,40] Documented 24-hour efficacy of PGAs[41–46] is important in reducing ischemic damage to the optic nerve caused by nocturnal episodes of systemic hypotension, especially in subjects with NTG. Topical β-blockers are unable to suppress aqueous secretion, hence reduce IOP, during sleep.[47] Enhanced aqueous flow may also act to carry nutrients and remove waste products, important in the maintenance of anterior segment health.[21]

Other effects

Reduced or increased ocular blood flow (OBF) may respectively accelerate or prevent glaucomatous progression in some subjects. Latanoprost significantly increased pulsatile OBF in healthy volunteers,[48,49] and OAG[50,51] and NTG[52–54] subjects, although not consistently found.[55] A randomized double-masked crossover study[56] found a more favorable effect on ocular perfusion pressures (OPP) (which are directly related to OBF) with latanoprost than timolol.[56] Using color Doppler ultrasound, Koz et al[57] demonstrated that latanoprost, travoprost and bimatoprost increased blood flow velocity and OPP, and latanoprost and travoprost decreased the resistive index of the ophthalmic artery and central retinal artery (CRA). Alagoz et al[58] found increased CRA blood flow with bimatoprost and travoprost use. Other studies have found no change in blood flow velocity or vascular resistivity of the retrobulbar vessels with latanoprost.[59–60] It is unclear if the effects on ocular hemodynamic parameters are related to IOP decrease or an independent phenomenon. Observation of conjunctival and scleral hyperemia with PGAs suggests vasodilatory actions, but vasoconstrictory effects may occur, often at higher concentrations.

Pharmacokinetics of prostaglandin analogs

After administration of a single drop (30 μL) of tritium-labeled latanoprost 50 μg/mL (thus 1.5 μg of drug), the maximum concentration of latanoprost averaged 32.6 ± 20.6 ng/mL at 2.5 hours.[62] The elimination half-life of latanoprost acid from the aqueous humor was 2.5 hours. The concentration 24 hours after administration was ≤0.2 μg/L.[62] After one drop in each eye, the maximum plasma concentration of the free acid was 10^{-10} M and the plasma half-life was 17 minutes. Latanoprost undergoes extensive first-pass metabolism in the liver via β-oxidation to its (1, 2)-dinor and (1, 2, 3, 4)-tetranor metabolites, then is eliminated by urine (87.9%) and feces (15.3%).[62]

After one drop of travoprost 0.004% (1.2 μg of drug) in each eye, the maximum plasma concentration of the free acid was 10^{-10} M and the plasma half-life 45 minutes (Travatan product information, Alcon).[7] The free acid is metabolized to inactive metabolites via β-oxidation of the α-chain to yield the 1, 2 dinor and 1, 2, 3, 4, tetranor metabolites, via oxidation of the 15-hydroxyl moiety, as well as via reduction of the 13, 14 double bond. Less than 2% of the topical ocular dose of travoprost was excreted in the urine within 4 hours as the travoprost acid.[7]

After one drop of bimatoprost 0.03% in each eye (9 μg of drug), the maximum plasma concentration of bimatoprost amide was approximately 10^{-10} M (Lumigan product info, Allergan), peaked within 10 minutes of dosing and fell below the lower limit of detection within 1.5 hours.[5] Mean maximum blood concentration and area under the curve values were similar on days 7 and 14 at 0.08 ng/mL and 0.09 ng/h/mL respectively, indicating steady state levels after one week of ocular dosing.[5] It is likely that bimatoprost enters the eye via the sclera as corneal tissue lacks specific amidases to form the active acid hydrolysis product.[10] Bimatoprost levels were 10- to 100- times higher in the ciliary body and iris compared with aqueous humor. Bimatoprost undergoes oxidation, n-de-ethylation, and glucuronidation to form a diverse variety of metabolites. No drug accumulation occurs. Up to 67% of the administered dose was excreted in the urine whereas 25% was recovered in the feces.[7]

Clinical efficacy and differential impact

Studies of PGA therapy vary by way of randomization, masking, drug cross-over, patient selection, medication run-in and wash-out periods, and sponsorship. IOP measurement can be diurnal (usually mean of 3 daily measurements

taken between 0800 and 1800 hours), investigated over a 12-[63,64] or 24-[46,65,66] hour period, and/or measured at specific time points (peak or trough).[64,67,68] The primary endpoint in most trials is the mean reduction in IOP from baseline. Because of the large number of clinical studies of variable scientific quality evaluating latanoprost 0.005%, bimatoprost 0.3% and travoprost 0.004% as mono-, concomitant or combination therapy for OH and OAG,[63,64,68–83] selected randomized control trials and meta-analyses will be discussed in this review. Meta-analyses may be preferable in evaluating drug effectiveness.[84] However, meta-analyses are unable to fully overcome heterogeneity of participant characteristics and IOP measurement time-points, and may be subject to publication bias with inclusion of unpublished data and often exclusion of non-English trials or lack of notating industry-sponsored trials. Quality of a meta-analysis depends on the quality of trials included. Selected meta-analyses involving PGAs as monotherapy are outlined in Table 1.

Selected multicenter, single- or double-blind, randomized control trials of greater than 1-month duration comparing the efficacy of prostaglandin analogues in OH and OAG are shown in Table 2. The studies used various end-point parameters including mean IOP reduction, %IOP reduction (%IOPR) from baseline, or target IOP levels. Baseline demographic parameters were similar among groups within each study. Mean IOP reduction was similar for latanoprost, bimatoprost, and travoprost and documented at 8.6 mmHg, 8.7 mmHg, and 8.0 mmHg respectively for one study.[85] Four studies favored bimatoprost over latanoprost for IOP lowering.[63,64,78,86] This was significant for 2 of the 4 studies. One of these studies found a significant difference only at 1200 and 1600 hours time-points,[64] but the other study found a difference in IOP reduction between bimatoprost and latanoprost of 1.2 to 2.2 mmHg at all measured time-points (0800, 1200, 1600 hours).[86] Bimatoprost achieved target IOP $\leq$ 13 mmHg[64,86] or $\leq$15 mmHg[78] significantly more with than latanoprost. Bimatoprost also showed superiority over travoprost, but was significant only at the 0900 time-point; %IOP reduction from baseline for bimatoprost and travoprost was 27.9% and 23.3% respectively (P = 0.014).[87] Travoprost was superior to latanoprost in another study; mean IOP was 0.8 mmHg lower for travoprost vs latanoprost (P = 0.0191) and final IOP of $\leq$17 mmHg or $\geq$30% IOP reduction was 54.7% and 49.6% for travoprost and latanoprost respectively (P = 0.0430).[68]

Several meta-analyses[88–91] have directly compared the clinical efficacy of the three main PGAs, latanoprost, travoprost, and bimatoprost. Two independent meta-analyses, one[88] of 8[63,64,68,78,85–87,92] and the other[89] of 13 trials (including double-blind parallel[57,63,93] or cross-over studies[41,42] and single blind parallel[64,78,85,86,94–96] or cross-over studies)[97] found bimatoprost was superior to latanoprost in lowering morning IOP at all time points, supported by a later post-hoc meta-analysis of 2 independent trials with 6 months follow-up. Weighted mean difference (WMD) for %IOP reduction (%IOPR) was 2.59% (P = 0.004) at 1 month to 5.60% ($P < 0.001$) at 6 months for one meta-analysis[89] and weighted mean (WM) IOP change from baseline ranged from a minimum of 0.50 mmHg (P = 0.05) at 0800 hours to a maximum of 1.17 mmHg ($P < 0.001$) at 1200 hours in the other meta-analysis[88] favoring bimatoprost over latanoprost. Bimatoprost was superior in IOP lowering to travoprost only during the daytime (0800 and 1200 hours time-points), but latanoprost and travoprost were comparable at all time points ($P \leq 0.82$).[88]

An industry-sponsored meta-analysis[90] of travoprost vs latanoprost (15 trials, n = 1098),[57,68,85,93,95,96,98–100] travoprost vs bimatoprost (8 trials, n = 714),[57,85,87,93,95,96,101,102] and latanoprost vs bimatoprost (8 trials, n = 943)[57,64,85,86,93,95,96,103] found similar efficacy among the three PGAs. Studies comparing the PGA to other non-PGA glaucoma treatments, non-randomized, dose-finding or cross-over trials, and short-term evaluations (less than 3 months) were excluded, although a trial evaluating timolol plus travoprost versus timolol alone,[100] was included indicating that the PGA effect has the same relative effect as if it were compared with no treatment. Another industry-sponsored meta-analysis by Denis et al[91] of 9 randomized trials[63,68,78,85,86,92,93,101,104] (n = 1318) found adjusted IOP was similar for bimatoprost and travoprost, but more favorable than latanoprost treated subjects. Authors commented that 4 trials evaluating latanoprost vs timolol, were not included which may have lead to a lower IOP decrease for latanoprost compared with the meta-analysis by van der Valk.[84]

Four trials comparing latanoprost with unoprostone 0.15% twice daily for 1–2 months demonstrated superiority with latanoprost.[74,79,80,82] The mean IOP reduction was approximately twice as great with latanoprost as with unoprostone ($P < 0.001$), and 6–8 times as many latanoprost recipients achieved an IOP reduction $\geq$30% (44 and 45% vs 6 and 8%; P values not reported) in the two largest trials.[80,82]

In summary, bimatoprost appears to have superior IOP lowering effects over travoprost or latanoprost,[63,64,78,86,88,89] with the ability to achieve lower target IOP,[64,78,86] although not consistently found.[85,90,91,105]

Table 1 Summary of meta-analyses of randomized control trials of prostaglandin analog use as monotherapy in ocular hypertension and open-angle glaucoma

Author/year/sponsor	PGA randomized	No. of trials	N	Cross-over studies	Single-blind studies	Quality scores	Duration (months)	%Without OAG or OH	Summary of IOP-lowering efficacy
Cheng[89] /2008/Nil	Lat, Bim	13	1302	Yes	Yes	Jadad	1–6	17.0[a]	WMD %IOPR: Bim vs Lat = 5.60%, $P < 0.001$ in favor of Bim
Zhang[115] /2001/Nil	Lat, Tim	11	1256	Yes	Yes	Jadad	1–12	10.9	%IOPR: Lat 30.2% >Tim 26.9%. %IOP-lowering difference = 5% (1.6 mmHg), $P < 0.001$
Fung[146] /2007/Nil	Lat, Brim	14	1784	Yes	Yes	No	1–12	3.4	WMD %IOPR: Lat vs Tim = 1.10 mmHg, CI 0.57–1.63, $P = 0.001$ in favor of Lat
Einarson[145] /2000/Pharmacia	Lat, Brim	9	1168	NR	No	Jadad	Up to 6	NR	IOPR: Lat 8.0 mmHg > Brim 6.2 mmHg, $P = 0.045$
Aptel[88] /2008/Nil	Lat, Bim, Trav	8	1610	No	No	Jadad	1–6	0	IOPR: Bim > Trav (at 0800 and 1200 h) >Lat (all time points)
Eyawo[90] /2008/Pfizer	Lat, Bim, Trav	16	2664(IR)	No	Yes	No	3–12	8.7	WMD %IOPR: Trav vs Lat = –0.24 mmHg, CI –0.87–0.38, $P = 0.45$, Trav vs Bim = 0.88 mmHg, CI 0.13–1.63, $P = 0.02$, Lat vs Bim = 0.73 mmHg, CI 0.10–1.37, $P = 0.02$. Authors state similar efficacy effects
Denis[91] /2007/Alcon	Lat, Bim, Trav	9	1318	No	Yes	No	0.5–12	0.9	Difference %IOPR: Trav vs Lat = –0.98 mmHg, CI –2.08–0.13, $P = 0.08$. Bim vs Lat = –1.04 mmHg, CI –2.11; 0.04, $P = 0.06$. Pooled Trav or Bim vs Lat = –1.0 mmHg, CI –1.91, –0.10, $P = 0.03$ in favor of pooled Trav or Bim
Holmstrom[128] /2005/Allergan	Lat, Bim, Trav, Tim	42	9295	Yes	Yes	No	0–6	NR	WM %IOPR: Bim 30.3% > Trav 28.7% > Lat 26.7% > Tim 22.2%
Li[105]/2006/Nil	Lat, Bim, Trav, Tim	12	3048	NR	Yes	No	0.5–12	3.8	WMD %IOPR: Trav vs Tim = –0.81 mmHg, $P = 0.00001$ in favor of Trav, Trav vs Bim = 0.08 mmHg, $P = 0.8$. Trav vs Lat = –0.57 mmHg, $P = 0.07$ in favor of Trav
Hodge[158] /2008/Nil	Lat, Brim, Dorz	8	1722	Yes	NR	Jadad	3–6	5.8	WMD in IOPR: Lat vs Brim = –1.04 mmHg, $P = 0.30$. Lat vs Dorz = –2.64 mmHg, $P < 0.00001$ in favor of Lat
Cheng[186] /2009/Nil	Lat, Dorz + Tim	14	2149	Yes	Yes	Jadad	1–12	14.3 (IR)	WMD %IOPR: Subjects uncontrolled on timolol treatment: Lat vs Dorz/Tim = 3.12%, CI 0.47– 5.78, Significant. Subjects not on baseline timolol treatment: Lat is as effective as Dorz/Tim
Stewart[162] /2008/Nil	Lat, Bim, Trav, Tim, Brim, Dorz	11	386	Yes	Yes	Delphi	1–2	NR	24-Hour %IOPR: Bim 29% > Trav 27% > Lat 24%, >Tim 19% > Dorz 19% > Brim 14%
van der Valk[84]/2005/Nil	Lat, Bim, Trav, Btx, Tim, Dorz, Brinz, Brim	28	6953(trough) 6841(peak)	NR	Yes	Delphi	1–6	2.8 (IR)	%IOPR: At peak: Bim 33% > Lat 31% = Trav 31% > Tim 27% > Brim 25% > Btx 23% > Dorz 22% >Brinz 17% At trough:Trav 29% > Bim 28% = Lat 28% > Tim 26% > Btx 20% > Brim 18% > Brinz 17% = Dorz 17%

Abbreviations: Bim, bimatoprost 0.03%; Brim, brimonidine 0.2%; Brinz, brinzolamide 1.0%; Btx, betaxolol 0.5%; CI, 95% confidence intervals; IOP, intraocular pressure; IOPR, intraocular pressure reduction; IR, incompletely reported; Lat, latanoprost 0.005%; NR, not reported; OH, ocular hypertension; OAG, open-angle glaucoma; Trav, travoprost 0.004%; WM. weighted mean; WMD, weighted mean difference; Tim, timolol.
[a]Excludes NTG subjects.

Table 2 Selected multi-center, randomized control trials of greater than 1-month duration comparing efficacy of prostaglandin analogs in ocular hypertension and open-angle glaucoma

First author /year/sponsor	Design	Randomized PGA	Duration (months)	N	Mean age (yrs) /%female/% withdrawal	No. of OAG/OH/Other[a]	Results summary
Parrish[85] /2003/Pharmacia	SB-P	Lat vs Bim vs Trav	3	410	65/58.0/4.4	309/95/6	Mean ± SEM IOP reduction from baseline was equivalent among treatment groups: Lat 8.6 ± 0.3 mmHg, Bim 8.7 ± 0.3 mmHg, Trav 8.0 ± 0.3 mmHg, $P = 0.128$. Mean IOP level was similar across treatment groups at 12 weeks
DuBiner[63] /2001/Allergan	DB-P	Lat vs Bim	1	43	66.5/51.1/7.0	19/24/0	Greater non-significant mean IOP reduction (average of 4 diurnal readings) from baseline with Bim (6.96 mmHg) than Lat (5.48 mmHg), $P = 0.0572$, and IOP ≤15 mmHg (Bim 31.6% vs Lat 19.0%)
Gandolfi[64] /2001/nil disclosed	SB-P	Lat vs Bim	3	232	61.7/62.5/7.8	132/81/19	Greater significant mean IOP reduction from baseline with Bim at 1200 and 1600 h, but not at 0800 and 2000 has Lat. IOP ≤13 mmHg more frequent in Bim group ($P \leq 0.006$)
Noecker[86] /2003/Allergan	SB-P	Lat vs Bim	6	269	61.3/61.7/7.4	150/93/26	Mean difference in IOP reduction significantly favored Bim compared with Lat: 1.5 mmHg at 0800 ($P < 0.001$), 2.2 mmHg at 1200 ($P < 0.001$) , and 1.2 mmHg at 1600 ($P = 0.004$). Diurnal IOP was lower with Bim (16.5 to 17.4 mmHg) than Lat (17.6 to 18.9 mmHg), $P \leq 0.008$. IOP ≤13 mmHg was achieved significantly more in Bim group
Walters[78] /2004/Allergan	SB-P	Lat vs Bim	1	76	58.8/61.8/3.9	48/28/0	Mean IOP reduction and %IOP reduction from baseline was greater with Bim (9.3 mmHg, 40.3%) than Lat (7.4 mmHg, 33.3%) but not significant. Target IOP ≤15 mmHg achieved more often in Bim- than Lat-treated eyes, $P \leq 0.038$
Netland[68] /2001/Alcon	SB-P	Lat vs Trav	3	390	64.2/51.5/5.3	259/126/5	Mean IOP reduction from baseline was similar for Trav (6.6 to 8.1 mmHg) and Lat (6.2 to 8.1mmHg). Mean IOP at all treatment visits for Trav was 17.5 to 19.7 mmHg and for Lat, 17.9 to 19.5 mmHg. Mean IOP was 0.8 mmHg lower for Trav than Lat, $P = 0.0191$. Target IOP reduction of ≥30% or final IOP ≤17 mmHg was achieved with Trav (54.7%) more than Lat (49.6%), $P = 0.0430$
Cantor[87] /2006/Allergan	SB-P	Bim vs Trav	6	157	65.0/60.5/10.8	108/48/1	Mean IOP reduction and %IOP reduction from baseline was significantly favorable for Bim (7.1 mmHg, 27.9%) than Trav (5.7 mmHg, 23.3%) at 0900, $P = 0.014$, but not-significantly favorable at 1300 and 1600. Significantly more Bim- (64.5%) treated subjects achieved IOP reduction ≥25% than Trav- (39.5%) treated, $P = 0.002$

Abbreviations: Bim, bimatoprost 0.03%; DB-P, double-blind; parallel group; IOP, intraocular pressure; Lat, latanoprost 0.005%; NR, not reported; OH, ocular hypertension; PGA, prostaglandin analog; OAG, open-angle glaucoma; SB-P, single-blind; parallel group; Trav, travoprost 0.004%.

[a]Includes pseudo-exfoliative, pigment dispersion, and angle-closure glaucoma.

Vs timolol

Before the introduction of travoprost and bimatoprost, initial studies compared latanoprost 0.005% with other ocular hypotensives, in particular timolol 0.5%. Table 3 shows the characteristics and results of double-blind randomized controlled trials comparing PGAs with timolol 0.5% twice daily for POAG and OH.

Four of these studies[71–73,81] evaluated latanoprost 0.005% and timolol 0.5% use in OH and POAG. Latanoprost reduced mean baseline diurnal IOP by 6.2 to 8.6 mmHg (26.8% to 35%) significantly more than timolol (4.4 to 8.3 mmHg (19.9% to 32.7%)) over 3[81] or 6 months of treatment,[71,73] except for the study by Watson et al[72] which showed equivalence. Pooled analyses of 3 Phase III studies[71–73] showed a mean diurnal IOP reduction of 7.7 mmHg (31%) for latanoprost vs 6.5 mmHg (26%) for timolol after 6 months, a significant difference of 1.2 mmHg (18%), $P < 0.001$106 and no evidence of drift.[107] Higher baseline diurnal IOP resulted in a larger diurnal reduction during treatment with both drugs ($P < 0.001$). A further decrease in morning IOP of 0.7 mmHg (9%, $P < 0.001$) at 6 weeks from the initial morning IOP reduction obtained at 2 weeks was found with latanoprost,[106] which was maintained throughout 2 years of treatment,[108] supported also by the 1- and 2-year extension trials of the Phase III studies.[109–112] The adjusted risk of IOP treatment failure was 8% overall,[106] 3.6 and 6.1 times significantly higher in the patients with a baseline untreated IOP of 26–29 and 30–45 mmHg respectively. Pooling 8 studies,[113] the greatest difference in IOP lowering effect was observed with latanoprost in Mexican and Asian clinical trials. A prospective unmasked study (n = 76)[114] found latanoprost reduced IOP from 26.5 ± 6.6 mmHg to 17.4 ± 2.7 at 3 years in timolol unresponsive eyes.

An independent meta-analysis[115] of 11 randomized head-to-head trials[56,61,71–73,81,116–120] (n = 1256) comparing timolol with latanoprost documented mean (SE) percentage IOP reductions (%IOPR) from baseline of 31.2% (2.3) and 26.9% (3.4) for latanoprost and timolol respectively at 3 months, a significant difference in reduction of 5.0% (95% confidence interval [CI] 2.8, 7.3), $P = 0.00$, and a similar difference at 6 months.[115]

The International Travoprost Study Group[121] (see Table 3) found travoprost 0.004% reduced mean diurnal IOP by 8.0 to 8.9 mmHg, significantly more than timolol (6.3 to 7.9 mmHg), $P \leq 0.001$. Based on intent-to-treat data, the Travoprost Study Group[122] also found a statistically significant mean IOP change from baseline for travoprost 0.004% (−6.5 to −7.1 mmHg) than for timolol 0.5% twice daily (−5.2 to −6.8 mmHg). Higginbotham et al[123]

Table 3 Characteristics of double-blind randomized control trials of 1 to 9 months' duration comparing prostaglandin analogs with timolol 0.5% twice daily for ocular hypertension and open-angle glaucoma

Author/year/location	Design	Randomized PGA	Duration (months)	N	Mean age (yrs)/%female/%withdrawal	No. of OAG/OH/Other[a]	% diurnal IOP reduction from baseline		*P*-value
							PGA	Timolol	
Alm[71]/1995/Scand[b]	DB-P DB-C	Lat mane or nocte	6	267	67/56.6/6	91/123/53	35 (nocte) 31 (mane)	27	$P = 0.001$
Camras[73]/1996/USA[b]	DB-P	Lat nocte	6	268	62/57.5/7	84/170/14	27	20	$P = 0.001$
Watson[72]/1996/UK[b]	DB-P	Lat nocte	6	294	65/35.0/9	121/148/25	33.7	32.7	NS
Mishima[81]/1996/Japan	DB-P	Lat mane	3	178	57/51.1/11	NR	26.8	19.9	$P < 0.001$
Brandt[124]/2001/USA[b]	DB-P	Bim nocte or bd	3	596	62/56.0/7.4	373/218/5	35.2 (nocte) 30.4 (bd)	26.2	$P < 0.001$
Whitcup[125]/2003/USA[b]	DB-P	Bim nocte or bd	3	602	61/53.7/8.6	300/284/18	32.4 (nocte) 25.2 (bd)	22.7	$P < 0.001$
Goldberg[121]/2001/Various[b]	DB-P	Trav nocte	9	382	63/49.7/3.1	208/147/27	30.8–31.6	25.1–27.9	$P \leq 0.0001$
Fellman[122]/2002/USA[b]	DB-P	Trav nocte	6	396	NR/52.5/2.8	251/132/13	From pooled visits, Trav was superior to Tim		$P < 0.0130$

Abbreviations: bd, twice daily; Bim, bimatoprost 0.03%; DB-C, double-blind, cross-over; DB-P, double-blind, parallel; Lat, latanoprost 0.005%; mane, every morning; nocte, every night; NR, not recorded; NS, not significant; OH, ocular hypertension; OAG, open-angle glaucoma; PGA, prostaglandin analog; Scand, Scandinavia; Trav, travoprost 0.004%; wks, weeks; Tim, timolol.

[a]Includes pseudoexfoliative, pigment dispersion and other secondary glaucomas; [b]indicates sponsorship by Pharmacia Inc.

pooled 1-year results from the Bimatoprost Study Groups 1[124] and 2[125] (n = 1198) found bimatoprost 0.03% once daily was more efficacious than bimatoprost 0.03% or timolol 0.5% twice daily.[123] An IOP ≤ 17 mmHg was achieved in 58% of bimatoprost once daily patients compared with 37% of timolol treated subjects. Bimatoprost lowered IOP to the same extent in blacks and non-blacks, while timolol was less effective in blacks (by approximately 2 mm). Mean reduction with bimatoprost 0.03% once daily was sustained over 2[126] and 4[127] years, and remained lower than timolol ($P \leq 0.001$).

Holmstrom et al[128] analyzed efficacy of latanoprost (33 studies), bimatoprost (18 studies) and travoprost (8 studies) monotherapy, and combined latanoprost/timolol (11 studies), bimatoprost/brimonidine (1 study), and travoprost/timolol (2 studies). Difference in %IOPR was 6%; IOPR% was 27.2% for PGA use (collectively)[63,64,67,68,71–73,78,80–82,85,86,92,116,117,119,121,122,124,125,129–143] compared with 21.2% for timolol[67,68,71–73,78,81,116,117,119,121,122,124–126,131,134,135,137,139,142,143] with 0- to 1-month data, and 22.2% and 28.6% for timolol and PGA respectively for studies with 0- to 6-months data. Pooling all data[128] the WM %IOPR was 30.3%, 28.7%, and 26.7% for bimatoprost, travoprost, and latanoprost respectively. Latanoprost studies had a lower baseline IOP (WM baseline IOP 24.84 mmHg) compared with bimatoprost (25.74 mmHg) or travoprost (26.83 mmHg), possibly due to a larger percentage of patients with run-in timolol treatment (16%, 5% and 0% for latanoprost, bimatoprost and travoprost respectively). Another meta-analysis[105] found travoprost 0.004% was equivalent in lowering IOP compared with bimatoprost 0.03%[85,86,92,93,95] (WMD = 0.08, $P = 0.8$) or latanoprost 0.005%[68,85,93,95,98,104] (WMD = −0.57, $P = 0.07$), but superior to timolol.[68,121,122,144]

In summary, the vast majority of studies support IOP-lowering superiority of latanoprost,[71,73,81,106] travoprost,[121,122] and bimatoprost,[124,125,137] over timolol, and although not entirely consistent.[72] PGAs were effective in eyes unresponsive or inadequately controlled with timolol, and remained effective long term.

Vs brimonidine

Two meta-analyses[145,146] comparing efficacy of latanoprost and brimonidine both favored latanoprost for IOP lowering.[145] In one meta-analysis,[145] the estimated absolute decrease in IOP from baseline for latanoprost and brimonidine was respectively −8.4 and −6.5 mmHg at 3 months ($P = 0.004$) and −8.0 and −6.2 mmHg at 6 months ($P = 0.045$). Head-to-head trials post-dated the study hence studies comparing the medication in question and timolol[71–73, 81,116,119,147,148] or betaxolol[149] were included. In contrast, head-to-head trials,[43,52,53,59,70,76,77,83,150–157] only were analyzed for the second meta-analysis.[146] The pooled summary estimate significantly favored latanoprost (weighted mean difference (WMD) = 1.10, 95% CI 0.57 to 1.63) over brimonidine. A third meta-analysis[158] did not find a significant reduction in mean IOP when latanoprost was compared with brimonidine (WMD = −1.04; $P = 0.30$). This pooled result did not change when only two higher-quality studies[70,76] were analyzed; one study part funded by Pharmacia[70] favored latanoprost (adjusted mean diurnal IOP reduction = 5.7 mmHg) over brimonidine (3.1 mmHg) and the other study supported by Allergan[76] did not find a significant difference between treatments; mean %IOPR was 27.8% vs 27.0% for latanoprost and brimonidine respectively. Clinical success (based on IOP lowering efficacy, tolerability and patient satisfaction) at 3 months was greater with the brimonidine group (91% vs 74%, $P = 0.01$),[76] although the former study[70] experienced 5 times more adverse effects from brimonidine use. In summary, 2 of 3 meta-analyses found improved efficacy of latanoprost than brimonidine in IOP lowering.

Vs dorzolamide

Hodge et al[158] also compared latanoprost with dorzolamide through a meta-analysis of 3 studies[75,159,160] (n = 328). Mean IOP was lower in the latanoprost compared with the dorzolamide group (WMD = −2.64 mmHg; $P < 0.00001$). The largest of the studies analyzed[75] documented a significant lowering of diurnal IOP with latanoprost (8.5 mmHg) than dorzolamide (5.6 mmHg; $P < 0.001$).[75]

Rank order of ocular hypotensives as monotherapy

Pooled one-month IOP-lowering effect from baseline to peak (n = 6953) and trough (n = 6841) of 8 commonly used ocular hypotensives was reported by van der Valk et al.[84] At peak, greatest %IOPR was achieved by bimatoprost (33%), followed by latanoprost (31%), travoprost (31%), timolol (27%), brimonidine (25%), betaxolol (23%), dorzolamide (22%), brinzolamide (17%), and a placebo (5%). At trough, greatest%IOPR was achieved by travoprost (29%), followed by bimatoprost (28%), latanoprost (28%), timolol (26%), betaxolol (20%), brimonidine (18%), brinzolamide (17%), and dorzolamide (17%). A network meta-analysis also by van der Valk[161] found mean IOP reduction at peak was greatest with bimatoprost, travoprost and latanoprost, followed by other ocular hypotensive agents, and at trough

bimatoprost, latanoprost, and travoprost followed by other ocular hypotensive agents.

Stewart et al[162] evaluated studies of ocular hypotensive therapy efficacy measured over 24 hours. Greatest 24-hour IOP reduction was found with bimatoprost (29%) and travoprost (27%) than latanoprost (24%), combination dorzolamide and timolol (19%), or brimonidine (14%). Mean reduction of night-time points was statistically lower than that of day time points for latanoprost ($P = 0.031$), timolol ($P = 0.032$), and brimonidine ($P = 0.050$) but not for dorzolamide ($P = 0.60$), bimatoprost ($P = 0.057$) and travoprost ($P = 0.064$). Latanoprost showed greater 24-hour efficacy with night dosing (24%) than morning dosing (18%). For travoprost, there was no a significant difference between night (27%) or morning (26%) dosing ($P = 0.074$).

Twenty-four-hour IOP measurements may provide better information for clinical decision-making than daytime IOPs alone.[162] Higher peak pressure[163,164] may be an independent risk factor for glaucomatous progression and IOP measurements outside normal office hours can change the peak pressure assessment in 69% to 75% of cases.[165,166] In other studies, mean reductions in IOP were lower with latanoprost than with timolol 0.5% during both the daytime and night-time hours ($P \leq 0.05$)[46,66] as timolol did not reduce IOP as much at night ($P = 0.04$).[66] Flattening of the 24-hour IOP curve, thus reduction in IOP fluctuations was documented for bimatoprost[63,143,163] and latanoprost,[168] importantly for NTG subjects in the latter. The 24-hour diurnal IOP was statistically lower with bimatoprost compared with latanoprost in a double-masked cross-over comparison (n = 42), although the difference was small and latanoprost better tolerated with regard to conjunctival hyperemia.[41]

However, for NTG a meta-analysis[169] found IOP reduction was greatest for brimonidine (24%), followed by bimatoprost (21%), latanoprost (20%), timolol (15%), and dorzolamide (14%) at peak, and greatest for latanoprost (20%), followed by timolol (18%) and bimatoprost (18%), dorzolamide (12%), and brimonidine (11%) at trough. Ten of the 15 trials involved a PGA.[44,53,56,103,114,169,170–173]

Subjects (n = 1571) switched to latanoprost from previous glaucoma monotherapy and fixed and unfixed combination therapies maintained IOP to an acceptable level through a 2-year period.[174] Latanoprost-insensitive patients developed IOP lowering with bimatoprost in a randomized prospective study with two 30-day treatment phase and 30-day washout phase.[136] IOP on bimatoprost (18.1 ± 1.7 mmHg) was significantly lower than either baseline (24.8 ± 1.1 mmHg, $P < 0.0001$) or latanoprost (24.1 ± 0.9 mmHg, $P = 00001$) when rechallenged.

In summary, all three PGAs have documented superiority over other ocular hypotensives in various meta-analyses with respect to %IOPR[84] and 24-hour IOP reduction for OH and POAG.[162] %IOPR may be superior for brimonidine than PGA for NTG.[169] PGAs are as effective for IOP-lowering at night-time as for day-time.

Adjunctive therapy

In timolol-treated subjects, adjunctive latanoprost lowered IOP significantly more than adjunctive dorzolamide (–7.06 mmHg; 32% vs –4.44 mmHg; 20% for adjunctive latanoprost and dorzolamide respectively) after 3-months in one study[175] and more than adjunctive pilocarpine 2%, 3 times daily in another.[130,176,177] Addition of latanoprost to pilocarpine therapy does not appear to diminish uveoscleral outflow[178,179] but is instead additive,[178,180–183] contrary to thoughts that ciliary muscle contraction with cholinergics hinders uveoscleral outflow.[179] In subjects (n = 115) with uncontrolled IOP on β-blocker monotherapy, adjunctive latanoprost (23.5%) or brimonidine (22.8%) were comparable in%IOPR at peak effect at one month, but brimonidine was better tolerated than latanoprost.[151] As third-line agents, overall mean%IOPR was not significantly different between brimonidine (22.8%) and latanoprost (17.2%), although brimonidine (85%) had slightly higher although non-significant clinical success (≥15% reduction in IOP from baseline) than latanoprost (65%).[152]

An additive effect of latanoprost was seen in an open-label 1-week trial of subjects with uncontrolled IOP on concomitant timolol and dorzolamide twice daily[184] with an additional 16% reduction in IOP, and a 3-month study of subjects with uncontrolled IOP on fixed combination dorzolamide/timolol (FCDT) with a further 5.2 mmHg IOP reduction at peak and 3.5 mmHg at trough.[150] A retrospective analysis of 73 eyes with uncontrolled IOP on latanoprost documented better %IOPR with adjunctive dorzolamide (19.7%, $P < 0.001$) than β-blockers (12.3%, $P < 0.001$) or brimonidine (9.3%, $P = 0.0011$).[185]

Vs dual therapy

A meta-analysis[186] of 14 studies[43,50,60,99,133,187–195] (n = 2149) found latanoprost lowered diurnal mean IOP significantly more than concomitant dorzolamide/timolol (11/14 studies used FCDT) if subjects were uncontrolled on timolol monotherapy (WMD for mean %IOPR was 3.12 (95% CI, 0.47 to 5.78), but was of equal efficacy if no baseline timolol was given. Post-hoc analyses[196] from 2 randomized, multicenter,

double-masked trials[133] comparing latanoprost with FCDT independent of baseline timolol use found equal efficacy for mean IOP at each time-point, mean IOP reduction for high IOP at baseline, and 40% IOP reduction. FCDT and latanoprost have similar 24-hour IOP-lowering efficacy after 2-months, but latanoprost further reduced mean 24-hour IOP by 0.3 mmHg ($P = 0.01$) at 6 months.[195]

Bimatoprost decreased IOP from baseline by 6.8 to 7.6 mmHg, significantly more than FCDT (4.4 to 5.0 mmHg, $P < 0.001$) in a randomized 3-month double-masked trial of subjects (n = 177) inadequately controlled with timolol[132] Subjects achieving IOP s of ≤13, ≤14, ≤15, ≤16 mmHg were more than twice as high for bimatoprost than for FCDT (all $P \leq 0.008$). Similar efficacy was found between bimatoprost 0.03% and concomitant timolol and latanoprost in a randomized 6 month investigator masked study of 56 subjects with a timolol run-in.[140] To date, there are no published studies evaluating the efficacy of fixed or unfixed combinations of brimonidine/timolol with latanoprost, travoprost or bimatoprost.

PGA/timolol fixed combinations

Diurnal IOP levels were lower with fixed combination latanoprost 0.005%/timolol 0.5% (FCLT) solution (Xalacom®; Pfizer Inc., NY, NY) (19.9 ± 3.4 mmHg), compared with timolol (23.4 ± 5.4 mmHg) and latanoprost (20.8 ± 4.6 mmHg) monotherapy in a 6-month double-masked trial (n = 418).[137] The mean 24-hour diurnal curve was 19.2 ± 2.6 mmHg for latanoprost alone vs 16.7 ± 2.1 mmHg for FCLT in another trial.[197] A meta-analysis of randomized clinical trials of 1 to 3 months' duration[198] documented greater pooled IOP change from baseline with concomitant latanoprost and timolol (−6.0 mmHg),[67,130,176] than FCLT (−3.0 mmHg),[137,142] concomitant dorzolamide and timolol (−4.1 mmHg at trough and −4.9 mmHg at peak), or FCDT (−3.8 mmHg at trough and −4.9 mmHg at peak). Omission of the evening timolol dose with FCLT possibly explains the large difference in IOP between fixed and concomitant use. Studies evaluating add-on therapy pre-selects patients with higher untreated IOP or those unresponsive to timolol. Only one study reported the pre-run-in IOP.[198] No measurement of expected peak latanoprost effect was made for studies on FCLT, whereas at least 1 measurement at the expected peak latanoprost effect for studies evaluating concomitant treatment was done.[198] Subjects (n = 325) with inadequate IOP control (IOP > 16 mmHg) on mono- or dual therapy had lower diurnal IOP with FCLT (16.9 mmHg) than concomitant brimonidine and timolol (18.2 mmHg), $P < 0.001$, at 6 months,[156] also supported by a cross-over study with a 1-month timolol run-in period.[154]

Data from 3 Phase III clinical studies[199,200] have shown that the fixed combination of bimatoprost 0.03%/timolol 0.5% (FCBT) ophthalmic solution (Ganfort®; Allergan inc., Irvine, CA) was significantly more effective in lowering IOP, with a higher percentage achieving mean reduction in diurnal IOP of >20% or a target pressure of <18 mmHg, than timolol or bimatoprost monotherapy. From the pooled analysis of 2 trials,[199] mean reduction in IOP from baseline was 7.4 to 9.6 mmHg in the FCBT group, 6.7 to 8.8 mmHg in the bimatoprost group, and 5.2 to 7.4 mmHg in the timolol treated group. Some subjects were unresponsive to timolol prior to the study and one study had a run-in period of timolol twice daily. FCBT was non-inferior to concomitant administration of its component parts in a randomized, double blind, 3-week study of patients with OAG or OH naïve to treatment.[201] Mean diurnal IOP was 16.1 mmHg with FCBT, 15.6 mmHg with concomitant bimatoprost and timolol, and 17.1 mmHg with bimatoprost monotherapy.[201] Two randomized, parallel group 4-[202] and 12-week[203] studies found FCBT was superior to FCLT in reducing mean diurnal IOP versus baseline at each time point. In the 12-week study,[203] more subjects had a mean IOP reduction from baseline of ≥20% with FCBT than FCLT (61.7% vs 17.1%). Subjects in both studies were insufficiently controlled on PGA, and there was no wash-out period.

Fixed combination travoprost 0.004%/timolol 0.5% (FCTT) ophthalmic solution (Duotrav®; Alcon Inc., Fort Worth, TX) lowered IOP 1.9 to 3.3 mmHg more than timolol alone and 0.9–2.4 mmHg more than travoprost alone.[144] Adverse events rates were comparable. FCTT lowered absolute IOP level (2.4 mmHg) for the 24-hour curve and at all time points, compared with travoprost ($P \leq 0.047$), and the mean 24-hour IOP fluctuation was lower with FCTT (3.0 mmHg) compared with travoprost (4.0 mmHg, $P = 0.001$).[204] FCTT had similar efficacy to concomitant travoprost and timolol.[205] Mean differences between FCTT and concomitant treatment was ±0.4 to ±1.1 mmHg. Percent IOP reduction from baseline was 29.1% to 33.2% for combination, 31.5% to 34.8% for concomitant, and 19.3% to 27.0% for timolol therapy alone.[205] These findings are also supported by a 3-month study of 316 patients.[206] FCTT did not demonstrate significant differences in mean IOP or mean IOP change from baseline compared with concomitant latanoprost and timolol in 2 studies.[207,208] A 12-month randomized control, parallel-group trial showed statistically equal or better mean IOP for FCTT (16.4 to 17.1 mmHg) than

FCLT (16.7 to 17.7 mmHg),[100] supported by a retrospective, cross-sectional study.[210] However, ocular hyperemia rates were higher with FCTT (15%) compared with FCLT (2.5%).[100] Compared with FCDT, mean pooled diurnal IOP was significantly lower with FCTT (16.5 ± 0.23 mmHg vs 17.3 ± 0.23 mmHg; $P = 0.011$) in a randomized-control, parallel, double-masked trial (n = 319).[209] FCTT produced mean IOP reductions of 35.3% to 38.5%, FCDT reduced IOP 32.5% to 34.5%. There do not appear to be studies directly comparing FCTT with FCBT.

In summary, fixed combinations of PGA with timolol are superior to monotherapy with its constituent parts.[137,144,199] Non-inferiority compared with the unfixed combination was found for FCBT[201] and FCTT,[205] though not for FCLT.[198] FCBT and FCTT appear to be more efficacious than FCLT.

Adverse effects

Table 4 shows differential rates of adverse events among the 3 main PGAs as reported in the randomized control trials summarized in Table 2.

Ocular adverse events

Conjunctival hyperemia

Conjunctival hyperemia was the most common adverse effect from PGAs observed in several studies.[64,78,85–87,123] All studies outlined in Table 4 show significantly higher rates of ocular hyperemia with bimatoprost and travoprost compared with latanoprost, except one.[63] Travoprost and bimatoprost have similar rates.[87,211] A meta-analysis of 13 randomized control trials found reduced rates of ocular hyperemia in subjects using latanoprost than both travoprost (odds ratio [OR] = 0.51; 95% CI 0.39 to 0.67, $P < 0.0001$) or bimatoprost (OR = 0.32; 95% CI 0.24 to 0.42, $P < 0.0001$).[211] Ocular hyperemia rates of 49.5% for travoprost, 27.6% for latanoprost, and 14% for timolol 0.5% have also been reported.[17]

Hyperemia was generally mild in severity, began within 2 days after starting PGA and diminished around 2 to 4 weeks, although may persist over time.[85,123] Discontinuation rates due to hyperemia were 3.4% for bimatoprost daily (5.6% for twice daily dosing), and 0.4% for timolol. Variability in the occurrence of hyperemia among those treated with PGAs may reflect a chemical difference in their molecular structure.[213]

Table 4 Differential adverse event rates among prostaglandin analogs as reported in multi-center, randomized control trials summarized in Table 2

First author/year	N	Reported rates of adverse events	
		Ocular	Systemic
Parrish[85]/2003	410	CH: Bim 68.6%, Trav 58.0%, Lat 47.1%, $P = 0.001$ Bim vs Lat Moderate CH: Bim 15.3%, Trav 10.1%, Lat 5.9% Eye irritation: Bim 10.9%, Trav 4.3%, Lat 6.6% Eyelash growth: Bim 2.9%, Trav 0.7%, Lat 0% Skin discoloration: Bim 2.9%, Trav 2.9%, Lat 1.5%	Bim 18.2%, Trav 16.7%, Lat 16.9%. Events reported >2% were nasopharyngitis, upper respiratory tract infection, headache
DuBiner[63]/2001	43	CH: Bim 14.3%, Lat 14.3%	
Gandolfi[64]/2001	232	CH: Bim 36.1%, Lat 14.2%, $P \leq 0.001$. Mild Eyelash growth: Bim 12.6%, Lat 4.4%, $P = 0.026$ Ant uveitis: 1 subject each No CME or iris change	Headache: 4.4% Lat vs 0% Bim, $P = 0.026$
Noecker[86]/2003	269	CH (slit-lamp): Bim 55.4%, Lat 42.5%, $P < 0.001$ Eyelash growth: Bim > Lat, $P = 0.064$ Iris change: 1 subject Bim Ant uveitis: 1 subject Lat No CME	12 serious adverse events. None reported to be related to study medication
Walters[78]/2004	76	CH: Bim 39.5%, Lat 15.8%, $P = 0.021$. Mild 14/15 cases Eye pruritis: Bim 13.2%, Lat 2.6%, $P = 0.20$ Ant uveitis: 1 subject Lat No CME	–
Netland[68]/2001	390	CH: Trav 38.0%, Lat 27.6%, mainly mild Eyelash growth: Trav 57.1%, Lat 25.8% Iris change: Trav 3.1%, lat 5.2% No anterior uveitis, No CME	–
Cantor[87]/2006	157	CH: Bim 21.1%, Trav 14.8%, $P = 0.326$ Ocular itching: Bim 2.3%, Trav 7.4%, $P = 0.278$ Iris change: 1 subject Bim	–

Abbreviations: Ant, anterior; Bim, bimatoprost 0.03%; CH, conjunctival hyperemia; CME, cystoid macular edema; Lat, latanoprost 0.005%; Trav, travoprost 0.004%.

Phenyl-substituted analogs significantly reduced the surface hyperemic effect of PGF2α – isopropyl ester, based on reduced co-stimulation of the vasodilatory EP prostanoid receptors, although other mechanisms involving both sensory nerves and a release of nitric oxide (NO) are at play.[22]

Iris pigmentation

Iris darkening is a recognized, common, and significant ocular side effect of PGAs,[73,111,214] and changes appear to be irreversible or very slowly reversible.[215,216] Latanoprost-induced iris hyperpigmentation after 1 year was noted in 12%, 23%, and 11% of patients in the USA, UK, and Scandinavia, respectively, mostly in mixed-color eyes (green-brown, yellow-brown, and blue/grey brown).[68] Iris pigmentation change was lower in travoprost 0.004% (3.1%) than latanoprost (5.2%).[68] A third of subjects with hazel irides developed recognizable iris darkening by 5 years.[215] A high 12-month incidence of 42.8%[217] to 58.2%[218] of iris darkening in brown irides in Japan[214,216] and Taiwan[217] has been documented. Homogeneous blue, green, or grey eyes are rarely affected.[214,216] Iris pigmentation may appear as soon as 3 months after initiation, develop in most (75%) affected subjects within 7 months,[217] and stabilize from 12[126] to 36 months.[215]

Increased iris hyperpigmentation is likely to be related to PGA-stimulated increase melanogenesis,[22,219–222] and possible increase in iris stromal melanocyte numbers[223] or their migration to the anterior border region with no net gain in melanin or melanocyte numbers.[224] Latanoprost-exposed iridectomy specimens showed increased melanin within the stromal melanocytes, but no evidence of pre-malignant change.[225] Tissue culture[226,227] and light microscopy[216] experiments do not show division and replication of iris stromal melanocytes. *In vitro* increase in PGE2 by latanoprost also suggests its role as an intracellular signaling agent to promote gene transcription and melanogenesis.[22] Potential problems with excess melanin include melanin granule release and inflammatory response in the stroma, melanin-induced anterior uveitis, or secondary pigment-induced glaucoma.[228]

Hypertrichosis

Reported increase in length, number, color and thickness of eyelashes,[229,230] from all PGAs,[64] can affect between 45% and 57% of subjects after 6 to 12 months' treatment,[229,231] and interfere with drop instillation.[232] Also, additional lash rows, conversion of vellus to terminal hairs in canthal areas and regions adjacent to lash rows,[233] lash ptosis, trichiasis, reversal of alopecia and poliosis can occur.[234,235] Randomized studies over 3 months found over 3-fold increase with bimatoprost compared with latanoprost.[64,85] The increased number of lashes is consistent with the ability of the PGA to induce anagen (the growth phase) in telogen (resting) follicles while inducing hypertrophic changes in the involved follicles. The increased lash length is consistent with the ability of the PGA to prolong the anagen phase of the hair cycle. Initiation and completion of PGA induced hair growth effects occur very early in anagen and the likely target is the dermal papilla.[233]

Periocular skin pigmentation

Darkening of the skin of the lids or other sites around the eye has been reported as a side effect associated with PGA use,[236–242] including development in black[236] subjects. The incidence of acquired skin pigmentation was 1.5% for latanoprost and 2.9% for bimatoprost and travoprost in one trial,[85] although numbers were small, and follow-up only 12 weeks.[85] Pigmentation can develop within months, and possibly earlier with bimatoprost use compared with latanoprost (1 vs 3 months),[236] or take even as long as 3 years.[238] Periocular pigmentation resolves without sequelae within 3 to 12 months for bimatoprost[239] and weeks for latanoprost.[236–238] with medication cessation. PGA-induced increase in melanogenesis[216] and melanocyte proliferation[243] have been implicated,[244] although a contact dermatitis-like reaction with inflammation may contribute.[239,245] FP receptors have been localized in hair follicles.[216]

Cystoid macular edema

Endogenous prostaglandin release induced by anterior segment inflammation can lead to blood aqueous breakdown, inflammatory mediators reaching the macula, and cystoid macular edema (CME). Prostaglandin levels increase after cataract surgery[246] and CME can resolve with non-steroidal anti-inflammatory therapy (NSAID).[247,248] Laser flare cell meter shows latanoprost enhances breakdown of blood-aqueous barrier and increase in angiographic CME after cataract surgery,[249] although disputable.[71–73,81,250] CME is reported to be higher in patients with posterior capsular rupture with vitreous loss, chronic topical medication use including epinephrine[251] possibly due to increased prostaglandin synthesis induced by benzalkonium chloride (BAC),[248] diabetes, and following laser procedures including laser capsulotomy.[228] A definitive link between PGA and CME is, however, hard to establish, as eyes developing CME generally have an independent risk factor for CME.[250] Pharmacologic considerations indicate that concentrations of PGA reaching the posterior segment are too low to induce vascular actions.[250]

Anecdotal reports of CME[252–255] with PGA use (latanoprost, travoprost, bimatoprost or unoprostone) occurred in patients with CME risk factors including aphakia, complicated cataract surgery, ruptured PC, history of uveitis, and retinal inflammatory or vascular disease. One study found clinical CME in 2/136 eyes (1.2%), but one subject had a ruptured posterior capsule and anterior chamber lens and the other was pseudophakic and had active uveitis 1 month prior to starting latanoprost.[256] Another study found clinical CME in 3/212 (1.4%) post-cataract eyes on latanoprost therapy, all of whom had a ruptured posterior capsule requiring vitrectomy.[257] In a prospective study of latanoprost therapy in 33 pseudophakic eyes, with ruptured posterior capsules, 2 (6%) had clinical CME.[258] However, there were no cases of CME reported in Phase I and II latanoprost trials (about 800 subjects) and incidence was less than 1% in Phase III studies (about 2400 patients over 6 months).[250] A study of 605 patients (excluding subjects with ocular trauma or incisional eye surgery) reported no CME with travoprost use.[122] In 163 eyes of 84 consecutive patients with uveitis and raised IOP, there was no increase in the frequency of visually significant CMO ($P = 0.19$) or anterior uveitis ($P = 0.87$) with PGA treatment compared with no PGA treatment.[259]

Although CME risk appears extremely low to non-existent in low-risk eyes (no intraocular surgery or uveitis)[260] and that even high risk eyes have relatively low incidence, caution should still be exercised during use in high risk eyes.[250] CME is reversible with discontinuation, and preventable with a NSAID without loss of effectivity.[249]

Anterior uveitis

Anterior uveitis is a rare potential side effect of PGA. PGF2α may stimulate the release of PGE2, and hence activate phospholipase II, enhancing the production of inflammatory eicosanoids.[261] In support of an association between PGA and anterior uveitis, the inflammation appears to occur in the ipsilateral treated eye,[261] improve after cessation and recur after rechallenge.[256] Excessive doses may induce iritis.[262] Affected subjects may have history of prior inflammation and/or incisional surgery.[261] A case report[256] documents an anterior uveitis rate as high as 4.9%, although no increase was found in PGA-treated subjects with anterior uveitis compared with those not on PGA treatment.[259] No increase in uveitic relapse rates were found when latanoprost was compared with FCDT ($P = 0.21$).[263] Fluorophotometry and laser-flare cell meters have failed to detect an effect of latanoprost on aqueous flare intensity.[170]

Herpes simplex keratitis

Herpes simplex keratitis (HSK) associated with latanoprost use has been reported to recur with latanoprost rechallenge, be unresponsive to anti-viral therapy until latanoprost was stopped,[264] and cause recurrent disease when inactive for 10 years.[265] HSV type 1 infected white rabbit eyes[266] had an increased severity of active HSK within 5 days of initiating topical latanoprost, and a significant increase in the clinical recurrence of HSK, although increased doses were given, and lack of viral cultures could not exclude development of pseudo-dendrites with epithelial toxicity. Data extracted from the claims records of 93,869 glaucoma patients between 1996 and 2002, showed 411 patients with ocular herpes simplex virus, which is a similar rate to that found in the general population and did not correlate with any particular anti-glaucoma therapy.[267] The risk of activating an ocular herpes simplex infection through the initiation of PGA is thus quite low, but based on anecdotal[264] and laboratory reports, it is important to enquire about history of HSK before initiating therapy.

Iris cyst

Reversible iris cyst formation is a rare reported complication of latanoprost use.[268–271] Proposed mechanisms of iris cyst formation may be related to flow pressures on the ciliary muscle and intraepithelial space of the posterior iris created by increased uveoscleral drainage[269,272] in predisposed subjects, or influence on secretory functions of cyst epithelium. Rapid reversal and lack of recurrences makes any proliferative event unlikely.

Systemic adverse events

PGA related systemic adverse events occurring via nasopharyngeal mucosal absorption[273] are infrequently seen due to a relatively rapid elimination half-life. Thromboxane A2, PGF2 and PGE2 elicit contractile responses in isolated human bronchial smooth muscle with bronchial hyperresponsiveness and constriction, and changes in microvascular leakage airway smooth muscle.[273] PGAs are however, relatively selective PGF2α receptor agonists with minimal effects on the thromboxane receptor.[274] A randomized cross-over study exposing subjects with stable asthma to 6 days of latanoprost followed by a 2-week washout, found no significant effects on peak expiratory flow, asthma symptoms or requirement for asthma medications.[273] Latanoprost for 3 months did not affect peak expiratory flow, forced expiratory volume in 1 second (FEV_1), and FEV_1/forced ventilatory capacity in 33 patients with newly diagnosed glaucoma.[157] In a 6-month

clinical study, adverse respiratory events were similar for latanoprost (2%) and brimonidine (2%).[83] However, a Swedish study found discontinuation of latanoprost therapy ameliorated deterioration of asthma in three patients with pre-existing asthma,[275] and severe apnea occurred 30 minutes after administration of latanoprost in one patient, which disappeared within 1 hour.

Upper respiratory tract infection interestingly was the most common systemic adverse event from latanoprost observed in clinical trials and occurred at a rate of approximately 4%.[276] Other systemic events included chest pain, muscle/joint/back pain, and rash/allergic skin reaction.[276] Angina,[277] latanoprost-induced arterial hypertension and tachycardia,[278] facial and peripheral edema, and new-onset migraine 64[279] have been anecdotally reported. Concurrent use of vitamin E in 2 subjects with arterial hypertension[278] may have altered arachidonic acid metabolism, and hence prostaglandin quantities.[278] Intravenous infusion of latanoprost in cynomolgus monkeys at 10 times the clinical dose had no cardiovascular or pulmonary effects.[32]

Dosage and administration

PGAs are indicated for the reduction of IOP in OH and OAG. All PGAs are supplied as a sterile, isotonic, buffered aqueous solution with their respective active ingredient (latanoprost 0.005% [50 μg/mL], travoprost 0.004% [40 μg/mL], and bimatoprost 0.03% [0.3 mg/mL]) and benzalkonium chloride as the preservative. Travoprost has the lowest pH at 6.0, followed by latanoprost (6.7) and bimatoprost (6.8 to 7.8). A single drop of PGA once daily in the evening is the recommended dosage.[276] Increased PGA dosage frequency[24,129,143,280,281] or combined PGA therapy[282] can result in diminished action, possibly due to desensitization at the level of the FP receptor.[24]

Efficacy of eye drops is dependent on proper storage and preservation. Unopened bottles of latanoprost should be refrigerated between 2°C and 8°C, whereas opened bottles can be stored at room temperatures for up to 6 weeks. Bimatoprost can be stored at temperatures between 15°C and 25°C, and travoprost between 2°C and 25°C for up to 6 weeks.[281] If used in combination with other topical ocular hypotensive agents, the medications should be administered at least 5 minutes apart to avoid wash-out and precipitation with drops containing thimerosal.[276] Contact lenses should be removed prior to instillation for 15 minutes.[283] Polypropylene bottles are needed to dispense travoprost as polyethylene used for latanoprost and bimatoprost allow adherence of travoprost to the sides of the container, thus decreased concentrations.[17]

Contraindications include known hypersensitivity to the active or other ingredients, or benzalkonium chloride. Cautious use in patients with intraocular inflammation (eg, iritis or uveitis), renal or hepatic disease (as not investigated), pediatric patients, pregnancy (no adequate studies), and nursing mothers should be exercised.

Tolerance, medication persistency and patient-focused perspectives

The long-term side effect profile of latanoprost has been studied most, but the other currently available PGAs appear to have a similar spectrum of side effects, supporting also the notion of similar mechanisms of action.[12] A large 5-year, open-label, multicenter study of latanoprost safety[284] (n = 5854), found macular edema, iritis/uveitis, or corneal erosion rates of ≤2.72% and a serious adverse drug reaction (CME (n = 4), uveitis (n = 3), chest pain, eye irritation, headache, dermatitis due to eye drop allergy, conjunctivitis, dyspnea and macular degeneration (n = 1 each)) rate of 0.44% with latanoprost use, similar to the usual care group. Overall discontinuation rates with latanoprost (2.46%) were similar to usual care (2.24%), and most frequently attributed to macular edema and iritis/uveitis, although unmasked groups could have led to a biased association.[284] Discontinuation from respiratory disease was more frequent in the usual care group (60 vs 16 patients).[284] Another open-label, 5-year study[215] of adjunctive latanoprost therapy also found marked iris pigmentary change in 19.0% and moderate in 36.3% of eyes. Most other ocular adverse events (including visual field defects, cataracts, ocular hyperemia) were mild to moderate in intensity, and occurred independent of presence of increased iris pigmentation.[215]

Compared with other topical ocular hypotensive medications, higher discontinuation rates were found for bimatoprost (5.3%) than for timolol (1.7%)123 and dorzolamide/timolol combination than for latanoprost,[186] although similar for bimatoprost (3.3%) and FCDT (3.4%).[132] Compared with latanoprost, ocular adverse effects were similar to dorzolamide.[158] Ocular discomfort[188] and stinging[133] was greater with FCDT. Ocular hyperemia was found to be similar for brimonidine and latanoprost use in one review[158] but converse in a meta-analysis.[89] Serious ocular adverse events were similar between brimonidine and latanoprost; ocular inflammation (0.7% vs 1.3%) and CME (0.3% vs 1.3%).[89]

Rates of non-compliance with glaucoma treatment instructions are as high as 50%.[285] Persistency or maintenance of therapy, involves patient satisfaction with medication tolerability, physician satisfaction with IOP control, medication

costs, ease of administration and patient understanding of long term medication use especially where an immediate effect is not noticed.[212,286] The need for multiple medications with increasingly complex dosing regimens are real obstacles to good IOP control,[285,287] and clearly once daily dosing of PGA is preferred.[190]

The Glaucoma Adherence and Persistence Study (GAPS) analyzed persistency of PGA monotherapy among 6271 subjects followed for >12 months though retrospective review of pharmacy claims.[211] Eleven percent of index latanoprost (n = 4071) patients continuously refilled their medication throughout the course of the year, as compared to 9% of bimatoprost (n = 1199) patients and 5% of travoprost (n = 1001) subjects. Reasons for medication switch were lack of efficacy (43%) and adverse events (19%), especially hyperemia which accounted for 2/3 of adverse effect-related switches and 27% of discontinuations. Among subjects with hyperemia, 10% reported skipping doses due to red eyes, 30% claimed it was a problem when seeing other people, and 7% avoided social situations when their eyes were red.

A retrospective cohort study in 2003 of 28,741 claims records of patients on any topical ocular hypotensives found timolol prescribed most frequently (43%), followed by latanoprost (33%), and brimonidine (18%). Travoprost or bimatoprost were infrequently prescribed (1% each). Compared with latanoprost-treated patients, subjects treated with timolol, dorzolamide, travoprost, and bimatoprost were 37%, 41%, 58% and 72% respectively more likely to discontinue treatment, based on a single discontinuation event.[286] At 12 months, 23% of latanoprost-treated patients and 13% of patients treated with other ocular hypotensives had neither discontinued nor changed therapy.[286] No association between co-payments and persistency was found.[286]

It is estimated that after 5 years of treatment, nearly 40% of glaucoma patients require 2 or more different medications.[4] Availability of PGA combination therapy offers the advantage of 2 classes of medication in a simplified regimen of 1 drop per day. In a survey of ophthalmologists in the European Union, 98% of doctors believed fixed combination therapy improved patient care by better compliance and quality of life (QoL).[288] Other advantages include reduced washout if two or more drops are required, and reduced exposure to corneal toxic preservatives. Chronic BAC exposure induced sub-clinical inflammation may be associated with glaucoma filtration surgery failure.[289] Recently introduced, tafluprost is a fully preservative-free difluoroprostaglandin derivative of PGF2α. There are no published IOP-lowering efficacy rates of tafluprost compared with other topical ocular hypotensive agents as yet, but no difference between preserved and non-preserved formulations were found at 4 weeks ($P = 0.96$)[290] and ocular hyperemia rates were similar.[291] TravatanZ® (Alcon Laboratories Inc, Forth Worth, TX) has the *Sof*Zia™ preservative system.[292] TravatanZ retained equivalent efficacy as travoprost,[293] and a lower non-significant rate of ocular hyperemia was found for BAC-free travoprost (6.4%) than travoprost (9.0%).[293]

Existing estimates of the indirect costs of glaucoma are likely to underestimate the impact of visual field loss on functioning and QoL.[294] Self-reported difficulty in using eye drops was strongly associated with decreased QoL, using the 25-item National Eye Institute Visual Function Questionnaire (VFQ-25) and short-form Health Survey (SF-12).[295] Using a non-validated questionnaire, patients showed preference for latanoprost for many systemic and ocular QoL measures compared with their previous therapy,[296] also supported by studies where patients switched to latanoprost from monotherapy.[297–299] A review has identified 4 major types of barriers to effective patient adherence: medication regimen, patient factors, provider factors, and situational or environmental factors.[300] Interestingly, in this review, non-adherence (defined by failure to fill a prescription over the initial 12 months) was 2 times higher in subjects initially started on a single agent compared with multiple agents,[300] contrary to other reports.[190,285,287]

Place of PGA in the management of OH and OAG

Lowering IOP is unequivocally associated with reduced rates of glaucoma and glaucoma progression as documented in several large multicenter trials including the OHTS,[4] the Early Manifest Glaucoma Trial,[2,301] the Collaborative Normal-Tension Glaucoma Study Group,[3,302] and the Advanced Glaucoma Intervention Study.[303] Reduction in IOP is readily modifiable with topical ocular hypotensive agents, and these remain first-line treatment for OH and OAG.[304,305] If the IOP is not sufficiently lowered to the estimated predefined target IOP level or if there is glaucomatous progression, then additional agents are introduced guided also by the patients concurrent health issues and medications, ability to comply, and potential impact on QoL. Surgery (laser, filtering, or cyclodestructive surgery) may be warranted if topical ocular hypotensives are ineffective.

Although timolol was prescribed most frequently, followed by latanoprost and brimonidine in a US study[286] this choice may be governed by cost considerations, government or other institutional restrictions and familiarity by the

treating ophthalmologist.[306] PGA have at least equivalent if not superior efficacy over timolol and other ocular hypotensive agents, and advantages of once daily application and low risk of well-recognized life-threatening complications of β-blocker therapy such as bronchospasm, cardiac arrythmias, and exacerbation of congestive heart failure. Conjunctival hyperemia, the most common side effect of PGAs tend to be mild and reversible, but commonly encountered (up to 69% in one study with bimatoprost).[85] Cosmetic side effects such as eyelash growth, peri-ocular skin discoloration and iris pigmentation also occur but to a lesser extent.

The OHTS study documented that 39.7% of glaucoma patients require 2 or more different medications after 5 years of treatment.[4] Simplifying dose regimen with fixed combinations of 2 ocular hypotensive medications are preferred over concomitant administration.[305] Fixed combination PGA with timolol also show superiority to monotherapy of its constituent parts and equivalence to concomitant therapy to its constituent parts. Additional benefits include enhancement of adherence, reduction of medication wash-out effect, and minimization of preservative-toxicity on the ocular surface, although they should not be prescribed for patients with sensitivity to β-blocker therapy.

In summary, PGAs are powerful topical ocular hypotensive agents available in our current OH and glaucoma treatment armamentarium. The three main commercially available agents, latanoprost 0.005%, bimatoprost 0.03%, and travoprost 0.004% may differ in pharmacology, tolerability and efficacy, but only a few meaningful differences consistently demonstrated in studies using rigorous statistical and scientific criteria exist.[7] All three PGAs work primarily by the same prostanoid FP receptor although controversial. All three have fairly similar and superior effectiveness for IOP reduction than other topical hypotensive agents available. Additionally, 24-hour IOP control is better with PGAs than β-blockers. PGA have near absence of systemic side effects, although do have other commonly encountered side-effects including ocular hyperemia, iris pigmentation, eyelash growth, and peri-ocular pigmentary changes. Once daily administration and near absence of systemic side effects enhances tolerance and compliance. OH and OAG patients require lifelong treatment and follow-up care to halt progression of optic neuropathy, thus preserve remaining visual function and QoL.[307]

Disclosure

The authors declare no conflicts of interest.

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