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Four years later: A clinical update on latanoprost

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PURPOSE. *Almost five years have elapsed since the introduction of latanoprost on several markets and considering the large number of publications dealing with it, the authors felt that it was worth re-evaluating the drug.*
METHODS. *The criterion used to select trials for inclusion in the review was: all articles mentioning the drug in common electronic data-bases; these were then screened and considered, on the basis of methodological quality.*
RESULTS. *Experimental data suggest that latanoprost acts by remodeling the extracellular matrix in the ciliary muscle, thus increasing the flow of aqueous humor through the ciliary muscle bundles of the uveoscleral pathway.*
POAG: Latanoprost persistently improves the pulsatile ocular blood flow in primary open angle glaucoma (POAG). Recent trials confirmed the greater IOP-lowering efficacy of latanoprost vs. timolol, dorzolamide, brimonidine and unoprostone. Trials lasting up to 24 months showed that latanoprost is effective in long-term treatment of POAG and ocular hypertension (OH), with no signs of loss of efficacy when compared to timolol or dorzolamide. Latanoprost provides better control of circadian IOP. Non-responders to b-blockers should preferably be switched to latanoprost monotherapy before a combination therapy is started. The possibility of a fixed combination of latanoprost and timolol has been explored, with promising results.
NTG: Latanoprost is effective in normal tension glaucoma (NTG), lowering IOP, improving pulsatile ocular blood flow and increasing ocular perfusion pressure.
Other Glaucomas. Latanoprost may provide effective IOP control in angle-closure glaucoma after iridectomy, in pigmentary glaucoma, glaucoma after cataract extraction and steroid-induced glaucoma. However, latanoprost was effective in only a minority of pediatric cases of glaucoma and is contraindicated in all forms of uveitic glaucoma.
Safety. In the articles reviewed, new or duration-related adverse events were reported. (Eur J Ophthalmol 2003; 13: 162-75)

KEY WORDS. *Latanoprost, PGF, Glaucoma, NTG, POAG, Review, Safety, Efficacy, Xalatan*

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INTRODUCTION

Major causes of visual impairment associated with poor vision or blindness in elderly people include cataracts, glaucoma, macular degeneration, and diabetic retinopathy. Glaucoma is a family of diseases not defined by a specific intra-ocular pressure (IOP), but rather as an optic neuropathy that can occur with any IOP, depending on the susceptibility of the optic nerve. Glaucoma is the second leading cause of vision loss in the world and better methods of detection and therapy are urgently needed (1). Glaucoma

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is responsible for approximately 5.2 million blind people (15% of the total burden of world blindness) (2) and the incidence rises significantly with age. With only half of the patients being diagnosed, glaucoma is a major eye health problem whose importance will increase as the population ages (3).

Extraordinary progress has been made in the last five years in improving the understanding of the molecular causes of various glaucomas. The hope of primary prevention for the various glaucomas, once a distant dream, may become reality within our lifetime (4).

The recent recognition of normal-tension glaucoma (NTG) as a major form of open-angle glaucoma may lead to a new definition of open-angle glaucoma and raise the prevalence of open-angle glaucoma due to the increasing number of patients diagnosed with NTG. Routine follow-up examinations of patients with glaucoma must include measurements of IOP, visual field examination, gonioscopy and evaluation of the optic discs. Especially for patients with NTG, careful interpretation of glaucomatous disc findings is critical, as misreading or misdiagnosis may significantly alter the prognosis for such patients. Pachymetry is also important as patients with NTG and thin corneas have in fact higher tension than is measured.

Aim of the review

In 1998 several prostaglandins (PGs), their prodrugs, and analogues were shown to reduce IOP. Generally, PGF2α derivatives have unacceptable side effects, including conjunctival hyperemia and ocular irritation. However, the 17-phenyl substituted PGF2α analogue latanoprost, reduced IOP by 30-40% for at least 24 hours, and was very well tolerated (5). This was the first in a new class of drugs for the treatment of open angle glaucoma. Several successors such as unoprostone, bimatoprost and travoprost are now available too. Its primary mode of action is by increasing uveoscleral aqueous outflow. Only longterm experience will exclude major, clinically relevant side effects and its influence on ocular circulation also needs further evaluation. Almost five years have passed since it was introduced on to the Swiss and other markets and we felt it was worthwhile re-examining the drug, particularly in view of the large number of publications dealing with it. Particular emphasis is laid here on aspects of clinical relevance.

METHODS

The criterion used to select trials for inclusion in the review was simply, all articles mentioning the drug; these were subsequently classified by date of publication, topic or indication, screened and weighted, on the basis of methodological quality (methods, participants, interventions, outcome measures and results).

Search strategy: The data sources used to identify trials were bibliographic databases (TOXLINE, PaperChase browsing the databases of the National Library of Medicine and the National Cancer Institute i.e. MEDLINE, HealthSTAR, AIDSLINE and CANCERLIT, Embase), reference lists from review articles and books, major international congresses and personal contacts with other experts in the area.

Material examined: The electronic databases identified latanoprost in 152 papers as a descriptor and PhXA34 was found five times as a descriptor. Two additional clinical studies were identified through other channels and scrutinised. In line with the concept of an update, the studies considered were all published in 1998 or later.

Statistics

Significance was accepted as such when $p < 0.05$, and for non-significance a threshold of $p > 0.1$ was considered; values between $p > 0.05$ and $p < 0.1$ are reported as trends.

RESULTS

Pharmacokinetics

Latanoprost is a prodrug which is rapidly hydrolysed to the corresponding free acid *in vivo*. The cornea seems to act as a slow-release depot to the anterior segment of the eye. One hour after administration, the maximal concentrations in the iris, anterior chamber and ciliary body are respectively 217.0 ± 12.9 pg eq/mg, 99.8 ± 7.4 pg eq/mg and 54.0 ± 4.9 pg eq/mg. The elimination half-life of total radioactivity from these tissues is 3-4 hours, although trace amounts (0.4-9 pg eq/mg) can still be detected 24 h after administration (6). The tissue distribution after i.v. and topi-

cal administration is similar, with metabolism (liver) and elimination (kidney) organs containing the highest concentrations.

After topical application much of the dose was found in the anterior ocular tissues but not in the posterior parts of the eye. The acid of latanoprost has a short half-life in plasma and is extensively metabolised mainly through ß-oxidation before it is excreted into the urine and faeces (the main metabolite in urine and faeces was identified as the 1,2-dinor acid of latanoprost. In a similar way a more polar fraction from urine was identified as the 1,2,3,4-tetranor metabolite of the acid of latanoprost) (7). No induction or inhibition of the metabolism occurred upon repeated administration and no indications of accumulation of the drug or its metabolites have been reported. The pharmacokinetics of latanoprost were similar whether the topical dose was single or repeated (8).

Mechanism of action

The prostaglandin analogue latanoprost is an effective topical medication for reducing IOP (9). Prostaglandin analogues act primarily by increasing uveoscleral outflow and therefore have a substantial additive effect when used with agents that

- reduce aqueous production (e.g., β-blockers or carbonic anhydrase inhibitors) or
- increase trabecular outflow facility (e.g., pilocarpine).

The cellular mechanism by which PGFs lower IOP is not known. Immunohistochemical data have shown that the IOP reduction with topical PGF2α is associated with a reduction of collagens within the uveoscleral outflow pathway (10). Cell cultures of human ciliary muscle were treated with latanoprost for 1-2 days then immunostained against various extracellular matrix components and metalloproteinases. In response to latanoprost, collagens I, III, and IV, fibronectin, laminin and hyaluronan were reduced, while metalloproteinases 2 and 3 were increased. These results suggest a role for latanoprost in the remodeling of extracellular matrix in the ciliary muscle which might then increase the flow of aqueous humour through the ciliary muscle bundles (11). The ciliary body thickness 2 mm from the scleral spur is positively correlated with an increased pressure-lowering effect of latanoprost (Pearson r=0.5, p<0.05) (12).

Therapeutic studies

Primary open-angle glaucoma (POAG)

Long-term studies

Latanoprost is effective in the long-term treatment of POAG and OH, with no signs of loss of efficacy or 'drifting' as has been shown in several trials with a duration ranging from 8 months (13); to 12 (14, 15) and 24 months (16, 17) totalling more than 1000 patients, IOP reduction is, more marked with higher baseline IOP, but is independent of trial duration (Tab. I). One shortcoming of these publications is that they report data of patients "on treatment" only, while an "intent to treat" analysis would have provided a better overall picture.

In a retrospective analysis (18), a significant difference between groups was observed in the success rate of therapy with latanoprost (70%), brimonidine (58%) and dorzolamide (40%) (P = 0.008) when added to a β-blocker. No significant differences between groups were observed for rate or type of adverse events leading to suspension of therapy.

In a noncomparative case series (19) of patients with chronic glaucoma with IOP uncontrolled by maximum-tolerated medications, patients were treated with latanoprost additive therapy on a compassionate basis. The criterion for success was avoiding glaucoma surgery with an IOP decrease of 20% or greater and final IOP less than 22 mmHg. The cumulative success rate of the latanoprost additive therapy was 70% at 1 month, 42% at 3 months, 40% at 6 months, and 30% at 12 months.

This suggests it is worth trying latanoprost additive therapy before glaucoma surgery in such patients (irrespective of pilocarpine therapy and the pilocarpine dosage). Latanoprost is particularly promising if the IOP is less than 25 mmHg and/or when previous incisional glaucoma operations are less than three. Two further twelve-months studies are described in the sections on pigmentary glaucoma and on angle-closure glaucoma.

Circadian IOP

In patients treated with topical β-blockers as monotherapy, the IOP at night was significantly high-

er than during the day (20). Thirty-four percent had an increase of more than 5 mmHg at night, and 15% had 10-18 mmHg. In these patients the median circadian IOP variation was 7 mmHg, and the diurnal IOP variation was 4 mmHg.

Latanoprost provides adequate reduction of IOP throughout the day and night (21) since its effect remains unchanged during the night-time.

Latanoprost provided better control of circadian IOP than timolol or dorzolamide in a one month crossover trial (22), in which patients with POAG (n = 10) or ocular hypertension OH (n = 10) were treated with timolol, latanoprost or dorzolamide. All the drugs significantly reduced IOP in comparison with baseline at all times, except for timolol at 3 AM. Latanoprost was more effective in lowering IOP than the other drugs, timolol appeared to be less effective during the night-time hours and dorzolamide, while less effective than latanoprost, still led to a significant reduction in nocturnal IOP. A recent double trial comparing latanoprost and timolol confirmed these findings (23).

Combining latanoprost and a β-blocker

Once-daily β-blocker therapy is an effective ocular hypotensive adjunctive treatment for OH 24 hours after dosing when added to latanoprost, and timolol hemihydrate 0.5% solution and timolol maleate gel 0.5% appear equally effective and safe (24). A fixed combination of latanoprost and timolol was explored in one trial (25) with 139 patients, randomized to once-daily treatment with combination or monotherapy. The combination of latanoprost 50 mg/mL with timolol 0.5% od emerged as the most promising formulation (Tab. II).

In a double-blind four-weeks trial on 136 patients, the mean IOP reduction with timolol+unoprostone was 2.9 ± 2.4 mmHg while with timolol+latanoprost it was 5.3 ± 2.6 mmHg and with timolol+placebo it was 1.6 ± 2.3 mmHg. The combination timolol+latanoprost provided a greater IOP reduction than timolol+unoprostone (p=<0.001), which in turn was more effective than timolol monotherapy. Burning and stinging were more com-

TABLE I - SUMMARY OF LONG-TERM TRIALS WITH LATANOPROST IN POAG OR OH

Author	No. Patients		Diagnoses	Duration	IOP-0 mmHg	IOP-End mmHg	Delta IOP	Delta IOP%
	Admitted	Completed		(Months)	Mean SD	Mean SD	Mean	Mean
Camras,1996	247	173	POAG/OH/ Exfol.S. /PDS*	12	25.3 ± 3.0	17.4 ± 2.7	7.9	31.2
Watson,1998	132	49	POAG/OH	24	25.2 ± 3.2	17.4 ± 1.9	7.8	31.0
Watson,1998[#)]	145	53	POAG/OH	18	25.4 ± 3.6	17.1 ± 2.3	8.3	32.7
Martin, 1999[§)]	153	153	POAG/OH	8	24.4 ± 5.8	19.9	6.9	28.3
Shin, 1999	61	61	Uncontrolled IOP	13.9	23.5 ± 6.3	19.4 ± 6.7	3.9	16.6
Alm, 2000	183	66	POAG/OH	24	25.1 ± 3.5	17.4 ± 2.9	7.7	30.7
Alm, 2000[#)]	72	41	POAG/OH	18	24.3 ± 2.3	17 ± 2.7	7.3	30.0
Suzuki, 2000	124	N.D.	POAG/OH	12	23.5 ± 2.2	18.1 ± 2.9	5.4	23.0
Pooled	1117	596		16.2	24.8 ± 3.8	17.9 ± 2.8	7.2	29.2

* PDS = Pigment Dispersion Syndrome
[#] First six months timolol
[§] In 82 pts. as add-on

mon with timolol+unoprostone (20%) than with timolol+latanoprost (4.3%) or timolol+placebo (2.2%) (26).

Latanoprost as add-on

Latanoprost had an additive effect when used as a third drug for patients on timolol and dorzolamide needing further IOP reduction (N = 52) (27). These and other (19) results suggest that latanoprost may be effective in some patients with poorly controlled glaucoma on multiple therapies. However, one small study (28) suggests that brimonidine 0.2% bid may be more reliable than latanoprost 50 µg/ml od for glaucoma and OH when used as third-line adjunctive therapy. Both drugs were well tolerated and reduced IOP in most patients; however, clinical success was achieved in 17 of 20 patients who received brimonidine, compared with 13 of 20 patients (65%) who received latanoprost (not significant).

Ocular blood flow

In one trial, 12 patients (24 eyes) with POAG, aged between 37 and 48 years, non-smokers, refractions ± 3D, were studied. Each patient had one eye treated with latanoprost 0.005% and the other with timolol 0.5%. Choroidal perfusion was measured by Langham's POBF system during the first day of therapy and then after 7, 15, 30, 60, 90 and 180 days. The maximum pressure decrease after the first latanoprost dose was at 12 h; after six months the mean IOP reduction was 32.6%. POBF values increased up to 55.8% in the first day and then settled at 22.6% until the end of the study. Timolol achieved a similar pressure progress, but its hematic perfusion values were distinctly lower (29). Similar results were recently reported in a doublemasked study on 20 patients comparing latanoprost and brimonidine: pulsatile ocular blood flow increased 40% with latanoprost, but was unchanged with brimonidine; mid-peripheral retinal microcirculation also increased 23% with latanoprost (30).

No difference between the two drugs was reported in another study on 15 patients with POAG or OH: topical timolol and latanoprost significantly reduced IOP in OH and glaucoma patients without any substantial hemodynamic changes in the retrobulbar vessels (31).

Comparative studies

Several recently published trials have confirmed the efficacy of latanoprost as an IOP-lowering agent both in comparison to timolol (32) and to more modern agents (Tab. III). Irish investigators compared the effects on IOP and tolerance of a monotherapy with either latanoprost or dorzolamide in 224 patients with glaucoma or OH (33), in a three-months open- labelled, randomized study. Latanoprost was superior to dorzolamide in reducing the IOP, judged both from the effect on IOP at peak and trough and by the effect on diurnal IOP. In a prospective open label study with 226 patients, monotherapy with latanoprost once-daily was at least as effective as twice daily dorzolamide+timolol in patients with IOP uncontrolled by timolol alone (34).

An international European study group coordinated by H. Uusitalo (35) compared latanoprost with brimonidine 0.2% twice daily in an open randomized trial. The target IOP ≤ 18 mmHg was achieved in 57% of the latanoprost group and in 33% of the brimonidine treated patients ($p<0.001$).

Systemic adverse events and ocular allergy were significantly more frequent in the brimonidine group

TABLE II - FIXED COMBINATIONS OF LATANOPROST WITH TIMOLOL, COMPARED WITH THE INDIVIDUAL DRUGS (25)

	Timolol		Latanoprost	Delta IOP	C1 *vs.* C2	C2 *vs.* M2 & M1
C1	0.5%	+	10 µg/ml	3.7 mmHg	p < 0.001	
C2	0.5%	+	50 µg/ml	6.1 mmHg		
M1	0.5%			2.1 mmHg		p < 0.05 -
M2			50 µg/ml	4.9 mmHg		p < 0.001

($p \leq 0.005$). Similar results were obtained in an American retrospective study (36), which reported 70% responders (i.e. IOP-reduction ≥ 3 mmHg) with latanoprost and 40% with brimonidine 0.2% bid after six months; there were significantly more dropouts due to adverse events in the brimonidine group (dizziness, fatigue, foreign body sensation, etc.).

However, these results might be somewhat biased since there were significantly more African American patients in the latanoprost group and more patients with adult-onset diabetes in the brimonidine group.

Employing the "dummy" technique in a double blind study latanoprost od was compared with unoprostone 0.12% bid (37). Latanoprost was superior in reducing the IOP, judged both from the effect on mean IOP and on the number of patients with an IOP reduction > 30% of baseline, a threshold which was achieved in 42% of the latanoprost group but only 6% of the unoprostone patients ($p<0.001$). Unoprostone appears to have an adverse effect profile similar to latanoprost (38), but it may cause more corneal epithelial problems (39). One 8-weeks trial on 32 patients showed an additive effect of latanoprost and unoprostone (40) which others considered of limited relevance (41).

In a 12 months, multicenter, double-masked, prospective study, 801 patients received travoprost 0.0015%, travoprost 0.004%, latanoprost (od in the evening) or timolol (bid) The IOP-lowering efficacy of travoprost was enhanced during the day from 8 AM to 4 PM and was significantly greater than latanoprost at 4 PM. This difference suggests that travoprost 0.004% is significantly more effective than latanoprost and timolol in reducing IOP in black patients. Ocular hyperemia was more frequent in the travoprost groups (38% for travoprost 0.0015%, 49.5% for travoprost 0.004%) than with latanoprost (27.6%) or timolol (14%) (42). However, the IOP-reducing effects of bimatoprost and latanoprost are reportedly similar, as were their profiles of side effects (43).

Beta-blocker non-responders: add or switch to latanoprost?

Confronted with β-blocker non-responders, the treating physician has to choose between changing therapies or adding an agent. Bucci et al conducted a six-month study on 128 timolol non-responders. Diurnal IOP was significantly reduced from baseline in all groups. Adding latanoprost to the timolol treatment reduced diurnal IOP by 6.1 ± 0.3 mmHg, adding pilocarpine to timolol reduced diurnal IOP by 4.2 ± 0.3 mmHg and switching from timolol to latanoprost monotherapy reduced diurnal IOP by 5.5 ± 0.3 mmHg (44). Similar findings were reported by Nordmann et al (45) on 237 patients treated with topical ß-adrenergic antagonists, alone or in combination, with glaucoma or OH and IOP > 22 mmHg. After a run-in period, patients were randomized to either latanoprost 50 µg/ml od or to a fixed combination of timolol-pi-

TABLE III - RECENT COMPARATIVE STUDIES IN POAG / OH WITH MODERN IOP-LOWERING AGENTS

Author	Drug	No. Patients	Duration (months)	IOP-0 mmHg	Delta IOP mmHg
Hedman, 2000 *	Timolol	414	6	25.0	6.5
	Latanoprost	415	6	24.8	7.7
O'Donoghue, 2000	Dorzolamide	112	3	27.2	5.6
	Latanoprost	112	3	27.2	8.5
DuBosar, 2000	Brimonidine	187	6	25.0	5.2
	Latanoprost	188	6	25.0	7.1
Stewart, 2000	Brimonidine	65	6	23.7	1.8
	Latanoprost	92	6	21.6	4.5
Susanna, 2001	Unoprostone	54	2	24.1	3.3
	Latanoprost	54	2	24.1	6.7
Pooled	References	832	4.6	25.1	5.5
	Latanoprost	861	4.6	24.8	7.3

* Pooled analysis of three trials

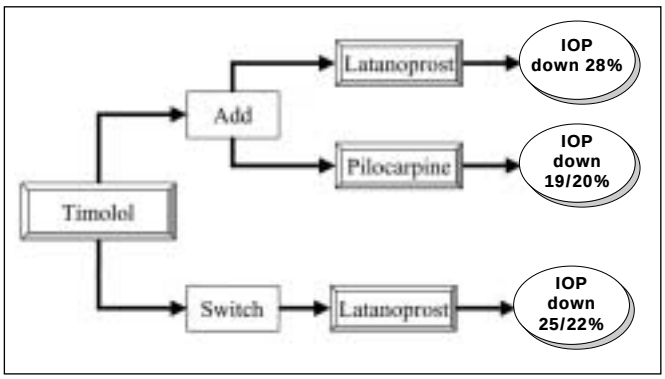

Fig. 1 - *Timolol non-responders, IOP reduction after adding latanoprost or pilocarpine or switching to latanoprost monotherapy (Data from Bucci et al (44) and Normann et al (45)).*

locarpine bid. Mean diurnal IOP was significantly lower than baseline in both groups (p<0.001).

Switching to latanoprost reduced mean diurnal IOP by 5.4 ± 0.3 mmHg while adding pilocarpine to timolol reduced it by 4.9 ± 0.4 mmHg. However, blurred vision, decreased visual acuity, decreased twilight vision, and headache were significantly more frequent in the timolol-pilocarpine group. These findings confirm earlier data showing the equivalence of adding dorzolamide to timolol therapy (-4.5 mmHg) or switching to latanoprost (-4.6 mmHg) (46). A large open trial in Germany confirms the viability of switching in a large sample of patients (47). These results suggest that a switch to latanoprost monotherapy should be attempted before starting combination therapy.

When combining latanoprost and pilocarpine, the order and timing of administration of the drugs can significantly influence their ocular hypotensive activity. Pilocarpine has been reported to be most effective when administered four times daily, and the bedtime dose should be administered 1 hour after latanoprost (48).

Normal tension glaucoma (NTG)

Latanoprost has been shown to be effective in NTG. While both latanoprost regimens significantly reduced IOP in patients with NTG (n = 30), 50 µg/ml od was more effective (IOP reduction 3.6 ± 1.9 mmHg, -21.3%, p < 0.001) than 15 µg /ml bid (IOP reduction 2.4 ± 1.5 mmHg, 14.2%, p < 0.001; placebo, IOP reduction 0.4 ± 1.8 mmHg, 2.4%, not significant) (49).

In a review of NTG studies, the ocular perfusion pressure was reported to improve more on once daily 50 µg/ml latanoprost than on other regimens tested (Fig. 2) or twice-daily 0.5% timolol. Thus, once-daily 50 µg/ml latanoprost appears to be an effective and convenient hypotensive agent for NTG. The IOP-lowering effect of latanoprost in NTG was confirmed in a recent open-label trial (50). However, long-term studies will be needed to establish the efficacy of this drug in delaying or preventing of the progression of visual field loss in NTG (51).

Ocular blood flow in NTG

Latanoprost improves pulsatile ocular blood flow (POBF) and ocular perfusion pressure (52, 53). The IOP reduction correlated with the IOP before treatment (p < 0.01) and was accompanied by an increase in median POBF from 656 to 796 µl/min (p < 0.001). Ocular perfusion pressure is important in glaucomatous patients. Latanoprost appears to have a better affect than timolol in patients with NTG, possibly because of its lack of systemic effects. Once-daily treatment with 50 µg/ml latanoprost provides a significant and stable IOP reduction in the majority of NTG patients after short-term treatment. This is accompanied by a significant increase in POBF.

In a small cross-over trial with NTG patients, latanoprost and dorzolamide both significantly lowered IOP without altering blood pressure; however, only latanoprost significantly raised the calculated ocular perfusion pressure (from 47.2 to 49.6 mmHg; p<0.01), while dorzolamide reduced the retinal dye transit time (from the superior temporal artery to the corresponding vein) (54).

Chronic angle closure glaucoma (CACG)

A preliminary double-blind study compared the IOP-reducing effect and side effects of 50 µg/ml latanoprost od and 0.5% timolol bid in 30 Asian patients with primary CACG, defined as glaucomatous optic neuropathy with a compatible visual field defect and at least six clock hours of synechial angle closure on gonioscopy. All patients had previous peripheral iridotomy with IOP > 21 mmHg after laser treatment and were thereafter controlled (IOP < 22 mmHg) with one

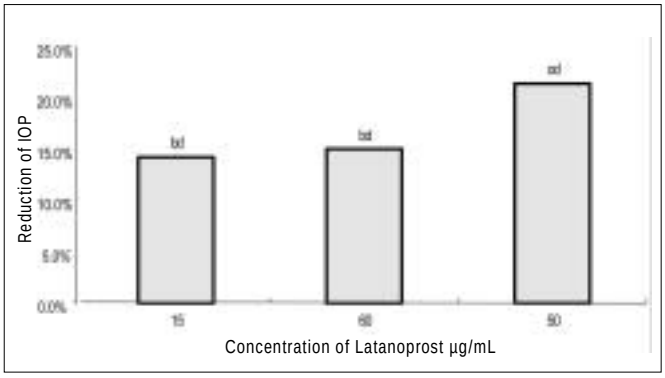

Fig. 2 - *Reduction of IOP in NTG after various concentrations and dosing schedules of latanoprost (According to Greve et al (51)).*

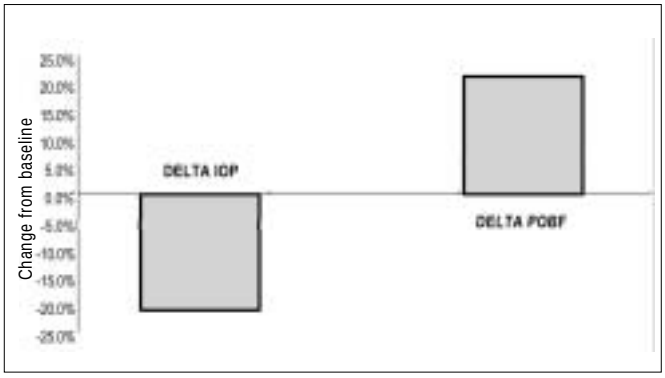

Fig. 3 - *Changes in IOP and pulsatile ocular blood flow in patients with NTG treated with latanoprost (According to McKibbin, (54)).*

or two pressure-reducing drugs. After 2 weeks of treatment, IOP was significantly reduced, by 8.8 ± 1.1 mmHg, in the latanoprost group, and by 5.7 ± 0.9 mmHg in the timolol group. The difference was 3.1 ± 1.5 mmHg in favour of latanoprost (p = 0.04) (55).

Residual primary angle-closure glaucoma (PACG) after iridectomy or iridotomy is an important issue among Asians, especially Chinese. Hung et al (56) tested the effectiveness of latanoprost as an IOP lowering agent in cases of residual PACG. Twenty-six eyes of 26 PACG patients with persistently elevated IOP after iridectomy, despite treatment with conventional IOP lowering drugs (ß-blockers and pilocarpine) were included. Latanoprost 50 µg/ml, one drop daily, was added adjunctively to all eyes. Measurements of IOP at baseline and after the start of treatment with latanoprost indicated a significant reduction. The IOP decreased by about 21% (p < 0.005) during the first three months, and by about 36% at the end of a year. At the one-year follow-up, IOP was well controlled (below 20 mmHg) in all eyes. These findings show that latanoprost, in combination with B-blockade and pilocarpine, can improve residual PACG after iridectomy and could potentially forestall the need for further therapeutic intervention.

Pigmentary glaucoma

This indication has been specifically examined in only one, relatively small trial (57). In this twelve-months study, both latanoprost [N = 18] and timolol [N = 18] caused a significant (p < 0.001) reduction of IOP at each hour of diurnal curve throughout therapy. The reduction of IOP was 6.0 ± 4.5 and 5.9 ± 4.6 with latanoprost and 4.8 ± 3.0 and 4.6 ± 3.1 with timolol after 6 and 12 months, respectively (difference p < 0.001 at 3, 6, and 12 months). Mean outflow facility was significantly enhanced (+30%) compared with the baseline only in the latanoprost-treated group.

Secondary glaucomas

Phacoemulsification: The data is still limited and the results remain controversial. Latanoprost may enhance uveoscleral outflow immediately after cataract extraction. In a reference study (58) on 103 eyes (latanoprost 53; control 50), latanoprost gave significantly lower post-operative IOP (16.4 ± 3.7 mmHg) than preoperative IOP (17.9 ± 3.0 mmHg) (p < 0.025). There was no decrease in post-operative IOP in the control group compared with pre-operative IOP (18.3 ± 2.6 mmHg). However, in another trial (59), a single dose of latanoprost after phacoemulsification and PC IOL implantation had no real IOP-lowering effect compared with a control group in the first 24 hours post-operatively. A single dose of timolol gel (0.5% Timoptol-XE®) produced a significant post-operative IOP decrease as early as 2 hours and up to 24 hours after surgery. Timolol gel and latanoprost were safe, but timolol was more effective than latanoprost in preventing post-operative OH.

In another study, six hours post-operatively, both dorzolamide and latanoprost were effective in reducing the IOP increase; however, at 20-24 hours, only dorzolamide was significantly active. Neither drug prevented IOP spikes of 30 mmHg or higher (1:34 each drug vs. 4:34 controls) (60).

Steroid-induced glaucoma: In a study with eight patients, monotherapy with latanoprost was safe and effective: initial IOP was 25.3 ± 9.1 mmHg, and with latanoprost it fell to became 18.3 ± 2.8 mmHg (61).

Uveitic glaucoma or any inflammatory states may be a contraindication for the use of latanoprost (62).

Topical prostaglandin analogues may be relatively contraindicated in patients with a history of uveitis (63).

Pediatrics

The hereditary factor is probably predominant in pediatric glaucoma. In a group of pediatric patients (64) (N = 48, evaluable 31) with a variety of glaucoma diagnoses and on various therapies, latanoprost was effective in only a minority of cases (6/31). In some patients, however, latanoprost showed "an impressive" ocular hypotensive effect, comparable with that in adults with open-angle glaucoma. (Responders were more likely to have juvenile open-angle glaucoma and tended to be older than non-responders). Mutations in the MYOC/TIGR gene are associated with juvenile open-angle glaucoma and in some cases may be involved in the formation of sporadic primary open-angle glaucoma in adults (65). The drug was well tolerated in this short-term study of pediatric patients with glaucoma.

Patients with Sturge-Weber syndrome and glaucoma (six months, open trial) responded poorly to adjunctive latanoprost (Responders: 3/18) and often required additional medical or surgical intervention (66).

Safety

In the long-term trials mentioned above (17-23), no treatment duration-related adverse events were reported. Confirming earlier studies, the most frequent adverse ocular event was mild conjunctival hyperemia and the only clinically significant side effect was increased pigmentation of the iris, most frequently seen in irides with a mixture of brown and blue/grey or green colours. No systemic side effect was observed. One retrospective study (67) reported high proportions of patients presenting signs and symptoms of ocular inflammation while receiving latanoprost: 6.4% had anterior uveitis, and 2.1% had cystoid macular edema. However, large clinical trials have not confirmed these rates.

Hypertrichosis

Latanoprost treated eyes may develop hypertrichosis and increased pigmentation of eyelashes in the region of treatment. Hypertrichosis involves the eyelashes and regional intermediate hairs of the upper and lower eyelids as well as vellus hair of the lower eyelid skin. Changes in appearance of the hair include increased number, length, thickness, curvature, and pigmentation (68).

Darkening of iris

Latanoprost-induced iris darkening may not appreciably lessen for several years and may even be permanent after discontinuing treatment. Some eyes that show latanoprost-induced darkening may have relative ocular sympathetic insufficiency (69). *In vitro* studies showed that latanoprost induced tyrosinase activity, but did not increase the mitotic index in any of the human melanoma lines studied. This suggests that the *in vivo* iris pigmentation effect of latanoprost may not result from increased cell division, but from elevated tyrosinase activity (70, 71).

Uveitis

In patients without any history of uveitis, a mild delayed uveitis may occasionally develop with latanoprost treatment. In patients with a history, mild delayed exacerbation may potentially occur and the IOP may not be lowered in active uveitis (72). Paradoxical elevation of IOP has been observed in patients with uveitis after treatment with latanoprost. Saccà et al (73) reported three cases of uveitic glaucoma, i.e. uveitic recurrence and secondary glaucoma, worsened by latanoprost and with positive dechallenge and rechallenge tests. Nonetheless, in most circumstances when patients develop a moderate anterior chamber reaction during latanoprost treatment, it seems to be due to a mere alteration of the blood aqueous barrier and is not an inflammatory process (74).

Cystoid macular edema

Reports of cystoid macular edema (CME) in eyes treated with latanoprost have led to concern regarding a possible causal relation. A review of all pub-

lished cases (75) (29 eyes in 26 patients) found that all eyes had independent risks for the development of CME, so no definite conclusions were established about a causal relation. In addition, controlled clinical trials and experimental studies with latanoprost have given no evidence that latanoprost causes clinical CME. Pharmacokinetic considerations (75) indicate that the concentration expected in the posterior segment of the eye is too low to have a pharmacological effect. Nevertheless, reports of a possible association between CME and latanoprost must be given serious consideration, and in eyes that are at risk of CME close surveillance is recommended.

The commercial preparation of latanoprost contains benzalkonium chloride. This product enhances disruption of the blood-aqueous barrier and increases the incidence of angiographic CME in early postoperative pseudophakias. Because eyedrops such as diclofenac seen to prevent this adverse effect of preparations containing the preservative (76) while maintaining their ability to lower IOP, its concurrent application has been suggested (77).

Corneal tolerance

No clinically important differences between latanoprost and timolol have been observed as regards ocular surface effects as all the effects remained within the normal range (78). However, latanoprost, among its diverse pharmacological effects, may mediate inflammation in the eye. Prostaglandins may be a final common pathway for stimulating the recurrence of Herpes simplex keratitis, as shown by some cases with positive rechallenge, and clinicians should be aware of this possible association (79).

Isolated case reports: There have been isolated reports of optic disc edemas (80, 81), and a possible systemic respiratory effect with positive dechallenge (82).

DISCUSSION

Latanoprost has all the elements of a first line IOP-lowering medication in POAG and OH: higher efficacy than the classical reference compounds, convenient administration schedule, and long-term efficacy and safety. Certainly, the once-daily application promotes compliance; additionally, this is a "forgiving" drug, i.e. it is long-acting and the effect persists even if patients forget 1-2 doses (83).

The circadian IOP control obtained with latanoprost seems particularly important since high circadian fluctuations correlate with disease progression (84). Disease progression was positively correlated with the range of diurnal variations of IOP and with the range of variation of IOP over multiple days, thus confirming that diurnal fluctuations of IOP are an important risk factor which needs to be managed adequately. Latanoprost was also consistently effective in the treatment of NTG. The prevalence of angle closure glaucoma shows important regional and ethnic variations and so will the relevance of therapeutic studies. Latanoprost appears to be a therapeutic option even in this kind of glaucoma.

Latanoprost preserves or improves ocular blood flow or ocular perfusion pressure, suggesting a protection of the retinal cells. However, as with other novel treatments, data with hard clinical end-points such as cupping, perimetric loss of visual fields or incidence of blindness are not yet available. Older studies with other drugs, particularly ß-blockers (85-88), have examined these aspects, explaining why they are perceived as the "gold standard" for IOP-lowering.

It seems important to stress the safety of latanoprost. Experience has helped dissipate concerns we might have had some years ago (89), e.g. through elucidation of the mechanism of iris coloration.

The favourable risk/benefit ratio justifies the use of latanoprost as first-line medication in the treatment of POAG and OH.

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Abbreviations

bid	Twice daily
CME	Cystoid macular edema
IOP	Intra-ocular pressure
NPG	Normal pressure glaucoma; see NTG
NTG	Normal tension glaucoma

od Once daily
OH Ocular hypertension
PACG Primary angle-closure glaucoma
POAG Primary open angle glaucoma
CACG Chronic angle closure glaucoma

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