Latanoprost and cystoid macular edema: is there a causal relation?

Robert A. Schumer, MD, PhD,* Carl B. Camras, MD,† and Agneta K. Mandahl, MD, PhD‡

Published reports of the occurrence of cystoid macular edema (CME) in eyes being treated with latanoprost have led to concern regarding a possible causal relation between the two. Review of all published cases (28 eyes in 25 patients), plus another case reported here for the first time, indicates that all eyes had independent risk for development of CME, so that definitive conclusions about a causal relation cannot be established. In addition, controlled clinical trials and experimental studies with latanoprost have given no indication that latanoprost causes clinical CME. Pharmacokinetic considerations indicate that the concentration of latanoprost expected in the posterior segment of the eye is too low to have a pharmacologic effect, and latanoprost is not known to exhibit vasoactive or inflammatory properties. Nevertheless, reports of a possible association between CME and latanoprost use must be given serious consideration, and in eyes that are at risk for CME, an increased level of surveillance for its development is recommended. Curr Opin Ophthalmol 2000, 11:94–100

*Department of Ophthalmology, Mt. Sinai School of Medicine, New York, New York, USA; †Department of Ophthalmology, University of Nebraska Medical Center, Omaha, Nebraska, USA, and Senior Scientific Investigator, Research to Prevent Blindness; and ‡Pharmacia & Upjohn Company, Stockholm, Sweden

Correspondence to Robert A. Schumer, MD, PhD, 70 East 96th Street, New York, New York 10128, USA

Current Opinion in Ophthalmology 2000, 11:94–100

Abbreviations

CME	cystoid macular edema
COX	cyclo-oxygenase
FA	fluorescein angiogram
FML	fluorometholone
IOP	intraocular pressure
NSAID	nonsteroidal anti-inflammatory drug
PG	prostaglandin
RF	risk factor

ISSN 1040–8738 © 2000 Lippincott Williams & Wilkins, Inc.

Latanoprost (13,14- dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-1-isopropyl ester; Xalatan[C], Pharmacia & Upjohn Company, Peapack, NJ, USA) is a prostaglandin (PG) analogue that lowers intraocular pressure (IOP) in the treatment of glaucoma. It was introduced into the market in the United States in September 1996 and in many other parts of the world soon thereafter. Although many naturally occurring PGs have vasoactive properties, preclinical testing clearly demonstrated that latanoprost was not vasoactive even at concentrations well above those used therapeutically [1–3]. However, because other PGs were found to have pronounced effects on the blood-aqueous barrier when used in excessive doses, primarily in rabbits [4,5], considerable attention was devoted to the possibility of disruption of the blood-retinal or blood-aqueous barriers. Based on clinical response and pharmacokinetic studies conducted in phakic and pseudophakic primates and humans, latanoprost did not appear to pose a risk of breakdown of intraocular vascular barriers [6–11]. Nevertheless, following clinical release, published clinical reports and spontaneous adverse event reports describing the occurrence of CME have appeared, involving small numbers of eyes relative to the number that have been treated.

In this article, published reports dealing with CME are summarized and basic and preclinical studies are reviewed. The authors conclude that although there is suggestive clinical evidence of a connection, controlled clinical trials and basic pharmacologic and physiologic studies have not supported a causal role for latanoprost in the genesis of CME. Further study of this important issue will be required before definitive conclusions can be reached.

Case reports of cystoid macular edema with latanoprost

During the course of a compassionate-use program prior to commercial availability, an isolated case of CME arose during the course of treatment with latanoprost. This case, observed by one of the authors (R.A.S.), was reported to the manufacturer in June 1995 and is described here in the accompanying case history report. Beginning shortly after market release in September 1996, the manufacturer received a series of spontaneous reports of the apparent occurrence of CME in association with latanoprost use. Beginning in early 1998, a series of case reports were published, each involving relatively small

numbers of eyes. Currently, 12 such publications [12–23] have appeared, describing 28 eyes in 25 patients, as summarized in Table 1.

Of interest, all 28 eyes described in prior publications, and also the eye described here, had widely accepted risk factors (RFs) for the occurrence of CME. Table 1 lists the clinical history of these eyes. Twenty-seven of the 29 eyes had undergone prior cataract surgery. Twenty-one had an open posterior capsule. There were no reports of CME occurring in eyes that were phakic and without risk for development of CME.

The occurrence of CME in an eye at risk is not unusual. For example, a recent meta-analysis of complications of cataract surgery concluded that clinically apparent CME occurs in 0.6% to 6.0% of eyes after phacoemulsification (median duration of follow-up: 228 days) and 0% to 7.6% of eyes after extracapsular cataract extraction (median duration of follow-up: 421 days) [24]. The incidence of

Case history

A 65-year-old caucasian male with primary open-angle glaucoma in both eyes, without history of diabetes mellitus or systemic hypertension, had retinal detachment in the left eye (OS) treated with cryotherapy and scleral buckle in 1989. He then underwent argon laser trabeculoplasty in both eyes (OU). He had a combined planned extracapsular cataract extraction and trabeculectomy OS in 1989, at which time inadvertent rupture of the posterior capsule occurred. Anterior vitrectomy was performed, and an anterior chamber intraocular lens (Cooper Cilco MT5U00 lens) was inserted without complication. Vision improved to 20/15 OS. Six months postoperatively, using timolol maleate 0.5% OS, he spontaneously noted a reduction in vision OS to 20/25. Yellowish pigmentary macular changes in a petalloid distribution were noted, and FA confirmed vascular macular leakage. Treatment with topical prednisolone acetate 1% twice daily was undertaken for several weeks; vision returned to 20/15 and the macular petalloid pattern resolved fully soon after its initial appearance. The patient was closely followed by a retinologist after the episode of CME and was stable for 5½ years until enrollment in the latanoprost compassionate-use program in May 1995.

The patient had long-standing paracentral arcuate scotomas OU related to glaucoma. In the right eye, the scotoma ultimately involved fixation with loss of most of the superior hemifield and resultant acuity of 20/70. The patient was intolerant of oral carbonic anhydrase inhibitors and had developed an allergic reaction to topical apraclonidine. Pilocarpine was avoided because of the history of retinal detachment. Dipifevrin and other epinephrine compounds were avoided because of the disrupted posterior capsule and the risk of CME. Using timolol maleate 0.5% OU twice daily, IOPs had averaged 20 mmHg OD and 17 mmHg OS; these IOPs were deemed inadequate for glaucoma control.

After informed consent had been obtained (as approved by the Institutional Review Board of the Mt. Sinai School of Medicine in New York City, NY, USA), the patient was provided with latanoprost through a manufacturer-sponsored compassionate use protocol. Dilated stereobiomicroscopy of the optic nerve head and macular region and visual field testing were performed. The discs showed advanced cupping, and the maculae were normal. The patient was begun on latanoprost 0.005% OU, used once daily between the hours of 6–8 pm.

Beginning several days after initial use of latanoprost, the patient noticed haziness of vision in the left eye. About two weeks later, this progressed to a distinct blur that was present each morning but which resolved by afternoon. Four weeks after beginning latanoprost treatment, the blur became more profound, so that the patient could no longer read, and the blur did not resolve as the day proceeded. He contacted his ophthalmologist (R.A.S.), was instructed to discontinue use of latanoprost, and was examined the following morning. He was found to have best-corrected acuity of 20/70 OD and 20/50- OS, with unchanged refractive error and stable anterior segment exam result. In particular, there was neither corneal haze, epitheliopathy, or irregularity, nor were there media opacities or signs of anterior segment inflammation. IOPs were 18.5 mmHg OD and 19 mmHg OS. Distinct yellowish petalloid macular changes were noted, which had not been seen previously. FA was obtained the same day and demonstrated vascular leakage OS. Latanoprost was discontinued OU, and the patient was told to begin use of diclofenac 0.1% OS four times daily and prednisolone acetate 1% OS four times daily, but the patient elected not to use the prednisolone acetate. He was seen one day later. The petalloid pattern was still present, and vision had improved to 20/20- OS. Subjectively, the blur was largely resolved. On the following day, vision was 20/25 OS. IOPs were 18 mmHg OD and 18.5 mmHg OS. The petalloid macular pattern was undetectable. He was seen again one week and two weeks afterward, and on both days vision was 20/15-1 OS, and IOPs on these occasions were 20 mmHg and 18 mmHg, respectively. At the time of most recent examination, over four years following the events described above, visual acuity OS has remained 20/15-1, and there have been no further episodes of blurred vision.

Table 1. Published reports of the occurrence of cystoid macular edema in association with latanoprost use

Publication	Eyes, #	Patients, #	Clinical history*
Avakian *et al.* 1998 [12]	2	2	1. ACIOL, DPC, AV 2. PCIOL, endo-CPC
Ayyala *et al.* 1998 [13]	6	4	1. CE, DPC 2. CE, DPC 3. ICCE, aphakia, DPC 4. ICCE, aphakia, DPC 5. PCIOL, DPC 6. PCIOL, uveitis (concurrent), prior CME
Callanan *et al.* 1998 [14]	2	2	1. PCIOL, DPC 2. sutured PCIOL, DPC, AV, trab x 2
Gaddie & Bennett 1998 [15]	2	2	1. PCIOL, DPC 2. ACIOL, DPC, uveitis
Heier *et al.* 1998 [16]	1	1	ACIOL, lens exchange, AV, DPC, PK
Reis *et al.* 1998 [17]	1	1	PCIOL
Rowe *et al.* 1997 [18]	1	1	PCIOL, prior CME
Thorne *et al.* 1998 [19]	2	1	ACIOL each eye
Wardrop & Wishart 1998 [20]	1	1	RDR (3 times), vitrectomy, PCIOL, CryoTx
Warwar *et al.* 1998 [21]	2	2	1. ACIOL, DPC, prior CME 2. PCIOL, recent uveitis
Moroi *et al.* 1999 [22]	7	7	1. BRVO, ERF, prior CME 2. ERF, uveitis, PCIOL, trab, Ahmed 3. HLA B27 + uveitis, subluxated lens, TS, AV 4. PCIOL, DPC, PLS, PPV, MP 5. PCIOL, DPC, prior CME 6. PCIOL, DPC, ERF 7. PCIOL, DPC, PPV
Weisz *et al.* 1999 [23]	1	1	PCIOL, DPC, vitreous to wound
This article	1	1	ACIOL, DPC, AV, RDR, prior CME
Totals	26	29	

*As derived from publication.
ACIOL, anterior chamber intraocular lens implant; Ahmed, Ahmed glaucoma valve implant; AV, anterior vitrectomy; BRVO, branch retinal vein occlusion; CE, cataract extraction; CME, cystoid macular edema; CPC, cyclophotocoagulation; CryoTx, cryotherapy; DPC, disrupted posterior capsule; ERF, epiretinal fibrosis; HLA, human leukocyte antigen; ICCE, intracapsular cataract surgery; MP, membrane peeling; PCIOL, posterior chamber intraocular lens implant; PK, penetrating keratoplasty; PLS, posterior lip sclerectomy; PPV, pars plana vitrectomy; RDR, retinal detachment repair; trab, trabeculectomy; TS, thermal sclerostomy.

CME was reported to be 8% for anterior chamber intraocular lens implantation and 3.5% for posterior chamber intraocular lens implantation within one year of surgery [25]. After neodymium:YAG laser capsulotomy, the incidence of reported CME ranges from 0.5% to 4.9% [26].

Importantly, the number of eyes developing CME described in published reports is small in comparison with the number of eyes that have been treated with latanoprost worldwide. The manufacturer estimates this number to be over 1,700,000 eyes treated as of June 1999. In addition to the 28 already published cases of CME, less than 120 other cases were known to the manufacturer (almost entirely through spontaneous reports) as of June 1999. In such a large group of treated eyes, many of which are at risk for the development of CME, it would be expected that a far greater number of cases of CME should have developed. Under-reporting of putative cases of CME may have occurred because of physicians' possible assumption that CME was caused by other risk factors and not by latanoprost. Over-reporting, on the other hand, may actually have occurred because of a widespread belief among ophthalmologists that PGs are pro-inflammatory and can cause CME [27]. It nevertheless appears that CME rarely occurs.

In three cases, the affected eye was rechallenged with latanoprost after the initial episode of CME [12,14,19]. Latanoprost was discontinued in all three eyes, and visual acuity returned to within one line of the baseline of 20/20 to 20/25 in all eyes. In two eyes that had a fluorescein angiogram (FA) repeated just prior to rechallenge, persisting angiographic CME was demonstrated in one [12], whereas no CME was seen in the other [19]. In one rechallenged eye, there was no evidence of recurrence of CME after three separate one-month-long rechallenges [19]. Two other rechallenged eyes [12,14] had decreased visual acuity of three and eight lines occurring two weeks and two months, respectively, after restarting latanoprost.

Prior preclinical and clinical studies

Latanoprost is a poor substrate for those PG receptors that mediate vasoactive responses. In addition, clinical

investigations reviewed elsewhere [6,28,29] have lent little credence to an action of latanoprost on the blood-aqueous barrier of humans. Whereas topical application of certain PGs produces marked anterior chamber flare reaction in rabbits [4,30–32], highly significant species-specific responses to PGs are well documented. Results concerning the blood-aqueous barrier obtained in the rabbit cannot be applied to the human [32]. In controlled clinical trials, slit-lamp biomicroscopic assessment after treatment with either PhXA34 (a compound consisting of the epimeric mixture of latanoprost and its considerably less active 15 S-epimer) or with latanoprost has consistently failed to show the development of flare. In addition, sensitive laser-flare meter and fluorophotometric measurements of anterior chamber flare and/or protein concentration also have failed to demonstrate alterations in blood-aqueous barrier integrity after treatment with either PhXA34, $PGF_{2\alpha}$-IE, or latanoprost in clinical studies [6]. Also, chemotaxis, a hallmark of inflammation, has not occurred in response to latanoprost or any PG analogue in clinical trials or, in fact, in controlled experiments involving any animal species. Indeed, the chemotaxis induced by leukotriene LTB_4 was inhibited by PGs, including $PGF_{2\alpha}$ [33].

Efforts to detect an effect of latanoprost on the blood-retina barrier have not yielded positive results either. Studies with monkeys failed to find angiographic or histopathologic evidence for CME following two weeks to six months of treatment with latanoprost or the related compound $PGF_{2\alpha}$-tromethamine salt [7,34,35]. In one study of latanoprost and CME [7], cynomolgus monkeys were subjected to unilateral extracapsular cataract extraction (without lens implant) and, beginning 14 weeks after surgery, were then treated bilaterally with latanoprost 0.035% (seven times the concentration used in human glaucoma therapy) once daily for six months. FAs, performed at one, three, and six months after the beginning of treatment, failed to show vascular leakage; also, there were no ophthalmoscopically-detected macular changes in any eye. However, none of the monkey eyes had posterior capsule disruption or underwent anterior vitrectomy. In another study, it should be noted, complicated and uncomplicated cataract surgery without latanoprost treatment produced histologically-proven disruption of the blood-retina barrier without angiographic CME in seven eyes of four monkeys [36]. However, the power of this study prevented definitive conclusions because only a single monkey eye was evaluated at each of seven time intervals following surgery.

In a study specifically designed to investigate the potential of latanoprost to induce CME in human pseudophakic eyes, 24 patients with posterior chamber lenses and with intact posterior capsules were treated unilaterally for four weeks [7]. Sixteen received latanoprost 0.006% twice daily (twice the clinical dose), and eight received placebo. They were examined with macular biomicroscopy and FA before and after treatment. There was no indication of macular edema nor was there a reduction in visual acuity in the latanoprost-treated eyes. One of the placebo-treated eyes had mild angiographic CME. None of the eyes had suffered a prior episode of CME, and all had intact posterior capsules.

Corticosteroids have been claimed to ameliorate uveitis-associated CME, though no randomized prospective trials have shown this. Nonsteroidal anti-inflammatory drugs (NSAIDs) are believed to reduce the likelihood and/or severity of postcataract surgery CME [37–40]. Either corticosteroids or NSAIDs can inhibit the production of PGs and other prostanoids from arachidonic acid. Based on these and other observations, a causal role for PGs in the pathogenesis of aphakic CME has been proposed [41,42]. However, corticosteroids and NSAIDs are nonspecific, having many effects independent of their ability to inhibit PG synthesis [43]. As cyclooxygenase (COX) inhibitors, NSAIDs also inhibit the formation of thromboxanes, prostacyclin, and other prostanoids. In addition, they may inhibit the activity of phosphodiesterases [44] and protein kinases [45], and they may reduce transmembrane calcium flux [46]. Corticosteroids inhibit phospholipase A_2 and therefore inhibit PG synthesis, but they also have an even broader spectrum of activity than NSAIDs. They inhibit migration of macrophages and neutrophils; induce lymphocytopenia, eosinopenia, monocytopenia, and neutrophilic leukocytosis; reduce capillary permeability and suppress vasodilation; inhibit neutrophil and mast cell degranulation; stabilize lysosomes and suppress action of lymphokines; and decrease leukotriene formation [47]. Surgical trauma stimulates not only the production of PGs but also many other eicosanoids and inflammatory mediators [5,48,49]. Therefore, the apparent palliative role of corticosteroids or NSAIDs in CME, and the increased levels of PGs during inflammation, in and of themselves do not prove a causal role for PGs in producing CME.

To further explore this issue, Miyake *et al.* [50] performed a randomized double-masked comparison of the effect of latanoprost therapy versus placebo on FA following cataract surgery in eyes with ocular hypertension, normal pressure glaucoma, or primary open-angle glaucoma. They also compared postoperative treatment of these same eyes with either diclofenac sodium or fluorometholone (FML), though this part of the study was open-label. All eyes underwent clear-corneal temporal phacoemulsification with implantation of an acrylic, foldable posterior chamber intraocular lens implant through a 3-mm incision. Thirty-five to 37 eyes were treated in each of four groups, receiving either latanoprost and diclofenac, latanoprost and FML, placebo and diclofenac, or placebo and FML. Latanoprost or placebo was used once every morning from two days before until five

weeks following surgery. Diclofenac or FML was used three times daily until five weeks following surgery. FA was performed five weeks postoperatively. No patient in any group experienced CME, as there was no difference in acuity between any of the four groups. Each group had average best-corrected visual acuity greater than 20/25 by five weeks. All groups had similar presurgical IOP, but latanoprost-treated eyes had significantly lower postoperative IOPs, regardless of concomitant therapy with either FML or diclofenac. The incidence of angiographic leakage was higher in latanoprost-treated than in placebo-treated eyes when FML was used postoperatively, but not when diclofenac was used. The authors conclude that latanoprost increases the likelihood of angiographic leakage and that diclofenac, but not FML, effectively protects against the development of leakage. However, the relevance of this study to clinical CME is unclear because no group demonstrated impairment of visual acuity [51].

Because diclofenac, a NSAID and COX-inhibitor, protects against the development of angiographic CME, latanoprost cannot be the direct cause of angiographic CME. The protective effect of the COX-inhibitor has no antagonistic action on the exogenously applied PG analogue, as demonstrated by the inability of diclofenac to inhibit the latanoprost-induced decrease in IOP. It could, though, inhibit the synthesis of a secondary COX-derived inflammatory mediator whose production was stimulated by latanoprost [50,51].

Pharmacologic and pharmacokinetic considerations

Latanoprost is a PG analogue modified from its parent compound, the naturally occurring $PGF_{2\alpha}$. Latanoprost differs from $PGF_{2\alpha}$ by addition of an isopropyl ester group on C_1, by 17-phenyl substitution, and by reduction of a double bond at $C_{13\text{-}14}$. It is a lipophilic prodrug, hydrolyzed to the active free acid in the cornea. $PGF_{2\alpha}$ is one of a large class of related 20-carbon biologic molecules known as eicosanoids, many of which have potent vasoactive effects. For example, thromboxanes cause vasoconstriction, whereas prostacyclin is a potent vasodilator. Of the eight different prostanoid receptors and their subtypes—including DP, EP_1, EP_2, EP_3, EP_4, FP, IP, and TP receptors—vasodilation is known to be mediated by EP_2, DP, and IP receptors and vasoconstriction by TP receptors [52,53]. $PGF_{2\alpha}$, by acting on the "vasoactive" receptors, has either vasoconstrictive or vasodilatory properties, depending on its concentration and the vascular tissue under investigation [1–3].

Earlier $PGF_{2\alpha}$-related compounds tested for their IOP-lowering effect, such as $PGF_{2\alpha}$-IE, caused conjunctival hyperemia secondary to vasodilation [54,55]. In the rabbit eye, the hyperemic effect of $PGF_{2\alpha}$-IE was abolished by trigeminal nerve ablation or by nitric oxide synthase inhibitors, indicating that the vascular response is mediated by the trigeminal nerve and is dependent on nitric oxide synthesis [1,2]. Therefore, the hyperemia does not appear to be a direct vascular response to the PG [1,2]. In contrast, latanoprost had a minimal effect on conjunctival hyperemia in rabbits [2] and humans [56–58]. The high selective affinity of latanoprost for the FP receptor makes vascular actions for latanoprost extremely unlikely even at high concentrations [59]. Indeed, in a study of bovine ciliary artery and episcleral vein, latanoprost had no vasoactive effect, whereas $PGF_{2\alpha}$ caused vasoconstriction, which was abolished by TP receptor antagonists [3].

Latanoprost acid should not be able to reach the posterior part of the human eye, as latanoprost, similar to other PGs, is rapidly removed from the anterior segment by an organic anion transport system in the ciliary processes [60–63]. One drop of commercially supplied latanoprost 0.005% solution contains 1.5 μgm of latanoprost. About 1% (*ie*, 0.015 μgm) is expected to enter the anterior chamber [59]. Peak concentration of the free acid of latanoprost appears in the human anterior chamber 2–3 hrs after topical application and is about 10^{-7} mol/L [64]. The half-life for elimination of latanoprost from the human anterior chamber is 3–4 hours [64]. Pharmacokinetic studies in phakic cynomolgus monkeys indicate that topically administered latanoprost reaches the anterior but not the posterior segment in detectable amounts [65,66]. Although some diffusion of the administered latanoprost acid might occur in an eye with a disrupted posterior lens capsule, it would then be diluted from its anterior chamber concentration because of volumetric considerations, aqueous humor production, and active transport processes to concentrations less than 10^{-9} mol/L [67]. At this concentration, there is no known vascular action of latanoprost [1,3]. Indeed, intravitreal injection of more than 500 μgm of $PGF_{2\alpha}$ was required to produce leakage detected by FA in rabbits [68].

In addition to evidence failing to demonstrate a route through direct intraocular penetration, latanoprost cannot reach the posterior segment through systemic circulation. In humans, the peak plasma concentration of latanoprost acid is about 50 pgm/ml or 10^{-10} mol/L, with a half-life of 17 minutes [59,67,69]. Latanoprost acid is rapidly metabolized in the liver and excreted primarily in the urine [59,70].

Conclusions

Although a number of cases of CME in association with latanoprost use have been described, the numbers of implicated eyes are small in comparison with the number of eyes that have been treated with latanoprost. Also, all eyes described to date have had other RFs for the development of CME. Indeed, there is no evidence, so far, for CME developing in a phakic eye without RFs for

CME. Repeated rechallenges with placebo controls have not been performed in eyes developing CME. It therefore is impossible to conclude that latanoprost caused CME in any of the cases so far reported because, by definition, these eyes all might have developed CME regardless of whether latanoprost had or had not been used.

All 29 eyes described in previously published case reports and herein arose from uncontrolled clinical observations. Controlled and closely monitored clinical trials and experimental studies with latanoprost have given no indication that latanoprost causes clinical CME. Pharmacologic considerations indicate that the concentration of latanoprost expected in the posterior segment of the eye is far too low to have any effect on those PG receptors that mediate vascular actions. Further, the systemic metabolism and clearance of latanoprost is too rapid to allow latanoprost to reach the posterior segment in a pharmacologically meaningful concentration from a systemic route. In addition, latanoprost is not known to exhibit vasoactive or inflammatory properties.

Nevertheless, reports of a possible association between CME and latanoprost use must be given serious consideration. Latanoprost should be used with caution in eyes with multiple RFs for CME. In these eyes, an increased level of surveillance for the development of CME is recommended. Long-term, randomized, placebo-controlled studies are required to determine whether a causal relation between latanoprost and CME exists in eyes with multiple RFs. Unfortunately, such studies would be very difficult to undertake in view of the large numbers of patients required to provide adequate power to evaluate this rare potential side effect.

Acknowledgments

Supported in part by an unrestricted departmental grant from Research to Prevent Blindness, Inc., New York, New York, USA, and the Gifford Laboratory Fund, Omaha, Nebraska (CBC), USA.

Dr. Camras is a consultant to, and Dr. Mandahl is an employee of, the Pharmacia & Upjohn Company, Stockholm, Sweden.

References and recommended reading

1 Astin M, Stjernschantz J, Selén G: Role of nitric oxide in PGF2a-induced ocular hyperemia. Exp Eye Res 1994, 59:401–407.

2 Astin M, Stjernschantz J: Mediation of prostaglandin F2a-induced ocular surface hyperemia by sensory nerves in rabbits. Curr Eye Res 1997, 16:886–890.

3 Astin M: Effects of prostaglandin E2, F2a, and latanoprost acid on isolated ocular blood vessels in vitro. J Ocul Pharmacol Ther 1998, 14:119–128.

4 Eakins KE: Prostaglandin and non-prostaglandin mediated breakdown of the blood-aqueous barrier. Exp Eye Res 1977, 25:483–498.

5 Bito LZ: Prostaglandins. Old concepts and new perspectives. Arch Ophthalmol 1987, 105:1036–1039.

6 Toris CB, Camras CB, Yablonski ME, Brubaker RF: Effects of exogenous prostaglandins on aqueous humor dynamics and blood-aqueous barrier function. Surv Ophthalmol 1997, 41:S69–S75.

7 Hoyng PFJ, Rulo AH, Greve EL, Astin M, Gjotterberg M: Fluorescein angiographic evaluation of the effect of latanoprost treatment on blood-retinal barrier integrity: a review of studies conducted on pseudophakic glaucoma patients and on phakic and aphakic monkeys. Surv Ophthalmol 1997, 41:S83–S88.

8 Toris CB, Camras CB, Yablonski ME: Effects of PhXA41, a new prostaglandin F2a analog, on aqueous humor dynamics in human eyes. Ophthalmology 1993, 100:1297–1304.

9 Lindén C, Nuija E, Alm A: Effects on IOP restoration and blood-aqueous barrier after long term treatment with latanoprost in open angle glaucoma and ocular hypertension. Br J Ophthalmol 1997, 81:370–372.

10 Diestelhorst M, Roters S, Krieglstein GK: The effect of latanoprost (PHXA41) on the intraocular pressure and aqueous humor protein concentration. A randomized, double masked comparison of 50 mg/ml vs 15 mg/ml with timolol 0.5% as control. Invest Ophthalmol Vis Sci 95, 36:S823.

11 Hotehama Y, Mishima HK: Clinical efficacy of PhXA34 and PhXA41, two novel prostaglandin F2a-isopropyl ester analogues for glaucoma treatment. Jpn J Ophthalmol 1993, 37:259–269.

12 Avakian A, Renier SA, Butler PJ: Adverse effects of latanoprost on patients with medically resistant glaucoma. Arch Ophthalmol 1998, 116:679–680.

13 Ayyala RS, Cruz DA, Margo CE, Harman LE, Pautler SE, Misch DM, et al.: Cystoid macular edema associated with latanoprost in aphakic and pseudophakic eyes. Am J Ophthalmol 1998, 126:602–604.

14 Callanan D, Fellman RL, Savage JA: Latanoprost-associated cystoid macular edema. Am J Ophthalmol 1998, 126:134–135.

15 Gaddie IB, Bennett DW: Cystoid macular edema associated with the use of latanoprost. J Am Optom Assoc 1998, 69:122–128.

16 Heier JS, Steinert RF, Frederick AR: Cystoid macular edema associated with latanoprost use. Arch Ophthalmol 1998, 116:680–682.

17 Reis A, Althaus C, Sundmacher R: Latanoprost (Xalatan®) induziertes Makulaodem. Klin Monatsbl Augenheilkd 1998, 213:63–64.

18 Rowe JA, Hattenhauer MG, Herman DC: Adverse side effects associated with latanoprost. Am J Ophthalmol 1997, 124:683–685.

19 Thorne JE, Maguire AM, Lanciano R: CME and anterior uveitis with latanoprost use. Ophthalmology 1998, 105:1981–1983.

20 Wardrop DR, Wishart PK: Latanoprost and cystoid macular oedema in a pseudophake. Br J Ophthalmol 1998, 82:843–844.

21 Warwar RE, Bullock JD, Ballal D: Cystoid macular edema and anterior uveitis associated with latanoprost use. Experience and incidence in a retrospective review. Ophthalmology 1998, 105:263–268.

22 Moroi SE, Gottfredsdottir MS, Schteingart MT, Elner SG, Lee CM, Schertzer RM, et al.: Cystoid macular edema associated with latanoprost therapy in a case series of patients with glaucoma and ocular hypertension. Ophthalmology 1999, 106:1024–1029.

23 Weisz JM, Bressler NM, Bressler SB, Schachat AP: Ketorolac treatment of pseudophakic cystoid macular edema identified more than 24 months after cataract extraction. Ophthalmology 1999, 106:1656–1659.

24 Powe NR, Schein OD, Gieser SC, Tielsch JM, Luthra R, Javitt J, Steinberg EP, for The Cataract Patient Outcome Research Team: Synthesis of the literature on visual acuity and complications following cataract extraction with intraocular lens implantation. Arch Ophthalmol 1994, 112:239–252.

25 Stark WJ, Worthen DM, Holladay JT, Bath PE, Jacobs ME, Murray GC, et al.: The FDA report on intraocular lenses. Ophthalmology 1983, 90:311–317.

26 Steinert RF, Puliafito CA, Kumar SR, Dudak SD, Patel S: Cystoid macular edema, retinal detachment, and glaucoma after Nd:YAG laser posterior capsulotomy. Am J Ophthalmol 1991, 112:373–380.

27 Camras CB: CME and anterior uveitis with latanoprost use. Ophthalmology 1998, 105:1978–1981.

28 Toris CB, Camras CB: Prostaglandins. A new class of aqueous outflow agents. In: Singh K, Zimmerman T, eds. J Ophthalmology Clinics of North America. Philadelphia: W.B. Saunders Co.; 1997:335–355.

29 Camras CB, Bito LZ, Toris CB: Prostaglandins and prostaglandin analogues. In: Zimmerman TJ, Kooner KS, Sharir M, Fechtner RD. Textbook of Ocular Pharmacology. Philadelphia: Lippincott–Raven; 1997:315–328.

30 Camras CB, Bito LZ, Eakins KE: Reduction of intraocular pressure by prostaglandins applied topically to the eyes of conscious rabbits. Invest Ophthalmol Vis Sci 1977, 16:1125–1134.

31 Lee P-Y, Podos SM, Severin CH: Effect of prostaglandin F2a on aqueous humor dynamics of rabbit, cat, and monkey. Invest Ophthalmol Vis Sci 1984, 25:1087–1093.

32 Bito LZ: Species differences in the responses of the eye to irritation and trauma: a hypothesis of divergence in ocular defense mechanisms, and the choice of experimental animals for eye research. Exp Eye Res 1984, 39:807–829.

33 Bhattacherjee P, Hammond B, Salmon JA, Eakins KE: Effect of lipoxygenase products on leukocyte accumulation in the rabbit eye. Adv Prostaglandin Thromboxane Leukot Res 1982, 9:325–330.

34 Camras CB, Bhuyan KC, Podos SM, Bhuyan DK, Master RWP: Multiple dosing of prostaglandin F2a or epinephrine on cynomolgus monkey eyes. II. Slit-lamp biomicroscopy, aqueous humor analysis, and fluorescein angiography. Invest Ophthalmol Vis Sci 1987, 28:921–926.

35 Camras CB, Friedman AH, Rodrigues MM, Tripathi BJ, Tripathi RC, Podos SM: Multiple dosing of prostaglandin F 2a or epinephrine on cynomolgus monkey eyes. III. Histopathology. Invest Ophthalmol Vis Sci 1988, 29:1428–1436.

36 Tso MOM, Shih C-Y: Experimental macular edema after lens extraction. Invest Ophthalmol Vis Sci 1977, 16:381–392.

37 Flach AJ, Stegman RC, Graham J, Kruger LP: Prophylaxis of aphakic cystoid macular edema without corticosteroids. A paired-comparison, placebo-controlled double-masked study. Ophthalmology 1990, 97:1253–1258.

38 Flach AJ, Jampol LM, Weinberg D, Kraff MC, Yannuzzi LA, Campo RV, et al.: Improvement in visual acuity in chronic aphakic and pseudophakic cystoid macular edema after treatment with topical 0.5% ketorolac tromethamine. Am J Ophthalmol 1991, 112:514–519.

39 Flach AJ: Cyclo-oxygenase inhibitors in ophthalmology. Surv Ophthalmol 1992, 36:259–284.

40 Rossetti L, Chaudhuri J, Dickersin K: Medical prophylaxis and treatment of cystoid macular edema after cataract surgery. Ophthalmology 1998, 105: 397–405.

41 Mishima HK, Masuda K, Miyake K: The putative role of prostaglandins in cystoid macular edema. In: Bito LZ, Stjernschantz J, eds. The Ocular Effects of Prostaglandins and Other Eicosanoids. New York: Alan R. Liss, Inc.; 1989: 251–264.

42 Miyake K, Shirasawa E, Hikita M: Hypotheses on the role of prostaglandins in the pathogenesis of epinephrine maculopathy and aphakic cystoid macular edema. In: Bito LZ, Stjernschantz J, eds. The Ocular Effects of Prostaglandins and Other Eicosanoids. New York: Alan R. Liss, Inc.; 1989:265–276.

43 Camras CB, Podos SM: The role of endogenous prostaglandins in clinically-used and investigational glaucoma therapy. In: Bito LZ, Stjernschantz J, eds. The Ocular Effects of Prostaglandins and Other Eicosanoids. New York: Alan R. Liss, Inc.; 1989:459–475.

44 Roy AC, Warren BY: Inhibition of cAMP phosphodiesterase by disodium cromoglycate. Biochem Pharmacol 1974, 23:917–920.

45 Dinnendahl V, Peters HD, Schönhöfer PS: Effects of sodium salicylate and acetylsalicylic acid on cyclic 3',5'-AMP-dependent protein kinase. Biochem Pharmacol 1973, 22:2223–2228.

46 Northover BJ: Effect of anti-inflammatory drugs on the binding of calcium to cellular membranes in various human and guinea-pig tissues. Br J Pharmacol 1973, 48:496–504.

47 Flach AJ: Nonsteroidal anti-inflammatory drugs. In: Tasman W, Jaeger EA, eds. Duane's Biomedical Foundations of Ophthalmology, volume 3. Philadelphia: J.B. Lippincott; 1994:1–32.

48 Bito LZ: A physiological approach to glaucoma management: the use of local hormones and the pharmacokinetics of prostaglandin esters. In: Bito LZ, Stjernschantz J, eds. The Ocular Effects of Prostaglandins and Other Eicosanoids. New York: Alan R. Liss, Inc.; 1989:329–347.

49 Bito LZ: Prostaglandins: a new approach to glaucoma management with a new, intriguing side effect. Surv Ophthalmol 1997, 41:S1–S14.

50 Miyake K, Ota I, Maekubo K, Ichihashi S, Miyake S: Latanoprost accelerates disruption of the blood-aqueous barrier and the incidence of angiographic cystoid macular edema in early postoperative pseudophakias. Arch Ophthalmol 1999, 117:34–40.

51 Camras CB: Latanoprost may trigger the biosynthesis of endogenous prostaglandins in early postoperative pseudophakias. Arch Ophthalmol 1999, 117:1265–1266.

52 Coleman RA, Smith WL, Narumiya S: International Union of Pharmacology classification of prostanoid receptors: properties, distribution, and structure of the receptors and their subtypes. Pharmacol Rev 1994, 46:205–229.

53 Woodward DF, Regan JW, Lake S, Ocklind A: The molecular biology and ocular distribution of prostanoid receptors. Surv Ophthalmol 1997, 41:S15–S21.

54 Villumsen J, Alm A: Prostaglandin F2a-isopropylester eye drops: effects in normal human eyes. Br J Ophthalmol 1989, 73:419–426.

55 Camras CB, Siebold EC, Lustgarten JS, Serle JB, Frisch SC, Podos SM, Bito LZ: Maintained reduction of intraocular pressure by prostaglandin F2a-1-isopropyl ester applied in multiple doses in ocular hypertensive and glaucoma patients. Ophthalmology 1989, 96:1329–1337.

56 Alm A, Stjernschantz J, the Scandinavian Latanoprost Study Group: Effects on intraocular pressure and side-effects of 0.005% latanoprost applied once daily, evening or morning. A comparison with timolol. Ophthalmology 1995, 102:1743–1752.

57 Watson P, Stjernschantz J, the Latanoprost Study Group: A six-month, randomized, double-masked study comparing latanoprost with timolol in open-angle glaucoma and ocular hypertension. Ophthalmology 1996, 103:126–137.

58 Camras CB, the United States Latanoprost Study Group: Comparison of latanoprost and timolol in patients with ocular hypertension and glaucoma. A six-month, masked, multicenter trial in the United States. Ophthalmology 1996, 103:138–147.

59 Stjernschantz J, Alm A: Latanoprost as a new horizon in the medical management of glaucoma. Curr Opin Ophthalmol 1996, 7:11–17.

60 Bito LZ: Accumulation and apparent active transport of prostaglandins by some rabbit tissues in vitro. J Physiol Lond 1972, 221:371–387.

61 Bito LZ: Comparative study of concentrative prostaglandin accumulation by various tissues of mammals and marine vertebrates and invertebrates. Comp Biochem Physiol A 1972, 43:65–82.

62 Bito LZ: Absorptive transport of prostaglandins from intraocular fluids to blood: a review of recent findings. Exp Eye Res 1973, 16:299–306.

63 Bito LZ, Stjernschantz J, Resul B, Miranda OC, Basu S: The ocular effects of prostaglandins and the therapeutic potential of a new PGF2a analog, PhXA41 (latanoprost), for glaucoma management. J Lipid Mediat 1993, 6: 535–543.

64 Sjöquist B, Almegård B, Khalifeh V, Alm A: The bioavailability of Xalatan® in the human eye. Invest Ophthalmol Vis Sci 1997, 38:S248.

65 Sjöquist B, Tajallaei S, Stjernschantz J: Pharmacokinetics of latanoprost in the cynomolgus monkey, 1st communication: single intravenous, oral or topical administration on the eye. Arzneimittelforschung 1999, 49:225–233.

66 Sjöquist B, Johansson A, Stjernschantz J: Pharmacokinetics of latanoprost in the cynomolgus monkey, 3rd communication: tissue distribution after topical administration on the eye studied by whole body autoradiography. Arzneimittelforschung 1999, 49:240–249.

67 Rulo AH, Hoyng PFJ: Author's reply to reduction of IOP with latanoprost. Ophthalmology 1997, 104:896–897.

68 Peyman GA, Bennett TO, Vlchek J: Effects of intravitreal prostaglandins on retinal vasculature. Ann Ophthalmol 1975, 7:279–288.

69 Sjöquist B, Byding P, Resul B, Stjernschantz J: The systemic pharmacokinetics of latanoprost in man after intravenous and topical administration. Invest Ophthalmol Vis Sci 1994, 35:2220.

70 Sjöquist B, Basu S, Resul B, Stjernschantz J: The pharmacokinetics of latanoprost in the cynomolgus monkey. Invest Ophthalmol Vis Sci 1993, 34:932.