Kobe J. Med. Sci., Vol. 53, No. 6, pp. 297-304, 2007

Intraocular Pressure Lowering Effect of Once Daily versus Once Weekly Latanoprost Instillation in the Same Normal Individuals

URTOGTAH DARHAD, MAKOTO NAKAMURA, MIYUKI FUJIOKA, YASUKO TATSUMI, AZUSA NAGAI-KUSUHARA, HIDETAKA MAEDA, and AKIRA NEGI

Division of Ophthalmology, Department of Surgery, Kobe University Graduate School of Medicine, Kobe 650-0017, Japan

Received 5 July 2007 /Accepted 26 July 2007

Key words: Glaucoma Pharmacology, Intraocular Pressure, Eye Drops, Efficacy

This study tested whether once weekly instillation of latanoprost exerts the similar IOP lowering effect as once daily instillation in the same individuals. Latanoprost was administered on right eyes of eight healthy male volunteers once daily first for 24 days, which was followed by the 31-day washout and the subsequent once weekly instillation for another 24 days. The mean baseline IOP was 12.06 ± 1.50 (range, 10.0 to 14.0) mmHg, whereas the mean IOP during once daily treatment was 9.87 ± 1.71 mmHg, which was significantly lower than the former (p=0.025). The mean washout IOP was 12.56 ± 2.16 mmHg, which was similar to the baseline IOP. The mean IOP during once weekly instillation of latanoprost was 11.34 ± 1.51 mmHg, which was not statistically different from the washout IOP. Four of the 8 subjects showed 15% or more reduction in IOP both during once daily and once weekly instillations, two of whom were overlapped. Since the magnitude of the IOP reduction with once daily use was higher than that with once weekly use even in the responders, the current protocol of once daily instillation should be respected.

Latanoprost is one of the prostaglandin-related anti-glaucoma medications with powerful ocular hypotensive effects (1) through facilitated uveoscleral outflow (2). Latanoprost is a prostaglandin F2α (PGF2α) analogue, which has the high affinity to the specific receptor FP (3). Although the currently recommended protocol of latanoprost administration in patients with glaucoma and ocular hypertension is once daily in the evening (4), a recent paper suggested that only once weekly instillation may be as effective as once daily instillation in terms of IOP reduction (5). The reduced frequency of instillation may also reduce ocular side effects of latanoprost such as conjunctival injection, increased pigmentation of iris and lid, increased growth of eyelashes, and cystoid macular edema (4). However, their study (5) used a different set of individuals (10 each) to compare the effectiveness of latanoprost between once daily and once weekly administrations. Since the magnitude of response to latanoprost is known to rather vary widely (6), their result may reflect the bias of latanoprost responders between groups with the small sample size. Thus, the comparison within the same group of individuals is more favorable to test their hypothesis.

The purpose of this study was to test whether once weekly instillation of latanoprost exerts the similar IOP lowering effect as once daily instillation in the same individuals.

Phone: 81-78-382-6048 FAX: 81-78-382-6059 E-mail: manakamu@med.kobe-u.ac.jp

MATERIALS AND METHODS

Eight healthy male volunteers were recruited for this study. The mean age (± S.D) was 36.5 ± 8.1, ranging from 27 to 53, years. Before enrolled into the study, all individuals were screened for ocular conditions to ensure their eyes were normal. None of them had any histories of taking drugs regularly, contact lens use, and refractive or other intraocular surgeries that affected the IOP measurement. The study protocol followed the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the Kobe University Graduate School of Medicine. Written informed consent was obtained from each participant.

All IOP measurements were made during 8 and 9 am with the same daily-calibrated Goldmann applanation tonometer (Carl-Zeiss). At IOP measurements, YT randomly set the dial around 10 mmHg and recorded the pressure, whereas MF applanated the cornea and turned the dial without looking. Three replicate measurements were performed each time. The means of last two readings for each eye were recorded and used for analysis. This is a standard method of IOP recording because the first measurement almost always yields an artificially higher IOP value due to testee's strain and the more repeated measurement results in an artificially lower IOP value due to too much compression of cornea (7).

Following the baseline IOP collection, the participants began taking 0.005% latanoprost in right eyes once daily at 10 pm for 24 days. The instillation started on Monday night (day 0) and the IOP was measured on Tuesdays and Fridays for 4 weeks, that is, on days 1, 4, 8, 11, 15, 18, 22, and 25. The participants then stopped the instillation for the following 31 days. Following the post-washout IOP measurement, latanoprost was administered on the same eyes every Monday night (10 pm) for 4 weeks. Then the IOP was measured as above.

The time for instillation of the evening drops was asked. A schedule deviation of more than 30 minutes was not allowed. Any subjective symptoms or objective signs of side effects during the study were registered. Left eyes did not receive eye drops and were used as controls.

Time course of changes in IOP from baseline, which were expressed as mean ± standard error of the mean, and the difference between eyes were used as the main response variables. In addition, the IOP reduction rate (%) during once daily instillation was defined as baseline IOP minus post-treatment IOP divided by baseline IOP, which was multiplied by 100. The reduction rate during once weekly instillation was defined as washout IOP minus post-treatment IOP divided by washout IOP, which was multiplied by 100. Responders were arbitrarily defined as those having the mean IOP reduction rate ≥ 15%, whereas non-responders as <15%.

Statistic analyses were performed in Microsoft Excel 2000 (Microsoft Corp, Seattle, WA, USA) and StatView version 5 (SAS Institute, Cary, NC, USA). Two-way repeated-measures analysis of variance (ANOVA) was performed to test significance of differences in IOP between the eyes. Student's paired two-tailed t-test was also used to compare the baseline IOPs with the washout IOPs or with IOPs at specific time points after initiation of latanoprost use within eyes and to test significant differences in IOP between the eyes. The mean baseline, washout, and post-treatment IOPs between once daily use and once weekly use were also compared with the paired t-test. Values of $p<0.05$ were considered statistically significant.

RESULTS

Raw data of IOP changes in the right eyes receiving once daily or once weekly instillation of latanoprost and in the left, untreated eyes are listed in Table 1.

The mean IOP at baseline was 12.06 ± 1.50 mmHg in the right eyes and 12.63 ± 1.79 mmHg in the left. There was no statistically significant difference in the mean baseline IOP between eyes (p=0.249). The mean IOP during once daily treatment of latanoprost was 9.87 ± 1.71 (range, 6.69 to 12.56) mmHg in the right eyes and 12.02 ± 1.88 (range, 8.31 to 13.88) mmHg in the left. The former was significantly lower than the latter (p=0.034). There was also significant difference between the mean baseline IOP and the mean post-once daily treatment IOP in the right eyes (p=0.025), whereas no difference between the corresponding values in the left eyes (p=0.315).

The mean IOP after the 28-day washout period was 12.56 ± 2.16 mmHg in the right eyes and 12.44 ± 1.95 mmHg in the left, which was not significantly different (p=0.298). These mean washout IOPs were not significantly different from the mean baseline IOPs either in the right eyes (p=0.598) or in the left (p=0.815).

The mean IOP during once weekly instillation of latanoprost was 11.34 ± 1.51 mmHg in the right eyes and 12.52 ± 1.56 mmHg in the left. There was no significant difference between the two (p=0.098). The difference between the mean washout IOP and the mean post-once weekly treatment IOP was not significant in the right eyes (p=0.055) or in the left (p= 0.849).

The averaged time course of changes in IOP after once daily and once weekly instillation of latanoprost is depicted in Figures 1 and 2, respectively.

Two-way repeated-measures ANOVA revealed the statistically significant difference in IOP between the right eyes receiving once daily latanoprost instillation and the left eyes (p=0.032, Figure 1), whereas no difference between the right eyes receiving once weekly latanoprost instillation and the left (p=0.204, Figure 2). The paired t-test disclosed that IOPs at days 4, 8, 18, 22, and 25 after initiation of once daily latanoprost use were significantly lower than the baseline IOP in the right eyes, while only IOP at day 4 was significantly different from the baseline IOP in the left eye (Figure 1). At days 11, 15, 22, and 25, the IOPs in the right eyes administered with once daily latanoprost were significantly lower than those in the left (Figure 1). As for the once weekly protocol, there was no significant difference in IOP at all but one time points (day 4) in the right eyes as compared with the washout IOP (Figure 2), whereas the inter-eye difference in IOP was significantly different at days 11 and 15 (Figure 2).

When responders were arbitrarily defined as those having the mean IOP reduction rate ≥ 15%, 4 out of the eight subjects were in average responders both during the once daily instillation (cases 2, 3, 6, and 8; Figure 3) and during the once weekly instillation (cases 2, 3, 5, and 7; Figure 4), two of whom (cases 2 and 3) were overlapped.

None of the participants exhibited serious ocular or systemic side effects. Cases 2 and 3 had mild conjunctival injection during once daily instillation, which spontaneously subsided during the washout period.

Table 1. Participants' age (years) and intraocular pressure (mmHg)

Case	1	2	3	4	5	6	7	8
age	55	41	38	34	37	34	32	28
Baseline	11.5/11.0	11.0/13.0	13.5/14.5	13.0/14.0	10.5/10.0	13.0/11.5	10.0/12.0	14.0/15.0
Post 1st	9.5/12.0	7.5/13.0	9.0/10.0	12.5/14.0	10.0/10.0	10.5/7.5	14.5/13.5	7.5/14.5
Post 4th	8.5/11.5	5.5/10.0	11.5/12.5	12.5/13.5	10.0/10.0	11.0/7.0	10.5/11.0	10.0/14.0
Post 8th	10.0/13.0	7.5/11.0	10.0/11.0	13.0/13.5	7.5/9.0	10.0/7.0	9.0/10.0	8.5/14.5
Post 11th	11.5/13.0	6.5/13.0	8.5/11.5	14.5/11.0	10.5/11.0	6.5/8.0	10.0/12.5	10.0/14.5
Post 15th	10.0/12.5	4.5/10.0	13.0/13.5	13.0/13.5	10.5/11.0	7.5/8.5	12.0/15.0	9.5/12.5
Post 18th	9.5/13.5	6.0/13.0	10.0/15.0	11.0/12.0	11.0/9.0	10.0/9.0	11.5/12.0	10.0/15.0
Post 22nd	11.0/12.5	6.0/14.0	8.5/12.0	12.0/13.0	9.0/10.0	8.0/8.5	12.5/18.0	8.0/13.0
Post 25th	10.0/13.0	10.0/18.0	11.0/12.0	12.0/13.0	10.0/10.5	10.5/11.0	10.5/11.5	9.5/13.0
Washout	12.0/12.0	10.0/11.0	15.5/13.0	14.5/14.0	12.5/12.0	9.5/9.0	14.5/15.5	12.0/13.0
Post 1st	10.5/11.0	10.0/13.0	13.0/13.0	14.0/15.5	10.5/9.5	12.5/10.5	12.5/14.0	10.5/12.0
Post 4th	10.5/9.5	7.5/12.0	15.5/14.5	14.0/12.0	8.0/9.0	10.5/12.0	11.5/14.0	9.5/12.5
Post 8th	11.0/13.5	6.0/13.0	10.0/12.0	14.0/18.0	11.0/11.0	12.0/10.0	12.0/13.5	12.5/15.0
Post 11th	13.5/12.0	7.0/10.0	10.5/14.0	13.0/15.5	8.5/11.5	10.5/10.5	12.5/12.5	11.0/15.5
Post 15th	10.0/12.0	8.0/12.0	12.5/14.5	13.0/13.5	9.5/10.5	11.5/11.5	9.5/11.5	12.5/15.0
Post 18th	14.0/13.0	14.0/15.0	12.0/13.0	14.0/13.0	11.0/12.0	10.5/7.5	14.0/14.0	9.5/13.5
Post 22nd	11.5/12.5	7.0/14.0	12.5/13.5	13.0/14.0	13.5/11.5	11.0/8.5	12.0/14.0	8.0/12.5
Post 25th	11.5/12.0	8.5/11.0	13.0/13.5	13.5/12.5	12.5/12.5	12.5/7.5	13.5/14.5	11.5/14.0

Intraocular pressure is expressed as right eye / left eye.

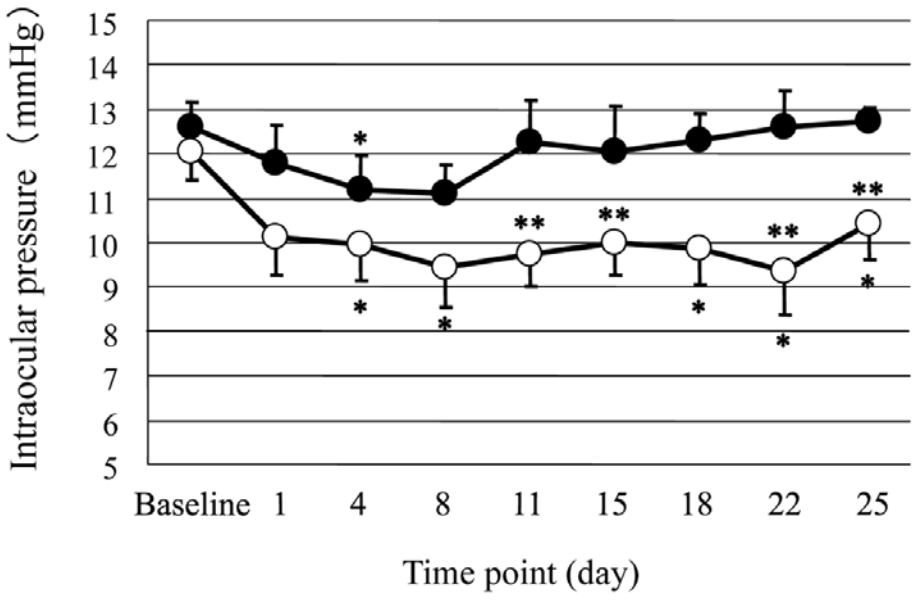

Figure 1. Time course of changes in intraocular pressure (IOP) at baseline and during once daily instillation of latanoprost. Open circles depict right eyes receiving 0.005% latanoprost at 10 p.m., whereas closed circles depict left eyes untreated. Bar stands for standard error of the mean. n = 8. *, $p<0.05$ as compared with baseline IOP. **, $p < 0.05$ between eyes.

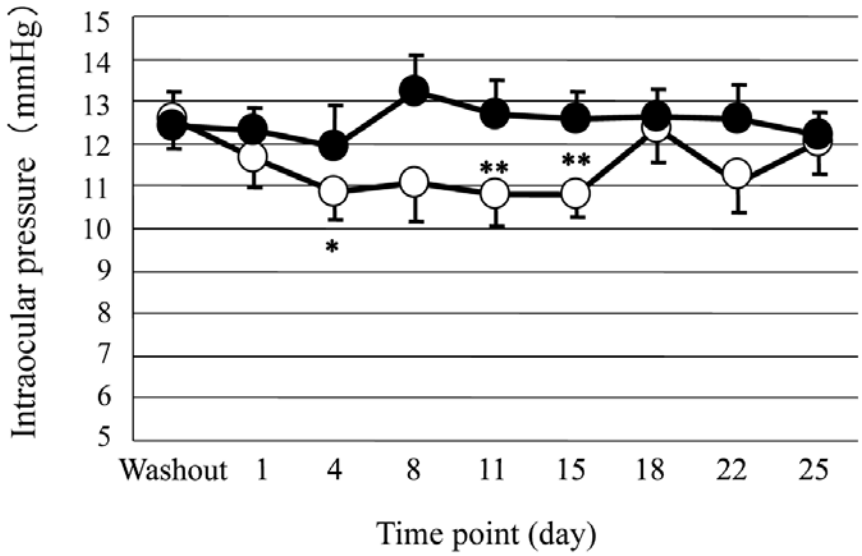

Figure 2. Time course of intraocular pressure (IOP) changes at 28 days after washout of the previous once daily instillation of latanoprost and during once weekly instillation of latanoprost. Open circles depict right eyes receiving 0.005% latanoprost at 10 p.m. on every Monday for 4 weeks, whereas closed circles depict left eyes untreated. Bar stands for standard error of the mean. n = 8. ∗, $p < 0.05$ as compared with baseline IOP. ∗∗, $p < 0.05$ between eyes.

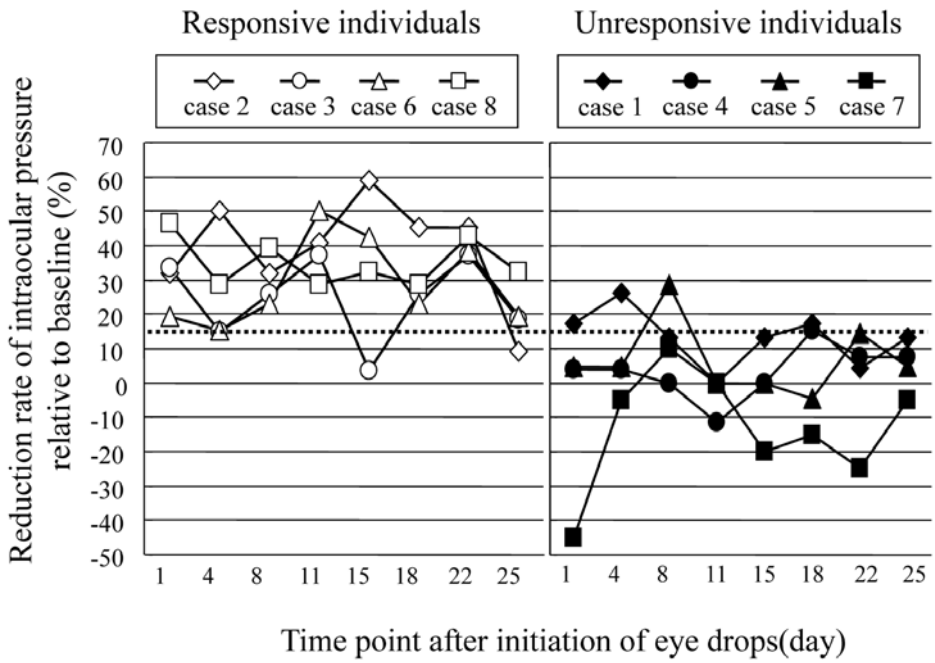

Figure 3. Time course of changes in the reduction rate of intraocular pressure (IOP) during once daily instillation of latanoprost. The IOP reduction rate (%) is defined as baseline IOP minus post-treatment IOP divided by baseline IOP, which is multiplied by 100. Dotted line indicates the border of 15% reduction rate.

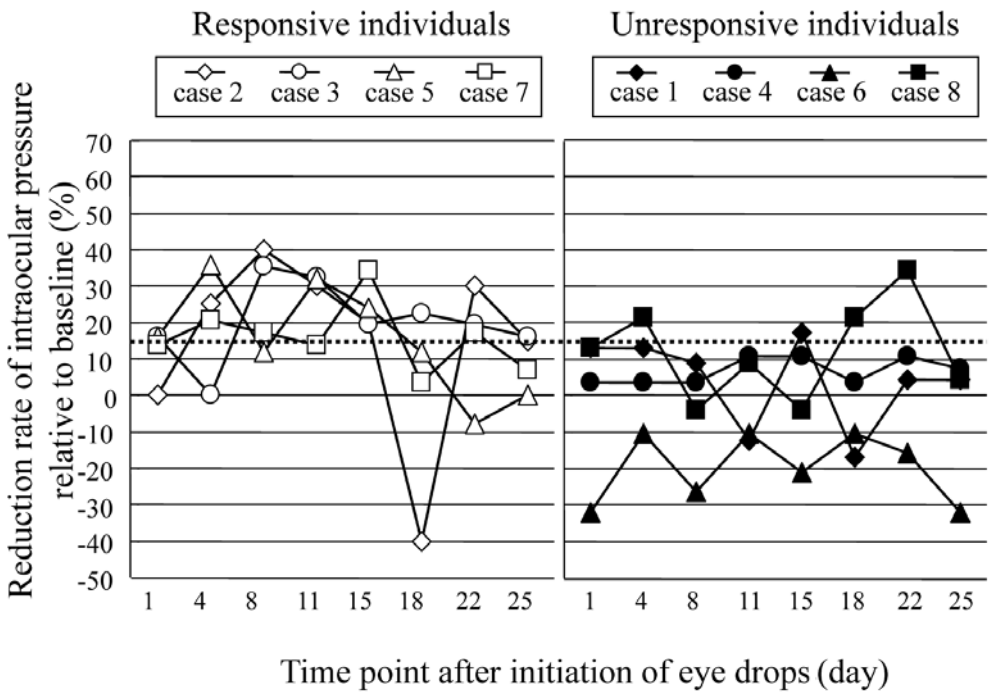

Figure 4. Time course of changes in the reduction rate of intraocular pressure (IOP) during once weekly instillation of latanoprost. The IOP reduction rate (%) is defined as washout IOP minus post-treatment IOP divided by washout IOP, which is multiplied by 100. Dotted line indicates the border of 15% reduction rate.

DISCUSSION

The current pilot study demonstrated that once daily instillation of latanoprost was superior in average to once weekly instillation regarding IOP reduction. On the other hand, 15% or more reduction in IOP was observed in half of the participants both during once daily administration and during once weekly administration, although the magnitude of the IOP reduction in the responders was greater during the once daily use than during the once weekly use. Thus, the overall superiority of IOP lowering effect with once daily instillation to once weekly instillation was attributed to the difference in magnitude of the IOP reduction in the responders under the two protocols.

Previous reports (6, 8, 9) indicated that some individuals required quite long time for washout IOP to return to baseline IOP after discontinuation of latanoprost use. For instance, Linden and Alm (9) showed that IOP three weeks after washing out latanoprost was significantly lower than the pretreatment IOP. If the IOP lowering effect had been sustained long after once daily instillation, the reduced IOP seen in some individuals during the once weekly protocol would have been artificial. However, this was not the case because of two reasons. First, the IOPs measured on 28 days after discontinuation of daily latanoprost instillation did not differ from the baseline IOPs. Second, 2 of the 4 subjects who showed 15 % or greater IOP reduction during the once daily use did not during the once weekly use and vice versa.

The mechanism why only once weekly instillation exerted the IOP lowering effect to some extent in some normal individuals is unknown. Recent studies demonstrated that

latanoprost is involved in the remodeling of the extracellular matrix in the ciliary muscle (10-12), trabecular meshwork (10), and sclera (13). Thus, one possible explanation is that some individuals who are very sensitive to latanoprost may undergo rapid and sustained alterations of extracellular matrix compositions in the uveoscleral outflow.

Another intriguing observation in the current study is partial discordance of IOP responders during once daily and once weekly instillation. It is well known that once daily dosing of latanoprost is superior to twice daily dosing in terms of IOP reduction (14-17). Although the precise mechanism of this is not clear, some claims a modest desensitization of the FP receptor (14). If this is the case, some individuals might be induced to desensitize the FP receptor even in the once daily instillation of latanoprost. However, caution must be made in defining the responders. As reported by Camras and his colleagues (6), the proportion of individuals who do not initially well respond and will become responders with prolonged use of latanoprost may be higher as compared with timolol use. Additional studies using different frequency of instillation with larger number of subjects are required to test this hypothesis.

Although the previous report (5) showed that latanoprost treatment once weekly was as effective as once daily treatment after 3 months follow-up, the overall IOP lowering effect with once weekly use was inferior to the once daily use of latanoprost in the current study. The discrepancy of our and their findings may be due to the small sample size and the difference in subject enrollment. The previous study tested patients with glaucoma or ocular hypertension (5), while the current one tested ophthalmologically normal individuals. The response to ocular hypotensive agents may be different between normal controls and patients with glaucoma. However, the present study indicated that even in individuals who had 15% or greater IOP reduction with once weekly instillation of latanoprost, the magnitude of IOP reduction was less than those with once daily instillation. Thus, the currently used regimen of once daily administration of latanoprost should be respected until further studies, which show that the reduced instillation frequency will apparently decrease the side effect and maintain the similar effectiveness in terms of IOP reduction.

ACKNOWLEDGEMENTS

This study is partly supported by Grand-in-Aid No. 16390499 (AN, MN) and No. 17591835 (MN) form the Ministry of Education, Culture, Sports, Science and Technology of the Japanese Government and by Suda Memorial Foundation for Glaucoma Research (MN).

REFERENCES

1. **van der Valk, R., Webers, C. A., Schouten, J. S., Zeegers, M. P., Hendrikse, F., and Prins, M. H.** 2005. Intraocular pressure-lowering effects of all commonly used glaucoma drugs: a meta-analysis of randomized clinical trials. Ophthalmology **112**: 1177-1185
2. **Toris, C. B., Camras, C. B., and Yablonski, M. E.** 1993. Effects of PhXA41, a new prostaglandin F2 alpha analog, on aqueous humor dynamics in human eyes. Ophthalmology **100**: 1297-1304
3. **Sharif, N. A., Kelly, C. R., Crider, J. Y., Williams, G. W., and Xu, S. X.** 2003. Ocular hypotensive FP prostaglandin (PG) analogs: PG receptor subtype binding affinities and selectivities, and agonist potencies at FP and other PG receptors in cultured cells. J Ocul Pharmacol Ther **19**: 501-515
4. **Alm, A., and Stjernschantz, J.** 1995. Effects on intraocular pressure and side effects of

0.005% latanoprost applied once daily, evening or morning. A comparison with timolol. Scandinavian Latanoprost Study Group. Ophthalmology **102**: 1743-1752

5. **Kurtz, S., and Shemesh, G.** 2004. The efficacy and safety of once-daily versus once-weekly latanoprost treatment for increased intraocular pressure. J Ocul Pharmacol Ther **20**: 321-327
6. **Camras, C. B., and Hedman, K.** 2003. Rate of response to latanoprost or timolol in patients with ocular hypertension or glaucoma. J Glaucoma **12**: 466-469
7. **Dielemans, I., Vingerling, J. R., Hofman, A., Grobbee, D. E., and de Jong, P. T.** 1994. Reliability of intraocular pressure measurement with the Goldmann applanation tonometer in epidemiological studies. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie **232**: 141-144
8. **Stewart, W. C., Holmes, K. T., and Johnson, M. A.** 2001. Washout periods for brimonidine 0.2% and latanoprost 0.005%. Am J Ophthalmol **131**: 798-799
9. **Linden, C., and Alm, A.** 2001. The effect on intraocular pressure of latanoprost once or four times daily. Br J Ophthalmol **85**: 1163-1166
10. **Zhao, X., Pearson, K. E., Stephan, D. A., and Russell, P.** 2003. Effects of prostaglandin analogues on human ciliary muscle and trabecular meshwork cells. Invest Ophthalmol Vis Sci **44**: 1945-1952
11. **Ocklind, A.** 1998. Effect of latanoprost on the extracellular matrix of the ciliary muscle. A study on cultured cells and tissue sections. Exp Eye Res **67**: 179-191
12. **Lindsey, J. D., Kashiwagi, K., Kashiwagi, F., and Weinreb, R. N.** 1997. Prostaglandins alter extracellular matrix adjacent to human ciliary muscle cells in vitro. Invest Ophthalmol Vis Sci **38**: 2214-2223
13. **Weinreb, R. N., Lindsey, J. D., Marchenko, G., Marchenko, N., Angert, M., and Strongin, A.** 2004. Prostaglandin FP agonists alter metalloproteinase gene expression in sclera. Invest Ophthalmol Vis Sci **45**: 4368-4377
14. **Linden, C., and Alm, A.** 1998. Latanoprost twice daily is less effective than once daily: indication of receptor subsensitivity? Curr Eye Res **17**: 567-572
15. **Linden, C., and Alm, A.** 1997. Effects on intraocular pressure and aqueous flow of various dose regimens of latanoprost in human eyes. Acta Ophthalmol Scand **75**: 412-415
16. **Watson, P., and Stjernschantz, J.** 1996. A six-month, randomized, double-masked study comparing latanoprost with timolol in open-angle glaucoma and ocular hypertension. The Latanoprost Study Group. Ophthalmology **103**: 126-137
17. **Camras, C. B.** 1996. Comparison of latanoprost and timolol in patients with ocular hypertension and glaucoma: a six-month masked, multicenter trial in the United States. The United States Latanoprost Study Group. Ophthalmology **103**: 138-147