Clinical Study

A Prospective Study Evaluating IOP Changes after Switching from a Therapy with Prostaglandin Eye Drops Containing Preservatives to Nonpreserved Tafluprost in Glaucoma Patients

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Purpose. To compare the ocular hypotensive effect of tafluprost with prostaglandin analogues (PGAs) in glaucoma patients.

Methods. 89 primary open-angle glaucoma patients treated with bimatoprost, latanoprost, or travoprost for at least 3 months complaining for ocular discomfort were switched to tafluprost. IOP was assessed at baseline and 3 months after switching the therapy by daily curve. Primary outcome was to compare the mean daily IOP of tafluprost with PGAs. Results. The mean daily IOP was 16 ± 2.1 and 16.6 ± 2.0 mm Hg at baseline and after switching to tafluprost, respectively (P > 0.05). When analysis was carried out between tafluprost and each previous PGAs, the comparison between latanoprost and tafluprost and travoprost and tafluprost did not show any statistically significant difference in mean daily IOP and at each time point. The comparison between bimatoprost and tafluprost showed a statistically significant difference in mean daily IOP (P < 0.05) and at each time point (P < 0.05). Conclusions. After 3 months of switching tafluprost showed an overall IOP lowering effect similar to others PGAs. When each PGA was compared with tafluprost, bimatoprost showed to provide a statistically significant additional IOP lowering effect.

1. Introduction

Intraocular pressure (IOP) is known to be the main risk factor for development and progression of glaucoma [1, 2]. Lowering intraocular pressure is the only evidence-based method for treating glaucoma, reducing the risk of visual field progression from 13% to 19% per 1 mmHg of IOP lowering [3, 4].

According to the European Glaucoma Society Guidelines, topical monotherapy is the first step in the medical management [1].

Among the many topical hypotensive medications, prostaglandin analogues (PGAs) are proved to be the most potent in lowering IOP and with very few systemic side effects [5, 6].

PGAs were first proposed for glaucoma treatment by Camras et al. in 1977 [7]. Nowadays, derivatives of prostaglandin F₂α, that is, latanoprost, travoprost, unoprostone, prostamide, and bimatoprost are commercially available. In van der Valk’s meta-analysis, latanoprost reduced IOP by 28%–31% from baseline, travoprost by 29%–31%, and bimatoprost by 28%–33%. Latanoprost and travoprost are selective prostanoid FP receptor agonists, and by binding to these receptors they exert their IOP-lowering effect [7, 8].

Bimatoprost is a prostamide, with a molecular mechanism of action not clearly understood [9, 10].

All these compounds decrease IOP by increasing aqueous outflow, mainly through the uveoscleral (unconventional) route [11].
2. Methods

This prospective clinical study was carried out at the Eye Clinic of the University of Milan, San Giuseppe Hospital, Milan, Italy, and it was approved by the local Ethical Committee conducted according to ICH/GCP guidelines. Patients of 18 years or older who fulfilled the eligibility criteria were recruited consecutively during routine visits and included in the study.

2.1. Inclusion Criteria. Patients with diagnosis of primary open-angle glaucoma based on the European Glaucoma Society Guidelines criteria, [5] treated with latanoprost, travoprost, or bimatoprost monotherapy for at least 3 months, complaining for ocular surface discomfort with baseline IOP less than 21 mmHg at all-time point with target IOP reached as set by the treating physician, were considered for the study.

2.2. Exclusion Criteria. Exclusion criteria included closed or barely open anterior chamber angle, or history of acute angle closure ocular trauma, history of ocular surgery, argon laser trabeculoplasty, ocular inflammation or infection occurring within 3 months before the baseline visit, neovascular glaucoma, history of refractive surgery, inability to adhere to the treatment and visit plan, other abnormal condition, or symptom preventing the patient from entering the trial, according to the investigator’s judgment.

2.3. Study Plan. Patients treated with latanoprost, travoprost, or bimatoprost monotherapy for at least 3 months, IOP less than 21 mmHg, target IOP reached with ocular surface discomfort were enrolled in the study. At the baseline visit, a medical history was taken for all the subjects. All the subjects underwent a complete ophthalmic examination including anterior segment biomicroscopy and fundus examination, refraction and measurement of best-corrected visual acuity (BCVA) by means of Snellen chart. A masked operator (SR) measured IOP at 8 AM, 11 AM, 2 PM, 5 PM, and 8 PM by Goldmann application tonometry. If both eyes fulfilled the eligibility criteria, one eye was randomly selected for the study.

Patients were switched to tafluprost monotherapy without washout between the treatments. Assessment of IOP and tolerability were carried out 3-month after switching the therapy by the same masked operator (SR). The investigator could choose to have a nonscheduled safety visit between the scheduled visit. IOP mean value at each time point was calculated as a mean of three IOP diurnal curves carried out within three weeks at baseline and after 3 months.

2.4. Study Outcomes. The primary outcome was to compare the mean diurnal IOP from the daily curve after 3 months of tafluprost treatment compared to preservative prostaglandin analogue (latanoprost, travoprost, and bimatoprost). Secondary outcome was to compare the diurnal mean IOP of the tafluprost treatment after 3 months with each previous preservative PGAs treatment group as mean IOP and for each time point separately (8 AM, 11 AM, 2 PM, 5 PM, 8 PM).
2.5. Clinical Tolerability Assessments. Best-corrected visual acuity (BCVA) by means of Snellen chart, biomicroscopy, and ophtalmoscopy were recorded at the baseline visit and at each follow-up visit. Any kind of adverse event was recorded. Change of conjunctival hyperemia was recorded at the slit lamp using a standard scale ranging from 0 to 3 (where 0 is none, 1 is mild, 2 is moderate, and 3 is severe) with the help of a standardized photographic chart [26]. Superficial keratitis, defined as the presence of small circular epithelial erosion in the cornea, was also graded as none, mild, moderate, and severe (none: no staining; mild: rare stained erosion localized close to the lid margins; moderate: rare stained erosion localized in the 4 quadrants; diffuse: diffuse stained erosion involving the 4 quadrants).

2.6. Analysis. Data are presented as mean and 95% confidence intervals for continuous variables and frequencies for categorical variable. For the IOP recording, the mean values of 2 measurements at each time point were used in the calculations. If both eyes fulfilled the eligibility criteria, only one eye was randomly selected. An intent-to-treat approach was used to analyze the IOP variables. Categorical variables such as proportions and tolerability variable were analyzed using the Pearson chi-square test of Fisher exact test as appropriate.

Formal sample size was calculated in order to assess the difference between treatments. Assuming Δ 2.3 mmHg (based on previously published data) [27] and using the formula:

\[ n = \frac{\left( \Phi^{-1}(a/2) + \Phi^{-1}(\beta) \right)^2 \sigma^2}{\Delta^2}, \]  

where \( \alpha = 0.05 \) and \( 1 - \beta = 0.80 \), a sample of 85 patients was needed to ensure a 95% chance of detecting a difference between the different treatments groups.

3. Results

A total of 91 patients were enrolled in this study, and 89 (mean age 64.7 ± 10.4) were included in the analysis (29 patients were under latanoprost, 28 under travoprost, and 32 under bimatoprost). Two patients were lost to followup without performing any follow-up visit and were excluded from the analysis. During the study we did not observe any adverse events.

3.1. Primary Outcome. Table 1 reports the mean daily IOP at baseline and after 3 months of treatment with tafluprost. After 3 months of treatment, mean daily IOP was not statistically different significantly compared with the baseline (+0.6 mmHg, \( P > 0.05 \)). No interaction between drug and treatment sequence was detected, indicating no carry-over effects between drugs.

Figure 1 reports the mean IOP value for each time point from the daily curve of tafluprost and PGAs treatment group. For each time point, separately, no differences were detected in mean IOP between the two groups (15.4 ± 2.4 versus 16 ± 2.3 at 8:00 AM, 15.6 ± 2.3 versus 16.1 ± 2.4 at 11 AM, 16.0 ± 2.4 versus 16.5 ± 2.4 at 2 PM, 16.1 ± 1.8 versus 16.8 ± 2.1 at 5 PM, 16.7 ± 2.6 versus 17.4 ± 1.8 at 8 PM, \( P > 0.05 \) for each time point).

Globally, the incidence of local adverse events was similar in both treatments; mean conjunctival hyperemia was 1.2 ± 0.8 with preservative PGAs, and 1.0 ± 0.6 with tafluprost (\( P = 0.06 \)), mean punctuate keratitis was 0.8 ± 0.6 with PGAs, and 0.8 ± 0.6 with tafluprost (\( P = 0.2 \)).

In 75% of the patients, there was an improvement of ocular discomfort, in 21% of patients ocular discomfort was unchanged, and in 4% there was a worsening of ocular symptoms.

3.2. Secondary Outcome. Figure 2 reports the comparison among the mean IOP value for each time point from the daily IOP curve of the four treatment groups. Comparing latanoprost to tafluprost treatment, no differences were found in mean IOP (16.5 ± 2.3 versus 16.6 ± 2.0, \( P = 0.85 \)) and at each time point (15.9 ± 2.6 versus 16.0 ± 2.3 at 8:00 AM, 15.6 ± 2.3 versus 16.1 ± 2.4 at 11 AM, 16.0 ± 2.4 versus 16.5 ± 2.4 at 2 PM, 16.1 ± 1.8 versus 16.8 ± 2.1 at 5 PM, 16.7 ± 2.6 versus 17.4 ± 1.8 at 8 PM, \( P > 0.05 \) for each time point).

No differences were found in conjunctival hyperemia and punctuate keratitis between the two groups (\( P = 0.8 \) and \( P = 0.9 \), resp.).

Comparing travoprost to tafluprost treatment, no differences were found in mean IOP (15.9 ± 2.5 versus 16.6 ± 2.0, \( P = 0.15 \)) and at each time point (15.3 ± 2.5 versus 16.0 ± 2.3 at 8:00 AM, 15.5 ± 2.5 versus 16.1 ± 2.8 at 11 AM, 16.1 ± 2.8 versus 16.5 ± 2.4 at 2 PM, 16.1 ± 1.9 versus 16.8 ± 2.1 at 5 PM, 16.5 ± 2.7 versus 17.4 ± 1.8 at 8 PM, \( P > 0.05 \) for each time point).

No differences were found in conjunctival hyperemia and punctuate keratitis between the two groups (\( P = 0.1 \) and \( P = 0.3 \), resp.).
Comparing bimatoprost to tafluprost treatment a statistically significant difference was found in mean IOP (15.6 ± 1.8 versus 16.6 ± 2.0, *P = 0.01) with a mean increase of 1 mmHg of IOP.

A significant difference in IOP was found at each time point (15.0 ± 2.4 versus 16.0 ± 2.3 at 8:00 AM, 15.1 ± 1.7 versus 16.1 ± 2.4 at 11 AM, 15.1 ± 2.0 versus 16.5 ± 2.4 at 2 PM, 15.7 ± 1.6 versus 16.8 ± 2.1 at 5 PM, 16.5 ± 2.4 versus 17.4 ± 1.8 at 8 PM, P < 0.05 for each time point).

The severity of conjunctival hyperemia and punctuate keratitis was higher with bimatoprost compared to tafluprost (1.3 ± 0.9 versus 1.0 ± 0.6, *P = 0.02 for conjunctival hyperemia and 0.9 ± 0.7 versus 0.7 ± 0.6, *P = 0.04 for punctuate keratitis).

### 4. Discussion

This prospective study aims to compare the IOP lowering effect of tafluprost with other PGAs in patients with glaucoma, with signs and symptoms of ocular discomfort. Published studies suggest that the IOP lowering effect of tafluprost is similar to other PGAs with a better local safety profile due to the absence of BAK [14, 22, 24, 25]. Several study has been published about safety and efficacy profile of tafluprost in vitro [19, 21, 23] and in animal models [7, 12, 14, 22, 25, 26], but few studies analyse the IOP lowering effect in a clinical setting in patients with glaucoma and ocular hypertension [28–32].

The primary outcome of this study was to compare the IOP lowering effect of tafluprost with all other BAK preserved PGAs.

After 3 months of treatment the mean daily IOP was not statistically significant different compared with preserved PGAs.

The comparison among the single PGAs and tafluprost showed a comparable efficacy between latanoprost and tafluprost (*P = 0.85) and between travoprost and tafluprost (*P = 0.15). The mean daily IOP and the IOP at any time point did not show any significant difference.

The bimatoprost group showed a statistically lower mean IOP, as compared to tafluprost (*P = 0.01), and the IOP lowering effect was statistically greater at any time point of the diurnal IOP curve.

The analysis of the ocular surface disorders showed no statistically difference between latanoprost and tafluprost and between travoprost and tafluprost. Bimatoprost showed to induced a slightly higher conjunctival hyperemia and punctuate keratitis compared to tafluprost (*P < 0.05).

Only few published studies compared tafluprost with other PGAs [28–32]. Most of them compare tafluprost with latanoprost [30, 31, 33]. There is only one study comparing tafluprost with travoprost [28] and none with bimatoprost.

In a recently published study [28] comparing efficacy of tafluprost with travoprost in patients with glaucoma or ocular hypertension, the authors found a statistically significant greater IOP lowering efficacy with travoprost compared to tafluprost (16.9 mmHg versus 17.5 mmHg, resp., *P = 0.01), with a similar safety profile for both the treatments.

Our study involved only glaucoma patients, whereas glaucoma and ocular hypertension patients were enrolled in Schnober study [34]. The different population involved could explain the different results.

In the study by Mochizuki et al. [28], the comparison between tafluprost and latanoprost in a group of healthy volunteers showed a statistically greater IOP reduction with tafluprost. In this study tafluprost was associated with a higher rate of conjunctival hyperemia.

Uusitalo et al. [29] investigated the efficacy of tafluprost in patients treated with latanoprost exhibiting ocular surface side effects. 158 patients were switched from latanoprost to tafluprost. After 12 weeks, tafluprost maintained the IOP at the same value as latanoprost baseline (16.4 ± 2.7 mmHg versus 16.8 ± 2.5 mmHg, resp.) with a decrease in subjective symptoms and objective signs.

Another study by Traverso et al. [30] reports the IOP lowering efficacy of tafluprost in patients previously treated with latanoprost. A preservative formulation of tafluprost was used in this trial. The lowering effect at 24 months was
−7.1 mmHg and −7.7 mmHg in tafluprost and latanoprost group, respectively. Although a slightly larger IOP lowering effect of latanoprost, the ANOVA test showed a noninferiority of tafluprost to latanoprost.

Efficacy of tafluprost was compared with latanoprost in glaucoma and ocular hypertension patients in a recent published randomized, controlled study [31]. The mean IOP reduction was −9.7/−3.3 mmHg in the tafluprost group and −8.8 ± 4.3 mmHg in the latanoprost group, respectively. The difference was not significantly different, and the author concluded that both tafluprost and latanoprost have a comparable effect on IOP lowering effect.

In agreement with published studies conducted with glaucoma patients, we found a similar efficacy of tafluprost compared to latanoprost. In the Mochizuki study, healthy patients were enrolled. The different results of this study are likely to depend on the different population.

Hommer [31] recently published a large series of 544 patients with glaucoma or ocular hypertension treated with preserved eye drops and poor IOP control or poor local tolerance. In these patients previous medications were changed to BAK free PGAs (latanoprost 0.005%, travoprost 0.004%, bimatoprost 0.03%) with the new unpreserved PGA (tafluprost 0.0015%). Tafluprost demonstrated a IOP lowering effect similar to others PGAs and after 3 months of therapy with tafluprost the mean IOP showed no difference between tafluprost and BAK preserved PGAs.

Tafluprost showed, towards other PGAs, comparable efficacy and a safe profile. Furthermore in this study bimatoprost seems to provide a statistically significant additional IOP lowering effect compared to patients treated with tafluprost.

Disclosure

The authors do not have any proprietary or financial interest in this study.

References

[1] M. O. Gordon, J. A. Beiser, J. D. Brandt et al., “The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma,” Archives of Ophthalmology, vol. 120, no. 6, pp. 714–720, 2002.
[2] C. Wesselink, M. W. Markus, and N. M. Jansonius, “Risk factors for visual field progression in the Groningen Longitudinal Glaucoma Study: a comparison of different statistical approaches,” Journal of Glaucoma. In press.
[3] M. C. Leskea, A. Heijl, L. Hyman, B. Bengtsson, and E. Komaroff, “Factors for progression and glaucoma treatment: the Early Manifest Glaucoma Trial,” Current Opinion in Ophthalmology, vol. 15, no. 2, pp. 102–106, 2004.
[4] The AGIS Investigators, “The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration,” American Journal of Ophthalmology, vol. 130, no. 4, pp. 429–440, 2000.
[5] European Glaucoma Society (EGS), Terminology and Guidelines for Glaucoma, Editrice Dogma s.r.l., Savona, Italy, 3rd edition, 2008.
[6] T. Hamacher, J. Airaksinen, V. Saarela, M. J. Liinamaa, U. Richter, and A. Ropo, “Efficacy and safety levels of preserved and preservative-free tafluprost are equivalent in patients with glaucoma or ocular hypertension: Results from a pharmacodynamics analysis,” Acta Ophthalmologica, vol. 86, supplement 242, pp. 14–19, 2008.
[7] C. B. Camras, L. Z. Bito, and K. E. Eakins, “Reduction of intraocular pressure by prostaglandins applied topically to the eyes of conscious rabbits,” Investigative Ophthalmology and Visual Science, vol. 16, no. 12, pp. 1125–1134, 1977.
[8] T. Nakajima, T. Matsugi, W. Goto et al., “New fluoroprostaglandin F2α derivatives with prostanoid FP-receptor agonistic activity as potent ocular-hypotensive agents,” Biological and Pharmaceutical Bulletin, vol. 26, no. 12, pp. 1691–1695, 2003.
[9] T. Ota, M. Aihara, S. Narumiya, and M. Araie, “Effects of prostanoid-analogues on IOP in prostaglandin FP receptor deficient mice,” Investigative Ophthalmology & Visual Science, vol. 46, no. 11, pp. 4158–4163, 2005.
[10] T. Ota, M. Aihara, S. Narumiya, and M. Araie, “Effects of prostanoid-analogues on IOP in prostaglandin FP receptor deficient mice,” Investigative Ophthalmology & Visual Science, vol. 26, no. 12, pp. 1691–1695, 2003.
[11] D. J. Oh, J. L. Martin, A. J. Williams, P. Russell, D. E. Birk, and D. J. Rhee, “Effect of latanoprost on the expression of matrix metalloproteinases and their tissue inhibitors in human
trabecular meshwork cells,” *Investigative Ophthalmology and Visual Science*, vol. 47, no. 9, pp. 3887–3895, 2006.

[12] N. Ishida, N. Odani-Kawabata, A. Shimazaki, and H. Hara, “Prostanoids in the therapy of glaucoma,” *Cardiovascular Drug Reviews*, vol. 24, no. 1, pp. 1–10, 2006.

[13] S. F. Nilsson, E. Drecoll, E. Lutjen-Drecoll et al., “The prostanoid EP2 receptor agonist butaprost increases uveoscleral outflow in the cynomolgus monkey,” *Investigative Ophthalmology & Visual Science*, vol. 47, no. 9, pp. 4042–4049, 2006.

[14] M. Aihara, “Clinical appraisal of tafluprost in the reduction of elevated intraocular pressure (IOP) in open-angle glaucoma and ocular hypertension,” *Clinical Ophthalmology*, vol. 4, no. 1, pp. 163–170, 2010.

[15] Y. Takagi, T. Nakajima, A. Shimazaki et al., “Pharmacological characteristics of AFP-168 (tafluprost), a new prostanoid FP receptor agonist, as an ocular hypotensive drug,” *Experimental Eye Research*, vol. 78, no. 4, pp. 767–776, 2004.

[16] C. Baudouin, “Side effects of antiglaucomatous drugs on the ocular surface,” *Current Opinion in Ophthalmology*, vol. 7, no. 2, pp. 80–86, 1996.

[17] J. Shimazaki, K. Hanada, Y. Yagi et al., “Changes in ocular surface caused by antiglaucomatous eyedrops: Prospective, randomised study for the comparison of 0.5% timolol v 0.12% unoprostone,” *British Journal of Ophthalmology*, vol. 84, no. 11, pp. 1250–1254, 2000.

[18] D. Pozarowska, P. Pozarowski, and Z. Darzynkiewicz, “Cytometric assessment of cytostatic and cytotoxic effects of topical glaucoma medications on human epithelial corneal line cells,” *Cytometry Part B - Clinical Cytometry*, vol. 78, no. 2, pp. 130–137, 2010.

[19] G. Martone, P. Frezzotti, G. M. Tosi et al., “An in vivo confocal microscopy analysis of effects of topical antiglaucoma therapy with preservative on corneal innervation and morphology,” *American Journal of Ophthalmology*, vol. 147, no. 4, pp. 725–735, 2009.

[20] M. De Saint Jean, C. Debbasch, F. Brignole, P. Rat, J. M. Warnet, and C. Baudouin, “Toxicity of preserved and unprepared antiglaucoma topical drugs in an in vitro model of conjunctival cells,” *Current Eye Research*, vol. 20, no. 2, pp. 85–94, 2000.

[21] H. Liang, C. Baudouin, A. Pauly, and F. Brignole-Baudouin, “Conjunctival and corneal reactions in rabbits following short- and repeated exposure to preservative-free tafluprost, commercially available latanoprost and 0.02% benzalkonium chloride,” *British Journal of Ophthalmology*, vol. 92, no. 9, pp. 1275–1282, 2008.

[22] M. Centofanti, F. Oddone, M. Vetrugno et al., “Efficacy of the fixed combinations of bimatoprost or latanoprost plus timolol in patients uncontrolled with prostaglandin monotherapy: a multicenter, randomized, investigator-masked, clinical study,” *European Journal of Ophthalmology*, vol. 19, no. 1, pp. 66–71, 2009.

[23] H. Mochizuki, H. Itakura, T. Yokoyama, M. Takamatsu, and Y. Kiuchi, “Twenty-four-hour ocular hypotensive effects of 0.0015% tafluprost and 0.005% latanoprost in healthy subjects,” *Japanese Journal of Ophthalmology*, vol. 54, no. 4, pp. 286–290, 2010.

[24] H. Usualto, L. E. Pillunat, and A. Ropo, “Efficacy and safety of tafluprost 0.0015% versus latanoprost 0.005% eye drops in open-angle glaucoma and ocular hypertension: 24-month results of a randomized, double-masked phase III study,” *Acta Ophthalmologica*, vol. 88, no. 1, pp. 12–19, 2010.

[25] C. E. Traverso, A. Ropo, M. Papadia, and H. Usualto, “A phase II study on the duration and stability of the intraocular pressure-lowering effect and tolerability of tafluprost compared with latanoprost,” *Journal of Ocular Pharmacology and Therapeutics*, vol. 26, no. 1, pp. 97–104, 2010.

[26] A. Hommer, O. Mohammed Ramez, M. Burchert, and F. Kimmich, “IOP-lowering efficacy and tolerability of preservative-free tafluprost 0.0015% among patients with ocular hypertension or glaucoma,” *Current Medical Research and Opinion*, vol. 26, no. 8, pp. 1905–1913, 2010.

[27] M. Centofanti, F. Oddone, S. Gandolfi et al., “Comparison of travoprost and bimatoprost plus timolol fixed combinations in open-angle glaucoma patients previously treated with latanoprost plus timolol fixed combination,” *American Journal of Ophthalmology*, vol. 150, no. 4, pp. 575–580, 2010.

[28] H. Usualto, E. Chen, N. Pfeiffer et al., “Switching from a preserved to a preservative-free prostaglandin preparation in topical glaucoma medication,” *Acta Ophthalmologica*, vol. 88, no. 3, pp. 329–336, 2010.

[29] D. Schnober, G. Hofmann, H. Maier, M. L. Scherzer, A. B. Ogundele, and M. C. Jasek, “Diurnal IOP-lowering efficacy and safety of travoprost 0.004% compared with tafluprost 0.0015% in patients with primary open-angle glaucoma or ocular hypertension,” *Clinical Ophthalmology*, vol. 4, no. 1, pp. 1459–1463, 2010.