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ORIGINAL RESEARCH

Effects of tafluprost treatment for 3 years in patients with normal-tension glaucoma

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Purpose: To evaluate the effects of tafluprost treatment for 3 years on intraocular pressure (IOP) and visual field performance.

Methods: The IOP of 55 patients with normal-tension glaucoma was monitored every 1–3 months for 3 years. The Humphrey visual field test was performed every 6 months after treatment and results compared with before-treatment results. Visual field performance was also evaluated by trend and event analysis.

Results: After 3 years' tafluprost single-use vials treatment, the IOP (12.8 ± 2.8 mmHg [mean ± standard deviation]) was significantly lower than before treatment (15.7 ± 2.2 mmHg; $P < 0.0001$). When comparing before-treatment Humphrey visual field test findings with those after 3 years of treatment, no change was found in the mean deviation and pattern standard deviation. Visual field performance had worsened in four patients and three patients according to trend analysis and event analysis, respectively. Adverse reactions appeared in ten cases and one patient (1.8%) discontinued treatment due to an adverse reaction.

Conclusion: Tafluprost single-use vials treatment was effective in reducing IOP over the 3 years of this study, but visual field performance worsened by 10.3%–13.8% in patients with normal-tension glaucoma. Safety was satisfactory.

Keywords: intraocular pressure, visual field, trend analysis, event analysis

Introduction

There are many glaucoma patients in Japan, particularly those with normal-tension glaucoma.[1] Intraocular pressure (IOP) decreasing therapy is the only therapy that has been found to control the progression of the visual field in normal-tension glaucoma patients.[2,3] The treatment of choice to decrease IOP is usually eye drops. Prostaglandin analogs are known to have strong IOP-decreasing efficacy, few systemic adverse reactions, and the convenience of once-a-day administration. For these reasons, prostaglandin analogs are the first-choice eye-drop treatment.

Tafluprost eye drops are one such prostaglandin analog that can be used in Japan and Europe. However, the formulation differs in each country. In Japan, benzalkonium chloride (BAK) is included as a preservative, but the formulation is preservative-free in Europe. Tafluprost eye drops are known for their safety and high IOP-decreasing efficacy,[4–12] and these have been reported to be equal in both BAK-containing and preservative-free drop formulations.[4] In Europe, most studies have considered patients with open-angle glaucoma and ocular hypertension,[5–9] while, in Japan, research has normally addressed patients with normal-tension glaucoma patients.[10–12] However, there are few reports concerning the IOP-decreasing efficacy and safety of long-term

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administration of tafluprost eye drops,[5] and, as far as we are aware, there have been no reports on administration for over a year in normal-tension glaucoma patients. The final goal of glaucoma treatment is preservation of the visual field, but this requires long-term follow-up in order to judge the extent of preservation. To the best of our knowledge, there have been no reports that have addressed this.

In the study presented here, tafluprost eye drops were administered for 3 years as a monotherapy to patients with normal-tension glaucoma and change in IOP, visual field progression, and safety were prospectively investigated.

Subjects and methods

A total of 55 eyes of 55 patients (male/female = 32/23) diagnosed with normal-tension glaucoma were included. The study was reviewed and approved by the Institutional Review Board of Inouye Eye Hospital at all participating sites. All participating subjects provided written informed consent prior to participation, and the study was conducted in full compliance with all tenets of the Declaration of Helsinki.

Tafluprost eye drops were newly administered as a monotherapy to all subjects from January to December 2009 at Inouye Eye Hospital. Follow-up was conducted for 3 years. The average age (± standard deviation [SD]) of the subjects was 56.1 (±11.2) years (range, 31–81 years old). The examination findings indicating normal-tension glaucoma – and thus, the inclusion criteria for the study – were: an IOP lower than 21 mmHg when measured several times including diurnal variation; thinning of the optic disk marginal region and deficit in the fiber layer; an abnormal visual field, as detected by highly reliable and repeatable means, that was not caused by other eye diseases or congenital abnormality; and normal open angles in both eyes, as revealed by gonioscopy. Patients would be excluded if: their best-corrected eyesight was under 10/20; they had any history of inner-eye surgery, laser surgery, or local or systematic steroid treatment; or any abnormality was recognized in the otolaryngology or neurosurgery examinations. All 55 patients had at least one eye that met the inclusion criteria; if both eyes met the inclusion criteria and did not match any of the exclusion criteria, the right eye was chosen.

Tafluprost eye drops (administered once per day at night) were administered. IOP was evaluated by Goldmann applanation tonometer at almost the same time every 1–3 months. The Humphrey 30-2 SITA-Standard Test was used every 6 months. Any case that produced false positive or false negative poor fixation results of over 20% was excluded from the analysis. Adverse reactions were evaluated at every check-up.

IOP was determined and recorded before tafluprost treatment commenced, and at 6, 12, 18, 24, 30, and 36 months of treatment. The mean deviation (MD) and pattern standard deviation (PSD) of the IOP measurements before treatment commenced, and at 1 year, 2 years, and 3 years during treatment, were compared using analysis of variance (ANOVA) as well as multiple comparison (Bonferroni/Dunnet). IOP measurements taken before tafluprost treatment were divided into four groups: ≥15 mmHg, <15 mmHg, ≥16 mmHg, and <16 mmHg. IOP-decreasing efficacy was compared after 3 years of administration (Mann–Whitney *U* test). Significance was set at $P < 0.05$.

Visual field defectiveness was evaluated by trend analysis[13] and event analysis.[14] Trend analysis showed visual field defectiveness as statistically significant. Linear regression analysis was used to analyze MD values. The change in MD values (dB/year) was calculated by the unit per year.[13] In the event analysis, the examination results of the first two follow-ups were used as baseline results, and then the findings of following examinations were compared. Progression was judged to have occurred at the point at which more than a certain level of deterioration was recognized.[14] Glaucoma progression analysis was used to judge whether there was progression or not. If a significant decrease in more than three adjacent measurement points were determined twice continuously, there was judged to be a "possibility of progression." If a significant decrease in more than three adjacent measurement points was found three times continuously, then this was determined to be a "tendency of progression." At the point at which "tendency of progression" was determined, this was considered progression of the visual field.

Results

Before tafluprost treatment, IOP (MD ± SD) was 15.7 ± 2.2 mmHg. Before treatment, the IOP was found to be 21 mmHg in one case, 20 mmHg in two cases, 19 mmHg in one case, 18 mmHg in seven cases, 17 mmHg in six cases, 16 mmHg in thirteen cases, 15 mmHg in eight cases, 14 mmHg in ten cases, 13 mmHg in three cases, 12 mmHg in two cases, and 11 mmHg in two cases. Mean average of the refractive value was –4.3 ± 4.3 D (range, –18.0 to +2.0 D). The MD before treatment was –6.75 ± 5.5 dB (range, –20.44 to +5.52 dB) and the PSD was 8.8 ± 4.7 dB (range, 1.7 to 17.0 dB).

IOP (mean ± SD) was 13.1 ± 1.5 mmHg after treatment for 6 months, 13.1 ± 1.8 mmHg after 12 months, 13.3 ± 2.2 mmHg after 18 months, 12.9 ± 1.7 mmHg after 24 months, 13.1 ± 2.0 mmHg after 30 months, and 12.8 ± 2.8 mmHg after 36 months. Thus, there was a

significant decrease in IOP when each observation point was compared with IOP measurements taken before treatment ($P < 0.0001$; Figure 1). The IOP-decreasing efficacy rate was 15.6% ± 11.4% after 6 months of treatment, 14.4% ± 12.5% after 12 months, 11.4% ± 16.9% after 18 months, 14.4% ± 14.2% after 24 months, 12.9% ± 15.5% after 30 months, and 15.4% ± 18.7% after 36 months; no significant difference was therefore observed ($P = 0.5893$). Prior to treatment, the IOP was analyzed for each group, and the IOP-decreasing rate was found to be 19.9% ± 19.1% in the ≥15 mmHg group (mean IOP, 16.7 ± 1.5 mmHg), 7.4% ± 15.5% in the <15 mmHg group (mean IOP, 13.2 ± 1.1 mmHg), 22.9% ± 20.3% in the ≥16 mmHg group (mean IOP, 17.2 ± 1.4 mmHg), and 7.9% ± 13.6% in the <16 mmHg group (mean IOP, 13.8 ± 1.2 mmHg). Patients with an IOP of more than 15 mmHg or 16 mmHg had a significantly higher IOP-decreasing efficacy rate ($P < 0.05$) than patients in either of the other two groups.

The MD of visual field was −5.4 ± 4.9 dB at 1 year of treatment, −5.4 ± 4.7 dB at 2 years, and 5.5 ± 4.8 dB at 3 years, which was found to be nonsignificant when compared with the MD before treatment ($P = 0.165$; Figure 2A). The PSD of the visual field was 7.8 ± 4.8 dB after 1 year of tafluprost treatment, 8.3 ± 4.7 dB after 2 years, and 8.2 ± 4.5 dB after 3 years, which again was nonsignificant when compared with the PSD before treatment ($P = 0.945$; Figure 2B).

A total of 19 of 55 patients dropped out. Of the remaining 36 cases, five cases were excluded because of poor fixation of over 20% in the Humphrey visual field test, meaning that a trustworthy examination result could not be obtained more than five times. Two cases could also not be included in the analysis due to insufficient frequency. Therefore, trend and event analyses were conducted with the remaining 29 cases. In four cases (13.8%) in the trend analysis and three (10.3%) in the event analysis, there was determined to be a possibility of progression in visual field defect (Figure 3). No case in either the trend or event analysis was determined to have visual field defect progression.

Adverse reactions were experienced in ten cases (18.1%): there were three cases of itchiness, three cases of conjunctival hyperemia, two cases of eyelid pigmentation, one case of ophthalmalgia, and one case of deepening of the upper eyelid sulcus. Eye drops were discontinued by one patient as a result of eyelid pigmentation after 18 months of treatment. Over the 3-year period of the study, 19 cases (34.5%; Table 1) dropped out: six cases due to being admitted to hospital, six cases due to their treatment being changed or added to because of insufficient IOP-decreasing efficacy, three patients due to relocation, three patients due to cataract operations, and one patient due to experiencing an adverse reaction (eyelid pigmentation).

Discussion

When administered to normal-tension glaucoma patients, the IOP-decreasing efficacy of tafluprost eye drops has been reported to be 14.3% ± 12.2%[10] and 22.7% ± 10.5%[11] after 12 weeks of treatment, and 21.9% ± 14.0%[12] after 48 weeks of treatment. The results of the present study are similar to the results of these reports.[10–12] IOPs before administration have been analyzed. Mizoguchi et al[10] divided their pretreatment IOP measurements into two groups – ≥15 mmHg and >15 mmHg – and found that the IOP-decreasing efficacy was 16.7% ± 10.8% in the former group (mean IOP, 16.9 ± 1.5 mmHg) and 10.2% ± 13.5% in the latter (mean

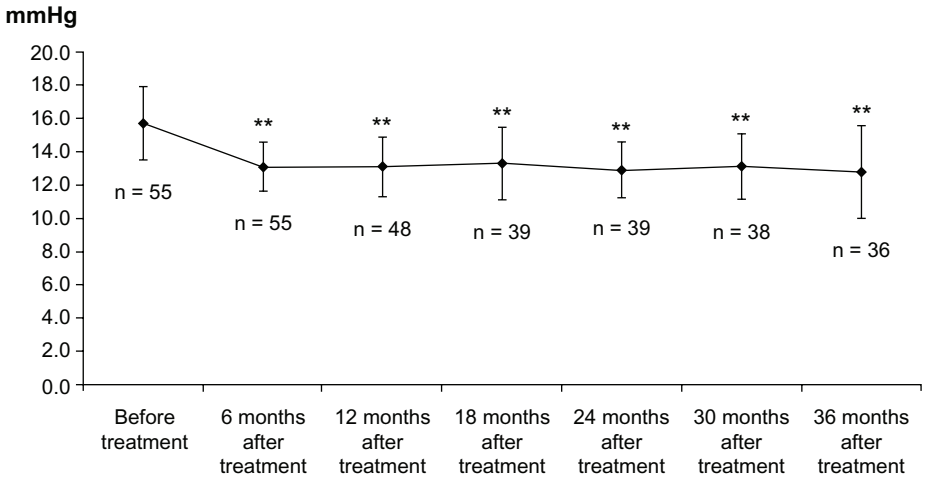

Figure 1 Intraocular pressure at baseline and after treatment with tafluprost.
Notes: Data shown as mean ± standard deviation; **$P < 0.0001$, analysis of variance.

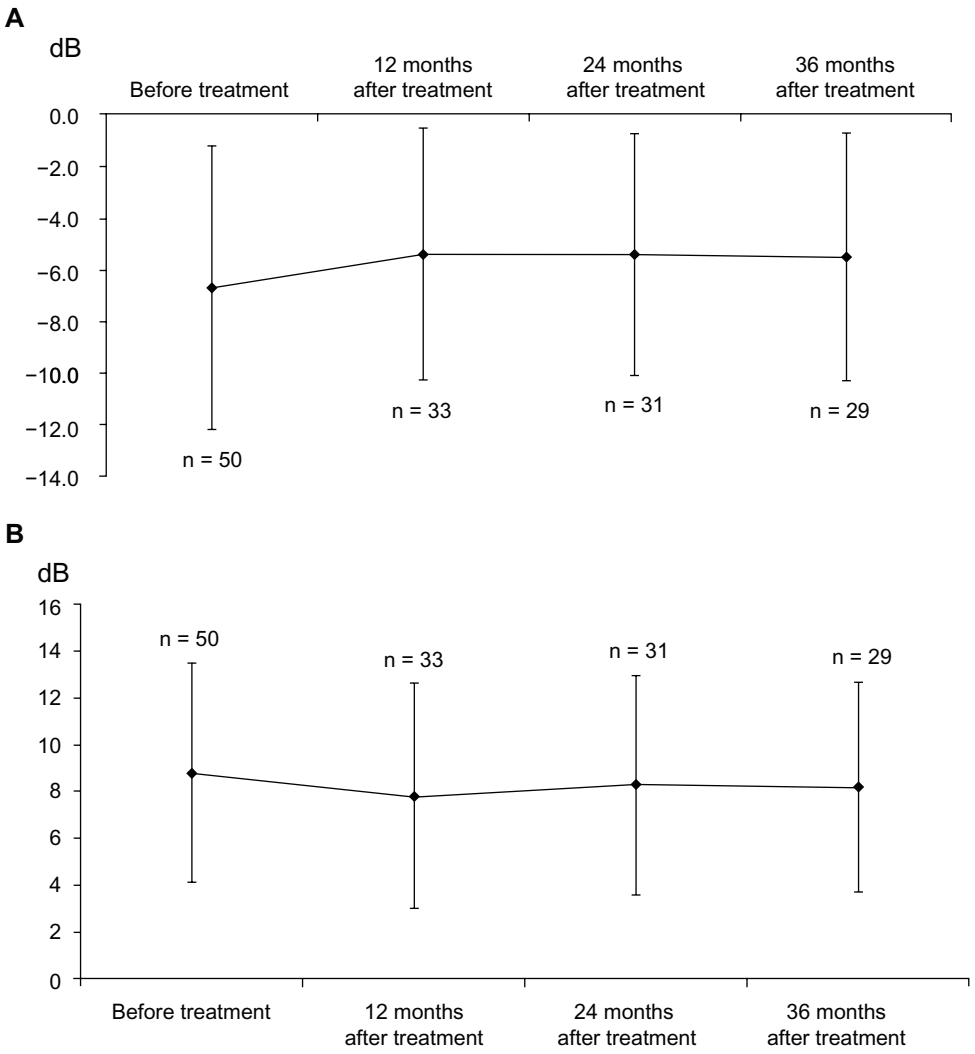

Figure 2 (**A**) Mean deviation and (**B**) pattern standard deviation (SD) at baseline, 1 year, 2 years, and 3 years after treatment with tafluprost. No significant difference was found in either case.
Note: Data shown as mean ± SD; analysis of variance.

IOP, 13.2 ± 1.3 mmHg). Nakano et al[11] measured IOP prior to treatment at ≤16 mmHg (mean IOP, 13.2 ± 1.3 mmHg), while Nakauchi et al[12] divided pre-treatment IOP measurements into two groups: ≥16 mmHg and >16 mmHg. They found that the IOP-decreasing efficacy rate was 24.8% in the ≥16 mmHg group (mean IOP, 18.2 ± 1.2 mmHg) and 13.6% in the <16 mmHg group (mean IOP, 14.1 ± 1.3 mmHg).[12] In our study, the high IOP value cases before treatment were almost the same as those reported in the previous literature,[10–12] while in low IOP value cases, the IOP-decreasing rate was slightly worse. The reasons for the IOP-decreasing rate being worse in the low IOP value group are unknown. From our

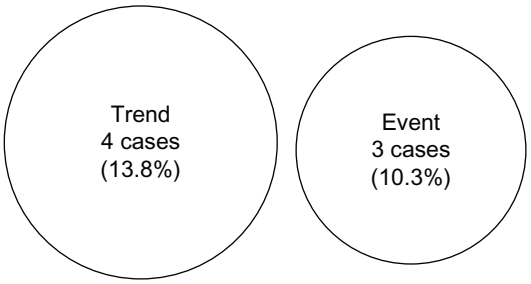

Figure 3 Analysis of progression in visual field deficit (left, trend analysis; right, event analysis).

Table 1 Discontinued cases (n = 19)

Reason for discontinuation	Case(s), n
Discontinued attending follow-up appointments	6
Insufficient IOP-decreasing efficacy	6
Patient relocation	3
Cataract surgery was conducted	3
Adverse reaction (eyelid pigmentation)	1

Abbreviation: IOP, intraocular pressure.

report, it can be seen that over the long-term (3 years), the IOP-decreasing efficacy before treatment can be preserved in high IOP value cases, but that it is impossible to preserve this in low IOP value cases.

Adverse reactions to BAK-containing tafluprost that have been reported include conjunctival hyperemia, itching, irritation, foreign body sensation, dryness, blurred vision, erythema of eyelid, photophobia, and increased lacrimation.[4,6,10–12] Uusitalo et al,[5] who administered eye drops for 24 months, reported adverse reactions such as eyelash growth, discoloration, and thickening as well as iris pigmentation. These are associated with prostaglandin analogs but appeared as adverse reactions. In our study, the adverse reactions (conjunctival injection, itchiness, eyelid pigmentation, ophthalmalgia, and deepening of the upper eyelid sulcus) were the same as has been previously reported.[4–6,10–12] Adverse reactions to prostaglandin analogs commonly appear around the eyelashes, irises, and eyelids, when administered long-term.[4–6,10–12] Various adverse reaction frequencies have been reported: 0.0%,[11] 1.8%,[12] 2.6%,[10] 16.7%,[4] 31.6%,[6] and 66.7%.[5] In our study, adverse reactions occurred in 18.2% of cases. In other studies, the rate of treatment discontinuation (due to insufficient IOP-decreasing efficacy, cataract surgery, admission to hospital, adverse reactions, etc) was 6.8%,[11] 13.8%,[10] and 22.8%.[12] These rates are lower than in our study (34.5%). This is because the treatment period in our study was much longer (3 years) than those in the cited studies (12–48 weeks).[10–12]

To the best of our knowledge, there have been no reports of visual field disorder occurring due to long-term administration of tafluprost eye drops. In the present study, there was no significant difference in MD and PSD when visual field was compared before treatment and after 3 years. In contrast, event and trend analyses, which were performed on individual cases, indicated that progression of visual field defect occurred in 13.8% (according to event analysis) and in 10.3% (according to trend analysis).

Finally, it should be noted that our study had some limitations. First, visual field was analyzed for 3 years using reliable data (achieved by using the exlusion criteria), and second, only 29 cases were included in our analysis.

Conclusion

BAK-containing tafluprost eye drops were administered to normal-tension glaucoma patients for 3 years as monotherapy. Treatment was effective, with IOP significantly decreasing over the 3 years. However, in 10.3%–13.8% of the cases, progression in visual field defect was seen. Adverse reactions occurred in 18.2% of cases and administration was discontinued in 1.8% of cases.

Disclosure

The authors declare no conflicts of interest in this work.

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