

The efficacy and safety of add-on 0.1% brimonidine tartrate preserved with sodium chlorite in on-treatment Japanese normal-tension glaucoma patients

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Background: To evaluate the efficacy and safety of newly formulated brimonidine (0.1% brimonidine tartrate preserved with sodium chlorite: brimonidine) as add-on therapy in on-treatment Japanese normal-tension glaucoma (NTG) patients.

Methods: Brimonidine was added to on-treatment NTG patients with intraocular pressures (IOP) of between 13 mmHg and 16 mmHg after three consecutive IOP measurements. The time courses of IOP, conjunctival hyperemia, superficial punctate keratitis, and adverse events were examined at 4, 8, and 12 weeks after brimonidine instillation.

Results: Though 75 of 83 patients (31 males and 52 females; mean age: 63.4±11.6 years) completed the study, six patients discontinued because of side effects and two patients withdrew. The mean IOP after brimonidine addition at week 4 (12.6±1.8 mmHg, $P<0.001$), week 8 (12.4±1.7 mmHg, $P<0.001$), and week 12 (12.6±1.8 mmHg, $P<0.001$) was significantly decreased compared with that before the addition of brimonidine (13.9±1.2 mmHg). No significant changes in superficial punctate keratitis or conjunctival hyperemia scores were observed throughout the study. Dizziness, sleepiness, eye pain, and itching (mild to moderate) were noted in five, four, three, and three patients, respectively.

Conclusions: The addition of newly formulated brimonidine to on-treatment Japanese NTG patients with IOP of 13–16 mmHg further reduced the levels of IOP with minimal side effects and adverse events.

Keywords: normal-tension glaucoma, 0.1% brimonidine tartrate with sodium chlorite, additive intraocular pressure reduction, side effect, adverse event

Introduction

Normal-tension glaucoma (NTG) is the most common type of glaucoma in Japanese individuals.^{1,2} Although monotherapy with prostaglandin (PG) analogs is mainly applied as the first-line treatment for NTG,^{3,4} additional treatment with second-line glaucoma ophthalmic solutions is frequently needed, as the target intraocular pressure (IOP) for NTG is relatively low compared with that in primary open-angle glaucoma (POAG).⁵

Brimonidine, an α_2 -adrenergic agonist, is postulated to be clinically useful for glaucoma treatment, in particular for add-on therapy, because it has a unique IOP-lowering mechanism of action.⁶

The concentration of brimonidine in ophthalmic solution was decreased from 0.2% to 0.1%, and the preservative was reformulated from benzalkonium chloride (BAK)

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to sodium chlorite (SC) in an effort to enhance tolerability in brimonidine usage.⁷ At present, this new formulation of brimonidine (0.1% brimonidine tartrate ophthalmic solution with SC: Aiphagan[®]; Senju Pharmaceutical Co., Ltd, Osaka, Japan) has been marketed in Japan since 2012.

To the best of the authors' knowledge, however, previous studies of the efficacy and safety of brimonidine in NTG treatment evaluated 0.2% brimonidine with BAK.^{8,9} No study has been conducted for the treatment of NTG using 0.1% brimonidine with SC.¹⁰

We therefore evaluated the IOP-lowering efficacy and safety of newly formulated 0.1% brimonidine preserved with SC as an add-on therapy in on-treatment Japanese NTG patients with IOP of 13–16 mmHg.

Materials and methods

Study design

This prospective, open-label, multicenter study was conducted over a period of 12 weeks at Fussa Hospital, Yoshikawa Eye Clinic, Ueno Eye Clinic, Nakano General Hospital, Kagurazaka Minamino Eye Clinic, and Irumagawa Hospital in Japan from June 2012 to January 2013. The study was carried out according to the ethical principles of the Declaration of Helsinki. All patients read and signed an informed consent form, and the Institutional Review Board of Fussa Hospital approved the study in advance. This study was registered in the University Hospital Medical Information Network (UMIN) clinical trials registry (No UMIN000012582).

Participants

Japanese NTG patients diagnosed according to Japanese glaucoma guidelines⁵ and receiving one to three drugs including PG, without a change of prescription for 3 months, were recruited.

Inclusion criteria for enrolled patients were as follows: 1) aged ≥ 20 years and ≤ 80 years who were diagnosed with NTG in both eyes; 2) patients undergoing treatment with PG and/or β -blockers who were judged to require the addition of brimonidine because they were unable to achieve target IOP on their current IOP-lowering therapy; 3) on-treatment IOPs in bilateral eyes of between 13 mmHg and 16 mmHg in at least three consecutive measurements; 4) patients with an IOP of 10–12 mmHg were eligible if the central corneal thickness was ≤ 470 μm ; 5) mean deviation (MD) values < -6 dB using the Humphrey central 30-2/24-2 Swedish Interactive Threshold Algorithm standard program (Carl Zeiss Meditec Inc., Dublin, CA, US), or any patients with central visual field

loss (Figure 1); 6) best-corrected visual acuity ≥ 0.5 ; and (7) spherical equivalent refraction $\geq -10\text{D}$.

Exclusion criteria were as follows: 1) abnormalities of the anterior segment that disturbed accurate IOP measurement with the Goldmann applanation tonometer; 2) apparent findings of dry eye; 3) any active ocular inflammation or blepharitis; 4) a history of laser therapy or surgical treatment of glaucoma; 5) patients requiring treatment with steroid eye drops during the study; 6) patients who had ocular fundus diseases that may affect visual field; and 7) patients judged ineligible by an investigator.

Procedure

One drop of brimonidine was added to instil into the bilateral conjunctival sac twice a day for 12 weeks at the predefined time (12-hour intervals) for each patient. Measurements of IOP, best-corrected visual acuity, slit-lamp examinations, and interviews for adverse events were conducted in each clinic at 4, 8, and 12 weeks after the addition of brimonidine.

IOP was measured twice consecutively between 9 am and 1 pm by a single examiner using a Goldmann applanation tonometer. The mean of the two IOP measurements at each time point was calculated and used for statistical analyses.

The degrees of conjunctival hyperemia and superficial punctate keratitis (SPK) were scored from 0 to 3 and 0 to 4 based on the standard photogram, respectively.^{11–13} For evaluation of adverse events, patients were examined with a slit lamp for the presence or absence of red eyelid, eyelid edema, conjunctival edema, and conjunctival follicles.

Each adverse event, such as ocular irritation, itching and foreign body sensation, and/or dry eye sensation, was classified into four grades: “nothing”, “almost nothing”, “sometimes” and “always”. Patients were interviewed at each visit to confirm their experiences of dizziness or sleepiness.

Blood pressure and pulse rate were measured for each patient at the start and end of the study. MD values were compared before and after the study.

Statistical analysis

All data collected from patients who fulfilled all of the inclusion criteria and did not meet any of the exclusion criteria were sent to Kinki University, Nara, Japan, and were analyzed by a statistician who did not directly collect data in the clinical study.

In each patient, one eye with a higher on-treatment IOP before the addition of brimonidine (the study eye) was used for statistical analysis. If both eyes had the same IOP values,

- (1) Patients with C30-2/C24-2 MD < -6.0 dB
 (2) Patients who have C30-2/C24-2 MD \geq -6.0 dB and meet either criteria A or B below:

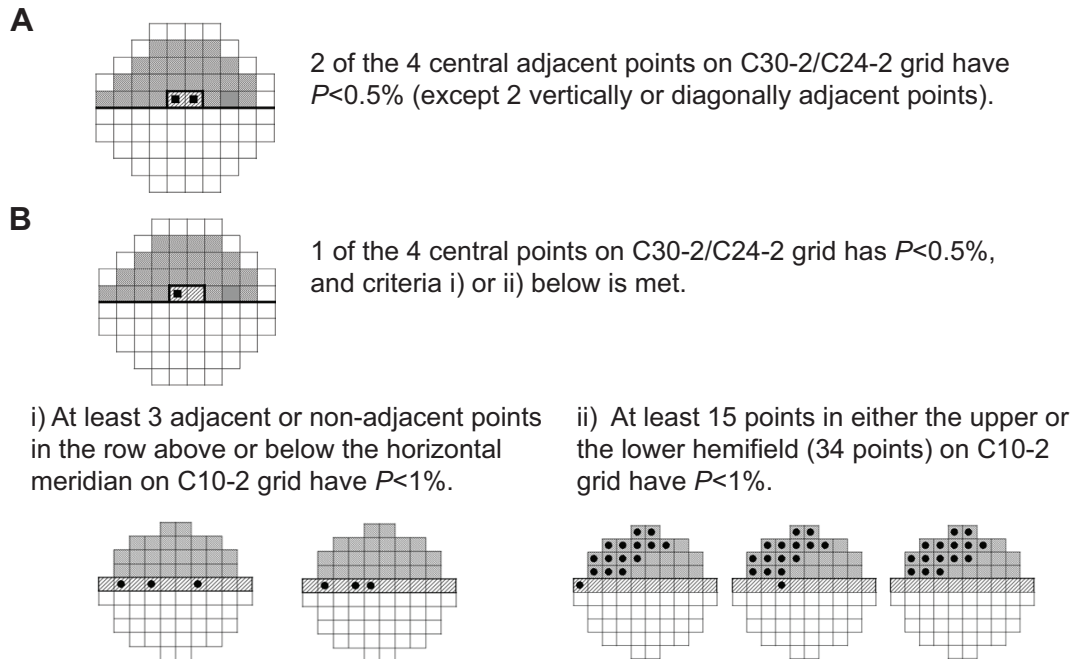


Figure 1 Visual field criteria required for patients' inclusion in the study.

Note: C30-2/24-2, C10-2: The Humphrey central 30-2/24-2 or 10-2 Swedish Interactive Threshold Algorithm standard program.

Abbreviations: dB, decibel; MD, mean deviation.

the eye with the lower MD value served as the study eye.¹⁴ In patients with the same IOP values and MD values in both eyes, the right eye was selected. IOPs obtained before and after add-on with brimonidine in the patients who were able to be followed up for at least 4 weeks were used in the analysis using a paired *t*-test with Bonferroni correction after repeated analysis of variance.

The relationship between the magnitude of IOP reduction in those eyes that were followed for up to 12 weeks, baseline characteristics, and the number of pretreated drugs was analyzed by multivariable logistic regression analysis.

Scores of conjunctival hyperemia and SPK in the study eyes were examined using a Wilcoxon signed rank test. Cumulative incidences of adverse events such as conjunctival and eyelid findings were calculated and statistically tested by a chi-square test. Blood pressures, pulse rates, and MD values before and after treatment with brimonidine were compared using a paired *t*-test. For statistical analysis, JMP[®] software (version 9.0.2; SAS Institute Inc., Cary, NC, USA) was used. *P*-values < 0.05 were considered to be significant.

Results

A total of 75 out of 83 enrolled patients (31 males and 52 females; mean age: 63.4 ± 11.6 years) completed the study (Table 1). Eight patients did not complete the study

due to dropping out (two patients) and adverse events (six patients; dizziness: three, sleepiness: one, eye pain: one, eye itching: one).

Compared with the IOPs before the addition of brimonidine, the IOPs in the study eyes showed a significant reduction at each time point ($P < 0.001$) (Figure 2). At 12 weeks, the IOP was lowered by 0–1 mmHg in 33 patients (44.0%), 2–3 mmHg in 25 patients (33.3%), and ≥ 4 mmHg in seven patients (9.3%). A 2 mmHg or greater reduction was observed

Table 1 Demographic characteristics of the study participants

Number of patients	83
Male/female	31/52
Eyes (R/L)	83 (40/43)
Age (years) ^a	63.4 ± 11.6 (range: 29–79)
RE (D) ^a	-2.97 ± 3.06 (range: -10.00 to +2.5)
MD (dB) ^a	-10.72 ± 4.63 (range: -19.90 to -1.59)
CCT (μm) ^a	520.6 ± 35.9 (range: 446–614)
Number of previous antiglaucoma drugs	2.0 ± 0.8
	1 drug: 29 (PG: 27, β-blocker: 2)
	2 drugs: 27 (PG + β-blocker: 15, PG + CAI: 11, PG + others: 1)
	3 drugs: 27 (PG + β-blocker + CAI: 26, PG + CAI + others: 1)

Note: ^aValue is presented as the mean ± standard deviation.

Abbreviations: CAI, carbonic anhydrase inhibitor; CCT, central corneal thickness; D, diopter; dB, decibel; L, left; MD, mean deviation; PG, prostaglandin; R, right; RE, refractive error.

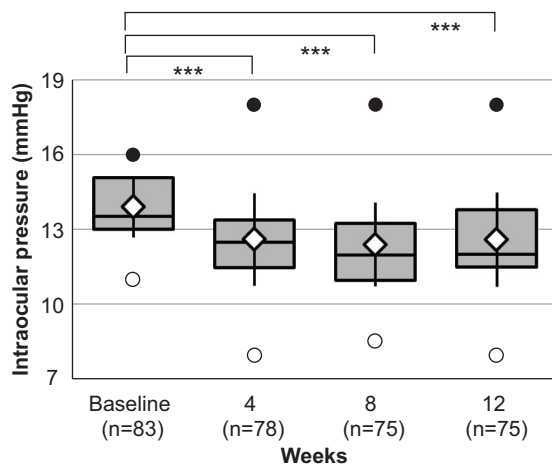


Figure 2 Intraocular pressure values in time course.³
Notes: ³The top of the box represents the 75th percentile, the bottom of the box represents the 25th percentile, and the horizontal line in the box represents the median. \diamond denotes the mean \pm standard deviation, \bullet denotes the maximum, and \circ denotes the minimum. $***P < 0.0001$, analyzed by paired t-test with Bonferroni correction after repeated analysis of variance.
Abbreviation: n, number of eyes.

in 32 of 75 eyes (42.7%). Brimonidine significantly lowered IOP compared with preaddition, regardless of the number of previous antiglaucoma drugs (Figure 3).

The correlation between various factors, including demographic characteristics, and the change from on-treatment IOP before the addition of brimonidine were analyzed using logistic regression analysis, and the magnitude of IOP reduction at 12 weeks significantly correlated with MD value and degree of refraction (Table 2).

Scores of conjunctival hyperemia in the study eyes were not significantly increased at each time point (Table 3). No significant differences in the SPK scores were observed at any time point in the study eyes (Table 3). Conjunctival edema, conjunctival follicles, reddish eyelid, and eyelid edema

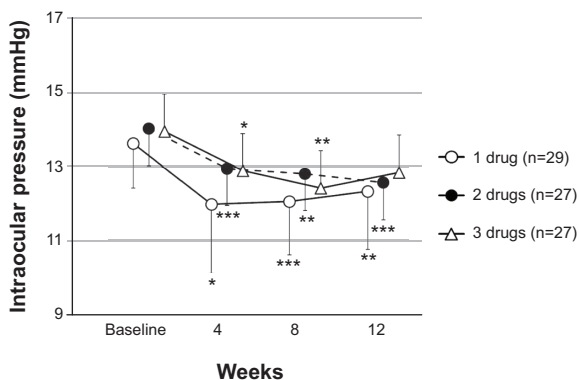


Figure 3 Change of intraocular pressure (IOP) in three groups with previous antiglaucoma drug administration.³
Notes: ³Eyes were classified into three groups based on the number of previous drugs. $*P < 0.05$, $**P < 0.01$, $***P < 0.0001$ for significant change of IOP compared with each baseline by repeated-measures analysis of variance with Bonferroni correction.

Table 2 Logistic regression analysis of 12 weeks IOP changes from on-treatment IOP before addition of brimonidine^a

Factor	Odds ratio	P-value (likelihood ratio test)
Baseline IOP	0.59	0.1071
Number of drugs	1.61	0.8106
MD value	0.84	0.02
Age	1.04	0.1328
Sex	1.75	0.3677
RE	20.8	0.0407

Notes: ^aTo explore baseline characteristics contributing to the IOP-lowering effect of brimonidine, subjects were divided into those experiencing an IOP reduction of ≥ 2 mmHg and those experiencing an IOP reduction of < 2 mmHg, and a multivariate logistic regression analysis was performed to calculate odds ratios.
Abbreviations: IOP, intraocular pressure; MD, mean deviation; RE, refractive error.

were observed in 1.2%, 4.8%, 2.4%, and 1.2% of patients, respectively, but no significant increase in frequency of these side effects was observed during the follow-up period (Figure 4). There were no significant changes in the cumulative incidence of adverse events over time (irritation, itching, foreign body sensation, and dry eye sensation) ($P=0.6561$, $P=0.8270$, $P=0.7932$, $P=0.8803$; Figure 5).

No apparent changes were observed in systolic and diastolic blood pressure (130.4 ± 18.2 mmHg, 80.5 ± 12.7 mmHg, 130.1 ± 19.2 mmHg, 79.9 ± 14.5 mmHg, $P=0.6849$, $P=0.4692$) or pulse rate (69.2 ± 9.2 bpm and 70.3 ± 9.2 bpm, $P=0.1685$) before or after add-on treatment with brimonidine.

Adverse events such as dizziness (five cases, 6.0%), sleepiness (four cases, 4.8%), eye pain (three cases, 3.6%), and itching (mild to moderate) (three cases, 3.6%) were observed in 15 of 83 cases (18.1%) during the study. There was no significant difference in MD values between before and after brimonidine instillation (10.72 ± 4.63 dB and -12.01 ± 4.94 dB, $P=0.9461$).

Discussion

Additive treatment with newly formulated brimonidine provided further IOP-lowering effects in Japanese NTG patients with on-treatment IOP between 13 mmHg and 16 mmHg who had been treated with one to three glaucoma eye drops,

Table 3 Time course of conjunctival hyperemia and superficial punctate keratitis (SPK) scores^a

	Baseline	4 weeks	8 weeks	12 weeks
Conjunctival hyperemia scores	0.5 ± 0.7	0.5 ± 0.7	0.5 ± 0.7	0.5 ± 0.7
P-value		0.2658	0.1607	0.1258
SPK scores	0.2 ± 0.3	0.1 ± 0.3	0.2 ± 0.3	0.2 ± 0.3
P-value		0.1006	0.912	0.8778

Notes: ^aScores are presented as the mean \pm standard deviation; analyzed by Wilcoxon signed rank test.

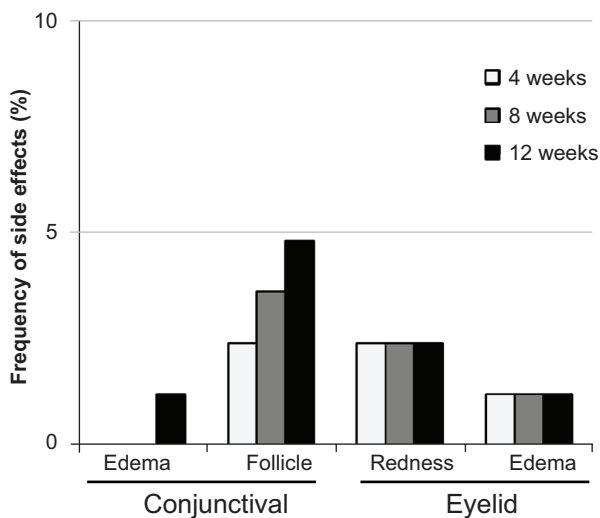


Figure 4 Side effects of conjunctiva and of eyelid in study eyes.

without serious local and systemic side effects or adverse events leading to discontinuation of administration.

As the main purpose of the present study was to examine the additive IOP-lowering efficacy of brimonidine in on-treatment Japanese NTG patients under a multicenter study design, inclusion criteria were strictly defined in respect of IOP levels and the visual field condition of the study candidates. Therefore, only those patients with on-treatment IOP between 13 mmHg and 16 mmHg were included, as IOP levels of ≤ 12 mmHg are generally considered not to need further IOP lowering,¹⁵ whereas those patients with on-treatment IOP of ≥ 17 mmHg might need to undergo surgery or laser therapy.⁵ The thickness of the cornea may affect the IOP measurement;^{5,16} however, patients with on-treatment IOP of 10–12 mmHg were eligible if the central corneal thickness was ≤ 470 μm . Regarding the grade of visual field defects, the necessity of add-on therapy for patients with mild visual

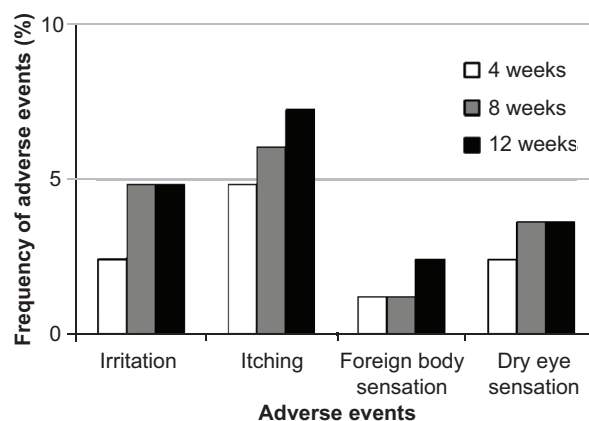


Figure 5 Adverse events experienced in study eyes.

field loss is thought to be low. Therefore, patients with an MD value $< -6\text{D}$ who were thought to have moderate visual field loss were recruited as study subjects. On the other hand, patients with central visual field defects, as shown by the Swedish Interactive Threshold Algorithm standard program (C10-2) visual field test, who met the new criteria provided in Figure 1 were enrolled because such defects may cause a threat to vision and such patients are thought to need further IOP lowering.¹⁷ Patients with severe myopia ($< -10\text{D}$) were excluded from the study because myopic optic neuropathy may be confused with glaucoma.

Although the speed of progression of visual field loss in NTG¹⁸ is recognized to be slower than that in POAG, it inevitably progresses. Therefore, IOP-lowering therapy is required for NTG, as it is with POAG. In the treatment of NTG, a decrease in IOP of around 20% from baseline was generally achieved by applying PG analogs as monotherapy.¹⁹ However, in those cases with visual field loss progression, additive treatment is required,^{20–22} and a proportion of NTG patients receive multiple antiglaucoma drugs. The magnitude of IOP reduction observed in the present study was 1.3 mmHg, a 9.4% reduction from preaddition of brimonidine in on-treatment NTG with IOP of 13–16 mmHg. The IOP reduction of 1 mmHg, despite being small in amount, is reported to be valuable for slowing down visual field loss, as shown in POAG in the Early Manifest Glaucoma Trial (EMGT) study.²³ It is considered that IOP lowering of 1.3 mmHg is clinically relevant in NTG.

The IOP-lowering effects of brimonidine are suspected to have individual differences, as the magnitude of IOP reduction at 12 weeks was widely distributed, with 44.0% of patients having IOP lowered by 0–1 mmHg, and 42.7% lowered by ≥ 2 mmHg, including 9.3% of patients by ≥ 4 mmHg. Therefore, we tried to identify potential factors contributing to IOP reduction. The baseline IOP in patients was relatively low and the additive mean IOP-lowering efficacy was 1.3 mmHg. We selected a logistic regression for this analysis. A cutoff value of 2 mmHg in IOP reduction should be used considering IOP measurement fluctuation of ± 1 mmHg. The results of the present analysis suggest that IOP in patients with nonmyopia and better MD values would be further lowered by brimonidine.

Brimonidine is known to lower IOP by reducing aqueous humor formation and increasing uveoscleral outflow.⁶ It is known that myopic eyes are structurally elongated while having mechanically weakened ciliary muscles.²⁴ These changes in myopic eyes might alter the IOP-lowering effect of brimonidine.

Addition of brimonidine was statistically prominent in patients with worse MD value. The actual time period in which patients had received glaucoma treatment could not be confirmed. However, patients with severe visual field defect, ie, worse MD value, in general, used eye drops for a longer period of time. Although no significant difference in IOP-lowering efficacy was observed based on the number of pretreated drugs, it can be postulated that patients with severe NTG might have already reached a sufficient level of pretreatment efficacy.

Significant local side effects were not observed during the 3 months of brimonidine add-on therapy. Moreover, no exacerbation of SPK or hyperemia was noted, which might be attributable to the exclusion of patients with severe dry eye from the study. In the present study we evaluated the efficacy and safety of newly formulated brimonidine, which had a decreased concentration of brimonidine and a changed preservative with less irritation. Therefore, another possible factor contributing to this favorable safety profile was the presence of SC in the brimonidine formulation as a non-BAK preservative, which may have the potential to reduce corneal disorders.^{25–27}

The literature indicates that brimonidine therapy is associated with an increased risk of allergic reactions.²⁸ Patients in this study were therefore carefully monitored in combination with subjective symptoms and slit-lamp evaluation. However, a marked increase in allergic reactions was not evident in our 3-month study. A longer follow-up study may be warranted for evaluation of these findings.

During this study, blood pressure and pulse rate did not change after brimonidine add-on, as reported in the US.²⁸ However, some patients experienced dizziness and sleepiness. Brimonidine may lead to dizziness or sleepiness like other α_2 -adrenergic receptor agonists such as clonidine and apraclonidine, which can penetrate the blood–brain barrier.^{29,30} Therefore, before starting brimonidine therapy, patients should be informed about the risks of dizziness and sleepiness.³¹

Conclusion

The results of this study suggest that the addition of newly formulated brimonidine effectively lowered IOP in Japanese NTG patients with IOP of 13–16 mmHg, with minimal clinically significant side effects or adverse events. Therefore, brimonidine is thought to be useful as an add-on therapy for on-treatment NTG.

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Disclosure

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