



Efficacy and Safety of Omidenepag Isopropyl 0.002% Ophthalmic Solution: A Retrospective Analysis of Real-World Data in Japan

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ABSTRACT

Introduction: This study aimed to clarify the efficacy and safety of omidenepag isopropyl (OMDI) in a retrospective, real-world, multi-center setting.

Methods: A retrospective medical chart review of patients with glaucoma and ocular hypertension receiving OMDI from November 2018 to November 2019 with at least 12 weeks of follow-up was conducted in 11 eye clinics in Japan. The participants were categorized into three therapy groups, designated the naïve monotherapy, switching monotherapy, and concomitant therapy groups. The main outcome measures were the change in intraocular pressure (IOP) at week 4 and week 12 after the

initiation of OMDI treatment, and frequency of adverse drug reactions.

Results: Data were collected from 827 patients. The baseline IOP in the naïve group was 16.6 ± 4.2 mmHg. The mean IOP reduction at week 4 and week 12 was -2.9 ± 3.2 mmHg ($P < 0.0001$) and -2.5 ± 2.9 mmHg ($P < 0.0001$), respectively. Eyes with baseline IOP less than 16 mmHg also showed a significant reduction of IOP of -1.4 ± 2.0 mmHg at week 12. OMDI significantly reduced IOP not only in eyes with primary open-angle glaucoma but also in eyes with primary angle-closure glaucoma and secondary glaucoma. In the switching monotherapy group, IOP did not change significantly after switching from most classes of medications to OMDI, but further IOP reduction was observed in the case of switching from beta-blockers to OMDI. The frequency of adverse drug reactions was 14.1% in all participants, and the most common adverse reaction was ocular hyperemia (7.6%). No serious and severe side effects were observed in this study.

Conclusion: OMDI showed an IOP-lowering effect in eyes with various types of glaucoma and using various therapeutic regimens in real-world clinical practice. In addition, OMDI did not show any serious and severe side effects, suggesting the potential of OMDI as a first-line medicine for the treatment of glaucoma.

Trial Registration: University Hospital Medical Information Network (UMIN): 000040040.

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Keywords: Glaucoma; IOP-lowering effect; Omidenepag isopropyl; Prostanoid EP₂ receptor agonist; Retrospective real-world study

Key Summary Points

Why carry out this study?

Omidenepag isopropyl, a selective prostanoid EP₂ receptor agonist, was launched in Japan in 2018 as a treatment for glaucoma and ocular hypertension. Although previous clinical trials on omidenepag isopropyl demonstrated overall favorable outcomes of the drug, the efficacy and safety of the drug in many clinical situations, including combination therapy with other classes of glaucoma medications, real-world usage, and use in various types of glaucoma other than open-angle glaucoma, have not been sufficiently evaluated. The aim of the present study was to investigate the efficacy and safety of omidenepag isopropyl in various real-world clinical settings.

What was learned from the study?

Omidenepag isopropyl showed an intraocular pressure (IOP)-lowering effect in eyes with various types of glaucoma and using various therapeutic patterns without serious or severe side effects, suggesting the potential of omidenepag isopropyl as a first-line medicine for treatment of glaucoma and ocular hypertension.

INTRODUCTION

Elevated intraocular pressure (IOP) is a major and the only modifiable risk factor for glaucoma [1, 2]. Since medicinal therapy is usually the first choice for IOP reduction [3], a number of IOP-lowering drugs are currently being developed and used clinically. In order to obtain a

reliable and safe therapeutic effect, it is necessary to select an appropriate drug, on the basis of each patient's clinical conditions, complications, and lifestyle [4, 5]. Therefore, novel medications that offer both reliable IOP reduction and acceptable safety profile have been eagerly desired.

Omidenepag isopropyl (OMDI) was launched in Japan in 2018 as the first EP₂ receptor agonist to obtain regulatory approval for the treatment of glaucoma and ocular hypertension. OMDI exhibited an IOP-lowering effect that was not inferior to the FP receptor agonist latanoprost, without producing prostaglandin-associated periorbitopathy (PAP) which adversely affects adherence to therapy [6–10]. On the other hand, since OMDI caused rare but serious adverse events such as cystoid macular edema (CME) and decreased visual acuity in a previous study [11], further information on safety under clinical use is required.

In addition, critical information about the safety and efficacy of OMDI in various clinical situations, such as the efficacy in each type of glaucoma, the efficacy after switching from other antiglaucoma drugs, and the safety in combination therapy, is still limited.

The purpose of this study was to clarify the efficacy and safety of the EP₂ agonist OMDI in a retrospective review of real-world clinical practice.

METHODS

Study Design and Setting

This retrospective, multicenter study was conducted at 11 geographically diverse sites in Japan. The study protocol was approved by the Institutional Review Board of the Medical Corporation of Sapporo Yurinokai Hospital, was conducted in accordance with the tenets of Declaration of the Helsinki and clinical trial guidelines in Japan, and was registered with the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (<https://www.umin.ac.jp/ctr>) with the identifier UMIN ID 000040040. This study performed on the basis of opt-out consent. We provided

information about this study to patients and guaranteed their opportunity to refuse participation in the study.

Data Collection and Outcome Measures

Data were retrospectively collected from medical charts in individual study sites. The medical chart data specified in the study protocol was collected by creating an electronic clinical research form (eCRF) using the electrical data capturing (EDC) system under the responsibility of each research site. A database was created from eCRF and used for data analysis.

The inclusion criteria were glaucoma or ocular hypertension (OH) in patients who received OMDI (EYBELIS[®] ophthalmic solution 0.002%, Santen Pharmaceutical Co., Ltd.) for the first time during the observation period from November 2018 to November 2019. Patients were excluded if the IOP was not measured more than twice during the observation period including the start date of OMDI treatment, if the IOP measuring devices were different for each examination day, and if OMDI was used in eyes with contraindicated conditions such as pseudophakia or aphakia, and in combination with tafluprost. In this study, patients were categorized by therapy pattern into three groups, designated the naïve monotherapy, switching monotherapy, and concomitant therapy groups. These therapy patterns were defined as follows: naïve monotherapy, OMDI monotherapy at first in the absence of previous or concomitant glaucoma drugs; switching monotherapy, OMDI monotherapy resulting from the switch from at least one previous drug; concomitant therapy, addition of OMDI to other glaucoma drugs or switching to OMDI combined with other glaucoma drugs. In this study, the safety analysis included all cases that met the inclusion criteria. On the other hand, efficacy analysis was performed in the naïve monotherapy and switching monotherapy groups. The subjects of the concomitant therapy group were excluded from the efficacy analysis set because the patterns of combined drugs were too diverse to

obtain meaningful analysis results (see Table S1 in the electronic supplementary material).

The main outcome measures of this study were the changes in IOP from baseline (week 0, i.e., start date of OMDI treatment) to week 4 and week 12 after OMDI treatment. Other outcome measures included adverse drug reactions, and their incidence. Also, patient demographics (age, gender), types of glaucoma, current/prior glaucoma drugs, and IOP were recorded.

Statistical Analysis

Efficacy data were analyzed with one study eye per subject. For patients with bilateral glaucoma or OH, with both eyes meeting the eligibility criteria, the eye with the higher IOP at baseline was selected as the study eye; if the IOPs were equal in both eyes, the right eye was selected for this study. Changes in mean IOP after OMDI treatment were evaluated for each therapeutic pattern, i.e., naïve monotherapy and switching monotherapy. Subgroup analyses based on diagnosis and baseline IOP were also performed in the naïve monotherapy group. In the switching monotherapy group, changes in mean IOP were evaluated separately for each category of medicines.

All data were analyzed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). The main outcome measure (estimated mean change in IOP) was determined using a linear mixed-effects model for repeated measures, with the time point visit as the fixed effect and with the patient as the random effect, and was compared by paired *t* test with Bonferroni correction. The significance level was 5% (two-sided).

RESULTS

A review of medical records identified 827 potentially eligible patients who fulfilled the inclusion criteria for this study (Fig. 1). In all, 129 patients were excluded for the following reasons: 105 for missing IOP measurements, 22 for contraindications, and 2 for insufficient background information. After exclusion of these ineligible patients, there were 341 in the

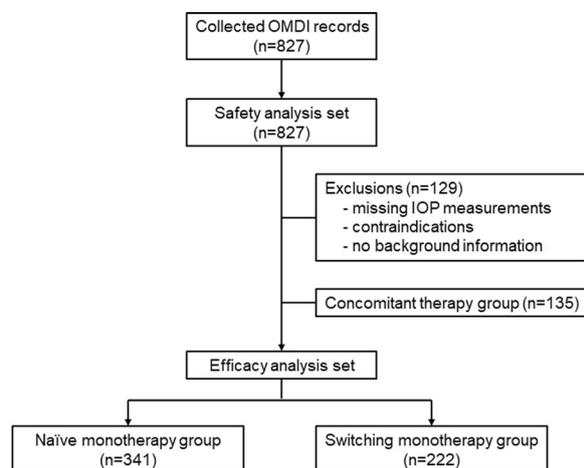


Fig. 1 A process flow diagram summarizing data collection and patient selection. OMDI, omidenepag isopropyl; IOP, intraocular pressure

naïve monotherapy group, 222 in the switching monotherapy group, and 135 in the concomitant therapy group. The mean age of all 698 included patients was 61.7 ± 13.2 years (range 14–89 years) and the most common diagnosis was primary open-angle glaucoma (POAG) and

normal tension glaucoma (NTG), followed by primary angle-closure glaucoma (PACG), secondary glaucoma and ocular hypertension (OH) (Table 1).

Efficacy

In the naïve monotherapy group, mean IOP decreased from 16.6 ± 4.2 mmHg at week 0 (untreated baseline) to 13.9 ± 3.4 mmHg at 4 weeks and 14.0 ± 3.3 mmHg at 12 weeks after OMDI treatment. The mean IOP change from baseline to week 4 and week 12 was -2.9 ± 3.2 mmHg ($P < 0.0001$) and -2.5 ± 2.9 mmHg ($P < 0.0001$), respectively (Fig. 2).

Subgroup analysis based on baseline IOP is shown in Fig. 3. In the naïve monotherapy group, the mean IOP of patients with baseline IOP ≥ 16 mmHg decreased from 19.4 ± 3.8 mmHg at week 0 (baseline) to 15.5 ± 3.1 mmHg at 4 weeks and 15.7 ± 3.1 mmHg at 12 weeks after OMDI treatment. The mean IOP reduction from baseline at week 4 and week 12 was -3.9 ± 3.4 mmHg (19.1% reduction, $P < 0.0001$) and -3.4 ± 3.1 mmHg (17.1%

Table 1 Subject demographics and characteristics in a retrospective real-world clinical study of omidenepag isopropyl in Japan

	Naïve (<i>n</i> = 341)	Switching (<i>n</i> = 222)	Concomitant (<i>n</i> = 135)	Overall (<i>n</i> = 698)
Age, mean \pm SD, years	58.9 ± 14.0	63.9 ± 11.6	65.2 ± 11.9	61.7 ± 13.2
Gender, <i>n</i> (%)				
Male	147 (43.1)	77 (34.7)	54 (40.0)	278 (39.8)
Female	194 (56.9)	145 (65.3)	81 (60.0)	420 (60.2)
Diagnosis, <i>n</i> (%)				
POAG/NTG	283 (83.0)	192 (86.5)	121 (89.6)	596 (85.4)
PACG	17 (5.0)	6 (2.7)	4 (3.0)	27 (3.9)
Secondary glaucoma	12 (3.5)	10 (4.5)	8 (5.9)	30 (4.3)
Other glaucoma	22 (6.5)	7 (3.2)	1 (0.7)	30 (4.3)
OH	7 (2.1)	7 (3.2)	1 (0.7)	15 (2.1)
Baseline IOP, mean \pm SD, mmHg	16.6 ± 4.2	14.7 ± 3.6	15.5 ± 5.4	15.8 ± 4.4

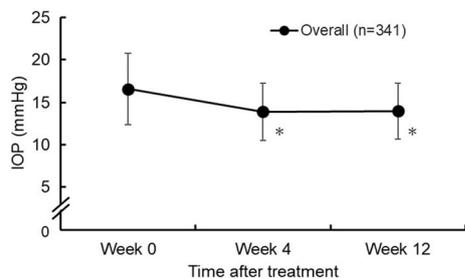


Fig. 2 Time course of IOP after OMDI treatment in naïve monotherapy patients with glaucoma and ocular hypertension, evaluated in a retrospective real-world study in Japan. * $P < 0.0001$ vs week 0 (untreated baseline) using the paired t test with Bonferroni correction. IOP, intraocular pressure; OMDI, omdinenepag isopropyl

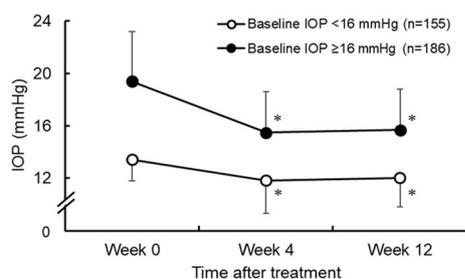


Fig. 3 Time course of IOP after OMDI treatment in naïve patients, evaluated in a retrospective real-world study. The IOP data for the low baseline IOP (less than 16 mmHg) group and high baseline IOP (at least 16 mmHg) group are indicated by open circles and closed circles, respectively. * $P < 0.0001$ vs week 0 (untreated baseline) using the paired t test with Bonferroni correction. IOP, intraocular pressure; OMDI, omdinenepag isopropyl

reduction, $P < 0.0001$), respectively. Mean IOP of patients in the naïve monotherapy group with baseline IOP < 16 mmHg decreased from 13.4 ± 1.6 mmHg at week 0 (baseline) to 11.8 ± 2.5 mmHg at 4 weeks and 12.0 ± 2.0 mmHg at 12 weeks after OMDI treatment. The mean IOP reduction from baseline at week 4 and week 12 in the low baseline IOP group was -1.6 ± 2.3 mmHg (11.7% reduction, $P < 0.0001$) and -1.4 ± 2.0 mmHg (9.8% reduction, $P < 0.0001$), respectively. Subgroup analysis in the naïve monotherapy group based on the diagnosis is shown in Fig. 4.

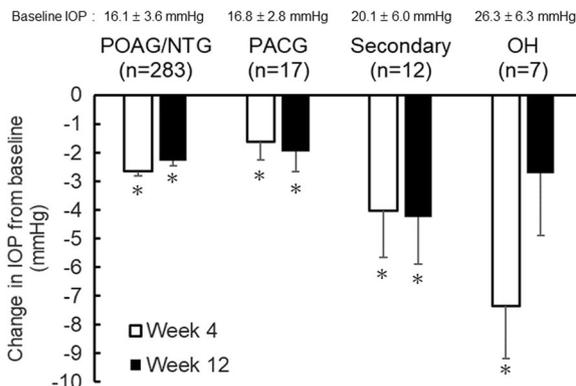


Fig. 4 Change from baseline in mean IOP after OMDI treatment in naïve patients with each type of glaucoma, evaluated in a retrospective real-world study. * $P < 0.05$ vs baseline (week 0) using the paired t test with Bonferroni correction. IOP, intraocular pressure; OMDI, omdinenepag isopropyl

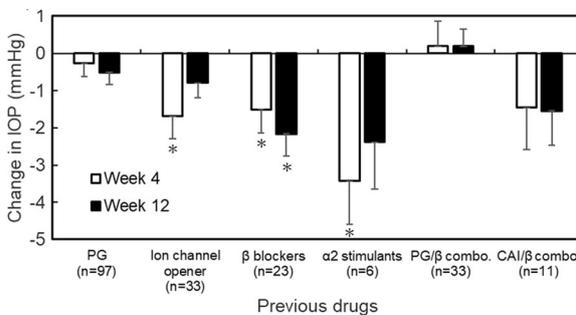


Fig. 5 Change in IOP after switching from various antiglaucoma drugs to OMDI monotherapy, evaluated in a retrospective real-world study. * $P < 0.05$ vs week 0 (switching time point) using the paired t test with Bonferroni correction. IOP, intraocular pressure; OMDI, omdinenepag isopropyl

The mean IOP reduction from baseline at week 4 in POAG/NTG, PACG, and secondary glaucoma was -2.7 ± 2.6 mmHg ($P < 0.0001$), -1.7 ± 2.8 mmHg ($P = 0.0360$), and -4.0 ± 6.6 mmHg ($P = 0.0466$), respectively. In the OH subgroup, the mean IOP reduction at week 4 and week 12 was -7.6 ± 4.3 mmHg ($P = 0.0090$) and -2.1 ± 4.7 mmHg ($P = 0.4952$), respectively.

Table 2 Summary of adverse drug reactions in the OMDI monotherapy and concomitant therapy groups

Adverse reactions	Overall (<i>n</i> = 827) patients, (%)	Naïve monotherapy (<i>n</i> = 341) patients, (% in group)	Switching monotherapy (<i>n</i> = 222) patients, (% in group)	Concomitant therapy (<i>n</i> = 135) patients, (% in group)
Ocular hyperemia	63 (7.6)	33 (9.7)	17 (7.7)	9 (6.7)
Eye pruritis	16 (1.9)	6 (1.8)	4 (1.8)	3 (2.2)
Vision blurred	9 (1.1)	3 (0.9)	4 (1.8)	1 (0.7)
Dry eye	7 (0.8)	5 (1.5)	2 (0.9)	0
Blepharitis	6 (0.7)	1 (0.3)	2 (0.9)	1 (0.7)
Eye pain	5 (0.6)	2 (0.6)	1 (0.5)	1 (0.7)
Foreign body eye sensation	5 (0.6)	1 (0.3)	2 (0.9)	0
Asthenopia	4 (0.5)	1 (0.3)	3 (1.4)	0
Conjunctivitis allergic	4 (0.5)	0	0	1 (0.7)
Eye irritation	4 (0.5)	1 (0.3)	3 (1.4)	0
Punctate keratitis	4 (0.5)	2 (0.6)	1 (0.5)	1 (0.7)
Visual acuity reduced	4 (0.5)	3 (0.9)	1 (0.5)	0
Iritis	3 (0.4)	3 (0.9)	0	0
Lacrimation increased	3 (0.4)	0	1 (0.5)	0
Blepharospasm	2 (0.2)	0	2 (0.9)	0
Eye discharge	2 (0.2)	0	1 (0.5)	0
Myopia	2 (0.2)	2 (0.6)	0	0
Photophobia	2 (0.2)	1 (0.3)	0	1 (0.7)

Results in the switching monotherapy group are shown in Fig. 5. The most commonly used medication before OMDI was prostaglandins (*n* = 97), followed by ion channel openers (*n* = 33), PG/beta-blocker fixed-combinations (*n* = 33), beta-blockers (*n* = 23), carbon anhydrase inhibitor (CAI)/beta-blocker fixed-combinations (*n* = 11), and alpha-2 receptor stimulants (*n* = 6). IOP was significantly

reduced in switching from beta-blocker to OMDI. The mean IOP reduction at 4 weeks and 12 weeks after switching from beta-blockers to OMDI monotherapy was -1.2 ± 2.7 mmHg ($P = 0.0472$) and -2.3 ± 3.1 mmHg ($P = 0.0015$), respectively. There was no significant difference in IOP before and 12 weeks after switching from prostaglandins, the ion-channel opener (unoprostone), alpha-2 receptor

Table 3 Categories of concomitant drugs with OMDI in a retrospective Japanese real-world clinical study

Concomitant drugs	No. of patients
One component	
+ α 1-blocker	5
+ α 1 β 1-blocker	7
+ α 2-stimulant	7
+ β -blocker	13
+ CAI	10
+ ROCK inhibitor	13
Two components	
+ α 1-blocker + CAI	2
+ α 1 β 1-blocker + ROCK inhibitor	1
+ α 2-stimulant + CAI	2
+ α 2-stimulant + ROCK inhibitor	2
+ CAI + ROCK inhibitor	6
+ CAI/ β combo	45
Three or four components	
+ CAI/ β combo + α 2-stimulant	7
+ CAI/ β combo + ROCK inhibitor	4
+ CAI/ β combo + α 2-stimulant + ROCK inhibitor	3
Other	8

CAI, carbon anhydrase inhibitor; ROCK, Rho-associated coiled-coil containing protein kinase; OMDI, omidenepag isopropyl

stimulants, or CAI and beta-blocker fixed-combinations.

Safety

The safety profiles in the present study are summarized in Table 2. A total of 153 adverse reactions were reported from 117 of the 827 patients (14.1%) in the safety analysis set. The most frequent adverse reaction was ocular

hyperemia (7.6%). Eye itching was documented in 1.9% of patients, and blurred vision was reported in 1.1% of patients. No systemic or local serious events were recorded. There was no case of cystoid macular edema and uveitis, as reported in the phase 3 RENGE study [8], and no PAP. The frequency of adverse reactions by therapy pattern was 15.8% in the naïve monotherapy group, 15.8% in the switching monotherapy group, and 13.3% in the concomitant therapy group (Table 2).

The combinations of drugs in the concomitant therapy group were diverse (Table 3). The most commonly used drug combination was the CAI/beta-blocker fixed-combination drugs ($n = 45$), followed by beta-blockers ($n = 13$) and rho kinase (ROCK) inhibitors ($n = 13$). There was no significant difference in the frequency of adverse reactions between the naïve monotherapy group and the concomitant therapy group ($P = 0.5711$, Fisher's exact test).

DISCUSSION

This real-world data survey provided several additional pieces of information about the efficacy and safety of the prostanoid EP₂ receptor agonist OMDI which have not been clarified in previous clinical trials. First, OMDI showed significant IOP reduction in patients with glaucoma and low baseline IOP (less than 16 mmHg). Second, OMDI was effective in various types of glaucoma such as PACG and secondary glaucoma. Third, switching from other classes of glaucoma drugs including prostaglandin-related drugs to OMDI maintained IOP at levels comparable to those achieved by previously prescribed drugs, or even further IOP reduction in the case of switching from beta-blockers. Fourth, no serious and high frequency side effect was observed in those receiving concomitant therapy with other class drugs.

Some of the clinical trials have been already reported. The phase 3 RENGE study was an open-label, multicenter evaluation of long-term IOP reduction with OMDI in Japanese patients with POAG or OH and high (22 mmHg to \leq 34 mmHg) or low (16 mmHg to $<$ 22 mmHg) baseline IOP [8]. After 6 months

of daily treatment with OMDI, mean IOP was reduced by 2.4 mmHg in the low baseline IOP group and by 4.9 mmHg in the high baseline IOP group. This RENGE study was conducted only in patients with baseline IOP of 16 mmHg or higher. Thus, the efficacy of OMDI in patients with NTG and low baseline IOP was unclear. The present study showed that OMDI has an IOP-lowering effect in patients with a baseline IOP of less than 16 mmHg, suggesting that OMDI reduces IOP even in patients with low baseline IOP. Another study by Inoue et al. reported the short-term efficacy and safety of OMDI in patients with NTG [9]. IOP was significant lower than baseline (15.7 ± 2.6 mmHg) after 1–2 months (13.5 ± 2.3 mmHg). The results of this research report are also similar to our retrospective analysis, indicating that treatment with OMDI may be beneficial for patients with NTG.

In general, most of the study subjects in the clinical trials of IOP-lowering drugs were patients with POAG. Therefore, at the time of drug launch, there were few data on the efficacy and safety of IOP-lowering drugs in eye with other glaucoma types such as PACG and secondary glaucoma. The results of the present study in the naïve monotherapy group showed that OMDI lowers IOP in patients with various types of glaucoma and OH. It is necessary to clarify the long-term efficacy and safety profile of OMDI for each type of glaucoma in the future, but our results suggest the favorable effect of OMDI regardless of glaucoma type.

There are some reports about efficacy after switching to OMDI monotherapy. Sakata et al. reported that switching patients with glaucoma from prostanoid FP receptor agonists to OMDI improved deepening of the upper eyelid sulcus (DUES) while maintaining IOP [12]. This clinical research showed that the mean IOP before switching, 1 month after switching, and 3 months after switching to OMDI was 15.3 mmHg, 15.6 mmHg, and 15.5 mmHg, respectively. Oogi et al. also reported no significant change in mean IOP after switching from PGF_{2α} analogues to OMDI [13]. Likewise in our study, there was no significant change in IOP after switching to OMDI from other classes of drugs including prostaglandin-related drugs.

The only exception was switching to OMDI from beta-blockers, which resulted in a further decrease in IOP. Currently, eye drops containing prostaglandin-related drugs are the most commonly used first-line medicines for glaucoma therapy [3]. Therefore, it is important that switching from this class of drugs to OMDI did not cause any adverse ocular events such as increased IOP. Treatment change to OMDI may help patients with cosmetic side effects because the risk of developing pigmentation, eyelash growth, and DUES, which are cosmetic side effects frequently associated with the use of prostaglandin F_{2α} analogues, is low with OMDI use [11].

In this retrospective study, the most frequent adverse reaction to OMDI was ocular hyperemia. Severe or serious side effects were not recorded in this study. Signs of eye inflammation, CME, and uveitis were reported in phase 3 trials [6, 8], but they were not observed in this study. In addition, iritis or decreased visual acuity was less frequent. PGE₂ is generally known to have vasodilator and vascular permeability effects which can enhance inflammation [14, 15]. Therefore, on the basis of this clinical and non-clinical knowledge, the careful use of OMDI has been recommended in patients with ocular inflammation. The reason for the low frequency of adverse reactions in this study may be related to the proper and careful use of this drug in the real world. PAP was not observed in our study. Also, there were no cosmetic adverse reactions to OMDI. Since the observation period of this study was short (12 weeks), further long-term observation is necessary for the safety evaluation of OMDI.

Evidence regarding the concomitant use of OMDI with other drugs has been limited except for beta-blockers in a phase 3 clinical trial report [8]. Since eye drops are often used in combination to achieve the patient's target IOP, it is important to obtain information on the optimal combination of drugs and their possible side effects. In our study, diverse medications were concomitantly used with OMDI, and many types of drugs were used before and after the medications concomitantly used with OMDI. Therefore, it was impossible to obtain sufficient number of cases for valid statistical analyses.

However, no serious safety risk was observed in eyes with OMDI concomitant therapy. This was supported by the fact that there was no significant difference in the frequency of adverse reactions between the naïve monotherapy and concomitant therapy groups. In an experimental animal study, OMDI enhanced the IOP-reducing effect in combination with beta-blocker, α_2 stimulants, CAI, and ROCK inhibitors [16]. This pharmacologic experimental data theoretically supports the efficacy of OMDI in combination with various categories of drugs in clinical situations.

There are some limitations to this study. First, the study has a short observation period and the findings from the study may not be generalizable to all clinical course and events. Second, in the subgroup analysis by glaucoma type, the number of cases may too small to have enough statistical power. Third, the unknown status of compliance with eye drop therapy in individuals may have affected the examination data. In the near future, it will be necessary to clarify the efficacy and safety of OMDI through longer-term cohort studies.

CONCLUSION

OMDI, a prostanoid EP₂ receptor agonist, achieved favorable IOP reduction in various types of glaucoma and using various therapeutic patterns in real-world clinical practice. In addition, OMDI showed no serious or severe, systemic or local adverse drug reactions, suggesting that OMDI can be a first-line medicine for the treatment of glaucoma.

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Compliance with Ethics Guidelines. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research

committee and with the Helsinki Declaration. This study was approved by the institutional review board, and was registered as a clinical trial (UMIN ID 000040040).

Data Availability. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis. The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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