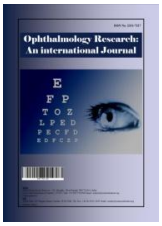

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Effect of Continuous 0.5% Ganciclovir Eye Drop Treatment in Secondary Glaucoma Associated with Cytomegalovirus Anterior Uveitis

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Authors' contributions

This work was carried out in collaboration among all authors. Authors TO and KY drafted the manuscript. Authors KY, TK and SN collected the data. Authors SN and KK reviewed the literature. Authors TO and KY interpreted the data and critically reviewed the manuscript. Author TK critically reviewed the final version of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Purpose: The purpose of this study was to investigate the treatment outcomes of secondary glaucoma caused by cytomegalovirus (CMV)-anterior uveitis (AU) with continuous 0.5% ganciclovir eye drop.
Study Design: Retrospective observational study.
Place and Duration of Study: Department of Ophthalmology, Oita University Hospital, between January 2012 and December 2017.
Methodology: Nineteen eyes of 19 patients with secondary glaucoma associated with CMV-AU diagnosed by a polymerase chain reaction analysis from human aqueous samples were enrolled. They were treated with continuous 4-times-daily topical 0.5% ganciclovir in addition to topical steroids and anti-glaucoma medications. We performed glaucoma surgery for patients with poorly medically controlled intraocular pressure (IOP).
Results: Anterior chamber inflammation and IOP were controlled without systemic ganciclovir or glaucoma surgery during the follow-up period (mean: 59.2±27.0 months) in 9 (47%) eyes. Five (26%) eyes required systemic ganciclovir and ten (53%) eyes required glaucoma surgery. Patients

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were divided into two groups for the comparison: one group requiring glaucoma surgery and one treated with medication. The mean IOP and number of anti-glaucoma medications at the first visit were significantly higher in the surgery group than in the medication group. The mean number of IOP spikes per year (IOP >30 mmHg) was 1.4±0.9 in the surgery group and 0.4±0.5 in the medication group. The recurrence of anterior chamber inflammation was suppressed in both groups. The cumulative survival rate after glaucoma surgery was 80% at 12 months and 70% at 36 months.

Conclusion: The anterior chamber inflammation and IOP were controlled with continuous 0.5% ganciclovir eye drop treatment in half of the patients with CNV-AU. A high IOP at the first visit and frequent IOP spikes were risk factors for additional glaucoma surgeries.

Keywords: Cytomegalovirus; anterior uveitis; secondary glaucoma; ganciclovir; glaucoma surgery.

ABBREVIATIONS

AU : Anterior Uveitis
CEC : Central Corneal Endothelium Cell
CMV : Cytomegalovirus
DNA : Deoxyribo Nucleic Acid
HSV : Herpes Simplex Virus
IOP : Intraocular Pressure
MD : Mean Deviation
PCR : Polymerase Chain Reaction
TGF : Transforming Growth Factor
TM : Trabecular Meshwork
VZV : Varicella Zoster Virus

1. INTRODUCTION

Cytomegalovirus (CMV)-associated anterior uveitis (AU) (CMV-AU) is a cause of secondary glaucoma with a high intraocular pressure (IOP) [1,2]. CMV is a main cause of ocular infection, such as CMV retinitis in immunocompromised patients [3]. However, CMV-AU and corneal endotheliitis can also affect immunocompetent patients [4,5]. CMV-AU induces a very high IOP during active inflammatory episodes compared to Herpes simplex virus (HSV) -or Varicella zoster virus (VZV)-associated uveitis [6]. In addition, CMV-AU is often associated with a risk for developing glaucoma. Shirahama et al. reported that patients with CMV-AU may have a higher risk and faster progression of secondary glaucoma than patients with HSV/VZV-AU [7].

A polymerase chain reaction (PCR) analysis of CMV-DNA from a human aqueous sample is necessary to make an accurate diagnosis [8-11]. CMV has been confirmed as the etiology of what was previously considered to be Fuchs heterochromic iridocyclitis and Posner-Schlossman syndrome since the introduction of PCR testing at ophthalmological clinics [12].

Ganciclovir is effective for clearing the viral load, reducing the inflammation and assisting with IOP control in CMV-AU [13]. CMV-AU patients have been treated with a systemic ganciclovir and topical ganciclovir eye drops in addition to topical steroids and anti-glaucoma medications [1, 2, 14-16]. However, some cases do not respond to medications and require glaucoma surgery because of an uncontrolled IOP. In addition, systemic ganciclovir treatment may need to be discontinued because of its side effects [15-17].

CMV-AU may require continuous treatment with ganciclovir in order to suppress recurrence of inflammation and IOP spikes. The effectiveness of continuous topical ganciclovir treatment has not been reported. In this study, we treated patients with continuous topical 0.5% ganciclovir eye drop during the follow-up period and report its treatment outcomes.

2. MATERIALS AND METHODS

This retrospective observational study protocol was approved by the Institutional Review Board of Oita University Hospital. The study adhered to the tenets of the Declaration of Helsinki for research involving human subjects. Written informed consent was obtained from each patient. In this study, all medical records of patients with secondary glaucoma associated with CMV-AU who underwent treatment between January 2012 and December 2017 at the Department of Ophthalmology, Oita University Hospital, were reviewed. Eligible patients met the following criteria: (1) AU patients diagnosed as CMV-positive according to the results of PCR of aqueous humor taps in our facilities, and (2) patients with glaucomatous changes on an optic nerve head examination (neuroretinal rim narrowing, notching, and retinal nerve fiber layer defects) and/or glaucomatous visual field defects. The exclusion criteria were (1) patients who were already receiving ganciclovir treatment at other clinics, (2) eyes with another visually significant

ocular pathology, and (3) a history of glaucoma surgery.

Nineteen eyes of 19 patients were included in this study. The patients were treated with topical 0.5% ganciclovir eye drops 4 times daily in addition to any topical steroid eye drops and anti-glaucoma medications used before. Topical 0.5% ganciclovir eye drops were used during the follow-up period. Topical steroids eye drops and anti-glaucoma medications tapered when anterior chamber inflammation and high IOP were suppressed. In some cases, systemic ganciclovir was used for a month against poor control patients of inflammation and high IOP after starting 0.5% ganciclovir eye drop. In patients with medically uncontrolled IOP, glaucoma surgery was performed.

Clinical information on all patients was collected from their medical charts, including their age, anterior chamber inflammation, central corneal endothelium cell (CEC) density, IOP, number of anti-glaucoma medications, mean deviation (MD) at the first visit, duration of disease and follow-up duration. The cumulative probability for success of topical 0.5% ganciclovir treatment was studied using a Kaplan-Meier analysis. The patients with no need for systemic ganciclovir or any additional glaucoma surgery were deemed to be successful. Patients whose poor IOP could not be controlled were set to undergo glaucoma surgery.

The above clinical information was compared between two groups: the group requiring glaucoma surgery (surgery group) and the group treated with medications (medication group). In addition, the IOP and number of glaucoma medications at the first and final visit, the number of IOP spikes (IOP >30 mmHg) and recurrence of anterior chamber inflammation after topical 0.5% ganciclovir treatment were compared between the groups. Furthermore, the surgical success rates were evaluated in the surgery group. The patients with an IOP <21 mmHg and any additional glaucoma surgery were deemed to be successful.

Anterior chamber inflammation was detected by slit-lamp examinations. The CEC density was assessed using noncontact specular microscopy. The IOP was assessed using Goldmann applanation tonometry. Visual field data were obtained with a Humphrey field analyzer. All statistical analyses were performed using BellCurve for Excel (Social Survey Research Information Co., Ltd. Tokyo, Japan). Differences between the two groups were compared using either a *t*-test (continuous factors) or Fisher's exact test (categorical factors). *P*-values <0.05 were considered statistically significant.

3. RESULTS

Table 1 describes the demographic data and initial clinical manifestations of all patients. Nineteen eyes of 19 patients were included in this study. The mean age was 59.7±13.7 years old (range: 30-81 years old). Anterior chamber inflammation was found in 19 (100%) eyes at the first visit. The mean IOP at the first visit was 25.3±12.9 mmHg (range: 10-50 mmHg). The mean number of glaucoma medications at the first visit was 3.0±1.7 (range: 0-6).

Anterior chamber inflammation disappeared in 17 (74%) eyes, and the IOP was controlled in 12 (63%) eyes within 3 months after additional 0.5% ganciclovir eye drop treatment. The IOP in 5 eyes was not controlled to <30 mmHg within 3 months after additional 0.5% ganciclovir eye drop treatment (Table 2). So four eyes of 5 patients were used systemic ganciclovir. However, IOP was not controlled and glaucoma surgery was immediately required. Five of 14 eyes underwent glaucoma surgery at 7, 10, 18, 36 and 40 months after being regularly treated with 0.5% ganciclovir eye drops, respectively because of sharp uncontrolled IOP. Finally, glaucoma surgery was performed in 10 (53%) eyes during the follow-up periods. The cumulative success rate of treatment with additional topical 0.5% ganciclovir was 73.6% at 3 months, 63.1% at 12 months and 52.6% at 36 months of follow-up (Fig. 1).

The demographic data and initial clinical manifestations of the two groups are listed in Table 3. The mean IOP at the first visit was 33.8±11.2 mmHg in the surgery group (n=10) and 15.9±4.9 mmHg in the medication group (n=9), a significant difference (p=0.0008). The mean number of glaucoma medications was significantly higher in the surgery group than in the medication group at the first visit. The two groups did not differ markedly in the age and anterior chamber inflammation at the first visit, CEC density, MD of visual field, duration of disease and follow-up duration.

Fig. 2 shows the mean IOP at different time points after additional 0.5% ganciclovir eye drop treatment. The clinical outcomes after additional topical 0.5% ganciclovir treatment of the 2 groups are listed in Table 4. In the surgery group, the mean IOP and number of glaucoma

medications at the final visit before surgery were not significantly different from those at the first visit. The mean number of glaucoma medications at the final visit was significantly lower than at the first visit (P<0.05) in the medication group.

Three months after starting additional topical 0.5% ganciclovir eye drop treatment, an IOP spike (IOP >30 mmHg) was observed in 4 of 5 eyes of the surgery group (excluding 5 eyes that underwent surgery within 3 months after starting additional topical 0.5% ganciclovir eye drop treatment) until glaucoma surgery and 2 of 9 eyes of the medication group during the follow-up period, and the mean number of IOP spikes per year (IOP >30 mmHg) was 1.4±0.9 in the surgery group and 0.4±0.5 in the medication group. Recurrence of anterior chamber inflammation was 2 of 5 eyes in the surgery group and 2 of 9 eyes in the medication group. Recurrence of anterior chamber inflammation was suppressed in both groups by continuous additional 0.5% ganciclovir eye drop treatment (Table 5).

Fig. 3 shows the mean IOP at different time points after glaucoma surgery. Seven eyes underwent trabeculectomy, and three eyes underwent trabeculotomy. The decrease in the mean IOP was statistically significant for all points compared to the baseline value. The mean IOP decreased from 32±10.3 mmHg at baseline to 10.2±1.7 mmHg after 2 years. The mean number of antiglaucoma medications decreased from 4.1±1.0 at baseline to 0.3±0.7 after 2 years. Surgery successfully reduced the IOP to <21 mmHg in 71% (5/7) of trabeculectomy patients and 66.7% (2/3) of trabeculotomy patients after 3 years. Three failed eyes underwent additional trabeculectomy and obtained controlled IOP.

Table 1. Baseline demographic and clinical characteristic

Number of eyes	19
Age (years)	59.7±13.7 (30-81)
Anterior chamber inflammation	19 (100%)
Central corneal endothelium cell density (cell/mm^2)	2345±406 (1405-2887)
IOP (mmHg)	25.3±12.9 (10-50)
Number of glaucoma medications	3.0±1.7 (0-6)
MD (dB)	-8.5±9.0 (0.85- -28.8)
Duration of disease (months)	97.8±102.9 (1-336)
Follow up duration (months)	59.2±27.0 (27-104)

Data are presented as the mean±standard deviation; IOP: intraocular pressure, MD: mean deviation

Table 2. Anterior chamber inflammation and IOP within 3 months after additional 0.5% ganciclovir eye drop treatment

Anterior chamber inflammation disappeared	**17 (89%)**
IOP was controlled to <21 mmHg	12 (63%)
IOP was not controlled to <30 mmHg	5 (26%)

Table 3. A comparison of the baseline parameters between the two groups

Characteristics	Surgery group	Medication group	p value
Number of eyes	10	9	
Age (years)	60.3±9.7	59.1±16.5	0.43
Anterior chamber inflammation	10 eyes (100%)	7 eyes (77.8%)	0.21
Central corneal endothelium cell density (cell/mm^2)	2303±406	2393±377	0.32
IOP (mmHg)	33.8±11.2	15.9±4.9	<0.001
Number of glaucoma medications	3.7±1.8	2.2±1.0	<0.05
MD (dB)	-8.5±9.0	-4.1±2.0	0.09
Duration of disease (months)	105±108	89±89	0.37
Follow up duration (months)	66±26	52±25	0.14

Data are presented as the mean±standard deviation
p value by Fisher's exact test

Table 4. IOP and number of glaucoma medications of baseline and final visit

	Baseline	Final	*p* value
IOP			
surgery group	33.8±11.2	32.0±10.3	0.51
medication group	15.9±4.9	15.4±5.7	0.64
Number of glaucoma medications			
surgery group	3.7±1.8	4.1±1.0	0.56
medication group	2.2±1.0	1.1±1.8	<0.05

p value by the t-test

Table 5. A comparison between the 2 groups after 0.5% ganciclovir eye drops

Characteristics	Surgery group (N=10)	Medication group (N=9)	*p* value
Disappearance of anterior chamber inflammation	8 (80%)	9 (100%)	
Recurrence of anterior chamber inflammation	1 (20%)	2 (22.2%)	0.58
IOP spikes >30 mmHg	4 (80%)	2 (22.2%)	0.09
Mean number of IOP spikes per year	1.4±0.9	0.4±0.5	<0.05

p value by Fisher's exact test

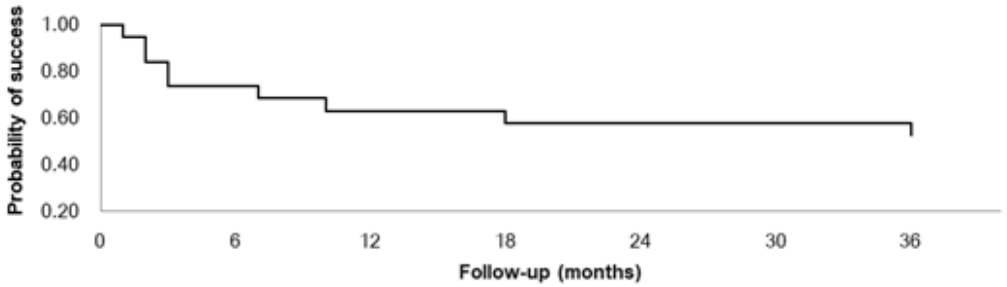

Fig. 1. Cumulative success rate in the patients treated with a topical 0.5% ganciclovir eye drop

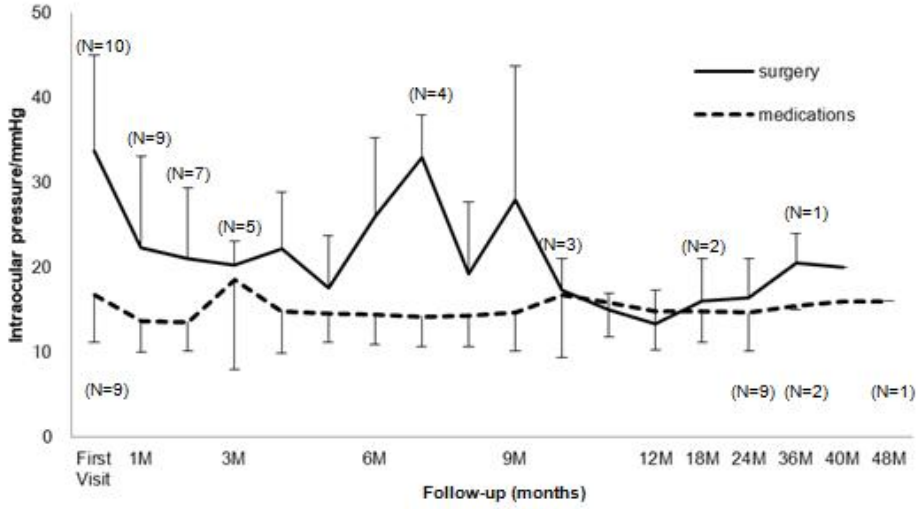

Fig. 2. Mean intraocular pressures (IOPs) ± standard deviation of the 2 groups after 0.5% ganciclovir eye drops at the follow-up points

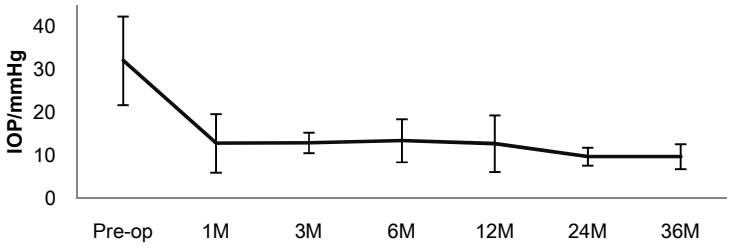

Fig. 3. The postoperative IOP values of the surgery group
Postoperative Period(months); p value by Fisher's exact test

4. DISCUSSION

Systemic ganciclovir has been recommended for CMV-AU because it suppresses the replication of the herpes virus. However, systemic ganciclovir has the risk of systemic side effects including granulocytopenia, thrombocytopenia, and anemia. Recently, many studies have confirmed the benefits of topical ganciclovir for CMV-AU treatment [15-18]. The concentration of the drug was reported to be 0.15% ganciclovir gel and 0.5% to 2% ganciclovir eye drops. Commercial topical 0.15% ganciclovir gel is available in many countries, although it has not been approved and marketed in Japan, so ganciclovir eye drops prepared at hospitals from vials for intravenous infusion are used. Therefore, 0.5% ganciclovir eye drops were used in this study for clinical research under the approval of institutional review boards.

In this study, the cumulative survival rate after continuous topical 0.5% ganciclovir eye drop treatment was 52.6% at 36 months. Anterior chamber inflammation disappeared in 17/19 (89%) eyes within 3 months after starting additional topical 0.5% ganciclovir eye drop treatment. Five eyes with severe anterior chamber inflammation and high IOP did not immediately respond to topical 0.5% ganciclovir eye drops. We used oral ganciclovir in addition to topical 0.5% ganciclovir eye drops for 1 month to treat these 5 eyes. The anterior chamber inflammation was controlled using oral ganciclovir. However, IOP were not controlled in these 5 eyes. Chee et al. [19] reported that oral valganciclovir and intravitreal ganciclovir were effective for suppressing inflammation of CMV-AU compared with 0.15% ganciclovir gel. Topical 0.5% ganciclovir eye drops may be insufficient to treat severe CMV-AU. Additional oral ganciclovir may be necessary in cases with severe anterior chamber inflammation and a high IOP.

Recurrence of anterior chamber inflammation was observed during the follow-up period in 3/14 (21%) eyes(surgery, 1/5 [20%]; medication, 2/9 [22%]) that did not undergo early surgery. This suggests that recurrence of anterior chamber inflammation may be suppressed by continuous 0.5% ganciclovir eye drop treatment. Chee et al. found that topical 0.15% ganciclovir gel was associated with lower recurrence rates than systemic ganciclovir. Furthermore, they reported that discontinuation of ganciclovir eye drop treatment induced recurrence of AU. Frequent recurrence of AU was reported with oral valganciclovir and intravitreal ganciclovir treatment (oral valganciclovir: 80%, intravitreal ganciclovir: 100%). The recurrence rates of 0.15% ganciclovir gel were 57.1% in eyes with acute AU and 25.0% in eyes with chronic AU [19]. Continuous topical 0.5% ganciclovir eye drop treatment did not cause systemic or ocular complications. No studies have reported significant side effects, such as ocular discomfort or corneal toxicity, with topical ganciclovir treatment [15,17,18]. Continuous 0.5% ganciclovir eye drop treatment may reduce the rate of recurrence of anterior chamber inflammation and result in the avoidance of glaucoma surgery.

In this study, 9 of 19 eyes had an IOP exceeding 25 mmHg at the first visit. The IOP at the first visit was significantly higher in the surgery group than in the medication group (33.8±11.2 mmHg vs. 15.9±4 mmHg; $P<0.001$). Eyes developed attack of high IOP over 30 mmHg after 3 months were 4/5 (80%) in the surgery group and 2/9 (22%) in the medication group. The number of IOP spike episodes (IOP >30 mmHg) was significantly higher in the surgery group than in the medication group (1.4±0.9 times per year vs. 0.4±0.5 times per year; $P<0.05$). The present study showed that surgery is often necessary if the IOP at the first visit is high and recurrence of IOP spikes is frequent.

The mechanism underlying the IOP elevation observed in CMV-AU associated with anterior chamber inflammation is considered to involve trabeculitis, steroid administration and trabecular blockage containing inflammatory materials. Some cases had uncontrolled IOP despite no anterior chamber inflammation after continuous 0.5% ganciclovir eye drop treatment. We believe that the IOP and anterior chamber inflammation are not correlated. Choi et al. reported that CMV infection enhanced the production of transforming growth factor (TGF)-β1, an upstream molecule that increases the resistance of the outflow pathway in human trabecular meshwork(TM)cells. When TM cells were exposed to different concentrations of ganciclovir, they found that ganciclovir significantly decreased the viral deoxyribo nucleic acid(DNA) accumulation. However, treatment with ganciclovir did not significantly affect the TGF-β1 production compared with exposure to CMV alone. Those authors therefore suggested that the acute elevation of TGF-β1 induced by CMV infection might be a key mechanism responsible for the elevation of the IOP [19].

The surgical success rates of trabeculectomy in eyes with inflammatory glaucoma were reported to differ among studies and were worse than the rates for other types of glaucoma [20, 21]. Iverson et al. reported the cumulative probability of success after 5 years of follow-up to be 38% (surgical failure defined as IOP >21 mmHg or not reduced by 20% below baseline at 2 consecutive follow-up visits after 3 months; IOP <5 mmHg at 2 consecutive follow-up visits after 3 months, reoperation for glaucoma; or loss of light-perception vision) [20]. You et al. reported a 90.9% success rate at 1 year and 62.3% at 4 years after mitomycin C trabeculectomy in secondary glaucoma in Fuchs' heterochromic iridocyclitis (success: IOP of 21 mmHg and IOP-lowering medications required to achieve this pressure) [21]. In the present study, we performed trabeculectomy in seven eyes and trabeculotomy in three eyes. trabeculectomy was performed in case of severe uncontrolled IOP and visual field defect progression. Trabeculotomy was performed in case of mild visual field defect progression. Trabeculectomy successfully reduced the IOP to <21 mmHg in 71% (5/7) of cases after 3 years. The IOP was controlled with additional trabeculectomy in all 10 patients. Trabeculectomy may be a good surgical intervention against secondary glaucoma associated with CMV-AU. However, a further study including a large number of patients is necessary.

Several limitations associated with the present study warrant mention. First, it was retrospective, included a limited small number of patients and had a short follow-up period. An analysis of a larger number of patients should be conducted to clarify the relationship between the recurrence of CMV-AU and continuous 0.5% ganciclovir eye drop treatment with a long follow-up period. Another limitation of our study is that overlapped use of two concomitant medications, such as topic ganciclovir and topical steroids. It may interfere positively in final control outcome of IOP and AU and the appreciation of their isolated effects. Topical steroids were continued and tapered off in 16/19 (84%) eyes for the follow-up period. Long-term topical steroids may affect IOP and anterior chamber inflammation control. Nonetheless, we examined the clinical outcomes of continuous 0.5% ganciclovir eye drop treatment for CMV-AU. The suppression of CMV-AU may therefore not have been entirely due to continuous 0.5% ganciclovir eye drop treatment.

5. CONCLUSIONS

In summary, continuous 0.5% ganciclovir eye drop is effective to control anterior chamber inflammation. The IOP was ultimately controlled with continuous topical 0.5% ganciclovir eye drop treatment in 9/19 (47%) of the patients with CNV-AU in this study. The rate of recurrence of IOP spikes was lower in the medication group than in the surgery group. A total of 53% cases required glaucoma surgery after continuous 0.5% ganciclovir eye drop treatment. Surgery is often necessary if the IOP at the first visit is high and recurrence of IOP spikes is frequent.

CONSENT

Written informed consent was obtained from each patient.

ETHICAL APPROVAL

This retrospective observational study protocol was approved by the Institutional Review Board of Oita University Hospital, in April 2020 (No1181). The study adhered to the tenets of the Declaration of Helsinki for research involving human subjects.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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