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Three-year visual outcomes after brolucizumab in patients with neovascular age-related macular degeneration

Yume Kobayashi[1], Maiko Maruyama-Inoue[1*], Tatsuya Inoue[1], Yasuo Yanagi[1] and Kazuaki Kadonosono[1]

Abstract

Background The purpose of this study is to investigate the 3-year outcomes of intravitreal brolucizumab and determine the factors that affect the visual acuity (VA) in patients with neovascular age-related macular degeneration.

Methods All received three consecutive, monthly, induction brolucizumab injections (6.0 mg/0.05 ml) and fixed-dose every 2-or-3-month treatment for 12 months, after which a pro re nata (PRN) or treat-and-extend (TAE) regimen began. Best-corrected VAs (BCVAs) on a Landolt C eye chart were compared before and 4, 12, and 36 months after initial treatment. Factors affecting VA improvements and morphologic characteristics associated with VA at 36 months were determined.

Results Fifty-nine eyes were assessed at 36 months. The mean logMAR BCVAs at baseline and 4, 12, and 36 months after the initial injection were 0.37 ± 0.39, 0.34 ± 0.48, 0.30 ± 0.47, and 0.36 ± 0.51 in the PRN group and 0.31 ± 0.28, 0.22 ± 0.27, 0.18 ± 0.28, and 0.20 ± 0.31 in the TAE group, respectively. In the PRN group, post-injection BCVA did not improve significantly compared with baseline throughout 36 months ($p = 0.999$, $p = 0.814$, and $p = 0.999$ at 4, 12, and 36 months, respectively). In the TAE group, the post-injection BCVA at 12 and 36 months improved significantly compared with baseline ($p = 0.006$ and $p = 0.032$, respectively). The baseline BCVA, central foveal thickness (CFT) and TAE regimen were associated with improved VA ($p < 0.05$ for all). Eyes with subretinal fluid (SRF) at 36 months had significantly better VA ($p = 0.019$).

Conclusion The TAE regimen achieved better visual outcomes at 3 years. Residual SRF should be tolerated during the maintenance phase if the change of CFT was little compared to the previous image.

Keywords Age-related macular degeneration, Polypoidal choroidal vasculopathy, Anti-vascular endothelial growth factor, Brolucizumab, Subretinal fluid

*Correspondence:
Maiko Maruyama-Inoue
maicoo@urahp.yokohama-cu.ac.jp
[1]Department of Ophthalmology, Yokohama City University Medical Center, 57 Urafune-cho, Minami-ku, Yokohama, Kanagawa 232-0024, Japan

Background

Age-related macular degeneration (AMD) is the leading cause of blindness in developed countries [1, 2]. Neovascular AMD (nAMD), which is caused by macular neovascularization (MNV), has been treated with intravitreal injections of anti-vascular endothelial growth factor (VEGF) agents and efficacious results have been shown using anti-VEGF treatment [3, 4]. However, there are still various problems with anti-VEGF agents, such as high cost, frequent injections, or long waiting time at hospitals. Therefore, it is important to keep being motivated for treatment in patients with nAMD. In fact, proactive regimen using aflibercept (Eylea, Bayer HealthCare, Berlin, Germany) was well tolerated over five years for nAMD although about 5 injections per year were needed after the first year [5].

Brolucizumab (Beovu, Novartis International, Basel, Switzerland), an approximately 26-kDa single-chain antibody fragment, was approved to treat nAMD in 2019 in the United States, and patients were maintained on every-12-week dosing intervals through 1 year in the phase 3, multicenter, randomized, double-masked HAWK and HARRIER studies [6]. Also, brolucizumab had stronger fluid control than aflibercept at week 96 [7], therefore, it was expected to reduce the treatment burden of the patients. However, in the HAWK and HARRIER trials, an independent Safety Review Committee reported that 4.6% of patients using brolucizumab developed intraocular inflammation (IOI) [8]. A multicenter study in Japan showed that 11.3% of patients with AMD treated with brolucizumab developed IOI [9], although they had a relatively good prognosis if treated at an early stage [10].

In a previous study, Matsumoto et al. reported that brolucizumab administered according to a treat-and-extend (TAE) regimen maintained the improved VA with a lower treatment burden for the 2-year follow-up [11]. Yoshida et al. also reported that brolucizumab achieved improved visual acuity (VA) using a TAE regimen and predefined discontinuation criteria [12]. However, no reports have described the 3-year outcomes of brolucizumab treatment for patients with nAMD. The purpose of this study was to investigate the 3-year outcomes of intravitreal brolucizumab (IVBr) and determine the factors that affect the VA in patients with nAMD.

Methods

We retrospectively studied 99 consecutive eyes of 96 Japanese patients aged 50 years or older who were diagnosed with treatment-naive nAMD. All patients had been treated initially at the Yokohama City University Medical Center between May 2020 and August 2021. The study was performed according to the principles of the Declaration of Helsinki and with the approval of the ethics committee of Yokohama City University Medical Center. All eligible patients provided informed consent.

Eligible patients were treated with three initial monthly loading doses of 6.0 mg/0.05 ml brolucizumab followed by every 8- or 12-week injections for 1 year. From 1 to 3 years, these patients were non-randomly assigned to the pro re nata (PRN) regimen (PRN group) or the TAE regimen (TAE group). In the PRN group, IVBr was repeated in cases of persistent or recurrent subretinal fluid (SRF), intraretinal fluid (IRF), or fluctuations in the pigment epithelial detachment (PED) on spectral-domain optical coherence tomography (SD-OCT) images and/or clinically detectable hemorrhages, and/or VA loss as judged by the same physician (M.M.) for each patient at the 1- or 2-month follow-up examination. The TAE group, which serves as a proactive treatment regimen, is based on the intervals at which the disease recurs. The treatment intervals are determined to minimize the need for evaluating patients from 8 to 28 weeks based on the presence of exudative findings on OCT or new hemorrhage detected by fundoscopy. In the TAE group, the interval was extended only when there was completely no fluid. Meanwhile, residual SRF was tolerated during the maintenance phase if central foveal thickness (CFT) increased 25 μm or less compared to the previous image. Patients who switched from the PRN regimen to the TAE regimen, or vice versa, during the 3-year period were included into PRN group.

The inclusion criteria included the presence of MNV diagnosed based on the presence of clinical, SD-OCT, fluorescein angiography (FA), and confocal indocyanine-green angiographic findings, a treatment-naïve status, and a baseline best-corrected VA (BCVA) on a Landolt C eye chart of 20/400 or better. Patients who had previously been treated for nAMD by laser photocoagulation, submacular surgery, or photodynamic therapy were excluded. Patients with an eye disease that affects the VA, such as glaucoma, macular hole, diabetic retinopathy, or rhegmatogenous retinal detachment, also were excluded.

The primary outcome measure was the BCVA changes between the pre-injection and post-injection BCVA at 4, 12, and 36 months after the initial treatment. The BCVA was converted to the logarithm of the minimum angle of resolution (logMAR) equivalent for statistical analysis. The secondary outcome was the factors that affected the VA improvement at 36 months. Multiple regression analyses were performed to determine the associations between the parameters, including baseline BCVA, age, sex, AMD type (polypoidal choroidal vasculopathy [PCV] or non-PCV), treatment modality (PRN or TAE), baseline CFT, baseline central choroidal thickness (CCT), and the differences between the pre- and post-injection BCVA at 36 months. The CFT and CCT were measured using a caliper function in the SD-OCT machine that passes through the fovea. The CFT was defined as the

distance from the internal limiting membrane (ILM) to Bruch's membrane at the fovea; the CCT was defined as the thickness between Bruch's membrane and the inner surface of the choroidal-scleral junction at the fovea. The changes in the BCVA were used as the dependent variable. We also analyzed the characteristics that affected the VA at 36 months. The association between the VA at 36 months and morphologic factors, such as IRF, SRF, PED, and macular hemorrhage, provided by SD-OCT as the possible factors that affected the VA at 36 months, also was investigated using multiple regression analysis.

The BCVAs before and after treatment were compared using one-way analysis of variance with Bonferroni correction. The numbers of injections were compared between the PRN and TAE groups using the unpaired *t*-test. Statistical analyses were performed using Statistical Package for the Social Sciences version 17 (IBM, Armonk, New York, USA). A p value < 0.05 was considered to denote statistical significance.

Results

Patient characteristics

Forty eyes did not complete the follow-up period and were excluded, leaving 59 eyes (56 patients; 37 men, 19 women; age range, 52–96 years; mean age ± standard deviation, 76.6 ± 8.2 years). Of the 59 study eyes, 26 eyes were in the PRN group and 33 eyes were in the TAE group in the maintenance phase. Of the 40 eyes that were excluded from the study, 22 patients (22.2%) stopped attending the outpatient clinic or were transferred to other hospitals, 11 eyes (11.1%) had IOI, and seven eyes (7.1%) were non-responders and were switched to other anti-VEGF agents. No cases had severe systemic complications. Table 1 shows the baseline characteristics and the comparison between the PRN group and TAE group. There were no significant differences between the two groups ($p > 0.05$, for all comparisons).

VA outcomes and number of injections

The mean logMAR BCVAs at baseline and 4, 12, and 36 months in all eyes after the initial injection were, respectively, 0.34 ± 0.33, 0.27 ± 0.38, 0.23 ± 0.37, and 0.27 ± 0.41. The post-injection logMAR BCVAs at 12 months, but not at 4 and 36 months, improved significantly compared with baseline ($p = 0.133$, $p = 0.004$, and $p = 0.189$ at 4, 12, and 36 months, respectively).

The mean logMAR BCVAs at baseline and 4, 12, and 36 months after the initial injection were 0.37 ± 0.39, 0.34 ± 0.48, 0.30 ± 0.47, and 0.36 ± 0.51 in the PRN group and 0.31 ± 0.28, 0.22 ± 0.27, 0.18 ± 0.28, and 0.20 ± 0.31 in the TAE group, respectively.

In the PRN group, the post-injection BCVA did not improve significantly compared with baseline throughout the 36-month period ($p = 0.999$, $p = 0.814$, and $p = 0.999$ at 4, 12, and 36 months, respectively). In the TAE group, the post-injection logMAR BCVA at 12 and 36 months, but not at 4 months, improved significantly compared with baseline ($p = 0.079$, $p = 0.006$, and $p = 0.032$ at 4, 12, and 36 months, respectively) (Fig. 1). During the 36-month study period, the mean numbers of brolucizumab injections administered were 7.9 ± 3.6 in the PRN group and 14.1 ± 3.1 in the TAE group, a difference that reached significance ($p < 0.001$). The average injection interval at 36 months in the TAE group was 14.7 ± 5.6 weeks.

Factors affecting BCVA improvement at 36 months

Multiple regression analysis (Table 2) indicated that worse baseline BCVA, TAE regimen in the maintenance phase, and lower CFT were associated significantly with the better improvement of BCVA at 36 months ($p = 0.021$, $p = 0.025$, and $p = 0.004$, respectively). No significant associations were observed between age, sex, AMD subtype, CCT, and the changes in the BCVA ($p > 0.05$ for all comparisons).

Table 1 Comparison between PRN group and TAE group

	Total ($n = 59$)	PRN ($n = 26$)	TAE ($n = 33$)	*P*-value*
Number of patients	56	24	33	
Number of eyes	59	26	33	
Age, mean ± SD, year	76.6 ± 8.2	75.2 ± 9.8 (range, 52 to 96)	77.3 ± 6.5 (range, 59 to 87)	0.316
Sex (Male/Female)(%)	37(66.1)/19 (33.9)	17(70.8)/7(29.2)	21(63.6)/12(36.4)	0.777
Lens status(phakic/IOL)(%)	35(59.3)/24(40.7)	14(53.8)/12(46.2)	21(63.6)/12(36.4)	0.594
AMD subtype (non-PCV/PCV) (%)	43(72.9)/16(27.1)	18(69.2)/8(30.8)	25(75.8)/8(24.2)	0.769
Mean baseline logMAR best-corrected visual acuity	0.34 ± 0.33	0.37 ± 0.39	0.31 ± 0.28	0.502
Mean baseline central foveal thickness (μm)	454 ± 180	425 ± 156	477 ± 197	0.272
Mean baseline central choroidal thickness (μm)	260 ± 130	289 ± 143	236 ± 133	0.146

PRN = pro re nata; TAE = treat and extend; SD = standard deviation; IOL = intraocular lens; AMD = age-related macular degeneration; PCV = polypoidal choroidal vasculopathy; logMAR = logarithm of the minimum angle of resolution

* *P*-value calculated using unpaired t test and the Fisher's exact test

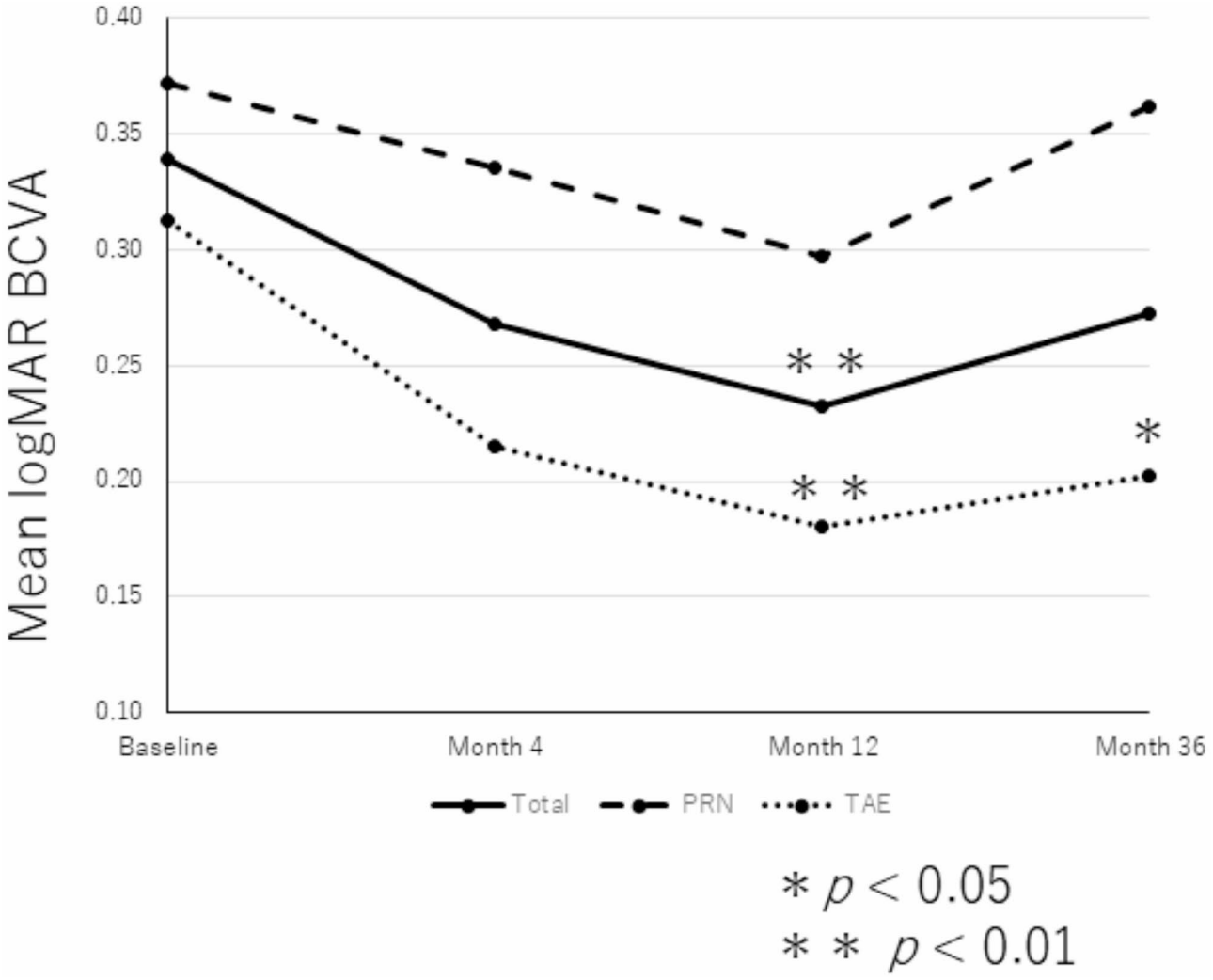

Fig. 1 Changes in the BCVA during the 36-month follow-up period. In all cases, the mean BCVA at 12 months, but not at 4 and 36 months, had improved significantly compared with the preoperative VA ($p = 0.133$, $p = 0.004$, and $p = 0.189$ at 4, 12, and 36 months, respectively). In patients treated according to the PRN regimen, the post-injection BCVA did not improve significantly compared with baseline throughout the 36-month period ($p = 0.999$, $p = 0.814$, and $p = 0.999$ at 4, 12, and 36 months, respectively). The logMAR BCVA in patients treated according to the TAE regimen improved significantly compared with the baseline value post-injection at 12 and 36 months, but not at 4 months ($p = 0.079$, $p = 0.006$, and $p = 0.032$ at 4, 12, and 36 months, respectively)

Table 2 Stepwise multiple regression analysis of the improvement of the BCVA

Independent variables	**Dependent Variable**		***p* value**
	Improvement of the visual acuity*		
	Partial Regression Coefficient	**Standard Error**	
Baseline BCVA	-0.2753	0.1160	0.021
AMD subtype (PCV or non-PCV)	-0.1431	0.0825	0.089
Age	0.0068	0.0046	0.150
Treatment modality (PRN or TAE)	0.1746	0.0756	0.025
Baseline CFT	0.0006	0.0002	0.004
Excluded variables: sex and baseline CCT.			

BCVA = best-corrected visual acuity; AMD = age-related macular degeneration

PCV = polypoidal choroidal vasculopathy; PRN = pro re nata; TAE = treat and extend

CFT = central foveal thickness; CCT = central choroidal thickness

* Improvement of the visual acuity = the difference between the baseline visual acuity and postinjection BCVA at 36 months

Table 3 Stepwise multiple regression analysis of the visual acuity at 36 months

Independent variables	Dependent Variable		*p* value
	Visual acuity at 36 months*		
	Partial Regression Coefficient	Standard Error	
Presence of SRF at 36 months	-0.3086	0.1280	0.019
Presence of IRF at 36 months	0.2975	0.1705	0.087
Excluded variables: Activity of PED and macular hemorrhage at 36 months.			

SRF = subretinal fluid; IRF = intraretinal fluid; PED = pigment epithelial detachment

Morphologic factors affecting VA at 36 months

Multiple regression analysis (Table 3) indicated that the presence of SRF at 36 months was associated significantly with better VA at 36 months ($p = 0.019$). However, no significant associations were seen between the presence of IRF, activity of PED, and macular hemorrhage, and the VA at 36 months ($p > 0.05$ for all comparisons).

Three of 26 eyes (11.5%) in the PRN group had SRF at 36 months and nine of 33 (27.3%) had SRF in the TAE group, a difference that did not reach significance ($p = 0.196$). Figure 2 shows the results for a patient with SRF at 36 months treated with brolucizumab using the TAE protocol.

Discussion

Previous studies have reported that aflibercept, administered using a proactive regimen, improved the vision of treatment-naive nAMD patients including PCV during follow-up of 3 years or more [13–15]. In addition, the long-term outcomes up to 2 years of brolucizumab in patients with nAMD showed that the drug was well tolerated [11, 12]. Yoshida et al. reported that the 2-year outcomes of brolucizumab using TAE and predefined discontinuation criteria showed favorable outcomes in patients with nAMD, with a 1-year recurrence rate of 5.6% [12]. In the current study, we showed that IVBr injections improved vision in treatment-naïve patients with nAMD who were treated according to the TAE regimen, as evaluated at a 3-year follow-up examination. However, patients who were treated using the PRN regimen did not have a significant improvement in the BCVA throughout the follow-up period. The present report is the first to describe the functional outcomes of IVBr injections up to 3 years and showed that the proactive regimen was superior for maintaining the improved VA for the long term. Furthermore, the presence of SRF at 36 months was associated significantly with better VA at 36 months.

Many reports have described visual deterioration using a PRN regimen. The HORIZON trials, in which patients were treated with ranibizumab (Lucentis, Genentech, Inc., South San Francisco, CA, USA), showed that the VA tended to decrease after changes in the treatment modality from monthly injections up to 2 years to PRN and finally returned to the baseline VA at the 5-year follow-up [16]. We also previously investigated the 3-year course of aflibercept for PCV and reported that the VA in the PRN group tended to decline after a 1-year follow-up [13]. We speculated that patients who are treated using a PRN regimen seem to be undertreated, and uncontrolled exudative findings would lead to decreased VA. Although brolucizumab showed greater fluid control than aflibercept in the HAWK and HARRIER trials [6], proactive treatment is still recommended to maintain VA over the long term.

In our study, while treatment protocols were identical for both PRN and TAE groups until the 12-month timepoint, significant visual improvement was observed only in the TAE group. Although there was a trend towards visual improvement until 12 months in PRN group, the reason why there was no significant improvement is that the numbers in this study might not be powered to show differences. However, this early divergence between the two groups might give its potential relationship to the superior visual outcomes in the TAE group at 36 months.

In this study, the worse baseline BCVA and lower CFT also were associated with better improvement of VA. The HORIZON trials using ranibizumab (Lucentis, Genentech, Inc., South San Francisco, CA) also described that worse baseline BCVA had more gains in BCVA at month 48 [16]. However, Roberts et al. described that the baseline CFT was associated with the baseline BCVA and not the BCVA at 12 and 24 months after treatment [17]. Recently, Sarraf et al. found that greater PED thickness was associated with poorer visual gains [18]. In our study, the CFT was defined as the distance from the ILM to Bruch's membrane, which includes the PED. Therefore, a thicker CFT might have been associated significantly with poorer visual gains in this study.

In addition, patients with SRF at 36 months on SD-OCT images tended to have better VA at 36 months. Because there was no significant difference between patients who were treated using the PRN and TAE regimens in the presence of SRF at 36 months, the treatment modality might not be associated with the presence of SRF at 36 months. This indicates that it may be difficult to suppress SRF in some cases even if the IVBr injections are administered at minimum of 8-week intervals. A similar result was achieved in the CATT Study, in that eyes with SRF had better VA than those without SRF by year

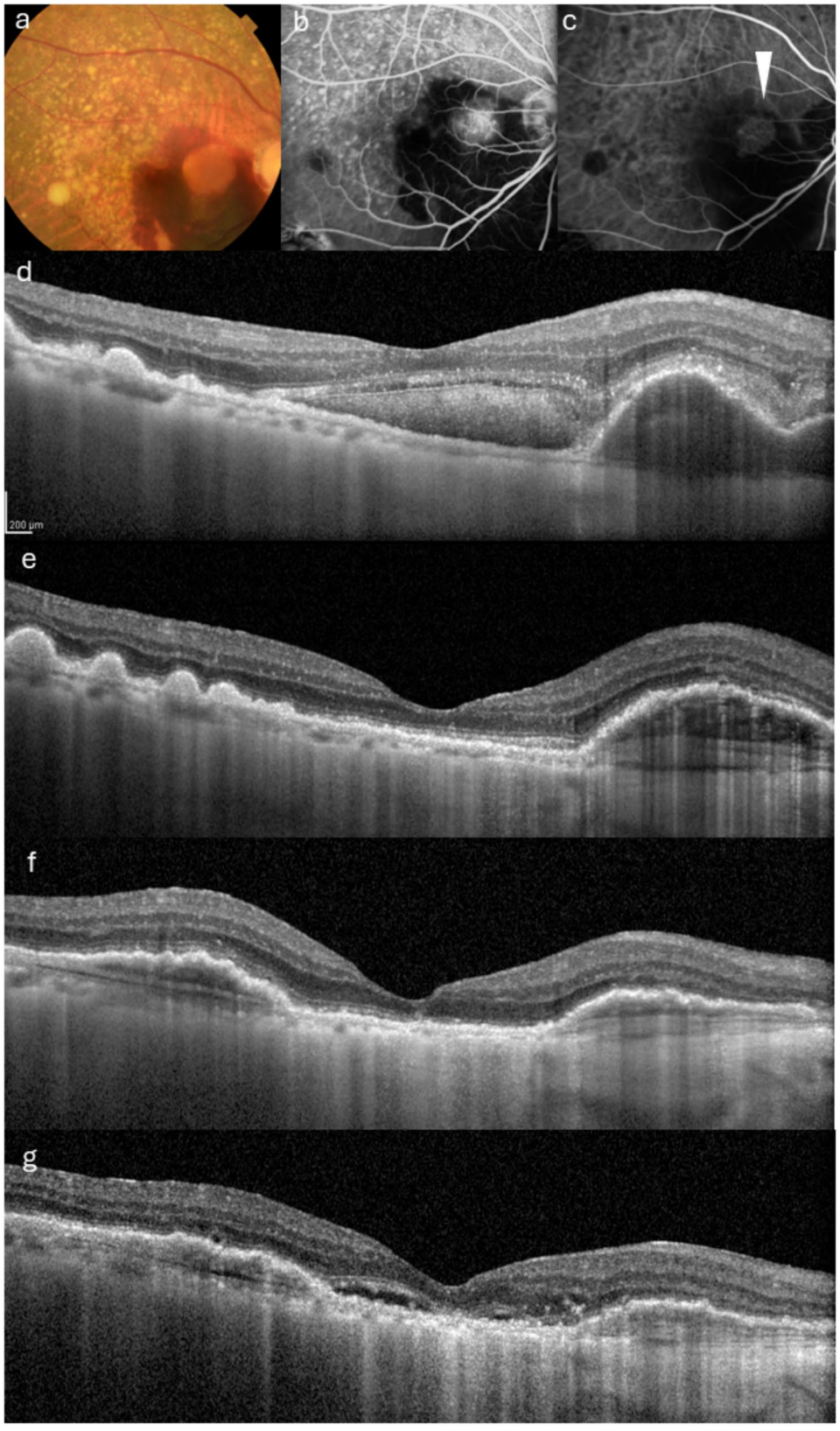

Fig. 2 (See legend on next page.)

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Fig. 2 The case of an 81-year-old man who presented with SRF in his right eye at 36 months. (**a**) The color fundus photograph shows MNV with a submacular hemorrhage (SMH). (**b**) The fundus FA image shows leakage corresponding to the MNV and blockage due to the hemorrhage. (**c**) Indocyanine green angiography shows MNV (arrowhead). (**d**) A baseline OCT image shows a hemorrhagic PED with a SMH. The VA was 20/20 in his right eye and the patient was diagnosed with type 1 MNV. The patient received three monthly IVBr injections during the loading phase. (**e**) An OCT image at 4 months shows regression of the SMH and reduced height of the PED. His VA was maintained at 20/20. During the maintenance phase, he received IVBr injections every 2 months for 1 year. (**f**) One year after the first treatment, the patient's VA was maintained at 20/20. SD-OCT showed reduced height of the PED. He was treated using the TAE regimen from 1 to 3 years. (**g**) Thirty-six months after the first treatment, the patient's VA was 20/16, although SD-OCT showed SRF

2 [19]. Bhavsar et al. described that some cases with type 1 MNV maintained good long-term VA with persistent SRF despite continuous intravitreal anti-VEGF therapy, and they hypothesized that type 1 MNV and a thicker CCT may protect the photoreceptor integrity [20]. Another possible reason is that the presence of shallow SRF may contain beneficial growth factors, which lead to better visual outcomes [21, 22]. Therefore, it seems desirable to tolerate residual SRF during the maintenance phase if increase of CFT was 25 μm or less compared to the previous SD-OCT image.

In this study, 11.1% of enrolled eyes had IOI and were excluded from the study, which was consistent with the previous study [9]. Although there is a possibility that other anti-VEGF drugs, such as aflibercept and faricimab, can cause IOI after injections in from 0.3–1.6% [23, 24], clinicians should be especially cautious about IOI after brolucizumab injections and treat promptly if IOI develops.

The main limitations of the current study were its small sample size, lack of a randomized control group, and the use of data from only one center. It was difficult to perform the randomized study because the wishes of the patient themselves also must be carefully considered before treatment to reduce their individual burdens. Therefore, it could introduce bias by patients who selected the TAE to require aggressive treatment. Furthermore, this study was conducted on Japanese subjects, so it is unclear whether this result applies to other ethnic groups. The results of this study need to be validated with further follow-up period involving more patients.

Conclusions

Three-year follow-up of brolucizumab showed good visual improvement, especially in cases treated according to the TAE regimen in the maintenance phase. Furthermore, patients with SRF on SD-OCT images at 36 months tended to have better VA. Tolerating the SRF may be considered acceptable if the change of CFT was little compared to the previous image.

Abbreviations

AMD	Age-related macular degeneration
nAMD	Neovascular age-related macular degeneration
MNV	Macular neovascularization
VEGF	Vascular endothelial growth factor
IOI	Intraocular inflammation
TAE	Treat-and-extend
VA	Visual acuity
IVBr	Intravitreal brolucizumab
PRN	Pro re nata
SRF	Subretinal fluid
IRF	Intraretinal fluid
PED	Pigment epithelial detachment
SD-OCT	Spectral-domain optical coherence tomography
CFT	Central foveal thickness
FA	Fluorescein angiography
BCVA	Best-corrected visual acuity
Log MAR	Logarithm of the minimum angle of resolution
PCV	Polypoidal choroidal vasculopathy
CCT	Central choroidal thickness
ILM	Internal limiting membrane

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Author contributions

YK and MM were involved in data collection. MM and TI were involved in data analyses. YK and MM were involved in writing of the manuscript. TI, YY and KK were involved in critical revision the manuscript. MM and TI were involved in design of the study.

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Data availability

The datasets used during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of the Yokohama City University, Japan (approval number: F230900008) and written informed consent was obtained from all patients enrolled in this study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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