Japanese Journal of Ophthalmology
https://doi.org/10.1007/s10384-022-00922-3

THE OFFICIAL INTERNATIONAL JOURNAL OF THE JAPANESE OPHTHALMOLOGICAL SOCIETY

CLINICAL INVESTIGATION

Short-term results for brolucizumab in treatment-naïve neovascular age-related macular degeneration: a Japanese multicenter study

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Received: 21 December 2021 / Accepted: 25 March 2022

Abstract

Purpose To investigate short-term treatment outcomes of intravitreal brolucizumab (IVBr) for treatment-naïve neovascular age-related macular degeneration (AMD) in a Japanese multicenter study.

Study design Retrospective case control study

Methods The subjects were 58 eyes of 57 patients with neovascular AMD (43 men and 14 women, mean age 74.6 years) of whom 43 eyes of 42 patients completed initial loading of 3 monthly IVBr injections and were followed for more than 3 months. Best-corrected visual acuity (BCVA) changes, anatomical outcomes, and complications were investigated.

Results Of the 43 eyes that completed loading doses, the AMD subtype was type 1 and type 2 macular neovascularization (MNV) in 51%, polypoidal choroidal vasculopathy (PCV) in 42%, and type 3 MNV in 7%. At 3 months after initiating treatment, BCVA significantly improved ($P=0.002$) and central retinal thickness significantly decreased ($P<0.0001$). At 3 months, complete retinal and subretinal fluid resolution was achieved in 91% of all eyes and complete regression of polypoidal lesions was achieved in 82% of PCV eyes. Iritis occurred in 8 eyes of 8 patients (14%), but resolved using topical or subtenon corticosteroid injection without visual loss in all cases.

Conclusions IVBr for treatment-naïve neovascular AMD was effective in the short-term, achieving significantly improved BCVA, good retinal fluid resolution, and a high rate of polypoidal lesion regression. However, iritis was noted in 14% of patients which may limit use of this drug.

Keywords Age-related macular degeneration · Polypoidal choroidal vasculopathy · Brolucizumab · Multicenter study · Treatment

Introduction

The incidence of neovascular age-related macular degeneration (AMD) is increasing in developed countries [1]. Treatment modalities include bevacizumab (Avastin; Roche Pharma AG), ranibizumab (Lucentis; Genentech) and aflibercept (Eylea; Regeneron and Bayer HealthCare). Since bevacizumab has not been approved for ocular use in Japan, intravitreal injections of two anti-vascular endothelial growth factor (VEGF) drugs, ranibizumab and aflibercept, are the main treatments available. However, treatment-resistance to aflibercept and ranibizumab, and the need for frequent injections, are problematic [2–4].

Brolucizumab (Beovu; Novartis) for neovascular AMD was launched in the United States in October 2019, with

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Published online: 21 May 2022

a therapeutic effect expected for treatment naïve cases [5, 6]. The features of brolucizumab include its low molecular weight and high-concentration dosage, which allows it to easily penetrate the retina [7]. However, several cases experienced intraocular inflammation (IOI) before sufficient clinical outcomes were demonstrated [8, 9]. Post hoc analysis of the HAWK & HARRIER trials, comparing brolucizumab with aflibercept, revealed a high incidence of IOI [10, 11]. Brolucizumab was also launched in Japan in May 2020, and reports of IOI have since been published [12–14]. However, studies on the outcomes of intravitreal brolucizumab injection (IVBr) for neovascular AMD mostly involved eyes switched from other drugs, and are still few in number [15, 16]. The HAWK & HARRIER studies found that although visual outcomes after IVBr were similar to those achieved with aflibercept, the fluid resolution rate after three IVBrs was significantly higher than that with aflibercept. Furthermore, approximately 50% of cases were able to maintain injection intervals at every three months in the brolucizumab arm [5]. In a Japanese cohort, a single-center study reports visual and anatomic outcomes after IVBr for type 1 choroidal neovascularization (CNV) in the short term [17]. Here, we report the outcomes obtained with three IVBrs at monthly intervals for treatment-naïve neovascular AMD in a multicenter study.

Methods

Subjects

We studied consecutive treatment naïve 58 eyes of 57 patients with neovascular AMD who visited Nihon University Hospital, University of the Ryukyus Hospital, Fukushima Medical University Hospital, Kyorin University Hospital, and the Tokyo Women's Medical University Hospital (JARC: Japan AMD Research Consortium) between June 2020 and February 2021. The protocol was approved by the Institutional Review Board at each university as a prospective study. All study procedures adhered to tenets established by the Declaration of Helsinki. Written informed consent was obtained from all patients included in this study. Inclusion criteria was untreated patients with neovascular AMD who were 45 years of age or older; we excluded myopia of more than -6 diopters, a history of uveitis, or a history of vitrectomy. Patients with no symptoms were examined one month after the injection. Fifty-eight eyes of 57 patients underwent IVBr once. Seven patients (7 eyes) developed complications and discontinued treatment, and eight patients (8 eyes) did not return for personal reasons. This resulted in 43 eyes of 42 patients that underwent IVBr once a month for three consecutive months; at baseline, one month and two months. The outcomes included visual acuity, fluid resolution rate, central retinal thickness (CRT), changes in pigment epithelium detachment (PED), the status of IOI, and the polypoidal lesion regression rate in polypoidal choroidal vasculopathy (PCV) at three months. Fluorescein angiography (FA) and indocyanine green angiography (ICGA) using a confocal scanning laser ophthalmoscope (Spectralis HRA+OCT; Heidelberg Engineering) were performed at baseline and followed for three months to determine the subtype of neovascular AMD, such as type 1 macular neovascularization (MNV), type 2 MNV [18], polypoidal choroidal vasculopathy (PCV) [19] and type 3 MNV [18]. PCV was diagnosed in the presence of polypoidal lesions on ICGA [19]. The diagnosis of type 3 MNV was established based on the identification of retinal–retinal anastomosis on early-phase FA or ICGA and the identification of a hot spot on late-phase ICGA [20].

In this study, best-corrected visual acuity was determined using the early treatment diabetic retinopathy study (ETDRS) visual acuity chart at Nihon University, and the Landolt C chart at the other four institutions. As the ETDRS chart is only used at Nihon University Hospital, and other institutions measure visual acuity in decimals, Best-corrected visual acuity (BCVA) was converted to a logarithm of the minimal angle of resolution (logMAR) units prior to the outcome analyses. The macula was considered dry when the OCT images showed complete resolution of subretinal fluid and intraretinal fluid. Central retinal thickness (CRT) was measured from the superior border of the retinal pigment epithelium (RPE) to the inner retinal layer border at the foveal center by manual, using DRI-OCT (Topcon) at the University of the Ryukyus and Tokyo Women's Medical University and Heidelberg Spectralis (Heidelberg Engineering Inc.,) at Nihon University, Fukushima Medical University, and Kyorin University.

The presence of PED was defined as one optic disc area or greater in the macula by FA, and its height was recorded for comparison with previous measurements. The changes in polypoidal lesions were recorded as complete regression, partial regression, or increase by comparing baseline findings with those at three months, as evaluated using ICGA. Greatest linear dimension was measured at the late phase of FA. Ultra-wide-angle fundus photography (Optos) was performed at each visit to detect IOI, which can be seen only in the peripheral retina.

Statistical analysis

Data are presented as mean ± standard deviation (SD). The Wilcoxon signed-ranked test was performed to assess changes in visual acuity, CRT after IVBr versus baseline. A value of $P < 0.05$ was considered to indicate a statistically significant difference. SPSS ver.26 (IBMSPSS, Inc) was used for statistical analyses.

Results

Subject background data are shown in Table 1. In terms of 43 eyes that completed three monthly IVBrs, there were 23 eyes (51%) with type 1 + 2 MNV, 17 eyes (42%) with PCV, and three eyes (7%) with type 3 MNV. BCVA improved compared to that of baseline at all timepoints, and CRT significantly reduced compared to that of baseline ($P < 0.01$, $P < 0.0001$, respectively) (Figs. 1 and 2). The fluid resolution rate was 67% at one month, 88% at two months, and 91% at three months, respectively. The 4 patients who did not obtain a dry macula at 3 months were 2 PCV and 2 type 1 + type 2 MNV, 3 men and 1 woman. Three of the four patients were characterized as not obtaining a dry macula in all 3 injections. PED was observed in 10 eyes (23%) at baseline. The PED resolved in one eye (10%) and decreased in height in eight eyes (80%) at three months. The mean maximum height of PED decreased from 474 μm at baseline to 264 μm at three months ($P = 0.009$). Polypoidal lesions in PCV showed complete regression in 14 eyes (82%), partial regression in two eyes (12%), and remained unchanged in one eye (6%) at three months. One PCV eye was excluded from evaluation due to no ICGA data at three months. A representative case is shown in Figure 3. We also analyzed the results based on AMD subtypes, and found that visual acuity and CRT tended to improve in all subtypes (Table 2). Dry macular rates at three months were 91%, 88%, and 100% for type 1 + type 2 MNV, PCV, and type 3 MNV, respectively. Of the 57 patients originally included in this study, fifteen patients dropped out before the 3 monthly injections. The reasons were: 1 retinal pigment epithelial tears, 1 hemorrhagic retinal detachment, and 5 of the 8 other IOIs were discontinued. In the other three cases of IOIs, injection was continued because the inflammation was quickly resolved by topical steroids. Thus, the three patients who continued the IVBr despite of IOI were included in this analysis. For unknown causes the remaining 8 patients did not come to the clinic on the day of their appointment. IOI occurred in eight patients (14%); iritis only in six eyes, vitritis in one

Table 1 Patient characteristics at baseline

	All participants	Participants who received three monthly injections
Number of patients (eyes)	57 (58)	42 (43)
Female, n (%)	14 (24%)	10 (24%)
Age (years ± SD)	74.2 ± 6.6	74.0 ± 7.0
Subtype, n (%)		
Type 1 + Type 2 MNV	29 (50%)	22 (51 %)
PCV	25 (43%)	18 (42%)
Type 3 MNV	4 (7%)	3 (7%)
BCVA (logMAR ± SD)	0.45 ± 0.39	0.41 ± 0.36
CRT (μm ± SD)	419 ± 253	399 ± 215
PED, n (%)	14 (24%)	10 (23%)
GLD (μm ± SD)	3837 ± 1723	3582 ± 1532

SD, standard deviation; MNV, macular neovascularization; PCV, polypoidal choroidal vasculopathy; BCVA, best-corrected visual acuity; MAR, minimal angle of resolution; CRT, central retinal thickness; PED, pigment epithelium detachment; GLD, greatest linear dimension

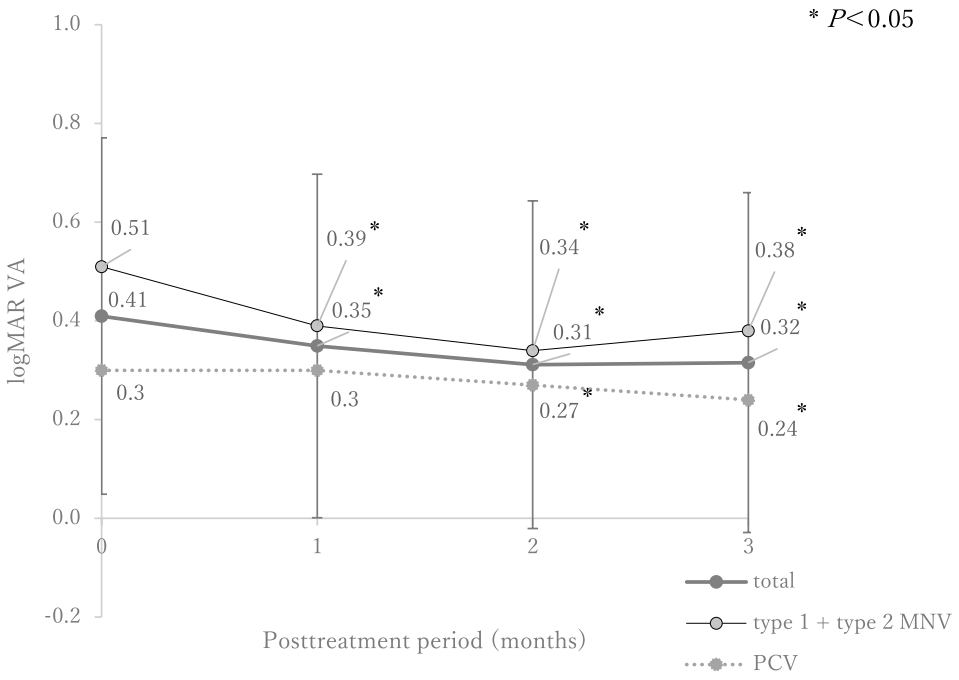

Fig. 1 Changes in mean best-corrected visual acuity (BCVA). MAR, minimal angle of resolution; P-value was calculated compared with baseline

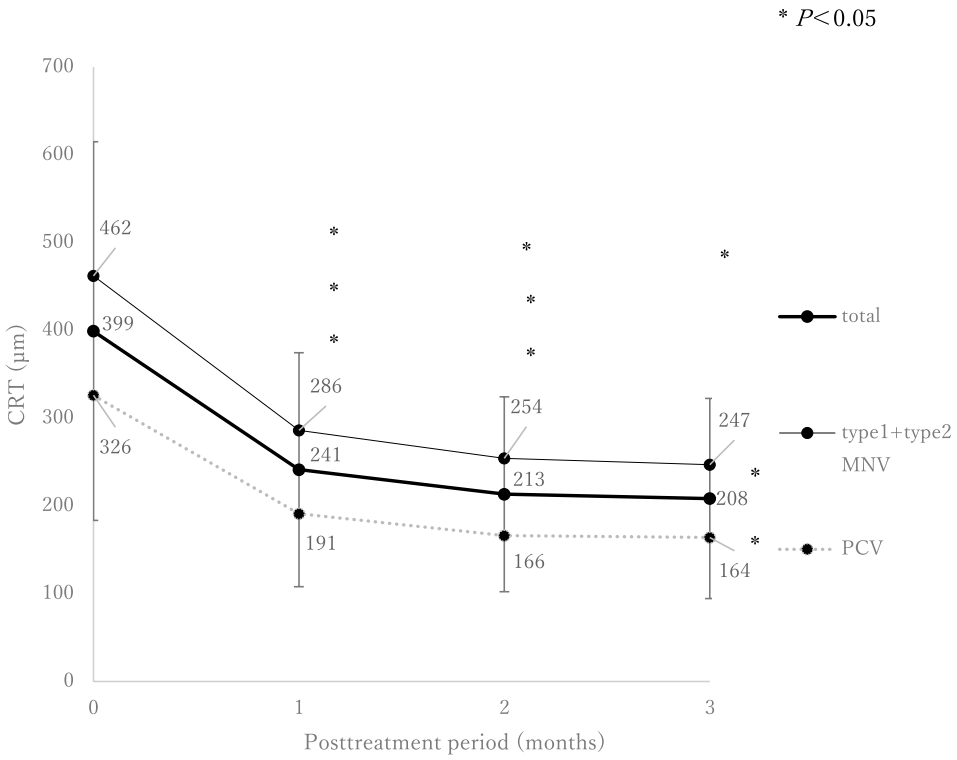

Fig. 2 Changes in mean central retinal thickness (CRT). P-value was calculated compared with baseline. MNV, macular neovascularization; PCV, polypoidal choroidal neovascularization

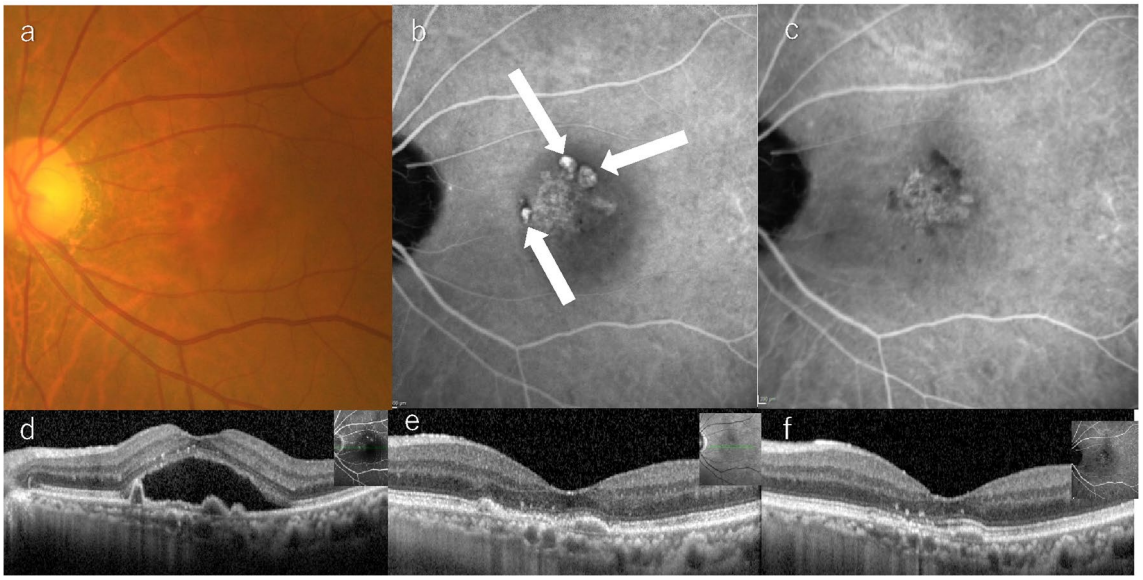

Fig. 3 Multimodal imaging of 75-years-old PCV patient. **a** Color fundus photograph at baseline showed orange-reddish lesions in the macula. **b** Indocyanine green angiography (ICGA) at baseline showed 3 polypoidal lesions (arrows). **c** ICGA at 3 months demonstrated complete regression of polypoidal lesions. **d** Optical coherence tomography (OCT) at baseline revealed subretinal fluid in the macula and irregular elevation of retinal pigment epithelium. **e** OCT at 1 month revealed complete resolution of subretinal fluid. **f** OCT still showed dry macula at 3 months

eye, and iritis combined with retinal vasculitis in one eye (2%), respectively. All IOI showed resolution with topical steroid or subtenon injection of triamcinolone acetonide, and no eyes experienced visual deterioration. The mean number of days from injection to IOI was 27. IOI was significantly more common in females; five of eight eyes with IOI were females. In the men, three of 44 eyes (7%), and in the women, five of 14 eyes (36%), developed IOI ($P=0.03$). None of the 57 participants had systemic complications such as arterial thromboembolism.

Table 2 Results of AMD subtypes

	Type 1 + Type 2 MNV	PCV	Type 3 MNV
Number of eyes, n (%)	22 (51%)	18 (42%)	3 (7%)
Female (%)	5 (23%)	5 (38%)	0 (0%)
Mean age (years)	74.7 ± 5.1	72.5 ± 8.4	80.0 ± 6.5
BCVA at baseline (logMAR)	0.51 ± 0.37	0.30 ± 0.31	0.37 ± 0.23
BCVA at 3 months (logMAR)	0.38* ± 0.35	0.24* ± 0.30	0.30 ± 0.29
Mean CRT at baseline (μm)	462.1 ± 228	326.6 ± 159	372.0 ± 264
Mean CRT at 3 months (μm)	247.1* ± 145	164.3* ± 32	188.3 ± 34
Dry macula at 3 months, n (%)	20 (91%)	16 (89%)	3 (100%)
Complete regression of polypoidal lesion at 3 months, n (%)	–	14 (82%)	–

*P < 0.05 compared with baseline. MNV, macular neovascularization; PCV, polypoidal choroidal vasculopathy; BCVA, best-corrected visual acuity; CRT, central retinal thickness

Discussion

In the HAWK & HARRIER trials, ETDRS visual acuity improved by 5-6 letters after three monthly IVBrs [5, 6]. In our study, logMAR BCVA improved from 0.41 to 0.32 after three monthly IVBrs. When converted to ETDRS visual acuity, the increase was about 4.5 letters, i.e., our cases had almost same results as the HAWK & HARRIER trials. CRT were significantly reduced after IVBr in our cases. In the report of Matsumoto [17] in which only Type 1 CNV was included, the logMAR BCVA improved significantly from 0.24 to 0.12. On the other hand, in our results, which included all types, there was a trend toward improvement in all subtypes.

The HAWK & HARRIER studies show the fluid resolution rate to be higher with brolucizumab than with aflibercept. The fluid resolution rate in these studies was 71% after three IVBrs. In our study, the rate was even higher—91%—suggesting better efficacy in Japanese subjects. This might be attributable to the HAWK & HARRIER trials having enrolled subjects with up to 78 letters on ETDRS, while 20% of cases included in the current study had ≥78 letters. Anti-VEGF therapy might be more effective in higher visual acuity cases, leading to a higher fluid resolution rate. Furthermore, CRT was also decreased in cases with type 1 + type 2 MNV, PCV or type 3 MNV in our report. Regardless of the AMD subtype, brolucizumab appears to be effective. A subanalysis of the 2-year results of Japanese PCV in the HAWK trial was recently reported [21]. Compared to aflibercept, the change in visual acuity was not significant, but the dry rate was high. Compared to our results, the dry rate after 3 injections was 87%, similar to our result of 91%.

The polypoidal lesion regression rate analysis of eyes with PCV showed complete regression in 82%, partial regression in 12%, and unchanged status in 6% at three months. Previous reports on aflibercept show a complete regression rate of 48% and a partial regression rate of 38% [22]. A recent report by Matsumoto et al. shows complete regression in 78.9% (15 of 19 eyes) of PCV eyes treated with brolucizumab, similar to that in our study [17]. These observations indicate that brolucizumab may be efficacious in achieving regression of polypoidal lesions of PCV. The efficacy of brolucizumab for PCV is likely due to its low molecular weight. Although the only data available at this time is from cattle, a low molecular weight reportedly facilitates penetration of the RPE [23].

PED, exceeding one optic disc area, was recognized in 10 out of 43 eyes at baseline. Of the 10 eyes, the PED disappeared completely in one eye, decreased in eight eyes, and remained the same in one eye. PED were reported to have improved in 18% of patients after three injections of aflibercept [24] and 44% of patients improved PED after one year of PRN treatment with ranibizumab [25]. IVBr reportedly has higher permeability into the choroid due to its low molecular weight than other anti-VEGF agents [26]. Ranibizumab also has a small molecular weight, but brolucizumab is reported to have an even smaller molecular weight and higher molar concentration. [27], this is likely to explain the high rate of PED decrease.

Since brolucizumab was first launched in the United States in 2019, IOI has been reported in several cases [8, 9]. The Safety Review Committee also reported an IOI rate of 12.9%, an IOI with vasculitis rate of 9.9%, and an IOI with vasculitis and vascular occlusion rate of 4.95% in the Japanese population [10]. In our multicenter study, IOI occurred in 14% of cases, while IOI plus vasculitis developed in 2%, i.e., there were relatively few serious side effects. In our 127 cases, including those switched from other anti-VEGF drugs to brolucizumab, the rates of IOI alone, IOI with retinal vasculitis, and IOI with retinal vasculitis and vascular occlusion were 9.9%, 3.1% and 1.6%, respectively, such that, similarly, there were few severe side effects [14]. The multicenter design of our study makes the results obtained particularly worthwhile since it covers the area extending as

far north as Fukushima, to Okinawa in the south, with inclusion of several regional facilities. In all cases, inflammation was reduced by topical steroid and/or subtenon injection of steroid. None of our cases developed severe loss of visual acuity, as reflected by a decrease of 15 letters or more on ETDRS. The mean number of days from injection to IOI was 27. More patients were found to have asymptomatic IOI in our study than in prior investigations, assumed to reflect the number of days between routine visits. 3 out of 8 patients continued IVBr after IOI as shown in Line19 in the result section on P5. Because it was a multicenter, retrospective study, and because we were not used to dealing with IOI at the beginning of the launch, 3 patients continued injections. They continued because they had mild iritis and improved with the topical steroid. However, as these three patients were at risk of developing severe IOI in the future, we made the decision to discontinue administration after three injections in each case. Fortunately, no further IOI appeared in these three patients.

IOI was significantly more common in women. Five of eight cases with IOI were women. Three of 44 eyes (7%) with IOI were in men, and five of 15 (33%) were in women. The reason for the female preponderance is unknown, but 22 of 25 (88%) cases with IOI in a previous report were also women [8]. In addition, the attached document for brolucizumab mentions 35–52% anti-brolucizumab antibodies from serum sample before the injection, were detected while anti-drug antibodies to ranibizumab and aflibercept are 0–5% [28–30]. IOI was hypothesized to be more likely to occur because anti-drug antibodies are more prevalent than in patients who received aflibercept or ranibizumab injections [31]. Further studies are needed to clarify this issue.

Treatment outcomes for each AMD subtype were also investigated. In the aforementioned report of the Japanese [17], IVBr was described as being highly effective for type 1 CNV. We also had good efficacy for other subtypes, improvement for both anatomical and visual acuity in the short-term.

This study had limitations, including the small number of participants and only a short-term follow-up. The multicenter design covered a large geographic area, and thus is applicable to the entire Japanese population, which is a major advantage of this study. This is the first report that covered all subtypes of MNV.

Our data indicate that IVBr for patients with treatment-naïve AMD significantly improved visual acuity, significantly reduced CRT, as well as achieving a high fluid resolution rate in all AMD subtypes and a high rate of polypoidal lesion regression. However, due to IOI developing in 14% of eyes, caution is necessary when administering this treatment. Our preliminary results merit further study with a larger cohort.

Conflicts of interest K. Tanaka, None; H. Koizumi, None; T. Tamashiro, None; K. Itagaki, None; M. Nakayama, None; I. Maruko, None; S. Wakugawa, None; N. Terao, None; H. Onoe, None; Y. Wakatsuki, None; A. Kasai, None; M. Ogasawara, None; H. Shintake, None; Y. Sugano, None; A. Yamamoto, None; K. Kataoka, None; T. Hasegawa, None; T. Izumi, None; M. Kawai, None; R. Maruko, None; T. Sekiryu, None; A. A. Okada, None; T. Iida, None; R. Mori, None.

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