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Clinical features and associated factors of intraocular inflammation following intravitreal brolucizumab as switching therapy for neovascular age-related macular degeneration

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Key messages

What was known

・A high incidence of intraocular inflammation (IOI) after intravitreal brolucizumab (IVBr) administration has been reported, and occlusive vasculitis, which can be associated with vision loss, has been considered as a severe phenotype of IOI.

・The risk factors of IVBr-associated IOI have not been fully elucidated.

What this study adds

・After IVBr administration as switching therapy for nAMD, 18 (20.6%) eyes developed IOI and 2 (2.3%) exhibited retinal artery occlusion.

・Macular atrophy and subretinal hyperreflective material on optical coherence tomography (OCT) increased the risk of developing IVBr-associated IOI.

Abstract

Purpose: To explore the clinical features and associated factors of intraocular inflammation (IOI) following intravitreal brolucizumab (IVBr) administration for neovascular age-related macular degeneration (nAMD).

Methods: This retrospective study included 87 eyes from 87 Japanese patients with nAMD who were followed up for 5 months after the initial administration of IVBr as switching therapy. Clinical pictures of IOI post-IVBr and changes in best corrected visual acuity (BCVA) at 5 months were evaluated between eyes with and without IOI (non-IOI). The association between IOI and baseline factors (age, sex, BCVA, hypertension and/or arteriosclerotic changes in the fundus, subretinal hyperreflective material [SHRM], and macular atrophy) was evaluated.

Results: Of the 87 eyes, 18 (20.6%) developed IOI and 2 (2.3%) developed retinal artery occlusion. There were 9 (50%) cases of posterior or pan-uveitis among eyes with IOI. The mean interval from initial IVBr administration to IOI was 2 months. The mean changes in logMAR BCVA at 5 months were significantly worse in IOI eyes than in non-IOI eyes (0.09 ± 0.22 vs. -0.01 ± 0.15, $P = 0.03$). There were 8 (44.4%) and 7 (10.1%) cases of macular atrophy and 11 (61.1%) and 13 (18.8%) cases of SHRM in the IOI and non-IOI groups, respectively. SHRM and macular atrophy were significantly associated with IOI ($P = 0.0008$ and $P = 0.002$, respectively).

Conclusion: In IVBr therapy for nAMD, eyes with SHRM and/or macular atrophy should be observed more meticulously, given the increased risk of developing IOI, which is associated with insufficient BCVA gain.

Keywords: brolucizumab, intraocular inflammation, uveitis, factor, age-related macular degeneration, retinal artery occlusion

Statements and Declarations

Financial interests

All authors declare no competing interests.

No funding was received for this study.

Author contributions

W.M. and R.S. designed the concept of this study.

W.M., R.S., KW. K., A.M., E. Y., Y.M., R.H., and S.K. collected data.

W.M. conducted statistical analysis.

W.M., S.K., and M.N. interpreted data.

W.M. and S.K. drafted work.

W.M., R.S., KW. K., A.M., E. Y., Y.M., R. H., S.K., and M.N. revised it critically for important intellectual content.

W.M., R.S., KW. K., A.M., E. Y., Y.M., R. H., S.K., and M.N approved of the version submitted for publication.
All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Introduction

Currently, anti-vascular endothelial growth factor (VEGF) therapy is the first line treatment for neovascular age-related macular degeneration (nAMD) [[1]]. Recently, brolucizumab, which is a 26-kDa humanized single-chain variable fragment antibody against VEGF-A, was approved as a new anti-VEGF drug by the US Food and Drug Administration in 2019. HAWK and HARRIEER, which are phase 3 clinical trials of brolucizumab for nAMD, showed the noninferiority of brolucizumab to aflibercept in terms of changes in visual acuity (VA) at 48 weeks from baseline. In addition, brolucizumab reduced the central subfield retinal thickness more than aflibercept. These trials also concluded that the overall safety of brolucizumab was similar to that of aflibercept [[2]]. However, in early 2020, two reports on retinal arteriolar occlusions and intraocular inflammation (IOI) after intravitreal brolucizumab (IVBr) administration were published [[3, 4]]. Moreover, 15 eyes from 12 patients that developed retinal vasculitis and IOI after administration of IVBr (6 mg/0.05 mL) for the treatment of nAMD were also reported [[5]].

In the HAWK and HARRIER trials, there were 399 cases of intraocular inflammation; 4.4% were treated with brolucizumab and 0.8% were treated with aflibercept. Of the 730 patients, 6 (0.8%) patients who received 6 mg brolucizumab developed IOI associated with retinal artery occlusion or thrombosis. Thereafter, a high incidence of IOI after IVBr administration has been widely reported, and occlusive vasculitis, which can be associated with vision loss, has been considered a severe ocular adverse effect (AE). A cohort study reported that the overall incidence of IOI and/or retinal vascular occlusion following IVBr administration was 2.4% (255 of 10,654 eyes from the IRIS Registry and 268 of 11,161 eyes from the Komodo Health database), whereas the incidence of retinal vasculitis and/or retinal vascular occlusion following IVBr administration was 0.6% (59 of 10,654 eyes from the IRIS Registry and 63 of 11,161 eyes from the Komodo Health database)[[6]]. In clinical settings, the incidence of IOI varied from 0% to 20% [[7]-[8]].

According to the post hoc analysis of the randomized HAWK/HARRIER clinical trials [[9]], in 6 of the 12 cases, IOI (other than retinal vasculitis) was reported before retinal vasculitis or retinal vascular occlusion occurred. Anterior chamber and/or vitreous cells may precede retinal vasculitis and/or retinal vascular occlusion in some IVBr-treated eyes. Thus, even if IOI is only in the anterior chamber and/or vitreous, its prevention and management in a patient who will receive IVBr are important to prevent severe AEs, including retinal vasculitis and/or retinal vascular occlusion. Previous studies have proposed a female sex, old age, and a Caucasian race as factors related to

IVBr-associated IOI. However, ocular findings have not been reported as a risk factor of IOI, and the mechanisms of IOI remain unclear. This retrospective case series of Japanese patients aimed to evaluate the factors and clinical findings associated with IOI after IVBr administration.

Methods

Study design and setting

This study enrolled patients with nAMD who were administrated with IVBr (6 mg/0.05 mL of brolucizumab) as switching therapy from other anti-VEGF drugs between May 2020 and May 2021 and were followed for >5 months in the Department of Ophthalmology at the Kobe University Hospital and Kakogawa Central City Hospital in Japan. This study was approved by the Institutional Review Board of the Kobe University Graduate School of Medicine and was conducted in accordance with the Declaration of Helsinki. This was an observational study involving the use of medical records, so the committee waived the requirement for informed consent.

All patients underwent detailed ophthalmological examinations, including best corrected VA (BCVA) measurements, slit-lamp biomicroscopy, color fundus photography (CFP), and spectral-domain optical coherence tomography (SD-OCT) (Spectralis; Heidelberg Engineering, Heidelberg, Germany) at every scheduled visit. BCVA was determined using a Landolt C chart in each visit and converted to a logarithm of the minimum angle of resolution (logMAR) value for calculation. Regarding SD-OCT measurements, all patients received one horizontal and vertical scan each through the fovea. Additionally, 25 horizontal raster scans or 8 radial scans centered on the fovea at rotational angular steps of 45° inter-scan angle, were performed. Fluorescein angiography and indocyanine green angiography (HRA2; Heidelberg Engineering) were performed to confirm nAMD.

In this study, all patients underwent ophthalmological evaluation a day after IVBr administration in accordance with the physicians' direction. The next visit was normally scheduled 1 month later. However, physicians were allowed to choose the protocol of pro re nata or treat and extend and modify the treatment protocol in the middle of the follow-up period based on disease activity, patient's request, and severity of IOI after IVBr administration. Physicians also explained that the patients had to undergo an ophthalmological exam as soon as possible if they had symptoms of IOI such as floaters or blurred vision.

IVBr-associated IOI

Regarding IVBr-associated IOI, we evaluated ocular inflammation based on the SUN criteria [[10]]. Although the SUN system does not specify a grading system for vitreous cells, the Multicenter Uveitis Steroid Treatment Trial employed the vitreous cell grading scale to evaluate ocular inflammation [[11]]. Thus, we focused on the presence of new anterior vitreous cells after IVBr administration to determine the presence or absence of IOI. Additionally, we regarded an eye with new keratic precipitates (KPs) after IVBr administration as an eye with IVBr-associated IOI [[12]]. IVBr-associated IOI included the presence of anterior chamber cells and occurrence of anterior chamber flare, anterior chamber inflammation, chorioretinitis, eye inflammation, iridocyclitis, iritis, KPs, retinal vasculitis, uveitis, and vitritis; these were also defined as IOI-related AEs in brolucizumab-treated eyes in the HAWK and HARRIER trials [[13]] IOI also included retinal vascular occlusion secondary to retinal vasculitis. Meanwhile, symptomatic subtle transient inflammation occurring within a few days after IVBr administration was not considered as IVBr-associated IOI as it is not a specific IOI [14].

Outcomes

The characteristics of IOI, including the anatomical classification of uveitis, time to IOI onset, and selected treatment for IVBr-associated IOI, were evaluated, and the change in BCVA at 5 months from baseline was compared between the IOI and non-IOI groups.

The following potential factors were also analyzed if a significant difference was found between eyes with and without IOI after IVBr administration: age, diabetes mellitus, history of cataract surgery, baseline BCVA, number of anti-VFGF injections before IVBr administration, presence of macular atrophy, hypertensive and atherosclerotic retinal vascular changes, and subretinal hyperreflective material (SHRM) on OCT. Two investigators (W.M. and R.O.S.) identified macular atrophy by reviewing the CFP and SD-OCT findings. CFP findings that fit the eligibility criteria were assessed based on a previous report [[15]]. The CFP eligibility criteria included a patch ≥250 μm in the longest linear dimension of partial or complete depigmentation in the CFP that had ≥1 of these characteristics: sharply demarcated borders seen in CFP; visibility of underlying choroidal vessels; and excavated or punched out appearance on stereoscopy. Retinal pigment epithelial and outer retinal atrophy (RORA) on SD-OCT were assessed according to the following: choroidal hypertransmission, attenuation of the retinal pigment epithelial (RPE) band, and collapse or thinning of the outer retinal layers [[16]]. We judged macular abnormality as macular atrophy when it met both criteria of CFP and RORA on SD-OCT. SHRM was also identified on OCT by two investigators (W.M.

and R.O.S.). It was defined as hyperreflective material bound anteriorly by the posterior-most aspect of the RPE based on a previous study.[17]

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows version 25 (IBM Corp., Armonk, NY, USA). Fisher's exact test was used to compare categorical variables. A *P* value of <0.05 was considered significant, except for the analyses of factors associated with IVBr-associated IOI. When potential factors associated with IOI after IVBr were compared between the IOI and non-IOI groups, a *P* value <0.005 was considered significant after Bonferroni correction.

Results

Patient characteristics

This study included 87 eyes from 87 Japanese patients with nAMD (53 eyes from Kobe University Hospital and 34 eyes from Kakogawa Central City Hospital) who were followed for >5 months after the initial administration of IVBr as switching therapy. No patients had a history of uveitis or ocular inflammation before IVBr administration. Of the 87 patients in the study, 19 (21.8%) were women, and 42 (48.2%) had polypoidal choroidal vasculopathy. The average age was 77.0 ± 7.6 (range, 62–93) years.

Clinical characteristics of IVBr-associated IOI

IOI occurred in 18 (20.6%) of 87 cases after IVBr administration. The anatomical classifications of inflammation were then identified. In 5 cases of anterior uveitis, 4 had new cells in the anterior chamber and 4 had new KPs. Four cases had intermediate uveitis with anterior vitreous cells, and 9 cases had posterior or pan-uveitis, which was the predominant anatomical classification of IOI in the study. Retinal vasculitis was seen in 4 of the 9 cases of posterior or pan-uveitis, and retinal artery occlusion was seen in 2 of the 4 cases of retinal vasculitis. Infectious endophthalmitis was not noted. All eyes received antibiotic eye drops such as moxifloxacin 4 times daily for at least four days after IVBr administration. None of the eyes received any systemic or local steroid therapy including steroid eye drops after IVBr administration until IOI occurred.

The time interval from initial IVBr administration to IOI onset are shown in Supplemental Figure 1. In 14 (77.8%) of the 18 cases, IOI occurred within 3 months after IVBr administration. Overall, 9 cases of posterior or pan-uveitis and 5 cases of anterior or intermediate uveitis occurred within 3 months, and 4 cases of anterior or intermediate uveitis occurred >3 months after IVBr administration (P = 0.08). The occurrence of anterior or intermediated uveitis was equally distributed from 1 month to 5 months after IVBr administration. In contrast, inflammation developed within 3 months after IVBr administration in all cases of posterior or pan-uveitis (Supplemental Figure 1). The mean interval from initial IVBr administration to IOI onset was 2.0 ± 1.5 months. IOI occurred after the first, second, third, and fourth IVBr administration in 12, 4, 1 and 1 eyes, respectively. Of the18 eyes with IOI, only 1 eye developed IOI >1 month after the last IVBr administration (3 months). Meanwhile, the other 17 eyes developed IOI within 1 month from the last IVBr administration; 1 eye developed IOI 0.5 months after the last IVBr administration.

Clinical factors associated with IOI after IVBr administration

Potential factors associated with IVBr-associated IOI are shown in Table 1. No significant differences in age, sex, diabetes mellitus, history of cataract surgery, baseline BCVA, atherosclerotic retinal vascular change, and number of anti-VEGF injections were found between the IOI and non-IOI groups. Hypertensive retinal vascular changes were observed in 72.2% (14/18) and 43.5% (30/69) of the cases in the IOI and non-IOI groups, respectively, but the difference was not significant (P = 0.014). Meanwhile, 8 (44.4%) and 7 (10.1%) cases of macular atrophy and 11 (61.1%) and 13 (18.8%) cases of SHRM were noted in the IOI and non-IOI groups, respectively. Macular atrophy and SHRM showed significantly increased odds (odds ratio [OR] = 7.08 and OR = 6.77, respectively) for IVBr-associated IOI (P = 0.002 and P = 0.0008, respectively).

	IOI(+)	IOI (−)	OR	P value
No. of eyes	18	69	−	−
Age (years), mean ±SD	79.4 ± 7.6	76.3 ± 7.5	1.06	0.14
Sex: male (%)	13 (72.2%)	55 (79.7%)	0.66	0.49
Diabetes mellitus (%)	2 (11.1%)	12 (17.4%)	0.59	0.52
Intraocular lens (%)	13 (72.2%)	38 (55.0%)	2.12	0.19
Baseline BCVA (logMAR), mean ± SD	0.38 ± 0.41	0.35 ± 0.40	1.20	0.73
Number of the other anti-VEGF drug injection, mean ±SD	15.5 ± 16.2	18.9 ± 12.9	0.98	0.19

Macular atrophy (%)	8 (44.4%)	7 (10.1%)	7.08	0.002
Hypertensive retinal vascular change (%)	14 (72.2%)	30 (43.5%)	4.55	0.014
Arteriosclerotic retinal vascular change (%)	14 (77.8%)	45 (65.2%)	1.86	0.31
SHRM (%)	11 (61.1%)	13 (18.8%)	6.77	0.0008

Table 1. Comparison of potential factors associated with intraocular inflammation following intravitreal brolucizumab administration between cases with and without intraocular inflammation.

BCVA, best-corrected visual acuity; IOI, intraocular inflammation; OR, odds ratio; VEGF, vascular endothelial-derived growth factor; SHRM, subretinal hyperreflective material. Significant p value <0.005 after Bonferroni correction.

Visual time course of IOI

Regarding VA changes, no difference was found in the baseline VA between the IOI and non-IOI groups (0.38 ± 0.41 vs. 0.35 ± 0.40, P = 0.73). In contrast, the change in VA 5 months after IVBr administration was significantly worse in the IOI group than in the non-IOI group (0.09 ± 0.22 vs. −0.01 ± 0.15, P = 0.03). Moreover, 3 (16.7%) cases in the IOI group and 2 (0.03%) cases in the non-IOI group had vision loss of >0.3 logMAR BCVA at 5 months after IVBr administration, but no significant difference was found between the groups. The mean total number of anti-VEGF injections during the 5-month follow-up period was not different between the groups (P = 0.82); 2.72 ± 1.40 injections (brolucizumab: 1.77 injections; aflibercept: 0.94 injections) in the IOI group and 2.78 ± 0.87 injections (brolucizumab: 2.68 injections; aflibercept: 0.10 injections) in the non-IOI group.

Representative cases

Two representative cases (cases 1 and 2) are shown in the Supplemental Figures.

Discussion

Clinical features of IVBr-associated IOI

This study showed that of the 87 eyes, 18 (20.6%) developed IOI and 2 (2.3%) developed retinal artery occlusion. However, the rates of IOI and vascular occlusion in a phase III study were 4.6% and 2.1%, respectively[[18, 19]]. Moreover, inflammation is more common in Japanese patients. In a subgroup analysis of Japanese patients, the rates of IOI and vascular occlusion were 2–3 times higher than that in other populations (12.9% and 4.3%, respectively) [[20]]. Racial or genetic differences may affect the development of IOI, as the distribution of uveitis differs

worldwide [[21]]. As IVBr-associated IOI was recognized as a concern during the study period, patients might have been more carefully monitored than usual, and even subtle inflammation may not have been overlooked.

According to the short-term results (3–6 months) regarding IVBr-associated IOI in Japan, the incidence of IOI was 9.6% in the study by Maruko et al. [[20]] and 19.0% in the report by Matsumoto et al. [[22]]. A recent study reported that 15 of 68 eyes (22.1%) developed IOI within 1 year in a Japanese population, [[23]] which is almost similar to that in the present study.

In a study of IVBr-associated IOI without retinal vasculitis reported to the American Society of Retina Specialists, IOI was anterior in 18%, posterior in 31%, and both anterior and posterior in 51% of the eyes [[24]]; the incidences are similar to those in the present study. These findings show that majority of cases of IVBr-associated IOI included ocular inflammation in the posterior segment.

According to the post hoc review of the HAWK and HARRIER trials, the median number of days from the last IVBr injection to the onset of event was 25.5 days for IOI [[19]]. Similarly, in the present study, the most probable interval from last IVBr injection to IOI onset was 1 month, and the most probable timing of IOI onset was after the first IVBr injection.

Factors associated with IOI after IVBr administration

In this study, macular atrophy and SHRM were significantly associated with IVBr-associated IOI. The mechanism of IVBr-associated IOI is still unclear. Although brolucizumab was expected to be less immunogenic because of the lack of a Fc portion in its structure, brolucizumab may actually be more immunogenic than other anti-VEGF agents due to its relatively small size and consequent ability to unfold, which exposes epitopes that may not be recognized by the immune system [[25]].

From the viewpoint of the ocular immune system, the eye has a unique ocular tolerance strategy against inflammation through the retina–immune barrier and blood–retina barrier (BRB), which use specialized mechanisms to suppress inflammation and subsequent immunopathology. The BRB which is maintained by the neurovascular unit, protects the retina from exogenous pathogens, separates tissues from the systemic immune system, and avoids immune surveillance [[26]]. Therefore, the stabilization of these functional barriers is important to prevent IOI caused by pathogens and foreign substances, including brolucizumab.

In the present study, SHRM was associated with the occurrence of IVBr-associated IOI. SHRM is a morphological component observed on OCT images as hyperreflective material external to the retina and internal to the RPE. SHRM can result from type 2 neovascularization, fibrosis, subretinal hyperreflective exudates, and hemorrhage [[27]]. In nAMD, breakdown of the BRB provides circulating immune cells with unusual access to a highly immunogenic environment, resulting in macrophage recruitment and activation. In addition, SHRM may be associated with inflammatory choroidal neovascularization. Fibrosis as a part of SHRM is associated with a pro-inflammatory milieu, including the expression of cytokines such as interleukin (IL)-1β, IL-6, and tumor necrosis factor-α [[28]]. Thus, the presence of SHRM may indicate an increased risk of developing IOI, especially after administrating IVBr as switching therapy.

Macular atrophy was also associated with IVBr-associated IOI in the present study. nAMD can lead to well-defined regions of RPE loss that meet the clinical and photographic criteria of geographic atrophy [[29]]. RPE is an important part of the retinal–immune barrier against inflammation and plays a pivotal role in retinal immunity [[30]]. Thus, RPE dysfunction causes instability of the ocular immune system. In nAMD eyes with macular atrophy, levels of some inflammatory cytokines, such as monocyte chemoattractant protein-1 (MCP-1), pre- and post-administration of intravitreal aflibercept were higher than those in nAMD eyes without macular atrophy [[31]]. Thus, macular atrophy in a patient with nAMD may potentially predict the development of IVBr-associated IOI.

Retrospective studies reported that women exhibited a higher risk of developing IOI [[6, 32]]. Meanwhile, the present study and a study by Maruko et al. did not show that women had a significantly higher risk of IVBr-associated IOI [20]. Although Mukai et al. reported old age, female sex, and history of diabetes as potential risk factors in their study of a Japanese population; these findings were also not observed in the present study [[32]].

Vison and IVBr-associated IOI

The relationship between IOI and BCVA is unclear; however, this study showed that change in VA 5 months after IVBr administration was significantly worse in the IOI group than in the non-IOI group. No cases of ≥3 (or ≥6) line vision loss was associated with IOI in the absence of vasculitis for over 2 years in the HAWK and HARRIER trials. In the present study, 3 (16.6%) of the 18 patients with IOI experienced vision loss of >0.3 logMAR BCVA at 5 months compared to that at baseline. This may indicate an association between IOI and poorer vision outcomes. However, as the IOI group had more cases with SHRM and macular atrophy, which may affect VA compared with

the non-IOI group, it should be further studied whether IOI is directly related to VA deterioration after IVBr administration. In addition, we compared the mean number of anti-VEGF injections during the 5-month follow-up period between the two groups to evaluate whether the cessation of IVBr due to IVBr-associated IOI influenced visual outcomes. However, there was no difference in the mean number of anti-VEGF injections between the two groups. In the present study, as aflibercept was administrated to the patient after the cessation of IVBr due to IVBr-associated IOI, the impact of cessation of IVBr on vision change would have been limited.

Limitations

This study has several limitations due to its retrospective design. As the study focused on patients with a history of anti-VEGF treatment who were treated with brolucizumab as switching therapy, some biases could not be completely removed. Those patients had a heterogeneous background, and the ocular environments of the patients in the present study may be different from those with naïve nAMD [[33]]. Regarding the timing of IOI onset, confirmation may have been delayed. Due to the retrospective nature of the study, all examinations including BCVA could be biased. In addition, this study did not have an adequate sample size to evaluate factors related to retinal vascular occlusion after IVBr administration because of its low incidence. Therefore, further studies with larger sample sizes and prospective studies are needed.

Conclusions

The incidence of IOI in this study was relatively higher than that in clinical trials or reports using large registry data. In terms of clinical characteristics of IOI, the findings of our study were comparable to those of other studies. In this study, macular atrophy and SHRM were significantly associated with IVBr-associated IOI. In addition, BCVA changes 5 months after the initial IVBr administration were worse in the IOI group than in the non-IOI group. Considering that there is evidence on IVBr-associated IOI, careful examination by a physician is necessary for patients who have previously been administrated IVBr. Furthermore, when using IVBr as switching therapy for nAMD, meticulous examination and careful monitoring should be performed, especially in eyes with SHRM and/or MA, given the increased risk of developing IOI, which is associated with worse BCVA.

Statements and declarations

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Data availability

The authors are able to provide all data relevant to the study according to the reader's request.

Compliance with Ethical Standards:

Funding: No funding was received for this research.

Conflict of interest: All authors declare no competing interests.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Review Board of the Kobe University Graduate School of Medicine and with the 1964 Helsinki declaration and its later amendments ethical standards.

Informed consent: The Institutional Review Board at the Kobe University Graduate School of Medicine approved this study prior to data collection and allowed it to waive the need for informed consent. Instead, the review board accepted the opt-out recruitment approach as this was a non-interventional study with rigorous measurement to anonymous the personal information.

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Supplemental figures

Supplemental Figure 1.Time interval from baseline to the onset of inflammation

In this study, 14 (77.8%) eyes developed IOI that presented within 3 months after intravitreal brolucizumab (IVBr) administration. In 11 eyes with IVBr-associated IOI, time interval from initial IVBr administration to the onset of inflammation was 1 month. The onset of anterior or intermediate uveitis was equally distributed from 1 month to 5 months after IVBr. In contrast, inflammation developed within 3 months after IVBr in all cases of posterior or pan-uveitis.

Supplemental Figure 2

Case 1: An 86-year-old man had a BCVA of 1.39 logMAR in the left eye at baseline after 35 injections of other anti-VEGF drugs for neovascular age-related macular degeneration (nAMD). Color fundus photography (CFP) of the left eye showed mild macular atrophy with RPE depigmentation (arrow). (a) OCT image of the left eye showed incomplete RORA with shallow SRF and PED at the macula before the initial intravitreal brolucizumab (IVBr) administration. (b) Four months after the initial IVBr administration when anterior uveitis occurred, his left eye vision was 1.52 logMAR BCVA. CFP showed no haze at 4 months. (c) OCT showed a decreased but still shallow SRF. (d) At that time, his left eye developed anterior uveitis with small KPs (arrowheads) and 1+ cells in the anterior chamber along with 1+ cells in the anterior vitreous. (e) CFP showed no remarkable findings aside from macular atrophy at 5 months. (f) OCT showed no change at 5 months (g) compared with OCT at 4 months (d). At that time, his left eye vision was 1.69 logMAR BCVA.

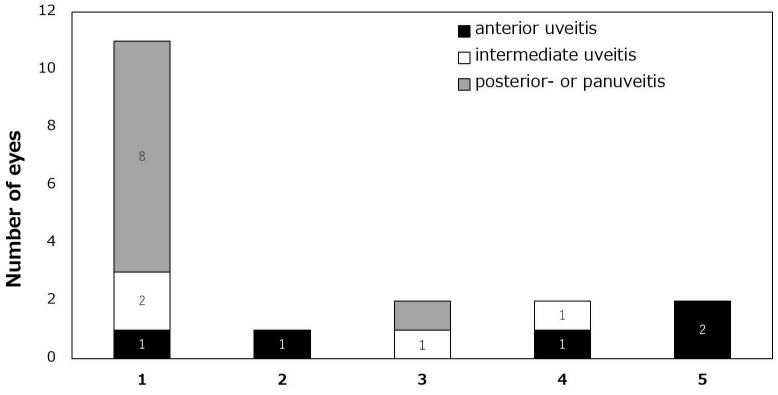
BCVA, best-corrected visual acuity; KP, keratic precipitates; OCT, optical coherence tomography; PED, pigment epithelial detachment; RORA, retinal pigment epithelial and outer retinal atrophy; SRF, sub retinal fluid

Supplemental Figure 3

Case 2: A 76-year-old man with neovascular age-related macular degeneration (nAMD) in the left eye. His left eye BCVA was 0.22 logMAR at baseline. At that time, color fundus photography (CFP) showed subretinal fluid at the macula (a), and OCT showed subretinal fluid and SHRM (arrow) at the macula. (b) One month later, he developed pan-uveitis in the left eye. His left eye vision decreased to 1.39 logMAR BCVA. CFP showed significant haze (2+). (c) No subretinal fluid and mild residual SHRM were noted on OCT. The image quality was poor because of vitritis.

(d) There were diffuse fine KPs (e) and fibrin in the anterior chamber (arrowheads) (f) with anterior inflammation in the left eye. He started betamethasone eye drops 4 times daily and received subtenon's triamcinolone acetonide 20 mg on his left eye. Two months later, his left eye was unremarkable, although his left eye vision was 1.04 logMAR BCVA. At that time, CFP showed no subretinal fluid at the macula (g), and OCT showed no subretinal fluid and no SHRM at the macula. (h)

BCVA, best-corrected visual acuity; OCT, optical coherence tomography; KPs, keratic precipitates; SHRM, subretinal hyperreflective material


12
10
8
6
4
2
0
Number of eyes
anterior uveitis
intermediate uveitis
posterior- or panuveitis
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1
1
1
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1
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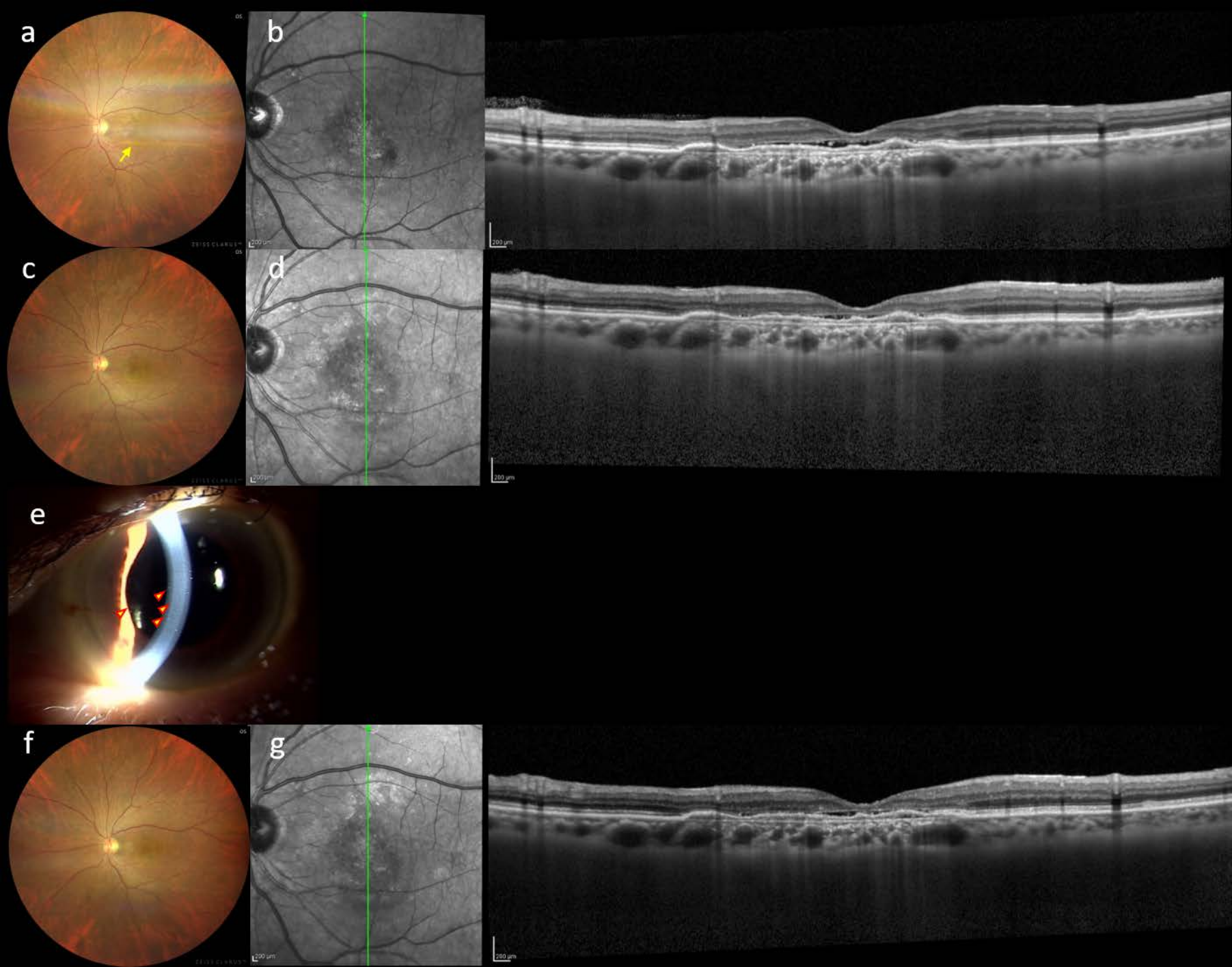
5
Time interval from initial intravitreal brolucizumab to the onset of inflammation (Month)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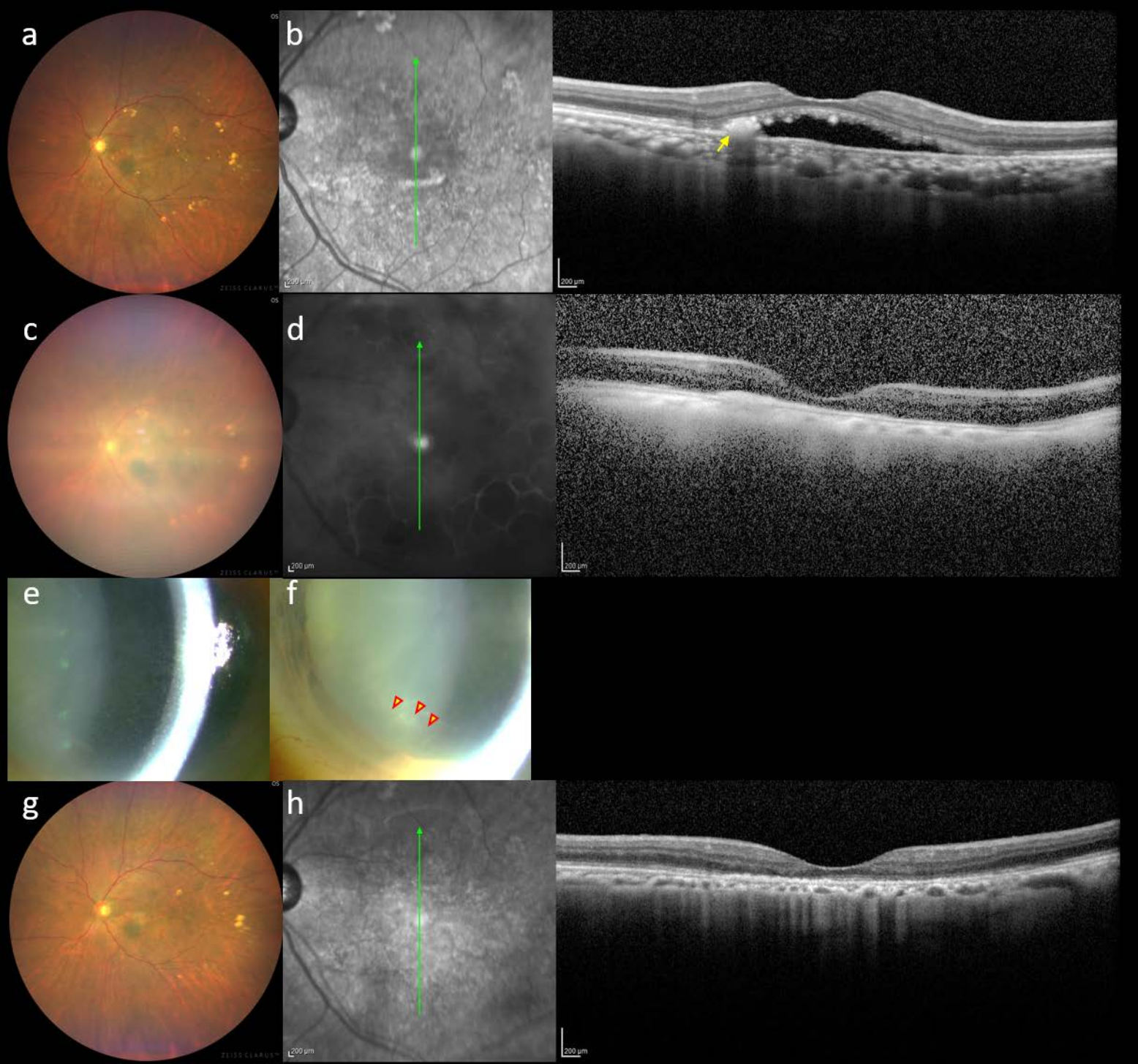
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b
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