



Subfoveal choroidal thickness after brolocizumab therapy for neovascular age-related macular degeneration: a short-term multicenter study

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Abstract

Background/purpose Observation of choroidal thickness after anti-vascular endothelial growth factor (VEGF) therapy may be important for the ideal management of neovascular age-related macular degeneration (AMD). This study investigated changes in subfoveal choroidal thickness (SCT) during loading doses of intravitreal injections of brolocizumab in eyes with neovascular AMD.

Methods This study included 73 eyes of 72 patients with neovascular AMD at five university hospitals in Japan. All 73 eyes underwent three monthly 6.0 mg intravitreal injections of brolocizumab at baseline, 1 month, and 2 months. The SCT at 3 months was evaluated using optical coherence tomography.

Results The 73 eyes were classified into the treatment-naïve group (43 eyes) and the switched group (30 eyes) that were switched from other anti-VEGF treatments. After three intravitreal injections of brolocizumab, SCT significantly decreased from $236.5 \pm 98.8 \mu\text{m}$ at baseline to $200.4 \pm 98.3 \mu\text{m}$ at 3 months (percent of baseline 84.7%, $P < 0.001$) in the treatment-naïve group. In the switched group, SCT also significantly decreased from $229.0 \pm 113.2 \mu\text{m}$ at baseline to $216.9 \pm 110.2 \mu\text{m}$ at 3 months (percent of baseline 94.7%, $P = 0.039$), although the decrease was not as marked compared to that of the treatment-naïve group.

Conclusion Intravitreal injections of brolocizumab for neovascular AMD significantly reduced the SCT in both the treatment-naïve and switched groups. Brolocizumab may cause significant anatomic changes in the choroid, particularly in treatment-naïve AMD eyes, possibly more than that previously reported for other anti-VEGF agents.

Keywords Age-related macular degeneration · Brolocizumab · Choroidal thickness · Choroidal neovascularization · Polypoidal choroidal vasculopathy · Retinal angiomatous proliferation

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Key messages

What is known

- Loading doses of intravitreal injections of brolocizumab reduced choroidal thickness in eyes with neovascular age-related macular degeneration (AMD) with or without prior treatment.

New information

- In the treatment-naïve AMD eyes, the decrease in choroidal thickness after brolocizumab therapy was greater than that reported for other anti-vascular endothelial growth factor agents.
- In the treatment-naïve AMD eyes, the decrease in choroidal thickness after brolocizumab therapy was associated with resolution of retinal fluid.

Introduction

Neovascular age-related macular degeneration (AMD) is one of the leading causes of acquired irreversible vision loss in developed countries [1]. To treat neovascular AMD, it is important to suppress the exudation induced by choroidal neovascularization (CNV) [2]. Various treatment strategies have been attempted, and in the last decade, intravitreal injections of anti-vascular endothelial growth factor (VEGF) agents have become the first-line therapy for neovascular AMD. The mainstay of current treatment includes ranibizumab (Lucentis; Genentech, South San Francisco, CA, USA) [3, 4] and aflibercept (Eylea; Regeneron, Tarrytown, NY, USA, and Bayer HealthCare, Berlin, Germany) [5]. However, due to the insufficient efficacy and/or refractoriness over time, frequent injections are required in many cases, imposing a burden on both patients and healthcare providers [2, 6–8]. In response to the need for more effective and longer-lasting drugs, brolocizumab (Beovu; Novartis, East Hanover, NJ, USA) has recently been introduced as a new anti-VEGF agent [9].

Brolocizumab is a humanized single-chain antibody fragment consisting of the tips of the Fab region of the antibody, linked by a peptide linker. Similar to ranibizumab, brolocizumab inhibits all isoforms of VEGF-A. In the global phase III HAWK and HARRIER trials, intravitreal injections of brolocizumab every 3 months after the loading phase yielded visual outcomes similar to those of intravitreal aflibercept injections administered every 2 months [9]. Moreover, brolocizumab therapy controlled exudation from CNV more strongly than did aflibercept therapy for subretinal fluid (SRF) and/or intraretinal fluid (IRF), and subretinal pigment epithelium (RPE) fluid, which are indicators of disease activity in neovascular AMD and are related to visual prognosis.

With the development of optical coherence tomography (OCT) technology in recent years, it has become possible to measure choroidal thickness in daily practice [10, 11].

Choroidal thickness varies according to the subtype of neovascular AMD [12–14]. Moreover, intravitreal injections of anti-VEGF agents affect choroidal thickness to varying degrees. Specifically, choroidal thickness is reduced to a greater extent by intravitreal injections of aflibercept than of ranibizumab [15–19]. Additionally, the decrease in choroidal thickness after aflibercept therapy proved to be related to better visual and anatomic outcomes at 1 year [19]. Therefore, observation of choroidal thickness after anti-VEGF therapy may be important for the optimal management of neovascular AMD. However, the effect of intravitreal injections of brolocizumab on choroidal thickness remains unclear.

In this multicenter study, we evaluated the changes in subfoveal choroidal thickness (SCT) after intravitreal injections of brolocizumab during the loading phase in cases recruited from five major university hospitals in Japan.

Patients and methods

This study retrospectively evaluated 73 eyes of 72 patients with neovascular AMD who received intravitreal injections of brolocizumab at the University of the Ryukyus, Nihon University, Fukushima Medical University, Kyorin University, and Tokyo Women's Medical University (JARC; Japan AMD Research Consortium) between May 2020 and February 2021. The study protocol was approved by the institutional review board of each university and was conducted in accordance with the guidelines of the Declaration of Helsinki. Written informed consent was obtained from all the patients included in this study.

The study included eyes with SRF and/or IRF in the central fovea, which underwent three monthly intravitreal injections of brolocizumab (6.0 mg/0.05 ml) for 3 months at baseline, 1 month, and 2 months.

Patients were excluded if they had any of the following: (1) infection or inflammation in the diseased or contralateral eyes; (2) history of idiopathic or autoimmune uveitis; (3)

severe allergy to fluorescein sodium, indocyanine green, or iodine; (4) treatment for serious systemic infection; (5) poorly controlled hypertension; and (6) history of cerebrovascular disease or myocardial infarction within the last 6 months.

Patients included in the study were classified into either the treatment-naïve group or the switched group (switched from other anti-VEGF agents to brolocizumab). Switching to three monthly intravitreal injections of brolocizumab was considered when SRF and/or IRF did not resolve even with monthly injections of other anti-VEGF agents.

All patients underwent an extensive ophthalmic examination, including best-corrected visual acuity (BCVA) testing, slit-lamp biomicroscopy using contact or non-contact lenses, color fundus photography, and OCT at every visit. Cross-sectional OCT was performed at the center of the fovea. Fluorescein angiography and indocyanine green angiography using a confocal scanning laser ophthalmoscope (Spectralis HRA + OCT; Heidelberg Engineering, Heidelberg, Germany) were performed to determine the subtype of neovascular AMD, namely, typical neovascular AMD, polypoidal choroidal vasculopathy (PCV) [20], and retinal angiomatous proliferation (RAP) [21], at the time of the initial treatment of AMD. Recently, the consensus on neovascular age-related macular degeneration nomenclature study group proposed a new consensus classification of neovascular AMD [22]. In that classification, typical neovascular AMD was classified into type 1 macular neovascularization (MNV), type 2 MNV, and mixed type 1 and type 2 MNV based on OCT findings, whereas RAP was renamed as type 3 MNV. However, the older classification into typical neovascular AMD, PCV, and RAP has been used for a long time, especially in the Asian cohorts [23]. Therefore, we mainly focused on the older classification in this manuscript to adequately compare the results with the previous reports.

In this study, BCVA testing was performed using the early treatment diabetic retinopathy study visual acuity chart at Nihon University and the Landolt C chart at the other four institutions. Central retinal thickness and SCT were measured using swept-source (SS)-OCT (DRI-OCT; Topcon, Tokyo, Japan) at the University of the Ryukyus and Tokyo Women's Medical University or enhanced depth imaging (EDI)-OCT (Heidelberg Spectralis; Heidelberg Engineering Inc., Heidelberg, Germany) at Nihon University, Fukushima Medical University, and Kyorin University. For each patient, the same OCT machine was used for each visit. Using SS-OCT, B-scan images were acquired by scanning 12 mm horizontally and vertically through the center of the fovea, and 128 images were averaged for each session. With EDI-OCT, B-scan images were obtained horizontally and vertically through the center of the fovea with a scan length of 9 mm, and 100 images were averaged for each session as previously described

[10]. SCT was manually measured as the vertical distance between the hyperreflective line corresponding to Bruch's membrane under the RPE and the inner boundary of the sclera at the foveal center, using the caliper function of the OCT. A macula was considered dry when the OCT images showed complete resolution of SRF and IRF.

The primary outcome was SCT changes in eyes treated with intravitreal injections of brolocizumab. The percentage of baseline in SCT at each time-point was also calculated. If no change in SCT was observed, the percentage of baseline was set at 100%.

All data were analyzed using frequency and descriptive statistics. The mean values were compared using paired and unpaired *t*-tests. BCVA was converted to the logarithm of the minimum angle of resolution (logMAR) units prior to calculation. The Wilcoxon signed-rank test was used to compare changes in BCVA, central retinal thickness, and SCT between baseline and each time-point. The correlation between changes in central retinal thickness and changes in SCT was assessed by the Spearman's rank correlation test. Data are shown as mean \pm standard deviation (SD). Statistical significance was set at $P < 0.05$. All data analyses were performed using Excel 2019 (Microsoft, Redmond, WA, USA) with the add-in software Statcel (OMS Publishing Co., Saitama, Japan).

Results

The 73 eyes of 72 patients included 14 eyes of 14 women (19.2%) and 59 eyes of 58 men (80.8%) with a mean age of 73.9 ± 7.2 years (range, 51–87 years). The treatment-naïve group included 43 eyes of 42 patients (10 women and 32 men), and the switched group included 30 eyes of 30 patients (4 women and 26 men). The switched group had received an average of 26.2 ± 22.8 (range 2–104) intravitreal injections of anti-VEGF agents prior to switching to brolocizumab. Five eyes had a history of one or two sessions of photodynamic therapy. The drugs used immediately before switching were aflibercept in 27 eyes (90.0%) and ranibizumab in three eyes (10.0%). The mean interval of injections immediately before starting brolocizumab was 4.8 ± 1.4 weeks. The AMD subtypes of the 73 eyes were classified as typical neovascular AMD in 36 eyes (49.3%), PCV in 33 eyes (45.2%), and RAP in four eyes (5.5%, including both eyes in one patient). In the treatment-naïve group, 22 eyes (15 eyes with type 1 MNV, two eyes with type 2 MNV, and five eyes with mixed type 1 and type 2 MNV), 18 eyes, and three eyes had typical neovascular AMD, PCV, and RAP, respectively. In the switched group, 13 eyes (12 eyes with type 1 MNV and one eye with mixed type 1 and type 2 MNV), 15 eyes, and two eyes had typical neovascular AMD, PCV, and RAP, respectively.

In the treatment-naïve group, BCVA improved from baseline to 3 months ($P=0.003$), and at baseline, 1 month, 2 months, and 3 months were 0.41 ± 0.36 , 0.35 ± 0.35 , 0.31 ± 0.33 , and 0.32 ± 0.34 , respectively. In the switched group, there was no significant change in BCVA between baseline and 3 months ($P=0.404$): at baseline, 1 month, 2 months, and 3 months were 0.36 ± 0.32 , 0.34 ± 0.30 , 0.29 ± 0.26 , and 0.33 ± 0.29 , respectively. In the treatment-naïve group, central retinal thickness decreased from baseline to 3 months ($P<0.001$), and at baseline, 1 month, 2 months, and 3 months were

$399.1 \pm 218.3 \mu\text{m}$, $241.2 \pm 134.7 \mu\text{m}$, $213.3 \pm 112.4 \mu\text{m}$, and $208.3 \pm 115.3 \mu\text{m}$, respectively. In the switched group, central retinal thickness also decreased from baseline to 3 months ($P=0.022$), and at baseline, 1 month, 2 months, and 3 months were $334.9 \pm 178.0 \mu\text{m}$, $260.1 \pm 164.3 \mu\text{m}$, $246.2 \pm 163.2 \mu\text{m}$, and $280.2 \pm 205.9 \mu\text{m}$, respectively. After three monthly intravitreal injections of brolucizumab, a dry macula was achieved in 38 of 43 eyes (88.4%) in the treatment-naïve group, whereas it was found in 12 of 30 eyes (40.0%) in the switched group.

Fig. 1 Changes in subfoveal choroidal thickness (SCT) in the treatment-naïve group and the switched group in eyes with neovascular age-related macular degeneration after three monthly intravitreal injections of brolucizumab. SCT in the treatment-naïve group at each time-point and at 3 months in the switched group are significantly decreased compared to baseline ($*P<0.05$; $**P<0.001$). Data are expressed as the average values

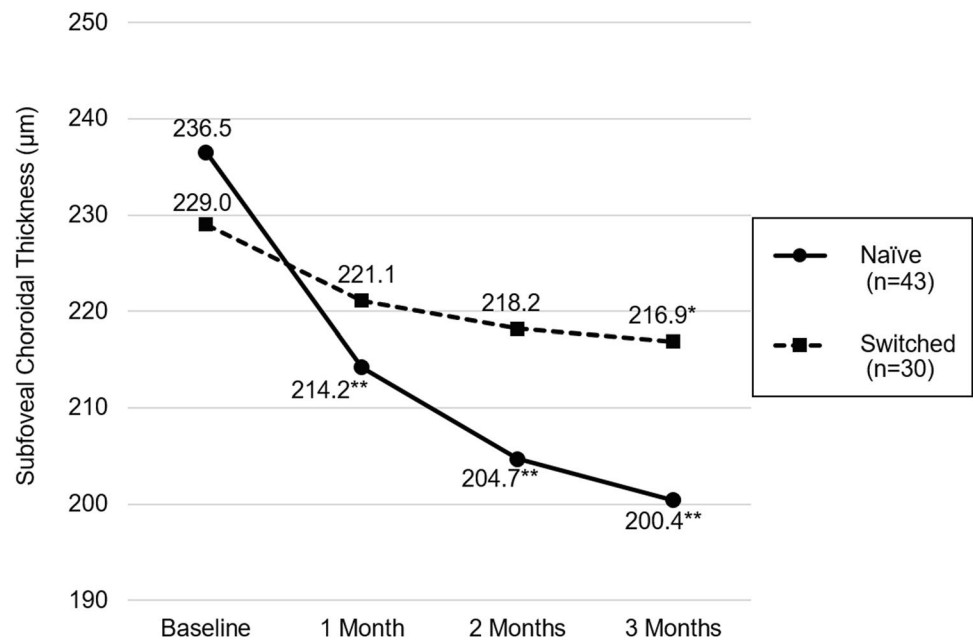
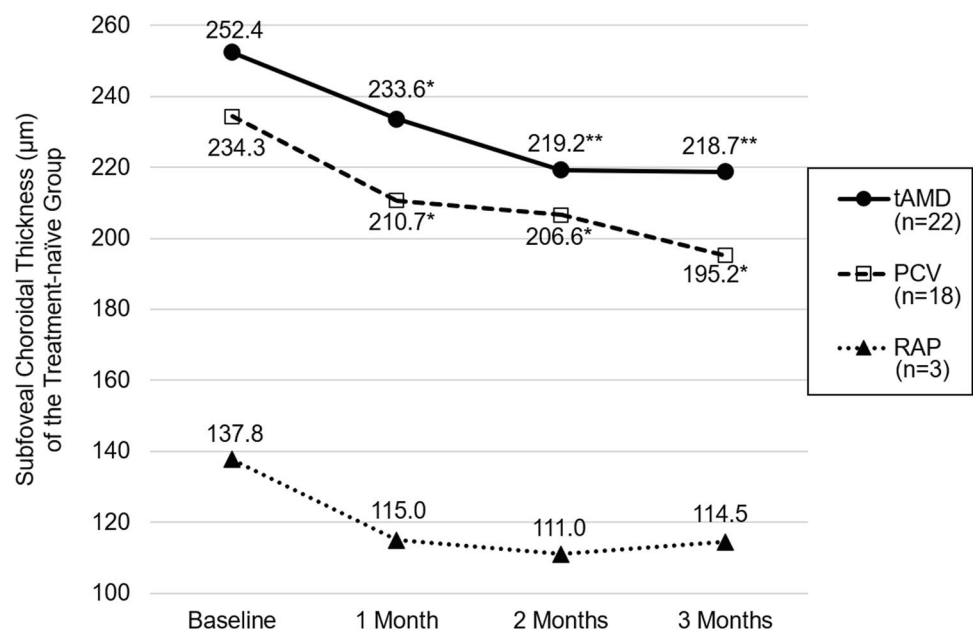


Fig. 2 Changes in subfoveal choroidal thickness (SCT) in eyes with typical neovascular age-related macular degeneration (tAMD), polypoidal choroidal vasculopathy (PCV), and retinal angiomatous proliferation (RAP) in the treatment-naïve group after three monthly intravitreal injections of brolucizumab. SCT in tAMD and PCV are significantly decreased at each time-point compared to baseline ($*P<0.01$; $**P<0.001$). Data are expressed as the averaged values



In the treatment-naïve group, SCT significantly decreased from $236.5 \pm 98.8 \mu\text{m}$ at baseline to $214.2 \pm 104.2 \mu\text{m}$ at 1 month (percent of baseline, 90.6%, $P < 0.001$), $204.7 \pm 102.0 \mu\text{m}$ at 2 months (86.6%, $P < 0.001$), and $200.4 \pm 98.3 \mu\text{m}$ at 3 months (84.7%, $P < 0.001$). SCT in the switched group also decreased significantly from $229.0 \pm 113.2 \mu\text{m}$ at baseline to $221.1 \pm 108.9 \mu\text{m}$ at 1 month (96.6%, $P = 0.096$), $218.2 \pm 105.6 \mu\text{m}$ at 2 months (95.3%, $P = 0.052$), and $216.9 \pm 110.2 \mu\text{m}$ at 3 months (94.7%, $P = 0.039$) (Fig. 1).

In the 22 eyes with treatment-naïve typical neovascular AMD, SCT decreased significantly from $252.4 \pm 103.3 \mu\text{m}$ at baseline to $233.6 \pm 112.7 \mu\text{m}$ at 1 month (92.5%, $P = 0.003$), $219.2 \pm 110.0 \mu\text{m}$ at 2 months (86.8%, $P < 0.001$), and $218.7 \pm 108.6 \mu\text{m}$ at 3 months (86.6%, $P < 0.001$). In the 18 eyes with treatment-naïve PCV, SCT decreased significantly from $234.3 \pm 92.6 \mu\text{m}$ at baseline to $210.7 \pm 89.2 \mu\text{m}$ at 1 month (89.9%, $P = 0.009$), $206.6 \pm 89.2 \mu\text{m}$ at 2 months (88.1%, $P = 0.006$), and $195.2 \pm 83.4 \mu\text{m}$ at 3 months (83.3%, $P = 0.004$). In the three eyes with RAP, the mean SCT tended to decrease: from $137.8 \mu\text{m}$ at baseline, $115.0 \mu\text{m}$ at 1 month (83.4%), $111.0 \mu\text{m}$ at 2 months (80.6%), and $114.5 \mu\text{m}$ at 3 months (83.1%); however, statistical analysis was not performed due to the small number of cases (Fig. 2). In the 14 switched eyes with typical neovascular AMD, SCT decreased significantly from $241.9 \pm 121.6 \mu\text{m}$ at baseline to $226.4 \pm 115.3 \mu\text{m}$ at 1 month (93.6%, $P = 0.017$), $225.9 \pm 110.8 \mu\text{m}$ at 2 months (93.4%, $P = 0.068$), and $220.5 \pm 116.6 \mu\text{m}$ at 3 months (91.2%, $P = 0.013$). In the 15 switched eyes with PCV, SCT did not change significantly over the observation period: $222.1 \pm 110.4 \mu\text{m}$ at baseline, $218.7 \pm 110.0 \mu\text{m}$ at 1 month (98.5%, $P = 0.609$), $213.2 \pm 107.3 \mu\text{m}$ at 2 months (96.0%, $P = 0.164$), and

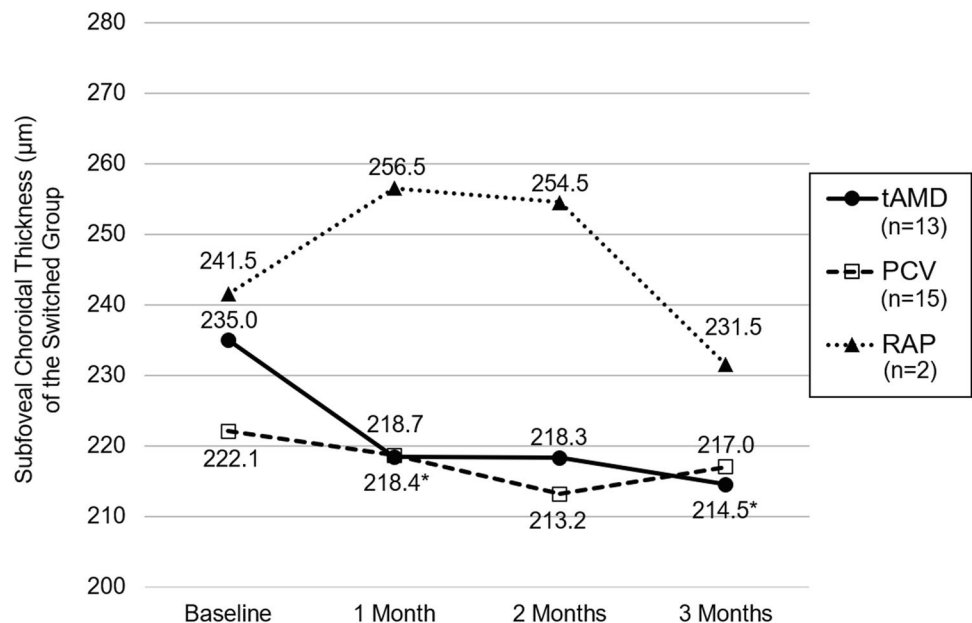
$217.0 \pm 111.1 \mu\text{m}$ at 3 months (97.7%, $P = 0.551$). In one eye with RAP, SCT was $152 \mu\text{m}$ at baseline, $183 \mu\text{m}$ at 1 month (120.4%), $185 \mu\text{m}$ at 2 months (121.7%), and $165 \mu\text{m}$ at 3 months (108.6%) (Fig. 3).

To evaluate the relationship of SCT changes with visual and anatomical outcomes, we performed further analyses. Of the 43 treatment-naïve eyes, eight eyes (18.6%) showed an improvement in BCVA of 0.3 logMAR units or more, 34 eyes (79.1%) remained unchanged, while BCVA in one eye (2.3%) worsened by 0.3 logMAR units or more. In the eight eyes with improved BCVA and the remaining 35 eyes without improved BCVA, SCT decreased significantly from $280.1 \pm 136.8 \mu\text{m}$ and $226.5 \pm 87.4 \mu\text{m}$ at baseline to $234.5 \pm 137.9 \mu\text{m}$ and $192.7 \pm 87.7 \mu\text{m}$ at 3 months, respectively ($P = 0.011$ and $P < 0.001$).

Of the 43 treatment-naïve eyes, the 38 eyes that achieved a dry macula showed a significant decrease in SCT from $238.4 \pm 102.6 \mu\text{m}$ at baseline to $199.4 \pm 102.1 \mu\text{m}$ at 3 months ($P < 0.001$). However, the remaining five eyes that did not achieve macular dryness did not show a significant decrease in SCT: $222.0 \pm 69.2 \mu\text{m}$ at baseline and $208.0 \pm 70.5 \mu\text{m}$ at 3 months ($P = 0.345$). Additionally, the decrease in central retinal thickness was not correlated with the decrease in SCT ($r_s = 0.066$, $P = 0.669$).

Of the 30 switched eyes, three eyes (10.0%) showed an improvement in BCVA of 0.3 logMAR units or more, 25 eyes (83.3%) remained unchanged, and two eyes (6.7%) worsened by 0.3 logMAR units or more. In the three eyes with an improved BCVA and the 27 eyes without improved BCVA, there was no significant change in SCT: $231.7 \pm 154.4 \mu\text{m}$ and $228.7 \pm 111.6 \mu\text{m}$ at baseline, and $208.0 \pm 139.4 \mu\text{m}$ and $217.9 \pm 109.8 \mu\text{m}$ at 3 months, respectively ($P = 0.109$ and $P = 0.102$). Of the 30 switched eyes, 12 eyes achieved

Fig. 3 Changes in subfoveal choroidal thickness (SCT) in eyes with typical neovascular age-related macular degeneration (tAMD), polypoidal choroidal vasculopathy (PCV), and retinal angiomatous proliferation (RAP) in the switched group after three monthly intravitreal injections of brolucizumab. SCT in tAMD are significantly decreased at 1 month and 3 months as compared to baseline ($*P < 0.05$). Data are expressed as the averaged values



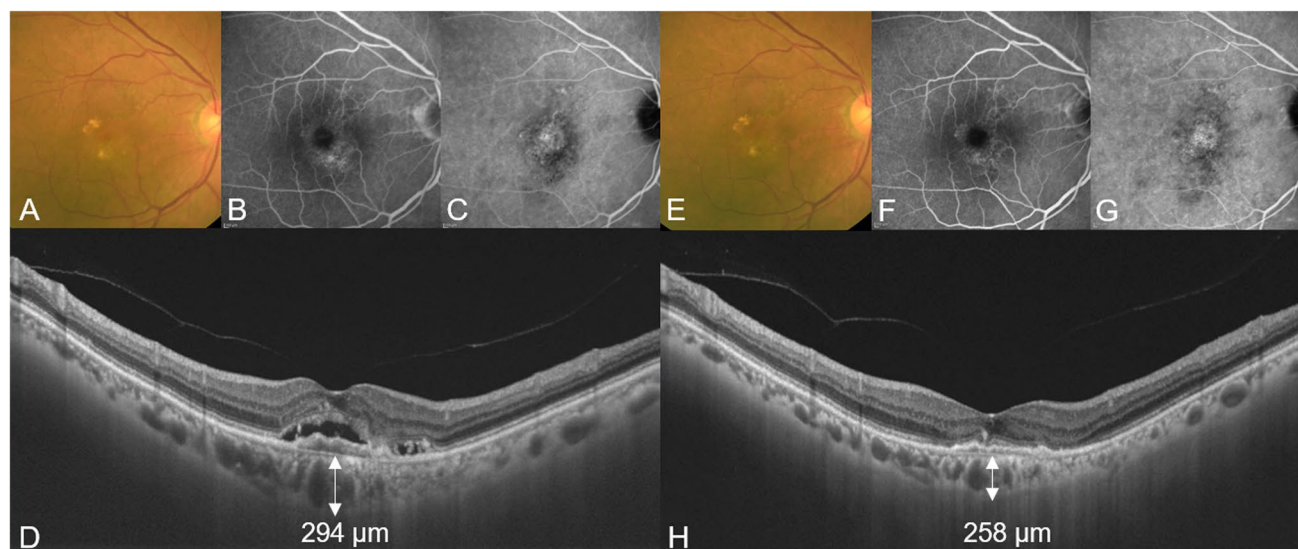


Fig. 4 The right eye of a 76-year-old male with polypoidal choroidal vasculopathy. At baseline, color fundus photography (**A**) shows small orange-reddish lesions in the macula and subtle exudation. Fluorescein angiography (**B**) demonstrates subtle leakage at the level of retinal pigment epithelium (RPE), suggestive of occult choroidal neovascularization. Indocyanine green angiography (**C**) shows a branching vascular network with small polypoidal lesions. The vertical optical coherence tomography (OCT) image (**D**) through the foveal center

demonstrates subretinal fluid with a shallow irregular RPE elevation. Subfoveal choroidal thickness (SCT) is 294 μm . At 3 months, color fundus photography (**E**) shows resolution of exudative changes. Fluorescein angiography (**F**) demonstrated attenuation of dye leakage. Indocyanine green angiography (**G**) shows partial regression of polypoidal lesions. The vertical OCT image (**H**) through the foveal center demonstrates resolution of subretinal fluid. The SCT decreases to 258 μm

macular dryness and 18 eyes did not, with no significant change in SCT from $202.5 \pm 124.5 \mu\text{m}$ and $246.6 \pm 104.9 \mu\text{m}$ at baseline to $186.3 \pm 121.7 \mu\text{m}$ and $237.3 \pm 100.2 \mu\text{m}$ at 3 months, respectively ($P=0.100$, $P=0.240$, respectively). However, the decrease in central retinal thickness was correlated with the decrease in SCT although with a borderline significance ($r_s=0.383$, $P=0.041$).

Of the 73 eyes included in this study, iritis developed in five eyes during the 3 months: three eyes in the treatment-naïve group, and two eyes in the switched group. Of the five eyes, iritis was detected in three eyes after the first injection, in one eye after the second injection, and in one eye after the third injection. The mean period from the latest injection to the detection of iritis was 22.2 days. The grade of anterior chamber cells was +0.5 in two eyes, +1 in one eye, and +2 in two eyes, based on the Standardization of Uveitis Nomenclature Working Group criteria [24]. One patient had noticed floaters, but the others had no symptoms. As soon as iritis was detected, four patients started topical corticosteroids (0.1% betamethasone eye drops), and the iritis ameliorated thereafter. In the remaining one patient, the iritis resolved without treatment. No eyes developed vitritis and retinal vasculitis with vision loss after the onset of iritis. After the completion of the loading doses, intravitreal injections of aflibercept were administered as needed. None of the patients experienced any systemic complications.

A representative case is shown in Fig. 4.

Discussion

This Japanese multicenter study investigated the changes in SCT during the loading phase of intravitreal injections of brodalumab in both treatment-naïve eyes and eyes switched from other anti-VEGF agents. The results showed that, in eyes with neovascular AMD that were treated with brodalumab, SCT decreased significantly in both the treatment-naïve group and the switched group after the loading phase, although the rate of decrease was lower in the switched group than in the treatment-naïve group. All neovascular AMD subtypes demonstrated a similar trend in SCT decrease in the treatment-naïve group, while there was a significant decrease in SCT in typical neovascular AMD in the switched group.

In the 43 treatment-naïve eyes treated with three monthly intravitreal injections of brodalumab, SCT decreased from 236.5 μm at baseline to 200.4 μm at 3 months, or 84.7% of baseline in SCT. In a Japanese cohort, the percent of baseline in SCT after three monthly injections of ranibizumab and aflibercept for treatment-naïve AMD eyes was 92.6% [16] and 86.5% [18], respectively. In terms of the AMD subtypes, the current study demonstrated that the loading doses of brodalumab for treatment-naïve eyes induced a decrease to 86.6% of baseline in SCT in typical neovascular AMD, 83.3% in PCV, and 83.1% in RAP eyes. Ellabban et al. [25] reported that the percent of baseline in SCT after loading doses of ranibizumab for treatment-naïve typical neovascular

AMD and PCV was 98.5% and 99.1%, respectively, which were not statistically significant. Other reports also revealed that the loading doses of aflibercept for treatment-naïve AMD caused a decrease to 84.8–87.8% of baseline in SCT in typical neovascular AMD [18, 26]. 85.4–87.0% in PCV [18, 26, 27], and 83.7% in RAP [28], respectively. Although the differences in the patient cohort need to be taken into consideration, the decrease in SCT after the loading doses of brolucizumab seemed to be much larger than that achieved with ranibizumab and to be comparable or even greater than that achieved with aflibercept. Recently, Matsumoto et al. [29] demonstrated that the percent of baseline in SCT after three monthly brolucizumab injections in eyes with type 1 CNV was 84.5%, identical to the results of the current study. Therefore, the pharmacological impact of brolucizumab on the choroid in eyes with neovascular AMD seemed to be stronger than that of the preceding anti-VEGF agents.

In the current study, SCT in the 30 switched eyes also decreased significantly, from 229.0 μm at baseline to 216.9 μm at 3 months, although the decrease to 94.7% of baseline in SCT was not as remarkable as that of the treatment-naïve eyes. With regard to switched therapy, Saito et al. [30] reported a decrease to 84.2% of baseline in SCT after switching from ranibizumab to three monthly loading doses of aflibercept. The reason for the lower decrease in SCT in this study compared to those of Saito et al. [30] might be frequent injections of aflibercept as the main drug and application of photodynamic therapy on some cases prior to switching to brolucizumab [17–19, 31].

We also analyzed the relationship of SCT changes and visual and anatomic outcomes. In treatment-naïve cases, we found that SCT decreased significantly only in eyes that achieved a dry macula. In addition, the decrease in central retinal thickness was correlated with the decrease in SCT in the switched cases, albeit with a borderline significance. The rate of macular dryness after administration of loading doses of brolucizumab in treatment-naïve eyes was 88.4%, which was greater than the reported rate of 71.6% after aflibercept therapy [18]. Ranibizumab is known to inhibit VEGF-A alone [32], while aflibercept inhibits VEGF-B and placental growth factor in addition to VEGF-A [33]. Similar to ranibizumab, brolucizumab inhibits VEGF-A alone, but because of its low molecular weight and high stability and solubility, it can be highly concentrated and administered in molar doses 12 times higher than that of aflibercept and 22 times higher than that of ranibizumab [9]. The anatomical impact of such high-dose administration of brolucizumab on the choroid might result in more effective resolution of SRF and IRF, in association with a decrease in SCT. However, a thinner choroid may cause macular atrophy in the long term [34], which could lead to severe vision loss. Although Japanese individuals seemingly develop less macular atrophy during anti-VEGF treatment than Caucasians [35, 36], the effects of brolucizumab on the choroid must be carefully monitored in the long term.

In terms of safety, iritis was observed in five of 73 eyes. Fortunately, there were no severe cases with retinal vasculitis and retinal vascular occlusions, and the iritis ameliorated with topical corticosteroid or without treatment in all five cases. Based on previous reports, brolucizumab is more likely to cause intraocular inflammation than precedent anti-VEGF agents with greater preponderance in Asians [37–39]. For the appropriate management of patients who underwent brolucizumab therapy, we should pay special attention to find and cope with intraocular inflammation as soon as possible.

The study has the advantage that it was a multicenter study with a relatively large number of patients treated with brolucizumab. However, this retrospective study had several limitations. First, the follow-up period was short. Second, all subjects were Japanese, and the results may not be applicable to other racial or ethnic groups. Third, due to the nature of multicenter studies, we could not unify the OCT devices among the institutions. However, we used the same OCT device for measurements of SCT at each time-point for each individual patient, and the correlation between these two OCT systems has been reported to be high [40]. Finally, the choroidal thickness was manually measured only at the foveal center. We need additional validation with an automated software and that at multiple choroidal locations.

Conclusions

Loading doses of intravitreal injections of brolucizumab reduced choroidal thickness in AMD eyes with or without prior treatment. In the treatment-naïve group, the decrease in choroidal thickness was greater than that reported for other anti-VEGF agents. Additionally, the decrease in choroidal thickness was associated with resolution of retinal fluid. Further studies with a larger number of patients and long-term follow-up are needed to verify the clinical significance of this study.

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Declarations

Ethics approval The study protocol was approved by the institutional review board of each university and was conducted in accordance with the guidelines of the Declaration of Helsinki.

Consent to participate Written informed consent was obtained from all the patients included in this study.

Conflict of interest Dr. Tamashiro reported personal fees from Alcon, Novartis, and Senju outside the submitted work. Dr. Tanaka reported personal fees from Alcon, Bayer, Novartis, Santen, and Senju outside the submitted work. Dr. Itagaki reported personal fees from Bayer and Novartis outside the submitted work. Dr. Nakayama has nothing to disclose. Dr. Maruko reported grants from JSPS KAKENHI (Grant Number JP20K09781); personal fees from Alcon, Bayer, Canon, Nidek, Novartis, Santen, Senju, and Topcon outside the submitted work. Dr. Wakugawa reported personal fees from Senju and Novartis outside the submitted work. Dr. Terao reported personal fees from Bayer, Nidek, Novartis, Senju, Santen, and Topcon outside the submitted work. Dr. Onoe reported personal fees from AMO and Novartis outside the submitted work. Dr. Wakatsuiki reported personal fees from Bayer outside the submitted work. Dr. Ogasawara has nothing to disclose. Dr. Sugano has nothing to disclose. Dr. Yamamoto reported personal fees from Alcon, Bayer, Novartis, Otsuka, and Santen outside the submitted work. Dr. Kataoka reported personal fees from Bayer, Novartis, Santen, and Senju outside the submitted work. Dr. Izumi reported personal fees from Senju and Topcon outside the submitted work. Dr. Kawai has nothing to disclose. Dr. Mori reported personal fees from Novartis, Bayer, Senju, Santen, Bausch & Lomb, JFC, Nikon, and Acula outside the submitted work. Dr. Sekiryu reported personal fees from Novartis, Bayer, Senju, Santen, Kowa, Allergan, and Chugai outside the submitted work. Dr. Okada reported consulting fees from Astellas, Bayer, Biocon Biologics, Daiichi Sankyo, HOYA, Kowa, and Novartis; personal support from Abbvie, Alcon, Bayer, Mitsubishi Tanabe, Novartis, Pfizer, Santen, and Senju outside the submitted work. Dr. Iida reported consulting fees from Bayer and Chugai; personal fees from AMO, Alcon, Bayer, Canon, HOYA, JFC, Kowa, Nikon, Nidek, Novartis, Otsuka, Pfizer, Santen, Senju, and Topcon outside the submitted work. Dr. Koizumi reported grants from JSPS KAKENHI (Grant Number JP21K09746); personal fees from Novartis, Alcon, Bayer, Canon, Senju, Santen, Kowa, HOYA, AMO, Otsuka, Pfizer, Allergan, Bausch & Lomb, JFC, Nidek, Topcon, Abbvie, TOMEY, Sumitomo Dainippon Pharma, Chugai, and SANOFI outside the submitted work.

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