

# Efficacy of Intravitreal Injection of Aflibercept in Neovascular Age-Related Macular Degeneration With or Without Choroidal Vascular Hyperpermeability

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**PURPOSE.** To compare therapeutic responses to intravitreal aflibercept and ranibizumab in neovascular age-related macular degeneration (AMD)-affected eyes with and without choroidal vascular hyperpermeability (CVH).

**METHODS.** Medical records of 216 consecutive patients (216 eyes) with treatment-naïve exudative AMD who had received three monthly intravitreal injections of aflibercept (2 mg) and ranibizumab (0.5 mg) at a single institution were analyzed. The associations of CVH with functional and morphologic changes were compared between the treatment groups.

**RESULTS.** Although foveal thickness ( $P = 0.85$ ) and visual acuity ( $P = 0.13$ ) changes were not significantly different between the treatment groups, subfoveal choroidal thickness (CT) ( $P = 0.001$ ) and pigment epithelial detachment (PED) height ( $P = 0.043$ ) decreased more profoundly in the aflibercept-treated group. The incidence of dry macula after treatments was lower in the ranibizumab-treated eyes with CVH than in those without CVH ( $P = 0.043$ ), but it showed no significant difference between the aflibercept-treated eyes with and without CVH ( $P = 0.74$ ). The aflibercept-treated eyes with CVH showed a higher incidence of dry macula ( $P = 0.04$ ) and greater decrease in subfoveal CT ( $P = 0.002$ ) than the ranibizumab-treated eyes with CVH.

**CONCLUSIONS.** Intravitreal aflibercept can achieve remission of exudative retinal changes in eyes with AMD even in the presence of CVH. In addition, it showed greater effects on the choroid and PED than intravitreal ranibizumab. The possible relationship between CVH suppression and decrease in CT warrants further study.

**Keywords:** age-related macular degeneration, polypoidal choroidal vasculopathy, choroidal vascular hyperpermeability, optical coherence tomography

Choroidal vascular hyperpermeability (CVH), which is visualized as multifocal hyperfluorescence in the middle and late phases of an indocyanine green angiography (ICGA), is a characteristic finding in some macular diseases such as central serous chorioretinopathy (CSC) and neovascular age-related macular degeneration (AMD). It reportedly occurs in 90% to 100% of eyes with CSC,<sup>1,2</sup> 9.8% to 59.3% of eyes with polypoidal choroidal vasculopathy (PCV; a subtype of AMD),<sup>3-5</sup> and up to 37.5% of eyes with typical AMD (tAMD).<sup>6</sup> Importantly, CVH influences therapeutic efficacy and other clinical characteristics in patients with tAMD or PCV. For example, eyes with tAMD or PCV as well as CVH have a thicker choroid.<sup>6</sup> Polypoidal choroidal vasculopathy-affected eyes with CVH also show persistent retinal fluid after three monthly intravitreal injections of the anti-vascular endothelial growth factor (VEGF) drug ranibizumab.<sup>4</sup> Further, photodynamic therapy (PDT) is more effective in PCV-affected eyes with CVH than in those without CVH.<sup>3</sup> Therefore, the optimal therapeutic option can differ depending on the presence or the absence of CVH in eyes with tAMD or PCV.

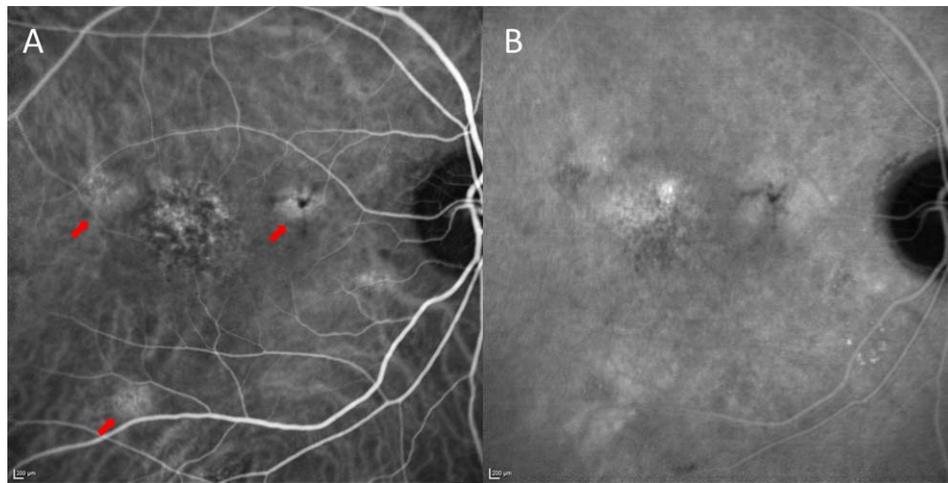
Aflibercept is a recombinant soluble decoy receptor fusion protein.<sup>7</sup> In contrast to the antibody-based VEGF-binding

strategy used by ranibizumab, aflibercept incorporates the second binding domain of the VEGF receptor-1 and the third domain of the VEGF receptor-2.<sup>8</sup> Aflibercept shows higher VEGF-binding affinity than ranibizumab.<sup>8-11</sup> According to the VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW 1 and 2) studies, aflibercept (2 or 0.5 mg monthly or bimonthly after three initial monthly doses) is clinically equivalent to ranibizumab (0.5 mg monthly) in maintaining visual acuity (VA) for 1 year.<sup>7</sup> Several studies have also shown the efficacy of aflibercept in some patients with AMD who were refractory to ranibizumab.<sup>12-16</sup>

Although CVH is associated with refractoriness to ranibizumab in eyes with tAMD or PCV, its influence on the therapeutic responses to aflibercept remains unknown. In this study, we compared the therapeutic responses to intravitreal aflibercept and ranibizumab in AMD-affected eyes with and without CVH.

## METHODS

This study was independently reviewed and approved by the Institutional Review Board of Kyoto University Graduate School



**FIGURE 1.** A representative case with choroidal vascular hyperpermeability. Choroidal vascular hyperpermeability was evaluated in the middle and late phases of indocyanine green angiography (ICGA). (A) In the middle phase of ICGA, choroidal vascular hyperpermeability is seen as multifocal areas of hyperfluorescence with blurred margins (red arrows). (B) In the late phase of ICGA, focal areas of hyperfluorescence expand and form a ring shape. The center of the initially hyperfluorescent area gradually becomes hypofluorescent.

of Medicine, and all study conduct adhered to the tenets of the Declaration of Helsinki. The patients had given written informed consent for the treatments. However, the Institutional Review Board waived the need for informed consent in the study because of the retrospective design.

We reviewed the medical records of 223 consecutive patients with treatment-naïve exudative AMD (223 eyes) who had received three consecutive monthly intravitreal injections of 0.5 mg ranibizumab (Lucentis; Novartis International AG, Basel, Switzerland) from December 2011 through November 2012 and 2 mg aflibercept (Eylea; Bayer HealthCare Pharmaceuticals, Berlin, Germany) from December 2012 through November 2013 at Kyoto University Hospital. The two inclusion criteria were diagnosis of symptomatic subfoveal exudative AMD and no previous treatment for exudative AMD. Eyes with other macular abnormalities (e.g., idiopathic choroidal neovascularization [CNV], pathologic myopia, presumed ocular histoplasmosis, angioid streaks, and other secondary CNV) were excluded. Prophylactic topical antibiotics had been applied regularly for 1 week after the injections.

Before the treatments, all the patients had undergone a comprehensive ophthalmologic examination including measurement of best-corrected VA with a Landolt chart, dilated indirect and contact lens slit-lamp biomicroscopy, automated refractometry, color fundus photography, fluorescein angiography (FA), ICGA using a confocal laser scanning ophthalmology

(HRA2; Heidelberg Engineering GmbH, Heidelberg, Germany), and spectral-domain optical coherence tomography (SD-OCT; Spectralis; Heidelberg Engineering GmbH). Measurement of best-corrected VA and SD-OCT had been repeated 1 month after the third injection. All the SD-OCT-derived images had been obtained by using an eye-tracking system, and 100 scans had been averaged automatically to improve the signal-to-noise ratio. Inverted images had also been routinely obtained by enhanced depth imaging (EDI) technique.<sup>17</sup> Enhanced depth imaging images were available for all patients in this study. The greatest linear dimension (GLD) had been measured on ICGA-derived images.

Choroidal vascular hyperpermeability was defined as multifocal areas of hyperfluorescence with blurred margins within the choroid (Fig. 1).<sup>18</sup> It was evaluated in the late phase of ICGA (approximately 10–15 minutes after dye injection) by two retinal specialists (MH, AO) who were blinded to all the other medical information. In cases of discrepancy, another retinal specialist (AT) made the final decision.

In the SD-OCT-derived images, foveal thickness (FT) was defined as the distance between the inner surface of the neurosensory retina and the retinal pigment epithelium (RPE) beneath the fovea. Subfoveal choroidal thickness (CT) was defined as the vertical distance between Bruch's membrane and the choriocleral interface. The subfoveal height of pigment epithelial detachment (PED) was defined as the

**TABLE 1.** Baseline Characteristics of Current Study Population

	Aflibercept-Treated Group			Ranibizumab-Treated Group		
	With CVH	Without CVH	Total	With CVH	Without CVH	Total
No. of eyes	27	56	83	46	87	133
Age, y	73.6 ± 7.0	75.9 ± 7.9	75.3 ± 7.5	71.7 ± 8.0	76.0 ± 8.1	74.5 ± 8.3
Sex, male/female	22/5	33/23	55/28	34/12	51/36	85/48
GLD, μm	3787 ± 1736	3769 ± 2244	3775 ± 2082	3652 ± 1512	3575 ± 1661	3602 ± 1605
Subtype, tAMD/PCV/RAP	13/14/0	26/23/7	39/37/7	20/26/0	41/40/6	61/66/6
Baseline VA, logMAR	0.38 ± 0.45	0.35 ± 0.36	0.36 ± 0.39	0.28 ± 0.28	0.36 ± 0.32	0.33 ± 0.31
Baseline FT, μm	291.6 ± 152.6	302.9 ± 148.4	299.2 ± 149.9	300.7 ± 125.7	337.8 ± 198.8	325.0 ± 177.3
Baseline CT, μm	331.7 ± 112.7	210.4 ± 85.8	250.3 ± 110.8	312.5 ± 121.3	218.3 ± 93.7	249.0 ± 112.1

RAP, retinal angiomatous proliferation.

**TABLE 2.** Mean Visual Acuities Before and After Intravitreal Injections of Aflibercept and Ranibizumab in Eyes With and Without Choroidal Vascular Hyperpermeability

Status	Treatment, n	Before, logMAR*	After, logMAR*	P†
With CVH	Aflibercept, 27	0.38 ± 0.45	0.27 ± 0.37	0.002
	Ranibizumab, 46	0.28 ± 0.28	0.23 ± 0.35	0.01
Without CVH	Aflibercept, 56	0.35 ± 0.36	0.27 ± 0.37	<0.001
	Ranibizumab, 87	0.36 ± 0.32	0.31 ± 0.32	0.003

\* Data are mean ± SD.

† Continuous variables compared by the paired-samples *t*-test at the significance level *P* < 0.05.

distance between the outer border of Bruch's membrane and the inner border of the RPE at the fovea. Only the height of subfoveal PED was measured regardless of how large the extrafoveal PED was. All the variables were manually measured by a trained ophthalmologist (MH), who was blinded to the study data, using the inbuilt caliber. We employed data from horizontal line scans. The subfoveal CT was measured in EDI-OCT through the center of the fovea. If the outer choroid was difficult to identify in the entire image, we chose 10 points at which the choriocleral interface was easily identifiable and created a segmentation line to measure subfoveal CT.<sup>17</sup> The posttreatment incidence of complete resolution of intraretinal or subretinal fluid (termed "dry macula") was also evaluated.

All data are presented as mean ± standard deviation. For statistical analysis, the measured best-corrected VA values were converted to logarithm of the minimum angle of resolution (logMAR) units. The independent-samples *t*-test was used to compare variables between the treatment groups and between the eyes with and without CVH. The paired-samples *t*-test was used to compare mean VA, FT, and CT before and after the treatments. The  $\chi^2$  test was used for categorical analysis. All statistical evaluations were performed using commercially available software (SPSS 20; IBM, Armonk, NY, USA). Values of *P* < 0.05 were considered to indicate statistical significance.

**TABLE 3.** Mean Foveal Thickness and Subfoveal Choroidal Thickness Before and After Intravitreal Injections of Aflibercept and Ranibizumab in Eyes With and Without Choroidal Vascular Hyperpermeability

Status	Treatment, n	Foveal Thickness			Subfoveal Choroidal Thickness		
		Before, $\mu\text{m}^*$	After, $\mu\text{m}^*$	P†	Before, $\mu\text{m}^*$	After, $\mu\text{m}^*$	P†
With CVH	Aflibercept, 27	291.6 ± 152.6	157.6 ± 82.8	<0.001	331.7 ± 112.7	304.5 ± 113.4	<0.001
	Ranibizumab, 46	300.5 ± 120.2	187.9 ± 79.6	<0.001	312.5 ± 121.3	307.2 ± 123.5	0.11
Without CVH	Aflibercept, 56	302.9 ± 149.8	156.7 ± 61.8	<0.001	210.4 ± 85.8	186.4 ± 79.1	<0.001
	Ranibizumab, 87	337.8 ± 198.8	175.5 ± 77.0	<0.001	218.3 ± 93.7	213.1 ± 93.8	0.003

\* Data are mean ± SD.

† Continuous variables compared by the paired-samples *t*-test at the significance level *P* < 0.05.**TABLE 4.** Comparison of Functional and Morphologic Changes Between Eyes Treated With Intravitreal Injections of Aflibercept and Ranibizumab

Parameter	Aflibercept-Treated Group, N = 83*	Ranibizumab-Treated Group, N = 133*	P†
VA change, logMAR	-0.09 ± 0.17	-0.05 ± 0.20	0.13
FT change, $\mu\text{m}$	-142.2 ± 136.2	-146.4 ± 169.3	0.85
Incidence of dry macula, %	86.7	72.2	0.63
Subfoveal CT change, $\mu\text{m}$	-25.1 ± 25.6	-5.2 ± 16.3	0.001
Subfoveal PED height change, $\mu\text{m}$	-86.9 ± 116.1	-44.0 ± 117.4	0.04

\* Data are mean ± SD unless indicated otherwise.

† Continuous and categorical variables compared by the independent-samples *t*-test and  $\chi^2$  test, respectively, at the significance level *P* < 0.05.

## RESULTS

Among the 223 enrolled patients, seven patients had not undergone angiography because of renal failure, so data of 216 patients (140 men, 76 women) were analyzed. The patient demographic and baseline characteristics are presented in Table 1. Of the 216 comprehensively assessed eyes, 100 had tAMD, 103 had PCV, and 13 had retinal angiomatous proliferation. Choroidal vascular hyperpermeability was present in 33 of the 100 eyes (33.0%) with tAMD and 40 of the 103 eyes (38.8%) with PCV. Before the treatments, the mean subfoveal CT was greater in the eyes with CVH than in those without CVH ( $331.7 \pm 112.7$  vs.  $210.4 \pm 85.8 \mu\text{m}$ , *P* < 0.001 in the aflibercept-treated group;  $312.5 \pm 121.3$  vs.  $218.3 \pm 93.7 \mu\text{m}$ , *P* < 0.001 in the ranibizumab-treated group).

The exudative change substantially decreased and VA significantly improved in all the treated eyes regardless of the CVH status (Tables 2, 3). In addition, the mean subfoveal CT significantly decreased except in the ranibizumab-treated eyes with CVH (*P* = 0.11; Table 3). Although changes in FT (*P* = 0.85) and VA (*P* = 0.13) were not significantly different between the treatment groups, subfoveal CT (*P* = 0.001) and PED height (*P* = 0.043) decreased more profoundly in the aflibercept-treated group (Table 4).

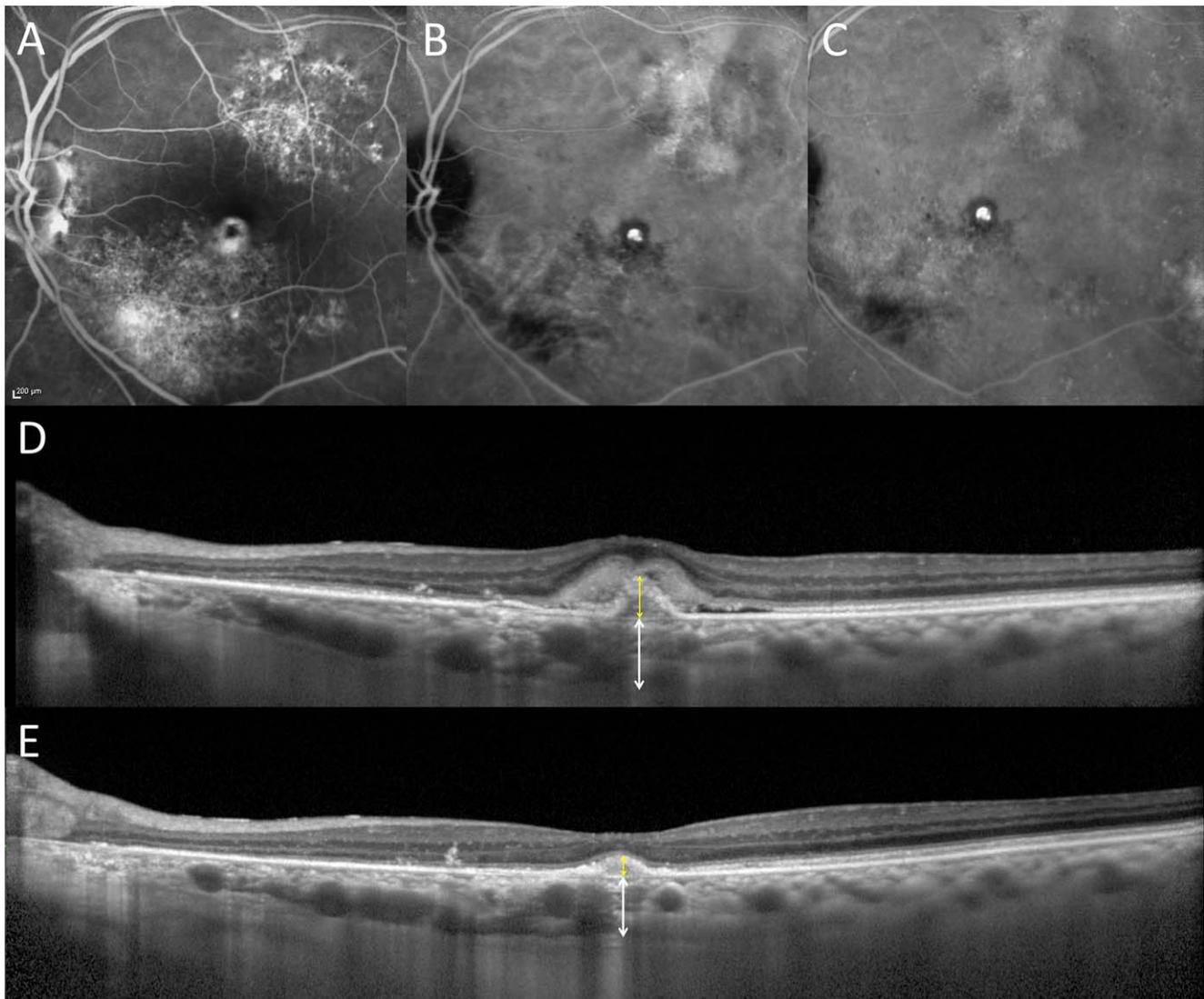
To evaluate the effect of CVH on the responses to treatments, we compared the eyes with and without CVH in each treatment group. In the ranibizumab-treated group, the posttreatment incidence of dry macula was significantly lower in the eyes with CVH than in those without CVH (60.9% vs. 78.2%, *P* = 0.043; Table 5). Moreover, the improvement in FT was marginally smaller in the eyes with CVH than in those without CVH (*P* = 0.07). In contrast, in the aflibercept-treated group, the change in FT (*P* = 0.71) and incidence of dry macula (*P* = 0.74) were not significantly different between the eyes with and without CVH. To investigate whether eyes with CVH showed different treatment responses between aflibercept and ranibizumab, we compared functional and morphological outcomes in the eyes with CVH between the aflibercept-treated group and ranibizumab-treated group. The eyes with CVH in the aflibercept-treated group showed a higher incidence of dry macula (*P* = 0.04) and a greater

**TABLE 5.** Comparison of Functional and Morphologic Changes Between Eyes With and Without Choroidal Vascular Hyperpermeability

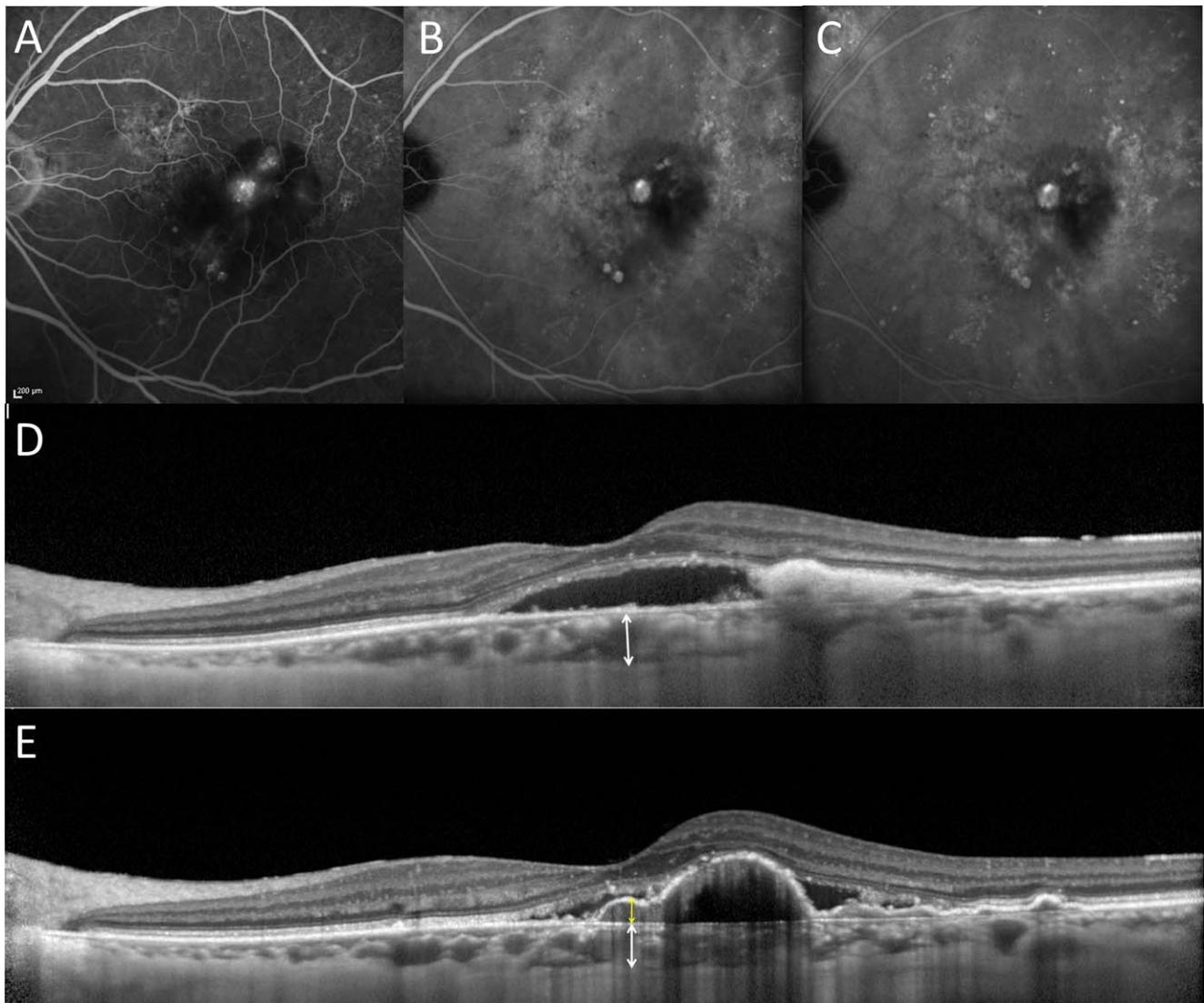
Parameter	Aflibercept-Treated Group, N = 83			Ranibizumab-Treated Group, N = 133		
	With CVH, n = 27*	Without CVH, n = 56*	P†	With CVH, n = 46*	Without CVH, n = 87*	P†
VA change, logMAR	-0.11 ± 0.17	-0.08 ± 0.17	0.48	-0.05 ± 0.19	-0.05 ± 0.20	0.86
FT change, μm	-134.1 ± 136.6	-146.3 ± 137.1	0.71	-112.6 ± 115.3	-162.3 ± 188.0	0.07
Incidence of dry macula, %	85.2	87.5	0.74	60.9	78.2	0.04
Subfoveal CT change, μm	-27.2 ± 30.4	-24.0 ± 23.1	0.60	-5.3 ± 20.6	-5.2 ± 13.9	0.98
Subfoveal PED height change, μm	-81.6 ± 84.9	-89.6 ± 130.1	0.83	-25.0 ± 128.8	-49.9 ± 112.8	0.32

\* Data are mean ± SD unless indicated otherwise.

† Continuous and categorical variables compared by the independent-samples *t*-test and  $\chi^2$  test, respectively, at the significance level  $P < 0.05$ .



**FIGURE 2.** A patient with treatment-naïve polypoidal choroidal vasculopathy and choroidal vascular hyperpermeability who received three monthly intravitreal injections of aflibercept. The pretreatment visual acuity (VA) was 0.3. (A) Fluorescein angiography revealed late leakage from choroidal neovascularization. (B) The middle and (C) late phases of indocyanine green angiography showed choroidal vascular hyperpermeability. (D) Pretreatment enhanced depth imaging-optical coherence tomography (EDI-OCT; cross-sectional view) revealed serous retinal detachment (SRD), subretinal exudation, fibrovascular pigment epithelial detachment (PED), and choroidal thickening. The subfoveal choroidal thickness (CT) was 317 μm (white arrow) and subfoveal PED height was 112 μm (yellow arrow). After three monthly injections, the VA was 0.4. (E) EDI-OCT (cross-sectional view) showed resolved SRD and decreased choroidal thickness. The subfoveal CT was 294 μm (white arrow) and subfoveal PED height was 57 μm (yellow arrow).



**FIGURE 3.** A patient with treatment-naïve polypoidal choroidal vasculopathy and choroidal vascular hyperpermeability who received three monthly intravitreal injections of ranibizumab. The pretreatment visual acuity (VA) was 0.8. (A) Fluorescein angiography revealed late leakage from choroidal neovascularization. (B) The middle and (C) late phases of indocyanine green angiography showed choroidal vascular hyperpermeability. (D) Pretreatment enhanced depth imaging-optical coherence tomography (EDI-OCT; cross-sectional view) revealed serous retinal detachment (SRD), subretinal exudation, and choroidal thickening. The subfoveal choroidal thickness (CT) was 247  $\mu\text{m}$  (white arrow). After three monthly injections, the VA was 0.9. (E) EDI-OCT (cross-sectional view) showed persistent SRD and pigment epithelial detachment (PED). The subfoveal CT was 237  $\mu\text{m}$  (white arrow) and subfoveal PED height was 124  $\mu\text{m}$  (yellow arrow).

decrease in subfoveal CT ( $P = 0.002$ ) than those with CVH in the ranibizumab-treated group. Figures 2 and 3 show representative FA- and SD-OCT-derived images of PCV-affected eyes with CVH in the aflibercept- and ranibizumab-treated groups, respectively.

## DISCUSSION

In this study, we evaluated the efficacy of intravitreal aflibercept and ranibizumab in eyes with treatment-naïve neovascular AMD with and without CVH. As expected, the eyes with CVH showed a poorer response to ranibizumab than those without CVH. In contrast, aflibercept improved exudative changes in all the treated eyes. It also achieved a greater decrease in subfoveal PED height than ranibizumab. Our results suggest that AMD-affected eyes with CVH will benefit more from intravitreal aflibercept than from intravitreal

ranibizumab. In contrast, aflibercept might have the disadvantage of choroidal thinning and RPE atrophy especially in eyes without CVH.

Both intravitreal aflibercept and ranibizumab caused significant improvements in VA and FT in eyes with neovascular AMD. The therapeutic effect was, however, less in the ranibizumab-treated eyes with CVH than in those without CVH. The result is compatible with previous reports showing a higher rate of persistent retinal edema after three monthly ranibizumab injections or deterioration of VA 6 months after anti-VEGF therapy (ranibizumab or bevacizumab) in PCV eyes with CVH.<sup>4,19</sup> Despite the lack of a significant difference in the visual outcome between the eyes with and without CVH in the short term, persistent and recurrent retinal fluid might further damage photoreceptors, resulting in poor visual prognosis in neovascular AMD. To prevent functional impairment, intravit-

real aflibercept rather than intravitreal ranibizumab may be recommended for AMD-affected eyes with CVH.

Aflibercept therapy improved exudative retinal changes in all the treated eyes regardless of the CVH status. The reason for its superior efficacy to ranibizumab in eyes with CVH is uncertain, but two possibilities can be considered. One is the binding properties of aflibercept to VEGF-A, which is a major molecule involved in increased vascular leakage and angiogenesis in AMD.<sup>20-22</sup> In fact, aflibercept has higher affinity to VEGF-A in vitro and a longer half-life than bevacizumab and ranibizumab.<sup>9</sup> The other possible reason is that some molecules influencing vascular permeability other than VEGF-A may be associated with eyes with CVH. Aflibercept can inhibit other VEGF family members, including VEGF-B and placental growth factor, which are not inhibited by ranibizumab.<sup>7-11</sup> Therefore, aflibercept could have greater therapeutic effects on AMD-affected eyes with CVH than ranibizumab.

Aflibercept also seems to have a superior effect on sub-RPE lesions compared to ranibizumab. Subfoveal CT and PED height were significantly reduced in all the aflibercept-treated eyes, but these parameters decreased only in the ranibizumab-treated eyes without CVH. The result is consistent with previous studies that showed no subfoveal CT change in eyes with CVH after ranibizumab injections<sup>4,6</sup> and reduction of CT in eyes with idiopathic subfoveal CNV and AMD (probably without CVH).<sup>23,24</sup> In the present study, furthermore, the greater reduction of subfoveal PED height was achieved in aflibercept-treated eyes, which is also in line with a previous report on the reduction of PED height after switching to aflibercept from prior anti-VEGF therapy.<sup>25</sup> Aflibercept reduced the thickness and number of fenestrations of the choriocapillaris in monkey eyes more profoundly than ranibizumab, possibly by an interaction between an Fc fragment and other molecules.<sup>26</sup> This property, which might be both beneficial and unfavorable, may explain the effect of aflibercept on CT and PED in the present study. Considering the association between CVH and CT, reduction in CT may indicate suppression of CVH after aflibercept treatments, though we did not evaluate the status of CVH after treatments. In contrast, this great effect on sub-RPE lesions may be a disadvantage: Excessive choroidal thinning causes RPE atrophy especially in the population without CVH. Further study is needed to confirm these hypotheses.

Photodynamic therapy is reportedly effective in eyes with CVH. The concept of PDT is selective nonthermal photothrombosis. Activated verteporfin produces reactive oxygen species and thrombosis mainly in neovascular tissue.<sup>27</sup> Although the treatment was initially considered to do little harm to normal tissue, vaso-occlusion occurs in the adjacent choroid.<sup>28,29</sup> Hypofluorescence of the choriocapillaris<sup>28</sup> or choroidal thinning<sup>3</sup> has been observed after PDT. The common feature between PDT and intravitreal aflibercept is choroidal thinning: The vaso-occlusive effect on the choroid would partly explain the response in the eyes with CVH, in which choroidal thickening indicates increased exudate from the choroidal vessels.<sup>4</sup>

This study has several limitations. In addition to the retrospective design and manual measurement of CT due to the lack of automated software, detection of CVH could have been performed in a subjective manner despite careful evaluation of all the ICGA-derived images by the blinded researchers. The acquisition of OCT images at the follow-up examination was performed without the follow-up mode of the eye tracker. Even with these limitations, our results indicate that intravitreal aflibercept can achieve remission of exudative retinal changes in AMD-affected eyes regardless of the presence of CVH. In addition, aflibercept showed greater effects on the choroid and PED than ranibizumab, which may

contribute to additional therapeutic or unfavorable effect in the long term. Long-term prospective studies are required to confirm the efficacy of intravitreal aflibercept in AMD-affected eyes with and without CVH.

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