Foveal structure during the induction phase of anti-vascular endothelial growth factor therapy for occult choroidal neovascularization in age-related macular degeneration

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Purpose: To evaluate the efficacy of monthly injections of aflibercept and ranibizumab on foveal structure after three months, for the treatment of occult choroidal neovascularization (CNV) in age-related macular degeneration (AMD).

Methods: We retrospectively studied 103 eyes with treatment-naïve neovascular AMD with occult and no classic CNV. Seventy-four of 103 eyes were treated with ranibizumab (intravitreal ranibizumab injection [IVR] group); 29 eyes were treated with aflibercept (intravitreal aflibercept injection [IAI] group). The best-corrected visual acuity and the retinal and choroidal structure at the fovea were evaluated using optical coherence tomography.

Results: The total foveal thickness, the height of serous retinal detachments, and subfoveal choroidal thickness were compared with baseline, and the incidence of retinal pigment epithelial elevation significantly decreased in the IAI group compared with the IVR group. In contrast, the thickness of the sensory retina at the fovea significantly decreased in the IVR group when compared with the IAI group. The logarithm of the minimum angle of resolution (logMAR) best-corrected visual acuity improved more significantly in the IVR group (−0.085±0.164) than in the IAI group (−0.020±0.125) at 3 months (P=0.017).

Conclusion: After intravitreal injection, aflibercept more rapidly reduced subretinal fluid and subfoveal choroidal thickness. In contrast, ranibizumab decreased the sensory retinal thickness compared with aflibercept. The responses of the retinal and choroidal tissue to these anti-VEGF agents may be different during the induction phase for eyes with occult CNV secondary to neovascular AMD.

Keywords: neovascular age-related macular degeneration, occult, ranibizumab, aflibercept, retinal thickness, outer nuclear layer

Introduction
Age-related macular degeneration (AMD) is the most common cause of irreversible blindness in the industrialized world.1 Emerging anti-vascular endothelial growth factor (VEGF) therapies are considered the standard of care for neovascular AMD. Anti-VEGF agents inhibit angiogenesis in the eye by suppressing abnormal blood vessel growth.2 Two landmark clinical trials using intravitreal injections of the humanized monoclonal antibody fragment ranibizumab (Lucentis; Genentech Inc., South San Francisco, CA, USA) in eyes with new-onset neovascular AMD showed that over 90% of the treated eyes lost fewer than 15 letters of vision after 24 months of follow-up, and the visual acuity (VA) improved in 33.3%–40% of the patients.3,4 Aflibercept showed a similar or superior effect on neovascular AMD.5,6
Ranibizumab is a Fab fragment that neutralizes all active forms of VEGF-A and does not possess the fragment crystallizable (Fc) domain. Aflibercept is a decoy receptor that is constructed by fusion of the second binding domain of the VEGFR-1 and the third binding domain of the VEGFR-2 to the crystallizable portion of immunoglobulin G (IgG) 1.5,7 Although there are definite biological differences between ranibizumab and aflibercept, the efficacies of the two anti-VEGF drugs in clinical practice are still inconclusive.

Spectral-domain optical coherence tomography (SD-OCT) provides a detailed anatomical assessment of the retinal layers, especially the photoreceptor layer and pigment epithelium. Moreover, a relatively new technique using SD-OCT, the enhanced depth-imaging technique, allows evaluation of the choroidal morphology.8 The retinal and choroidal thicknesses significantly decreased after intravitreal injections of ranibizumab or aflibercept.9−12 Regarding the choroidal thickness, previous studies suggested that a decrease of choroidal thickness might be more remarkable in the eyes treated with aflibercept.10,11 Microstructural changes in retina and choroid may differ between the anti-VEGF drugs. To our knowledge, the morphological difference between the eyes treated with ranibizumab and that with aflibercept has not been reported.

In this retrospective study, we compared the effects of ranibizumab and aflibercept on retinal and choroidal morphology during three consecutive monthly injections to treat choroidal neovascularization (CNV) secondary to AMD in the induction phase in humans. CNV with predominantly or minimally classic lesion is associated with less improvement in VA at anti-VEGF therapies in the multicenter study.13 The integrity of the retinal structure after treatment of neovascular AMD also varied among the CNV subtypes.14 We thought that occult CNV may be suitable to analyze the retinal structure changes because the location of CNV had little influence on the foveal retinal structure. In the current study, we therefore focused on eyes with pure occult CNV, that is, CNV with no classic lesions, to minimize the variations among CNV subtypes.

Methods
This was a retrospective interventional study of treatment-naïve patients who had occult CNV with no classic lesions secondary to neovascular AMD. After the potential risk and benefits were explained in detail, all patients provided written informed consent approved by Institutional Review Board at Fukushima Medical University. We analyzed the medical records of 103 eyes of 100 patients examined at Fukushima Medical University between March 2009 and December 2013. All patients underwent measurement of best-corrected visual acuity (BCVA), slit lamp biomicroscopy, color fundus photography, and OCT at baseline and 1 month, 2 months, and 3 months. The records of the eyes were discarded when there were no good fundus photographs or OCT images for analysis. The 74 eyes of 71 patients who visited from March 2009 to November 2012 were treated with a monthly intravitreal ranibizumab (0.5 mg) injection (IVR) for 3 months. The 29 eyes of 29 patients who visited from December 2012 to December 2013, aflibercept became available for medical use in Japan after December 2012, were treated with monthly intravitreal aflibercept (2 mg) injection (IAI) for 3 months. All treatment-naïve patients were treated within 3 months from onset.

The primary study outcomes were retinal and choroidal morphologic changes after IAI and IVR. To discriminate polypoidal choroidal vasculopathy from occult CNV, indocyanine green angiography (ICGA) was performed in all eyes. We used the BCVA measured with a Japanese standard decimal VA chart. The BCVA was converted to the logarithm of the minimum angle of resolution (logMAR) units before the calculations were performed.

The inclusion criteria were: a patient age of at least 50 years with a diagnosis of primary occult subfoveal CNV with no classic lesions secondary to AMD and juxtafoveal lesions with leakage affecting the fovea were allowed, a total occult CNV lesion on fluorescein angiography <12 disc areas, and a BCVA of 0.05 or better using the Japanese decimal VA chart.

The exclusion criteria were any of the following in either eye: CNV secondary to other macular disorders and eyes with polypoidal choroidal vasculopathy based on ICGA findings, which showed polypoidal structures at the border of the branching choroidal vascular networks16 and subpigment epithelial orange–red protrusions seen biomicroscopically that corresponded to the polypoidal lesions observed on ICGA. Other exclusion criteria included a spherical equivalent of −6.5 diopters (D) or less and/or chorioretinal atrophic changes secondary to pathologic myopia, a history of intraocular surgery within 6 months, a history of pars plana vitrectomy, a retinal pigment epithelial (RPE) tear at the first examination, or a systemic contraindication for IVR or IAI.

Measurements
The primary study outcomes were retinal and choroidal morphologic changes after IAI and IVR. To assess the retina
using OCT, 9 mm horizontal and vertical scans through the foveal center were routinely performed in all study eyes using SD-OCT (Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany). Additional scans were made through lesions of interest. The subfoveal choroidal thickness (SFT) was measured using the enhanced depth-imaging technique. All images were obtained using an eye-tracking system (ART, installed in Spectralis OCT), with 100 scans being averaged.

We measured the total foveal thickness (TFT), the distance from the surface of the RPE to the internal limiting membrane (ILM), the foveal retinal thickness (FRT, the distance from the ILM to the external limiting membrane [ELM]), the height of serous retinal detachments (HSRD, the distance from the ELM line to the surface of the RPE), and the SFCT (the distance between the hyperreflective line corresponding to Bruch’s membrane beneath the RPE and the inner surface of the sclera at the foveal center; Figure 1). The measurement was performed using the calliper function of the OCT instrument.

The structures of the ELM line, ellipsoid zone, the incidence of serous retinal detachment (SRD), intraretinal fluid (IRF), and the RPE elevation at the fovea were qualitatively assessed. RPE elevation included RPE separation from Bruch’s membrane and any type of pigment epithelial detachment that was detected at the fovea on OCT images. Regarding the line structures of the ELM or the ellipsoid zone, “disruption” was defined as complete disappearance or disruption of the line. Eyes with any lines or zones that were identified regardless of whether they were or were not clear did not meet the definition of disruption.

Two retinal specialists (MK and KI) who were masked to the patients’ information performed all quantitative and qualitative measurements. Regarding quantitative data, the mean value of the two graders was used for statistical analysis. Regarding qualitative data, when there were cases with inconsistent evaluations between the two graders, a third grader (TS) made the final decision. The institutional review board of Fukushima Medical University approved the study, which was conducted according to tenets of the Declaration of Helsinki.

**Statistical analysis**

The data obtained from all patients were analyzed with frequency and descriptive statistics. The logMAR BCVA and the mean measurement values were compared using the Mann–Whitney U test. Categorical data were tested using Fisher’s exact test. A P-value <0.05 was considered significant. All descriptive statistics were performed using JMP software version 11.0 (SAS Institute Inc., Cary, NC, USA).

**Results**

No significant differences in the baseline characteristics were observed between the two groups (Table 1). No systemic events were observed in two groups. The age of the patients ranged from 53 to 93 years (75±8 years [mean±standard deviation]) in the IAI group and 76±8 years in the IVR group (P=0.755). The IAI group included 27 male and two female patients, and the IVR group included 59 male and 12 female patients (P=0.339). The disc areas of the occult CNV seen on the fluorescein angiography images were 3.5±2.6 in the IAI group and 4.1±2.5 in the IVR group (P=0.334). The mean logMAR BCVAs before treatment did not differ significantly (P=0.721) between eyes treated with

**Table 1 Baseline characteristics of patients in the study**

<table>
<thead>
<tr>
<th></th>
<th>IAI</th>
<th>IVR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (eyes/patients)</td>
<td>29/29</td>
<td>74/71</td>
<td>0.339</td>
</tr>
<tr>
<td>Female: male</td>
<td>2:27</td>
<td>12:59</td>
<td>0.339</td>
</tr>
<tr>
<td>Age (years)</td>
<td>75±8</td>
<td>76±8</td>
<td>0.755</td>
</tr>
<tr>
<td>logMAR BCVA</td>
<td>0.29±0.309</td>
<td>0.29±0.271</td>
<td>0.721</td>
</tr>
<tr>
<td>Lesion size (DA)</td>
<td>3.5±2.6</td>
<td>4.1±2.5</td>
<td>0.334</td>
</tr>
<tr>
<td>TFT (µm)</td>
<td>249±85</td>
<td>267±115</td>
<td>0.634</td>
</tr>
<tr>
<td>FRT (µm)</td>
<td>110±72</td>
<td>120±68</td>
<td>0.190</td>
</tr>
<tr>
<td>HSRD (µm)</td>
<td>139±77</td>
<td>147±110</td>
<td>0.572</td>
</tr>
<tr>
<td>SFCT (µm)</td>
<td>242±93</td>
<td>239±95</td>
<td>0.866</td>
</tr>
<tr>
<td>ELM (disrupted)</td>
<td>1 (3.5%)</td>
<td>5 (6.8%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Ellipsoid zone (disrupted)</td>
<td>8 (27.6%)</td>
<td>3 (30.1%)</td>
<td>0.814</td>
</tr>
<tr>
<td>SRD</td>
<td>27 (93.1%)</td>
<td>62 (83.7%)</td>
<td>0.339</td>
</tr>
<tr>
<td>RPE elevation</td>
<td>25 (86.1%)</td>
<td>65 (87.4%)</td>
<td>1.000</td>
</tr>
<tr>
<td>IRF</td>
<td>6 (20.6%)</td>
<td>23 (31.0%)</td>
<td>0.338</td>
</tr>
</tbody>
</table>

**Note:** Measured data is expressed as mean ± standard deviation.

**Abbreviations:** IAI, intravitreal aflibercept injection; IVR, intravitreal ranibizumab injection; logMAR BCVA, the logarithm of the minimum angle of resolution best-corrected visual acuity; DA, disc area; TFT, total foveal thickness; FRT, foveal retinal thickness; HSRD, height of serous retinal detachment; SFCT, subfoveal choroidal thickness; ELM, external limiting membrane; SRD, serous retinal detachment; RPE, retinal pigment epithelium; IRF, intra retinal fluid.
afiblercept and those treated with ranibizumab (0.292±0.309 and 0.299±0.271, respectively). There were no significant differences in the TFT (P=0.634), FRT (P=0.198), HSRD (P=0.572), or SFCT (P=0.866; Table 1). The incidence rates of an abnormality in the layer structure, disruption of the ELM (P=1.000), disruption or absence of the ellipsoid zone (P=0.814), SRD (P=0.339), or RPE elevation (P=1.000) did not differ between the two groups.

The changes in each measured value are shown in Table 2 and Figures 2–6. The mean logMAR BCVA in the IVR group improved consecutively at 1 month, 2 months, and 3 months; those in the IAI group decreased at 1 month and improved at 2 months and 3 months. Significant differences between the two groups were seen at each time point, P=0.002, P=0.017, and P=0.017, respectively. To determine the visual prognosis, we investigated the BCVA changes at 6 months from the clinical records, although the treatment regimens differed. The IVR group received additional injections according to the criteria during the second year of the Prospective OCT Imaging of Patients with Neovascular AMD Treated with Intraocular Ranibizumab (PrONTO) study.15 The IAI group received bimonthly injections after 3 months of the loading dose. The changes in the logMAR BCVA from baseline at 6 months were 0.009±0.127 (n=27) in the IAI group and −0.064±0.199 (n=71) in the IVR group. No significant (P=0.281) difference was observed in the logMAR BCVA between the two groups at 6 months.

Table 2 Changes in the parameter values

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Month</th>
<th>IAI Mean</th>
<th>IAI SD</th>
<th>IVR Mean</th>
<th>IVR SD</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>logMAR</td>
<td>1</td>
<td>0.016</td>
<td>0.010</td>
<td>−0.064</td>
<td>0.130</td>
<td>0.002</td>
</tr>
<tr>
<td>BCVA change</td>
<td>2</td>
<td>−0.012</td>
<td>0.118</td>
<td>−0.084</td>
<td>0.155</td>
<td>0.017</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>−0.020</td>
<td>0.125</td>
<td>−0.085</td>
<td>0.164</td>
<td>0.17</td>
</tr>
<tr>
<td>TFT (μm)</td>
<td>1</td>
<td>−81</td>
<td>168</td>
<td>−29</td>
<td>103</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>−79</td>
<td>115</td>
<td>−49</td>
<td>113</td>
<td>0.016</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>−78</td>
<td>125</td>
<td>−52</td>
<td>115</td>
<td>0.043</td>
</tr>
<tr>
<td>FRT (μm)</td>
<td>1</td>
<td>−5</td>
<td>50</td>
<td>−24</td>
<td>56</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>−11</td>
<td>67</td>
<td>−21</td>
<td>53</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>−1</td>
<td>50</td>
<td>−18</td>
<td>57</td>
<td>0.001</td>
</tr>
<tr>
<td>HSRD (μm)</td>
<td>1</td>
<td>−85</td>
<td>86</td>
<td>−53</td>
<td>84</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>−90</td>
<td>93</td>
<td>−70</td>
<td>98</td>
<td>0.059</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>−79</td>
<td>111</td>
<td>−69</td>
<td>98</td>
<td>0.129</td>
</tr>
<tr>
<td>SFCT (μm)</td>
<td>1</td>
<td>−12</td>
<td>18</td>
<td>−7</td>
<td>17</td>
<td>0.279</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>−33</td>
<td>52</td>
<td>−13</td>
<td>23</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>−27</td>
<td>16</td>
<td>−15</td>
<td>24</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Abbreviations: IAI, intravitreal aflibercept injection; IVR, intravitreal ranibizumab injection; SD, standard deviation; BCVA, best-corrected visual acuity; TFT, total foveal thickness; FRT, foveal retinal thickness; HSRD, height of serous retinal detachment; SFCT, subfoveal choroidal thickness; logMAR, logarithm of the minimum angle of resolution.

The TFT decreased from baseline after anti-VEGF therapy in both groups at each visit. The differences in the TFT changes between the two groups were significant (1 month, P=0.002; 2 months, P=0.016; 3 months, P=0.043; Table 2). The FRT also decreased in both groups, and the change was greater in the IVR group than in the IAI group (1 month, P=0.001; 2 months, P=0.009; 3 months, P=0.001; Table 2). The HSRD significantly decreased after injections of both drugs. The change in the HSRD at 1 month was
significantly greater \((P=0.008)\) in eyes treated with aflibercept than in those treated with ranibizumab. The differences in the changes in the HSRD between the two groups did not reach significance at 2 months and 3 months \((P=0.059\) and \(P=0.129\), respectively\). The SFCT gradually decreased after treatment in both groups. Although the changes in the SFCT between the two groups were not significant \((P=0.279)\) at 1 month, the SFCT in the IAI group significantly decreased at 2 months and 3 months compared with that in the IVR group \((P=0.003\) and \(P<0.001\), respectively\). The rates of SFCT reduction at 3 months were 11.3\% in the IAI group and 6.3\% in the IVR group.

Regarding qualitative parameters, the incidence rates of SRD and RPE elevation were low in eyes treated with aflibercept at each observation point after the intravitreal injections. The incidence of SRD at 3 months was significantly lower \((P=0.036)\) in eyes treated with aflibercept. The incidence rates of RPE elevation at 2 months and 3 months also were significantly lower \((P=0.008\) and \(P=0.030\), respectively\) in eyes treated with aflibercept compared with eyes treated with ranibizumab. The incidence of disruption of the ellipsoid zone was low in the ranibizumab group at each observation point after the intravitreal injections. The differences between the two groups did not reach significance. The incidence rates of ELM disruption and IRF did not differ between the groups (Table 3). We analyzed the factors associated with logMAR changes at 3 months using stepwise analysis. The dependent variable was the change in the logMAR BCVA at 3 months. The explanatory variables were the treatment drugs and changes in the TFT, FRT, HSRD, SFCT, ELM, ellipsoid zone, SRD, and RPE elevation at 3 months. The minimal Bayesian information criterion was used as the stopping rule. The status of the FRT and the ellipsoid zone remained as probable factors. Fitting to a least squares model using the two probable factors showed that the decrease in the FRT was the only significant factor \((P=0.012)\) correlated with the improvement of the logMAR BCVA at 3 months (Table 4). The decreasing FRT was correlated with the logMAR BCVA improvement in each group (Figure 7).
Discussion

The foveal structure seen on OCT images was retrospectively evaluated during the initial three monthly intravitreal injections of aflibercept or ranibizumab in eyes with occult CNV secondary to neovascular AMD. The TFT, HSRD, SFCT, and the incidence of RPE elevation significantly decreased in the IAI group. In contrast, the FRT significantly decreased in the IVR group. The ellipsoid zone was restored in the IVR group but did not reach significance. The mean logMAR BCVA significantly increased in the IVR group but did not reach significance. The mean FrT significantly decreased in the IAI group. In contrast, the FRT significantly decreased in the IVR group. The ellipsoid zone was restored in the IVR group but did not reach significance. The mean logMAR BCVA significantly increased in the IVR group but did not reach significance. The mean FrT significantly decreased in the IAI group. In contrast, the FRT significantly decreased in the IVR group. 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IAI group at 3 months. We think that the FRT change might not be influenced by the baseline condition of the retina between two groups.

The difference in FRT change between two drugs is attributed to swelling of the photoreceptor cells due to the ischemic status of the choroid. After photodynamic therapy, choroidal ischemia induced retinal thickening.22 Bevacizumab, ranibizumab, and aflibercept affected the endothelium of the choriocapillaris, which resulted in thrombosis of the choroidal vessels.23,24 Because aflibercept has a higher affinity for VEGF than ranibizumab, the combined high affinity and longer half-life have led to a calculated duration of effect of intravitreal injection of 2 mg of aflibercept for 48–83 days.25 In addition, aflibercept reduced the intraocular concentration of VEGF to extremely low levels after intravitreal injection in humans. Based upon these reports, it is observed that aflibercept may cause choroidal ischemia. As a result, the sensory retinal thickness may be thicker in the aflibercept group than in the ranibizumab group. Furthermore, thinning of the choroidal thickness might be involved in circulatory changes of the choroid. However, a recent study reported that the retinal microstructure in healthy primate models did not change remarkably after aflibercept injection.19 A therapeutic dose of aflibercept injection in human eyes is therefore less likely to be associated with increasing FRT.

Another possibility of the difference in FRT change is immune complex inflammation through interaction of IgG with the Fcγ receptor. Aflibercept is constructed by fusion of the binding domains of the VEGFRs to the crystallizable portion of IgG1,6,7 whereas ranibizumab is a monoclonal antibody fragment (Fab) without the crystallizable (Fc) domain.2 Aflibercept was assumed to bind to vascular endothelial cells with the endothelial Fc receptor through formation of a protein complex. A recent report suggested that interaction of IgG with the Fcγ receptor possibly induced immune complex inflammation, in which microglia and macrophages were activated in the retina.27 An immune reaction involving the Fcγ receptor could be attributed to the increasing FRT in the aflibercept group. In an extended study, the change in BCVA did not differ significantly between the two groups 6 months after the intravitreal injections, and the BCVA in a longitudinal multicenter study showed that aflibercept was not inferior to ranibizumab.5 Immune reactions in the early phase might resolve when VEGF concentration decreased after serial injection of aflibercept. As we did not evaluate the parameter regarding inflammation in the current study, further studies are needed to confirm this possibility. Placental growth factor (PIGF) may have a protective effect on the retinal cells.28 Blockade of PIGF may be responsible for the change in the FRT.

The current study was limited because of its retrospective nature. All patients were Japanese, and they clinically and genetically differed from Caucasian and black patients, so racial differences may have affected the results.

Conclusion
In conclusion, after intravitreal injection, aflibercept more rapidly reduced subretinal fluid and SFCT. In contrast, ranibizumab decreased the sensory retinal thickness compared with aflibercept. The responses of the retinal and choroidal tissues to these anti-VEGF agents may be different during the induction phase for eyes with occult CNV secondary to neovascular AMD. Based upon these results, long-term investigations of the efficacies of these two treatments on retinal and choroidal tissue are needed in future studies.

Disclosure
The authors report no conflicts of interest in this work.

References


