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ORIGINAL RESEARCH

Comparisons of Early Changes of Vascular Structure After Treatment with Faricimab and Aflibercept in Eyes with Macular Neovascularization by OCT Angiography

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Objective: To evaluate whether Faricimab, which targets Ang-2, can reduce macular neovascularization (MNV) metrics on OCTA compared with Aflibercept in treatment-naïve nAMD.

Methods: Among 34 eyes treated with Aflibercept, 12 eyes were included; among 31 eyes treated with Faricimab, 14 eyes were included. Vessel area (Va) and junction density (JD) were measured using AngioTool over a 3-month loading period.

Results: In the Faricimab group, mean Va changed from 0.14 mm^2 at baseline to 0.15 mm^2 at 3 months; JD changed from 0.16 to 0.15/mm. In the Aflibercept group, Va decreased from 0.29 to 0.20 mm^2, and JD changed from 0.77 to 0.83/mm. Differences in Va and JD between groups were not statistically significant.

Conclusion: There were no significant structural changes in MNV with either drug over the short term. These findings suggest that vascular effects of Faricimab may require longer observation to become evident.

Keywords: Neovascular age-related macular degeneration, Faricimab, Aflibercept, Optical coherence tomography angiography

Introduction

Neovascular age-related macular degeneration (nAMD) is a major retinal disorder that can progress to a significant reduction in the visual acuity. Studies of nAMD are important because its prevalence is increasing in Japan and worldwide.[1–3] Currently, the first-line treatment for nAMD is the intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) drugs with the Treat and Extend (TAE) regimen.[4,5] However, even with this treatment protocol, it is difficult to resolve the macular neovascularization (MNV) completely in all nAMD patients.[6]

It has also become clear that mature vessels that are resistant to anti-VEGF drug exist, and the treatment prognosis factors related to the structure of MNVs have not been determined.[7] Thus, research into the structure of MNVs is important in eyes with nAMD.[8–10] Earlier, Takeuchi et al examined the structural changes of the MNV after an initial administration of Aflibercept in eyes with untreated nAMD.[8] They reported that the vascular areas (Va) of MNVs were transiently decreased after the initial administration of Aflibercept, but then rebounded and increased in size.[8] Optical coherence tomography angiography (OCTA) derived parameters such as vessel area (Va) and junction density (JD) have been proposed as non-invasive imaging biomarkers for evaluating the complexity and regression of neovascular networks in response to anti-VEGF therapy. JD reflects the density of vascular branching points and may indicate structural remodeling or pruning of immature vessels following treatment.[8]

A new anti-VEGF drug, Faricimab, has been approved for intravitreal use, and one of the features of Faricimab is that it is the first humanized bispecific IgG monoclonal antibody that binds to and neutralizes both VEGF-A and angiopoietin-2 (Ang-2)

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independently. Faricimab differs from conventional anti-VEGF drugs in that it promotes vascular stabilization by binding to Ang-2.[11]

We hypothesized that Faricimab, through its Ang-2 inhibitory action, may exert a stronger vascular regression effect on VEGF-refractory MNV compared to Aflibercept. This effect was expected to manifest as a greater reduction in vessel area and junction density, as quantified by OCTA. Since past studies have evaluated treatment responses during the anti-VEGF loading phase, we also focused on this early treatment period to investigate whether structural differences between the two agents could be detected.[8]

To test this hypothesis, we conducted a comparative analysis of short-term changes in MNV morphology after the loading phase using OCTA based parameters.

Methods

Study Design

The procedures used in this study were approved by the Ethics Committee of Mie University Hospital (approval number: H2021-088, UMIN000044144), and they conformed to the tenets of the Declaration of Helsinki. This study employed an opt-out consent process. The data for this study were analyzed anonymously to ensure participant privacy and confidentiality. The data were accessed between the 20th and 27th of November 2024. The authors had no access to information that could identify individual participants during or after data collection.

The medical records of nAMD patients treated between April 2009 and December 2023 with intravitreal injections of Faricimab (Vabysmo, Roche/Genentech, Basel, Switzerland) or Aflibercept (Eylea; Bayer, Basel, Switzerland) at the Mie University Hospital (Mie, Japan) were analyzed.

Patient Selection

Patients diagnosed with nAMD using fluorescein angiography (FA), indocyanine green angiography (ICGA), and structural optical coherence tomography (OCT) and were untreated were selected. All received intravitreal injection of either Aflibercept or Faricimab as a loading treatment and were followed monthly for three months. The time from diagnosis of neovascular AMD to the initiation of anti-VEGF treatment was not consistently documented in the medical records. However, all patients included in the study received treatment as early as possible following diagnosis, in accordance with clinical guidelines and physician discretion. Patients whose MNV was not clearly visible in the OCTA images or whose condition could not be accurately evaluated using the Angio tool (National Cancer Institute, NIH; version 0.6a) were excluded from the study. Because AngioTool cannot accurately quantify MNV morphology unless the lesion boundaries are clearly delineated, only eyes with well-visualized and analyzable MNV were included in this study.

OCTA Image Acquisition

All patients received three monthly loading injections and visited the clinic approximately one month after each injection. The first visit was defined as the baseline (BL) examination, and the postinjection examination times were at 1 month (M), 2M, and 3M. The OCTA (PLEX Elite 9000. Carl Zeiss AC, Jena, Germany) images were recorded at the BL and at each designated postinjection time. Macular cubes of the OCTA images of 3×3 mm or 6×6 mm scan patterns were used to evaluate the MNV so that the entire structure of the MNV could be measured. The MNV was then examined using the MNV mode embedded in the OCTA device. The images of the MNV were made clearer by adjusting the slab from the outer nuclear layer to either the RPE or Bruch's membrane. As in previous studies, the enface images of the MNV were cropped using the open-source GNU Image Manipulation Program (GIMP, version 2.8.14) to segment the MNV and eliminate surrounding signals.[12]

After processing the OCTA images, all MNV images were analyzed by Angio tool with the threshold parameters of 30 and 255; vessel thickness 5; and removal of small particles 80.[13,14] The AngioTool semi-automatically delineates and obtains the following metrics: vessel area (Va) and junction densities (JD) which is the internal branching points of the vessels.

Va refers to the total area occupied by the vascular structures within the region. It represents the overall extent of neovascularization detected within the MNV lesion. JD represents the number of vessel junctions reflecting the complexity

and branching architecture of the vascular network. In AngioTool, these junctions are indicated as blue dots, and junction density refers to the density of these blue dots within the defined measurement area.

These parameters were measured at each visit in both the Aflibercept group and the Faricimab group (Figure 1).

Statistical Analyses

The descriptive data are presented as numbers, percentages, medians with the first and third quartiles (Q1, Q3), and the 95% confidence intervals (CIs) when appropriate. OCTA-derived metrics (vessel area and junction density) were reported as means ± standard deviations. Fisher's exact tests were used to compare the baseline factors between the Aflibercept and the Faricimab groups for the ages, the number of cases of dry macula, and subtypes. The Mann–Whitney's *U*-test was used to compare the ages. The changes of the Va and JD from the baseline was examined using Tukey's multiple comparison tests. All *P* values were two-sided, and $P < 0.05$ was taken to be statistically significant. All statistical analyses were performed using R version 2.9.0.

Results

The medical records of 443 patients were examined, and 12 eyes of 12 patients with a median age of 67 [59, 74] years that met the inclusion criteria were placed in the Aflibercept group. There were 14 eyes 14 patients with a median age of 75 [70.7, 77.5] years that met the inclusion criteria that were placed in the Faricimab group (Figure 2). There were no significant differences between the two groups in the baseline age, sex distribution, and subtypes of nAMD. Although the median age was higher in the Faricimab group (75 years) than in the Aflibercept group (67 years), the difference was not

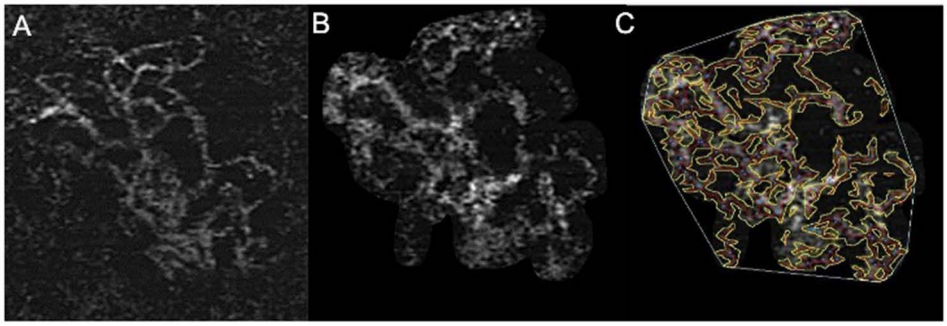

Figure 1 Fundus photographs and optical coherence tomography angiographic (OCTA) images of a patient with neovascular age-related macular degeneration. (**A**) En-face OCTA image of the MNV slab. (**B**) Manually segment the MNV and elimination of surrounding signals. (**C**) Images obtained from AngioTool analysis.

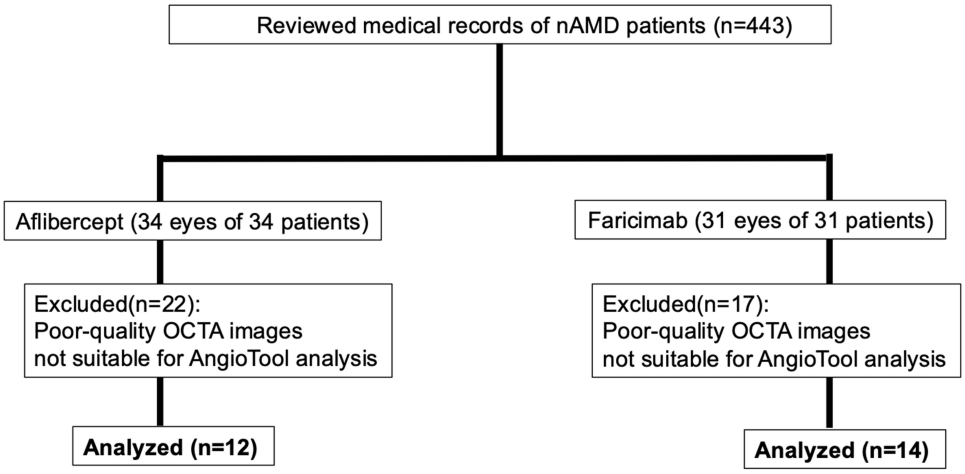

Figure 2 Flow chart showing the selection of patients with neovascular age-related macular degeneration (nAMD). Flow chart showing the selection of participants.
Abbreviation: nAMD, neovascular age-related macular degeneration.

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Table 1 Comparisons of Background Factors Between the Afribercept Group and Faricimab Group

	Aflibercept	Faricimab	P value
Sex (Male:Female)	12 (10:2)	14 (12:2)	0.67[+]
Age (Median)	67 [59, 74]	75 [70.7, 77.5]	0.07*
Subtype (type 1:type 2:type 3:PCV)	10:0:1:1	8:2:2:2	0.32[+]
Dry macula	11	11	0.56*

Notes: [+]Fisher's exact test; *Mann–Whitney's *U*-test.
Abbreviation: PCV, polypoidal choroidal vasculopathy.

statistically significant (P = 0.07). The number of cases that achieved a dry macula was 11 of 12 cases in the Aflibercept group and 11 of 14 cases in the Faricimab group ($P = 0.56$; Table 1).

In the Faricimab group, the average Va was 0.14 ± 0.10 mm^2 at the baseline (BL), 0.13 ± 0.05 mm^2 at 1 month (M), 0.13 ± 0.11 mm^2 at 2M, and 0.15 ± 0.16 mm^2 at 3M. The average values for the JD were 0.16 ± 0.10/mm at the BL, 0.17 ± 0.12/mm at 1M, 0.17 ± 0.13/mm at 2M, and 0.15 ± 0.1/mm at 3M. In the Aflibercept group, the average values of Va were 0.29 ± 0.26 mm^2 at the BL, 0.20 ± 0.18 mm^2 at 1M. 0.25 ± 0.17 mm^2 at 2M, and 0.20 ± 0.14 mm^2 at 3M. The mean values for the JD were 0.77 ± 0.26/mm at the BL, 0.93 ± 0.80/mm at 1M, 0.70 ± 0.39/mm at 2M, and 0.83 ± 0.6/mm at 3M. The differences in the Va and JD values were not significant for both the Aflibercept and Faricimab groups (all P > 0.05; Figures 3 and 4).

Discussion

We examined the structural changes of MNVs during the induction period of treatment for untreated nAMD and found no significant difference in the changes in the Va and the JD between the Aflibercept and Faricimab treated groups. We had hypothesized that the addition of the anti-VEGF will affect to the Ang2 inhibitory effect, a characteristic of Faricimab, and would then act on the VEGF-refractory MNVs. This would then result in a significant decrease in both the Va and the JD compared to Aflibercept. However, the results were not significantly different, and we rejected our hypothesis.

There are several possible reasons for this rejection. The first is the time of the progression of VEGF-independent angiogenesis mechanisms. Takeuchi et al reported that immediately after the start of the induction therapy, the Va and JD of the MNV are transiently decreased from that at the baseline, but at around 3 months after the first dose, the Va and JD

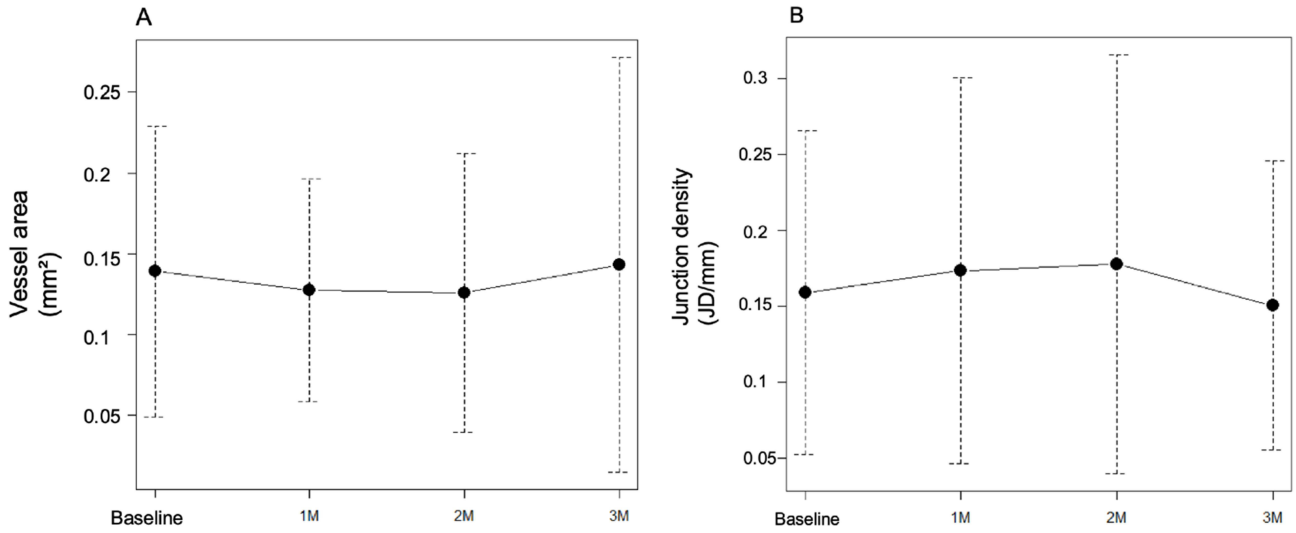

Figure 3 Mean changes in vessel area (mm^2) and junction density (JD/mm) from baseline in the Faricimab group. (**A**) Mean changes in vessel area (Va) from baseline. (**B**) Mean changes in junction density (JD) from baseline. There were no significant changes from baseline in Va or JD. Error bars represent standard deviations (SD).

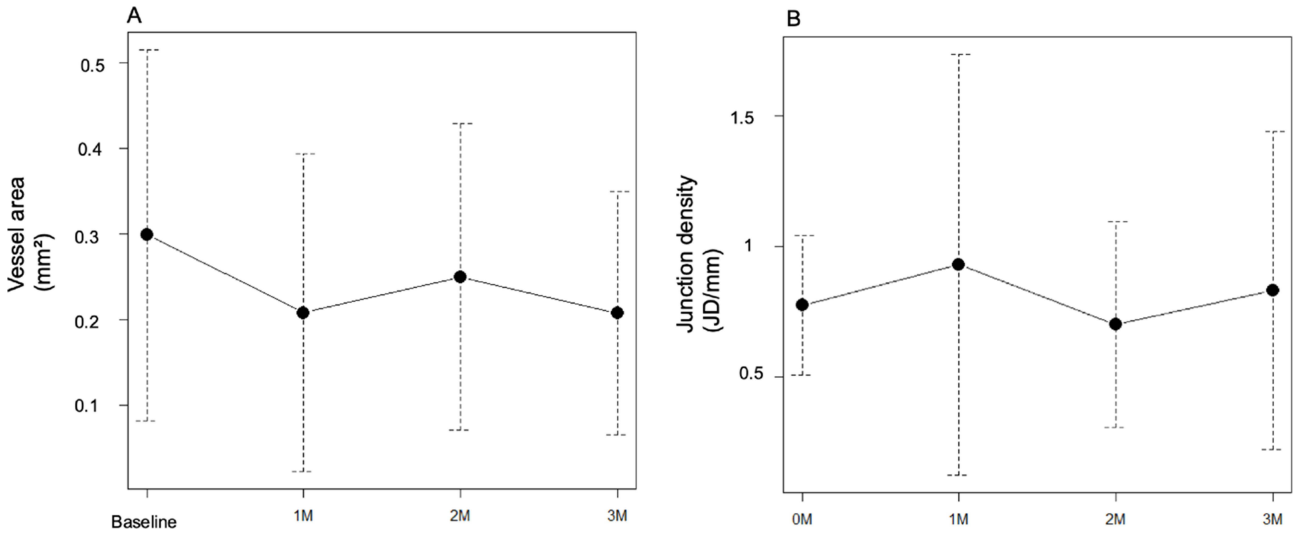

Figure 4 Mean changes in vessel area (mm^2) and junction density (JD/mm) from baseline in the Aflibercept group. (**A**) Mean changes in vessel area (Va) from baseline. (**B**) Mean changes in junction density (JD) from baseline. There were no significant changes from baseline in Va or JD. Error bars represent standard deviations (SD).

return to the baseline values.[8] In addition, Nakano et al reported that the mechanism of VEGF-independent angiogenesis may be initiated when the MNV is surrounded by pericytes.[10]

Based on this, we believe that immediately after the administration of the induction period, the MNV is not surrounded by pericytes, and the mechanism of VEGF-independent angiogenesis was not initiated. However, as the MNV is gradually surrounded by pericytes, VEGF-independent angiogenesis mechanisms are added at the end of the induction period. Thus, it is possible that the effect of the vascular stabilizing action of Faricimab will not be noticeable in the observation period examined in this study. Thus, it will be necessary to extend the observation period to examine this question in full.

The second reason is the possibility that the blocking effects of VEGF by Faricimab is less than that of Aflibercept. Aflibercept is then able to bind not only to VEGF with a greater affinity but also to other ligands, owing to the different domains that include VEGF-B, placental growth factor (PlGF), and galectin-1.[15–17]

Faricimab was designed with one antigen-binding site for VEGF and Ang-2, and it has an affinity equivalent to that of ranibizumab (3.3 vs 3.1 nM).[15,16] Thus, we considered the possibility that the effect of Faricimab on the MNVs in eyes with nAMD acts slowly including the loading phase. We suggest that this is the reason why there was no structural changes in the MNV in the induction period compared to aflibercept. In fact, according to Hara et al it was reported that Faricimab is slower than Aflibercept in improving visual acuity during the loading phase.[18]

However, according to the report by Fukuda et al, there is no significant difference in the visual acuity or central macular thickness between Faricimab and Aflibercept during the introduction period.[19] Furthermore, the results of the 2-year results of the TENAYA study (ClinicalTrials.gov identifier, NCT03823287) showed that Aflibercept was not inferior in terms of the degree of improvement of the corrected visual acuity 2 years after the initiation of the treatment compared to the baseline visual acuity.[20]

Thus, in the long-term, Faricimab was not inferior to Aflibercept due to the significant suppression of the vascular structure of MNV by the vascular stabilization effect which is a characteristic of Faricimab. To resolve this issue, further investigations are needed.

It has been stated that the Va and JD of MNVs would temporarily decrease and then rebound and increase but the results of this study did not confirm this. The dynamics of MNV when nAMD worsens may be a major factor in evaluating this trend. Choi et al reported that in nAMD, the vascular area temporarily increases before a fluid recurrence.[11] Thus, the results are likely to be affected by factors such as the duration of the subretinal fluid (SRF) during the observation period, and the number of cases that did not achieve a dry macula. However, both the previous

study and the present study had small sample sizes so the results may change depending on the timing of the achievement of dry macula and the number of cases. So, we suggest that it is necessary to conduct a study with a larger sample size.

Our results indicated that there was no significant difference in the structural changes of the MNV during the induction period between Faricimab and Aflibercept. However, the results may change if the observation period was extended, so further studies with an extended observation period are needed. We believe that with longer-term observation, the Ang-2 inhibitory effect of Faricimab may lead to stronger suppression of neovascular remodeling, resulting in a more significant reduction in Va and JD compared to other anti-VEGF agents.

Limitations

There are several limitations in this study. The first is the small sample size that was because this was a retrospective study, and many patients were excluded due to image quality issues, eg, the OCTA images of the MNV were not clear. As described in the Methods section, AngioTool cannot provide accurate quantification unless the MNV lesion is clearly delineated. Therefore, only cases in which the MNV was sufficiently visualized for reliable analysis were included, which resulted in a limited sample size. In future studies, increasing the number of cases or exploring alternative quantification tools will be considered.

The second limitation was the possibility of measurement errors. The measurements using AngioTool were determined by manually adjusting the parameters, which may have introduced variability. Therefore, in this study, we restricted our analysis to cases in which the MNV was clearly visualized and could be reliably quantified to minimize such errors. This restriction also contributed to the limited sample size.

The third limitation is that we were unable to examine each subtype. We would have preferred to classify and examine the samples according to whether they were derived from pachychoroid or drusen, but the small sample size made this not possible. In future studies, we aim to include a larger number of cases to address these limitations and to evaluate the relationships between OCTA-based vascular changes and retinal morphological features such as central macular thickness and SRF.

Conclusions

We determined the structural changes in the MNV after an initial intravitreal injection of Aflibercept or Faricimab in eyes with nAMD. The results showed there were no statistically significant changes with either drug. However, because the effects on the Faricimab characteristics may be reflected in the long-term, further studies with a longer observation period are needed.

Ethics Approval

The procedures used conformed to the tenets of the Declaration of Helsinki of the World Medical Association. All protocols were reviewed and approved by the Ethics Committee of Mie University Hospital (approval number H2021-088).

Consent to Participate

This retrospective study involved de-identified patient data, and the IRB of the Mie University Hospital approved to waive the written informed consent.

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Disclosure

All authors declare no competing interests in this work.

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