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CASE SERIES

Efficacy of Aflibercept (8 mg) for Diabetic Macular Edema in Vitrectomized Eyes Refractory to the Other Anti-VEGF Drug Therapies: A Report of Three Cases

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Introduction: To report the efficacy of aflibercept (8 mg) for diabetic macular edema (DME) in vitrectomized eyes refractory to other anti-VEGF drug therapies.

Case Presentations: This was a single-center retrospective case series. Three eyes with DME that developed after vitrectomy for diabetic vitreous hemorrhage were resistant to other anti-vascular endothelial growth factor (VEGF) drugs but improved with aflibercept (8 mg). Prior to treatment with aflibercept (8 mg), 2 eyes received multiple injections of faricimab and brolucizumab, and 1 eye received multiple injections of faricimab, but none of the 3 eyes showed morphological or functional improvement. Subsequently, aflibercept (8 mg) was administered, and a single dose of aflibercept resulted in marked improvement in all cases.

Conclusion: The efficacy of anti-VEGF therapy for DME in vitrectomized eyes is thought to be lower than that of DME in non-vitrectomized eyes. In this case, brolucizumab, which has a high anti-VEGF molar concentration, and faricimab, which has a low anti-VEGF molar concentration but anti-angiopoietin (Ang)-2 activity, were not effective, but aflibercept (8 mg), whose VEGF molar concentration was intermediate between the two, was effective. This may be due to the fact that aflibercept (8 mg) is a fusion protein rather than an antibody, has lower clearance than a small molecule like brolucizumab, and has a higher anti-VEGF molar concentration than faricimab. It is suggested that aflibercept (8 mg) may be effective for DME in vitrectomized eyes and may merit preferential administration in such cases.

Keywords: diabetic macular edema, anti-VEGF, aflibercept, vitrectomized, case series

Introduction

Anti-vascular endothelial growth factor (VEGF) agents have been the first choice of treatment for diabetic macular edema (DME).[1] Clinically, ranibizumab[2] and aflibercept[3] were approved as first-generation anti-VEGF agents for DME in the 2010s. In the 2020s, brolucizumab,[4] with its smaller molecular weight and higher molar concentration, and faricimab,[5] which combines an anti-VEGF antibody with an anti-Angiopoietin (Ang)-2 antibody, were introduced. With an increased range of drug choices, the question of which anti-VEGF drug should be chosen for DME patients remains debatable.

Aflibercept (8 mg) was developed by increasing the concentration of the conventional aflibercept (2 mg) formulation in the hope that it would allow for an increased dosage, thereby increasing the duration of efficacy.[6] A large-scale, multicenter, prospective study found that aflibercept (8 mg) can significantly prolong the maintenance interval, thus reducing the frequency of dosing, but also found no advantage over conventional agents of aflibercept (2 mg) in terms of improvement in visual outcomes or edema.[7]

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The clinical efficacy of anti-VEGF drugs for DME that develops in vitrectomized eyes is often diminished by the increased clearance of the drug into the eye.[8] However, it is unclear which drugs should be administered in these cases.

In this report, we describe three cases of DME after vitrectomy in which multiple doses of brolucizumab and/or faricimab were ineffective and were replaced with aflibercept (8 mg), which showed marked efficacy.

Case Report/Case Presentation

Case 1: The patient was a 59-year-old man had been developed DME with decreased vision in the left eye. He had undergone vitrectomy 2 months previously for vitreous hemorrhage associated with proliferative diabetic retinopathy (PDR). At that time, the best-corrected visual acuity (BCVA) of the left eye was 20/50, and the central macular thickness (CMT) was 636 µm (Figure 1a). First, a total of 5 consecutive monthly doses of faricimab (6.0 mg/0.05 mL) was injected intravitreally; however, the BCVA and CMT changed to 30/100 and 571 µm, respectively, which did not amount to a significant improvement (Figure 1b). Subsequently, a total of 6 consecutive monthly doses brolucizumab (6.0 mg/0.05 mL) was injected intravitreally, but not sufficiently effective for DME, with BCVA remaining 30/100 and CMT increasing to 635 µm (Figure 1c). The intravitreal injection of aflibercept (8 mg/0.07 mL) was performed, and 1 month after the initial injection, DME dramatically regressed with improvement in BCVA (20/50) and CMT (354 µm) (Figure 1d). Two additional monthly injections of aflibercept (8 mg) were administered, and BCVA and CMT at 1

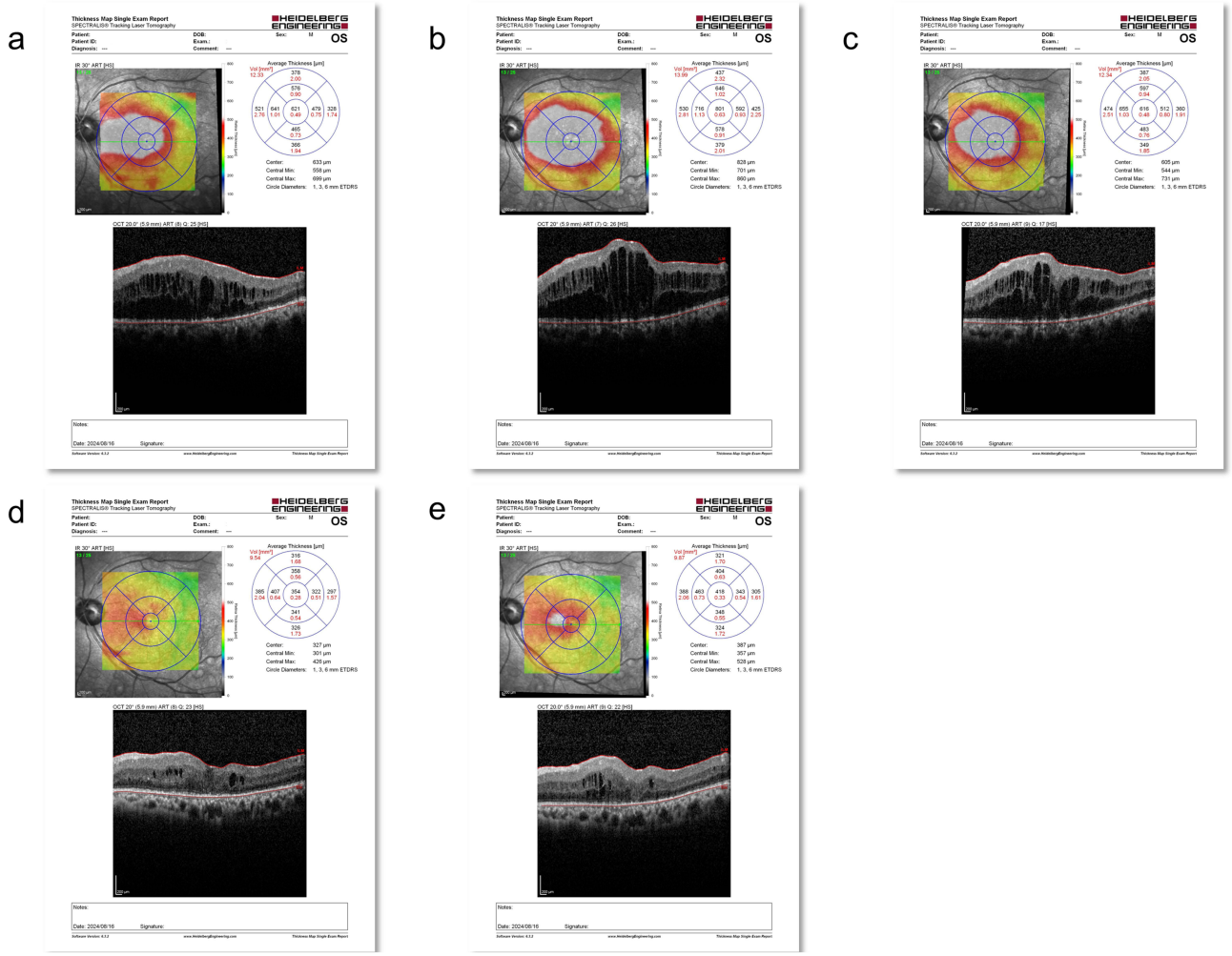

Figure 1 Case 1. Alteration of optical coherence tomography image (upper right: color map, upper left: average thickness map, lower: longitudinal image) at baseline (**a**), 1 month after the last injection of 5 consecutive monthly doses of faricimab (**b**), 1 month after the last injection of 6 consecutive monthly doses of brolucizumab (**c**), and 1 month after the initial injection of 8 mg aflibercept (**d**), and 1 month after the last injection of 3 consecutive monthly doses of aflibercept (8 mg) (**e**).

month after the last injection were 20/50 and 387 µm, respectively (Figure 1e). Systemic treatment for diabetes was provided using oral medications, and no changes in the drug regimen were reported during the clinical course of the disease.

Case 2: The patient was a 65-year-old man had developed DME in the right eye. He had undergone vitrectomy 2 months previously for vitreous hemorrhage associated with PDR. At that time, the BCVA of the right eye was 40/50 and CMT was 526 µm (Figure 2a). First, a total of 2 consecutive monthly doses of brolucizumab (6.0 mg/0.05 mL) were administered, but macular edema remained, and his BCVA and CMT changed to 90/100 and 540 µm, respectively (Figure 2b). Subsequently, faricimab (6.0 mg/0.05 mL) was injected intravitreally once, but did not have a sufficient inhibitory effect on macular edema with BCVA and CMT of 40/50 and 515 µm, respectively (Figure 2c). Then, we switched to aflibercept (8 mg/0.07 mL, intravitreally). One month after the initial injection, remarkable suppression of the DME was observed, with improvement in BCVA (60/50) and CMT (346 µm) (Figure 2d). Two additional monthly injections of aflibercept (8 mg) were administered and his BCVA and CMT were maintained at 60/50 and 383 µm, respectively (Figure 2e). Systemic treatment for diabetes was provided using oral medications, and no changes in the drug regimen were reported during the clinical course of the disease.

Case 3: The patient was a 58-year-old woman who had developed DME in her left eye. She had undergone vitrectomy for PDR 1 month previously. At that time, the BCVA of her left eye was 70/100, and the CMT was 532 µm (Figure 3a). First, a total of 13 consecutive monthly doses of faricimab (6.0 mg/0.05 mL) were administered, but macular edema

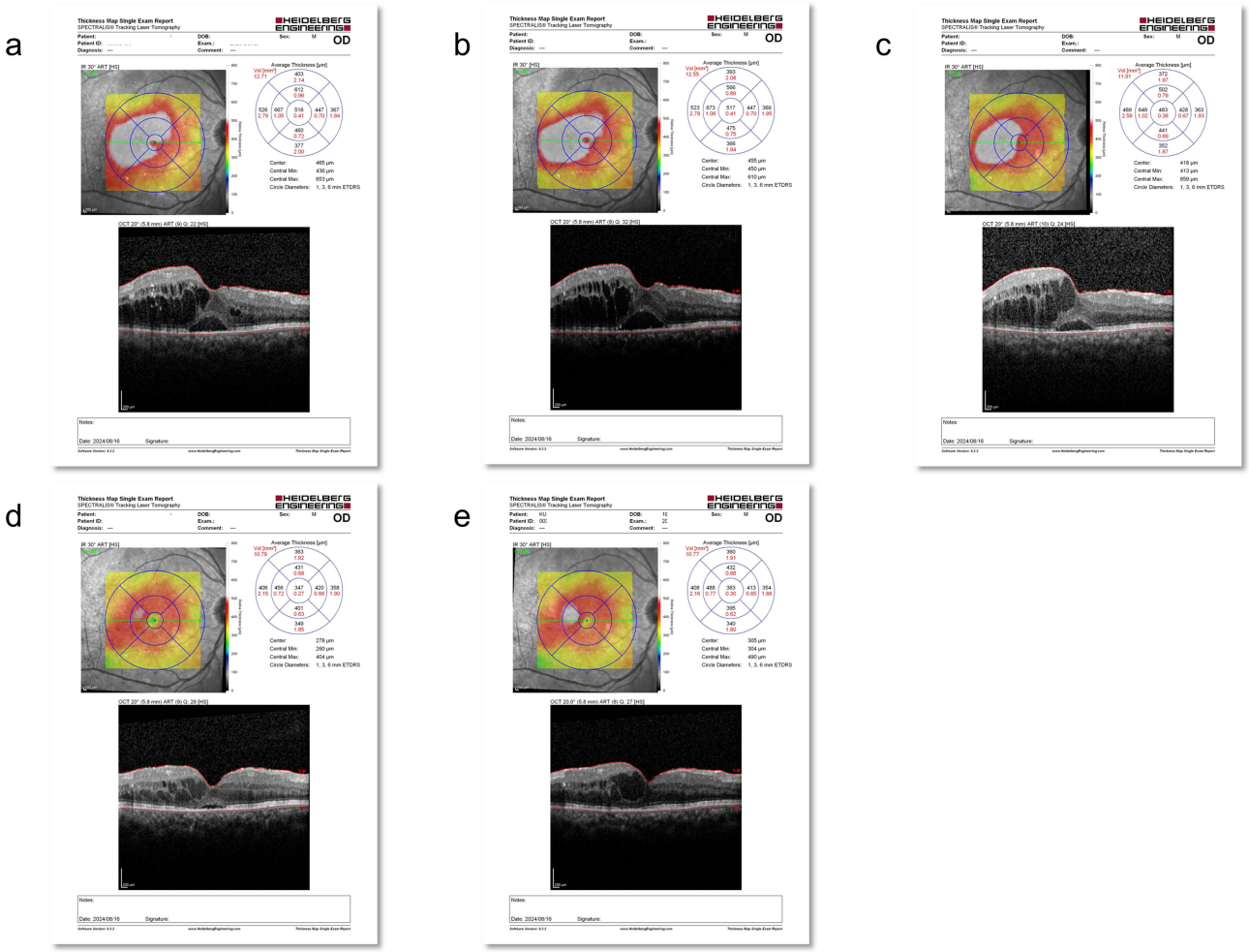

Figure 2 Case 2. Alteration of optical coherence tomography image (upper right: color map, upper left: average thickness map, lower: longitudinal image) at baseline (**a**), 1 month after the last injection of 2 consecutive monthly doses of brolucizumab (**b**), 1 month after the last injection of initial dose of faricimab (**c**), and 1 month after the initial injection of aflibercept (8 mg) (**d**), and 1 month after the last injection of 3 consecutive monthly doses of aflibercept (8 mg) (**e**).

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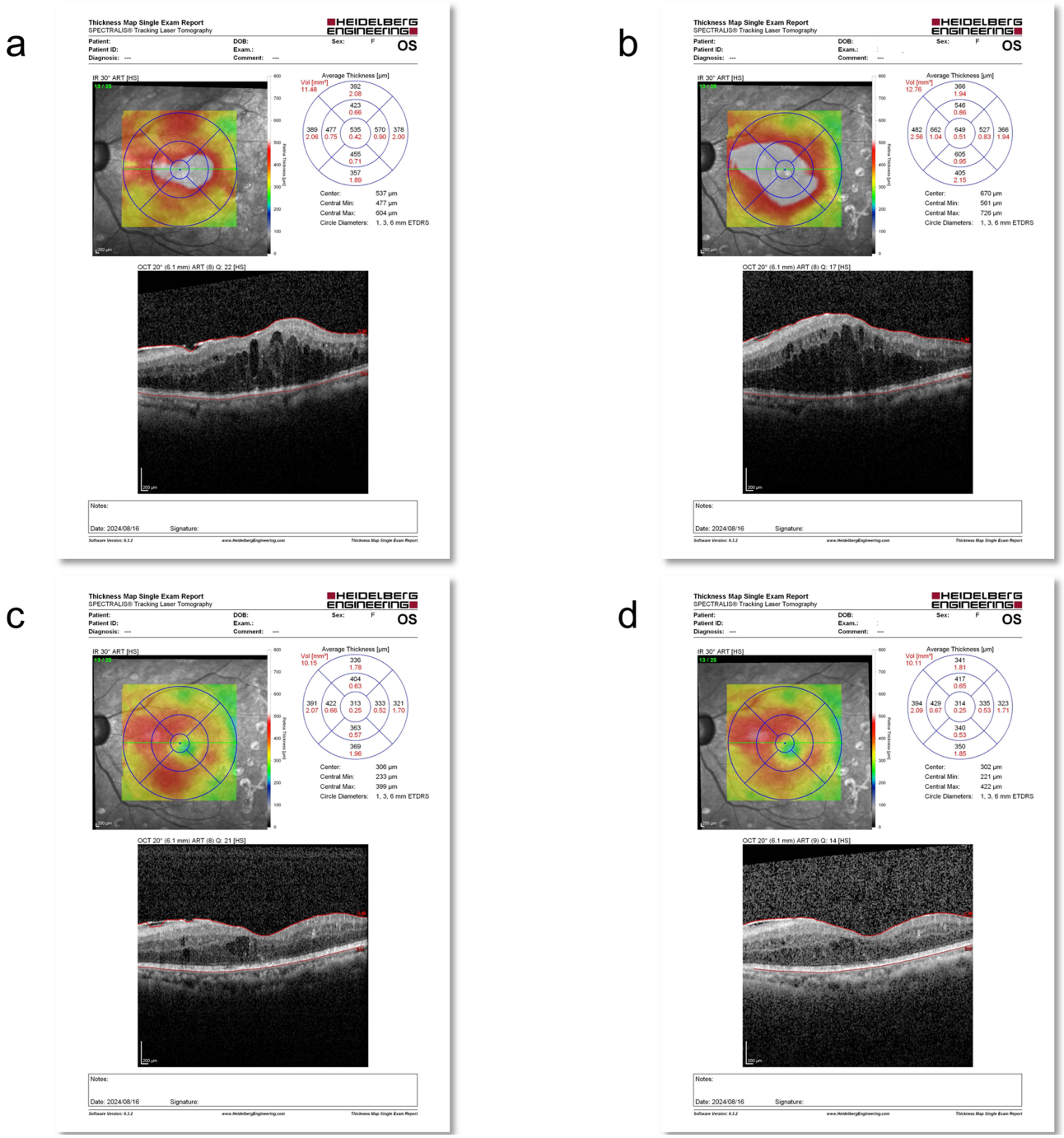

Figure 3 Case 3. Alteration of optical coherence tomography image (upper right: color map, upper left: average thickness map, lower: longitudinal image) at baseline (**a**), 1 month after the last injection of 13 consecutive monthly doses of faricimab (**b**), and 1 month after the initial injection of aflibercept (8 mg) (**c**), and 1 month after the last injection of 3 consecutive monthly doses of aflibercept (8 mg) (**d**).

remained, and the BCVA and CMT worsened to 20/50 and 649 µm, respectively (Figure 3b). Then, we switched to aflibercept (8 mg/0.07 mL, intravitreally). One month after the initial injection, remarkable suppression of DME was observed, with improvement in BCVA (30/50) and CMT (313 µm) (Figure 3c). Two additional monthly injections of aflibercept (8 mg) were administered, and BCVA and CMT at 1 month after the last injection improved to 70/100 and 314 µm, respectively (Figure 3d). Systemic treatment for diabetes was provided using oral medications, and no changes in the drug regimen were reported during the clinical course of the disease.

Discussion

In this case series, all patients had DME that developed after vitrectomy, in which multiple doses of brolucizumab or faricimab did not improve edema or vision, but aflibercept (8 mg) improved prominent edema. It is important to note that the efficacy of anti-VEGF drugs is usually judged by the state of macular edema at 1 month after administration and may not necessarily reflect the best state of the patient after administration. It is possible that the longer duration of action, rather than the pharmacological effect itself, caused the observed outcome. However, since the dosing interval of anti-VEGF agents is clinically limited to 1 month or longer, it seems reasonable to judge efficacy at the time point of 1 month after administration.

Generally, the efficacy of anti-VEGF drugs is thought to be reduced in vitrectomized eyes. Although definitive evidence exists, it is speculated that this is because removal of the vitreous affects the pharmacokinetics of the drug in the vitreous and increases the rate of decrease in drug concentration owing to increased clearance in the eye.[9] Therefore, attempts have been made to prolong the effects of anti-VEGF drugs by increasing the frequency of intravitreal administration, increasing the dosage, and selecting higher drug concentrations.[10]

Brolucizumab is a single-chain antibody fragment with a relatively low molecular weight of 26 kD and high affinity for VEGF. This allows a higher amount of drug to be delivered per injection compared to other anti-VEGF drugs, which is expected to result in effective tissue penetration and prolonged duration of action.[11] The clinical single dose of brolucizumab is 6.0 mg/0.05 mL, and the molar concentration administered is calculated to be 4615.5 nM.

Faricimab is a bispecific antibody with high affinity for both VEGF-A and Ang-2, with a molecular weight of 149 kD. The crystallizable fragment (Fc) region is designed to be easily metabolized in vivo, reducing Fc-mediated complications.[6] A single dose of faricimab is 6.0 mg/0.05 mL, and the molar concentration administered is calculated to be 805.4 nM.

Aflibercept is a fusion protein with a molecular weight of 115 kD and is a decoy VEGF receptor, fusing the major domains of human VEGF receptors 1 and 2 with the Fc domain of human immunoglobulin G1.[12] The aflibercept (8 mg) formulation is a higher concentration of conventional aflibercept (2 mg) and is expected to provide greater efficacy and prolonged duration of efficacy when administered in larger doses at one time.[13] The clinical single dose of aflibercept (8 mg) is 8.0 mg/0.07 mL, and the molar concentration administered is calculated to be 993.8 nM.

According to the calculated molar concentrations of each drug, the concentration of aflibercept (993.8 nM) was between brolucizumab (4615.5 nM) and faricimab (805.4 nM), and its molecular weight (115 kDa) was also between faricimab (149 kDa) and brolucizumab (26 kDa); thus, the reason why aflibercept (8 mg) was more effective than the other 2 drugs for DME in vitrectomized eyes was not due to differences in molar concentration or molecular weight. However, the total dosage volume of aflibercept (8 mg) was higher than that of the other 2 drugs (6.0 mg each).

Also, both brolucizumab and faricimab are antibodies, whereas aflibercept is a fusion protein; therefore, the formulations of the drugs are different. Unlike the other two anti-VEGF drugs of brolucizumab and faricimab, aflibercept traps not only VEGF but also placenta growth factor (PlGF)-1 which activates VEGF receptor-1,[14] and it may be contributing to improved efficacy to vitrectomized DME.

Another possible explanation for this is tachyphylaxis and/or tolerance.[15] Although the possibility of tachyphylaxis/tolerance to the antibody cannot be ruled out, it seems unlikely because neither brolucizumab nor faricimab were effective from the first dose in DME in vitrectomized eyes.

Although there are previous reports that aflibercept (2 mg) was also effective in vitrectomized DME eyes, no comparison with other agents has been made,[16] and to the best of our knowledge, there are no reports of aflibercept (2 mg) being more effective than other anti-VEGF agents in vitrectomized DME eyes. While, for DME in non-vitrectomized eyes, a comparative study of the efficacy of 2 mg and 8 mg doses of aflibercept reported no significant difference in either functional improvement or morphological regression.[7] The efficacy of aflibercept (8 mg) may be more pronounced in eyes with vitrectomized DME.

In view of the above, aflibercept (8 mg) may have demonstrated efficacy in DME in non-vitreous eyes owing to the combined effects of its non-antibody formulation and relatively high dosage. Although our case reports were retrospective and the number of cases was limited, it seems worthwhile to conduct a large prospective comparative study of

aflibercept (8 mg) versus other anti-VEGF agents, including aflibercept (2 mg), for DME in vitrectomized eyes in the future.

Of course, there is also the option of steroids for DME which is not responsive to anti-VEGF drugs. Although not approved in Japan, it is known that the intravitreal implant of steroid (dexamethasone) showed the same efficacy in both vitrectomized and non-vitrectomized DME eye.[17] In Japan, it is common to administer steroids (triamcinolone) locally with sub-tenon injection,[18] but it would also be interesting to compare this with local steroid administration based on this report.

In our case series, we showed an improvement in DME in vitrectomized eyes after the intraocular administration of aflibercept (8 mg). It is currently unclear why aflibercept (8 mg) was effective for DME in vitrectomized eyes, while brolucizumab, which has anti-VEGF activity at high molar concentrations, and faricimab, which has both anti-VEGF and anti-Ang-2 activities, were both ineffective. Our report suggests that the newly approved aflibercept (8 mg) is worth trying when DME in vitrectomized eyes is resistant to conventional anti-VEGF treatment.

Data Sharing Statement

Original data were recorded and kept in the medical records in the Tokyo Medical University Hospital. Any inquiries about the data dealt with in this study should be made by the corresponding author.

Statement of Ethics

Written informed consent has been provided by the patients to have the case details and any accompanying images published.

Ethical approval is not required for this study according to the guidelines, and institutional approval was not required to publish the case details.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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