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Two cases of diabetic macular edema with diminished areas of retinal non-perfusion and microaneurysms after intravitreal faricimab injections

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ABSTRACT

Purpose: To report two cases of diabetic macular edema (DME) treated with intravitreal faricimab injections (IVFs), including the assessment of retinal microaneurysms and extent of retinal capillary non-perfusion using fluorescein angiography (FA) and indocyanine green angiography (IA).

Observations: Case 1: A 72-year-old man presented with aflibercept-resistant DME in the left eye, with a best-corrected visual acuity (BCVA) of 20/16. FA showed areas of retinal capillary non-perfusion and focal leakage in the macular area of the left eye. IA revealed numerous microaneurysms in the temporal region of the macula. Four consecutive monthly IVFs were administered to the left eye, and DME eventually diminished. After the loading phase, the BCVA was maintained at 20/16 with reduced visual distortion. FA showed improvement of macular leakage and stable retinal capillary non-perfusion areas, and the foveal avascular zone was clearly observed. The disappearance of numerous microaneurysms was confirmed on IA images.

Case 2: An 80-year-old woman developed DME with macular vein occlusion in the left eye after panretinal laser photocoagulation for proliferative diabetic retinopathy. The patient's BCVA was 20/32. DME was resistant to subtenon triamcinolone injections. FA revealed focal areas of retinal capillary non-perfusion and persistent leakage in the macular area of the left eye. IA revealed scattered microaneurysms within the retinal arcade. Four consecutive monthly IVFs were administered to the left eye, and DME eventually diminished. After the loading phase, the BCVA was maintained at 20/32. FA showed improvement of macular leakage and stable retinal capillary non-perfusion areas. The reduction of microaneurysms was confirmed on IA images.

Conclusions and importance: These case reports highlight the potential of faricimab as an alternative anti-vascular endothelial growth factor drug for treatment-resistant DME, including reduction of retinal microaneurysms and stabilization of the areas of retinal capillary non-perfusion. However, continuation of a robust treatment regimen may be required to achieve these objectives.

1. Introduction

Diabetic macular edema (DME) is responsible for vision loss in patients with diabetes mellitus.

It has been approximately 20 years since anti-vascular endothelial growth factor (VEGF) drugs became the standard of care for the treatment of DME. Faricimab (Roche/Genentech, Basel, Switzerland), a novel anti-VEGF agent, was approved in Japan in 2022 for treating DME.[1] Faricimab is a bispecific antibody directed simultaneously against VEGF and angiopoietin-2 (Ang2); the inhibition of Ang2 stabilizes the loss of pericytes by different mechanisms as compared to other anti-VEGF agents.[2]

Visual acuity measurements, and anatomical and morphological examinations using optical coherence tomography (OCT) are common in clinical trials and practice to assess the effectiveness of anti-VEGF therapy for DME. Fluorescein angiography (FA) has been the gold standard for several decades to assess the inner blood-retinal barrier and pericyte function in diabetic retinopathy.[3] DME often originates from microaneurysms, and indocyanine green angiography (IA) is useful for visualizing the microaneurysms resistant to anti-VEGF therapy.[4]

The use of FA and IA has not been extensively studied with respect to faricimab. Herein, we report two cases of DME treated with four doses of monthly faricimab injections and assessed using FA and IA to investigate changes in the retinal leakage, microaneurysms, and areas of retinal capillary non-perfusion.

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2. Findings

2.1. Case 1

A male patient's first visit to our hospital was in 2015 to treat DME in the left eye at the age of 65 years. He was diagnosed with diabetes mellitus twenty years ago. Best-corrected visual acuity (BCVA) was 20/25 OS. Focal DME associated with perifoveal microaneurysms in the left eye was treated with direct focal laser photocoagulation, and resolved two months later. In 2016, hemodialysis was initiated due to renal dysfunction. In 2018, the patient visited our hospital again to treat recurrent DME in the left eye with severe visual distortion. BCVA was 20/32 OS. Three consecutive monthly intravitreal aflibercept injections (IVAs) were administered to the left eye, and DME was resolved. Cataract surgery was performed in 2019 with improvement of the BCVA to 20/20 OS; however, DME recurred in the left eye a few months later. Then, IVA was performed bimonthly. DME responded to the IVAs within 1 year. However, it became IVA-resistant and treatment was discontinued after a total of 12 injections. In 2022, DME deteriorated 5 months after the last IVA, and the patient claimed severe visual distortion. BCVA was 20/16 OS. FA showed areas of retinal capillary non-perfusion and retinal leakage from numerous microaneurysms in the macular area (Fig. 1A–C). IA revealed more microaneurysms than FA (Fig. 2A). Four consecutive monthly intravitreal faricimab injections (IVFs) were administered to the left eye. Sequential OCT revealed a gradual decrease in DME (Fig. 3). After the loading phase, BCVA was 20/16 OS and the visual distortion almost disappeared. FA and IA were performed again to assess DME status. Retinal leakage was improved and the areas of retinal capillary non-perfusion appeared to be stabilized in FA image (Fig. 1D–F). In addition, the foveal avascular zone was clearly observed (Fig. 1E). IA also showed almost complete disappearance of the microaneurysms (Fig. 2B). Four months later, DME recurred and promptly resolved upon additional IVF treatment.

2.2. Case 2

An 80-year-old woman visited our hospital in July 2022 to treat DME with macular vein occlusion in the left eye. At the referral hospital before visiting our hospital, panretinal photocoagulation was performed in the left eye with proliferative diabetic retinopathy, and cataract surgery was performed in 2013. Macular edema appeared in the left eye in 2021; subsequently, subtenon triamcinolone injections was administered twice.

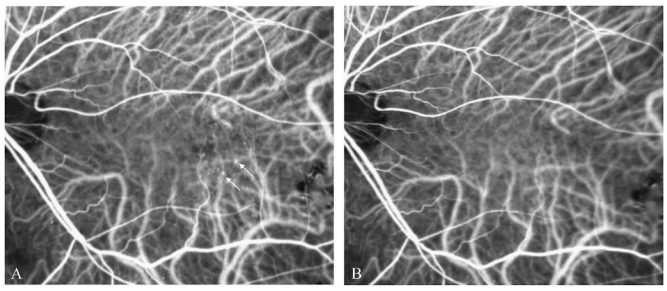

Fig. 2. Case 1. (A) The early phase of indocyanine angiography (IA) (1 min) at baseline showing numerous microaneurysms (arrows), predominantly seen in temporal in the macular area. (B) The early phase of IA (58 s) after the loading phase showing the disappearance of microaneurysms in the macular area.

At the first visit to our hospital, BCVA was 20/32 OS. DME dominated by intraretinal fluid was observed in the left eye (Fig. 4A). FA showed focal areas of retinal capillary non-perfusion and retinal leakage in the macular area (Fig. 5A–C). IA showed numerous microaneurysms in the macular area (Fig. 6A). Four consecutive monthly IVFs were administered to the left eye. After the second IVF, DME partially resolved (Fig. 4B–E). After the loading phase, the BCVA was 20/32 OS. Retinal leakage improvement and decreased areas of retinal capillary non-perfusion were observed in post-IVF FA image (Fig. 5D–F). IA showed reduction in the number of microaneurysms (Fig. 6B). Five months later, DME recurred and promptly resolved upon additional IVF treatment.

3. Discussion

We described two cases of treatment-resistant DME treated with IVF and assessed by FA and IA before and after the loading phase. OCT

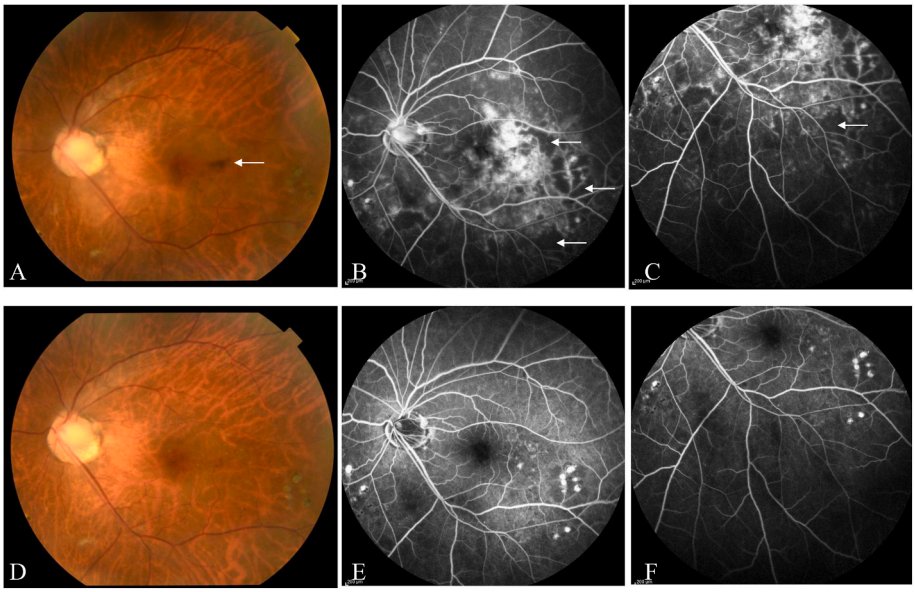

Fig. 1. Case 1. (A) Color fundus photography at baseline showing retinal hemorrhage (arrow) in the macular area. (B, C) The middle phase of fluorescein angiography (FA) (B: 5 min 42 s, C: 2 min 57 s) at baseline showing retinal leakage and areas of retinal capillary non-perfusion (arrows). (D) Color fundus photography after the loading phase showing the disappearance of retinal hemorrhage in the macular area. (E, F) The middle phase of FA (E: 4 min 34 s, F: 3 min 52 s) showing the resolution of retinal leakage and stability in areas of retinal capillary non-perfusion. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

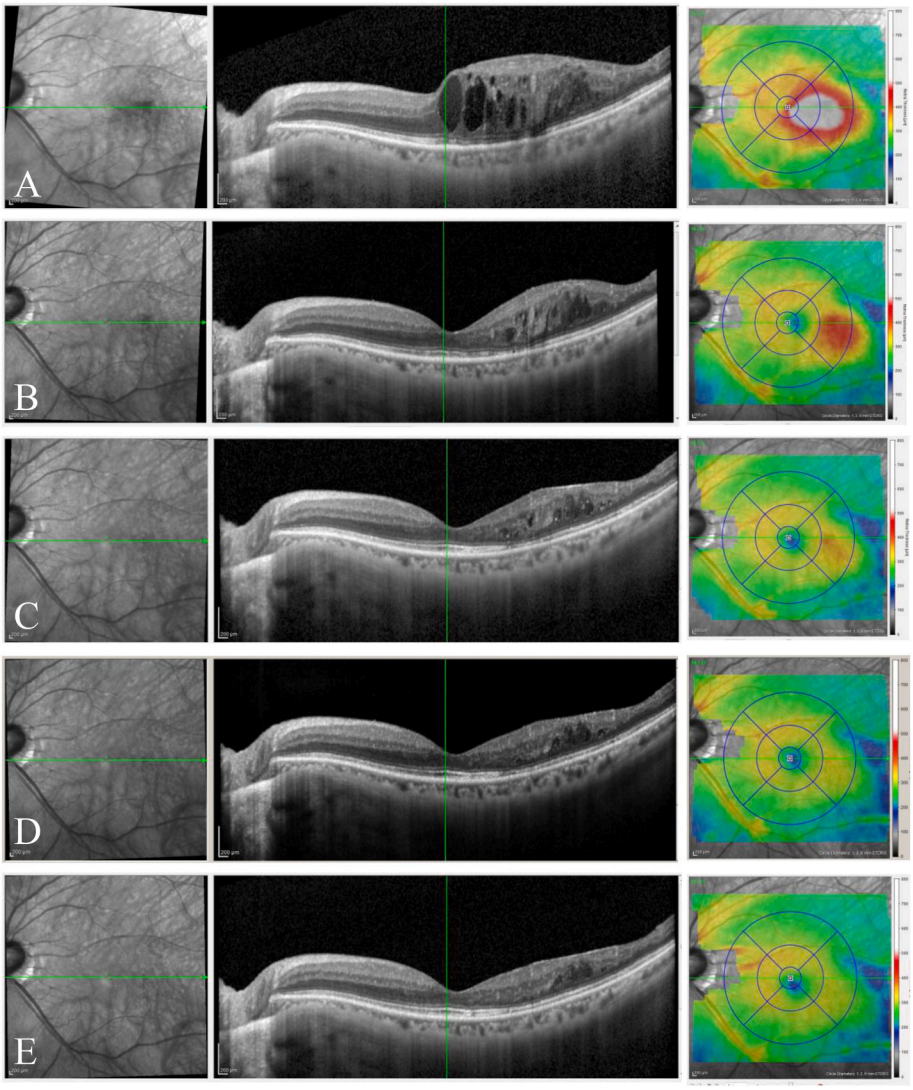

Fig. 3. Case 1. Horizontal section and maps on optical coherence tomography (OCT) at (A) baseline, (B) 1 month, (C) 2 months, (D) 3 months, and (E) 4 months. Sequential OCT images showing gradual reduction in diabetic macular edema.

images showed the gradual disappearance of DME following sequential IVFs. After four consecutive monthly injections, FA showed resolution of the macular leakage and the areas of retinal capillary non-perfusion appeared to have stabilized. The foveal avascular zone became more visible in Case 1. Moreover, IA revealed the disappearance of numerous microaneurysms in both cases.

In these two cases, DME gradually decreased on sequential OCT images following consecutive monthly injections, and the short-term effectiveness of faricimab in DME was confirmed by anatomical assessment. However, the BCVA remained unchanged throughout the loading phase. In the clinical trials of faricimab for DME in the YOSEMITE and RHINE studies with over 80% treatment-naïve participants, BCVA increased by approximately 10 letters from the baseline after the loading phase in the faricimab group.[5] In our two cases, improvement of visual acuity was limited probably owing to the high pre-treatment BCVA. The chief complaint in Case 1 was visual distortion, which disappeared after switching from aflibercept to faricimab. Slow decreases in DME and long-standing dry macula may contribute to ameliorating visual distortion.

In the FA images corresponding to the time frame of pre- and post-IVF, the resolution of retinal leakage following faricimab administration was remarkable. In addition, the areas of retinal capillary non-perfusion appeared to be stabilized after four consecutive IVFs in the loading phase. Retinal reperfusion in diabetic retinopathy following other anti-VEGF therapies, including ranibizumab or aflibercept, has been investigated in some studies.[6,7] In contrast to other anti-VEGF agents, faricimab has a potential to promote vascular stability by inhibiting Ang2.[8] However, information about retinal reperfusion after IVF is lacking. Reperfusion depends on the severity of retinal tissue ischemia. In our limited series of cases with retinal vessel dysfunction due to a long history of diabetes mellitus, faricimab had a potential to induce retinal reperfusion.

In addition, the disappearance of numerous microaneurysms was confirmed on IA images. Pericyte loss is noted in microaneurysms.[9] It is well established that DME results from microaneurysms that occur in the retina's blood vessels, leading to fluid accumulation within the macula. A previous study revealed that IA-stained microaneurysms are refractory to anti-VEGF therapy (ranibizumab and aflibercept)[10]; direct laser photocoagulation was expected to be the next treatment option. However, laser photocoagulation for microaneurysms close to the fovea is associated with the risk of sudden scotoma. Based on the present case series, faricimab may be preferable to treat IA-stained microaneurysms near the fovea.

DME and diabetic retinopathy exemplify the role of Ang2 in stimulating pericyte loss.[8] Data from clinical trials of faricimab have shown that dual Ang2/VEGF-A pathway inhibition may stabilize

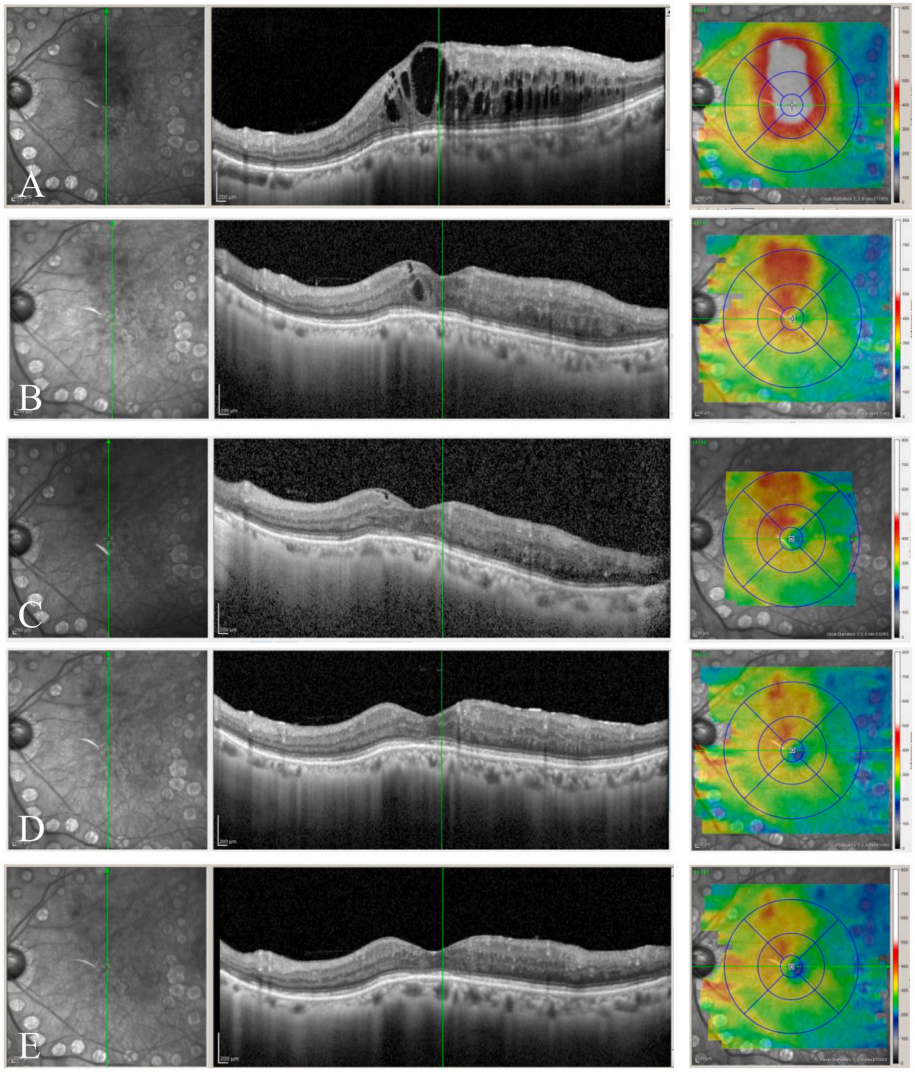

Fig. 4. Case 2. Vertical section and maps on optical coherence tomography (OCT) at (A) baseline, (B) 1 month, (C) 2 months, (D) 3 months, and (E) 4 months. Sequential OCT images showing gradual reduction in diabetic macular edema.

microaneurysms and extend treatment durability for DME.[1] In our two limited cases, dry macula was maintained for at least 4 months (4 months in Case 1 and 5 months in Case 2) after the final IVF of the loading phase in treatment-resistant DME. In order to prove the long-term durability of faricimab, more studies are needed to elucidate its benefit.

This case report has a limitation that assessment of retinal leakage in the FA images without such intense leakage after IVF might potentially give the false impression of a substantial reduction in the areas of retinal capillary non-perfusion after the treatment.

4. Conclusions

These two case reports highlight the advantage of faricimab in promoting stabilization of the blood-retinal barrier in recalcitrant DME owing to its bispecific antibody mechanism. Further study of faricimab on DME with a much more robust sample size is warranted to confirm the observations made in our study.

Patient consent

The patients' legal guardians orally consented to the publication of the cases. This report does not contain any personal information that could lead to the identification of the patients.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

CRediT authorship contribution statement

Miki Sawa: Conceptualization, Data curation, Writing – original draft, Investigation, Supervision. **Norihiko Nakagawa:** Writing – review & editing. **Takuya Shunto:** Data curation, Formal analysis. **Issei Nishiyama:** Data curation, Formal analysis.

Declaration of generative AI and AI-assisted technologies in the writing process

None.

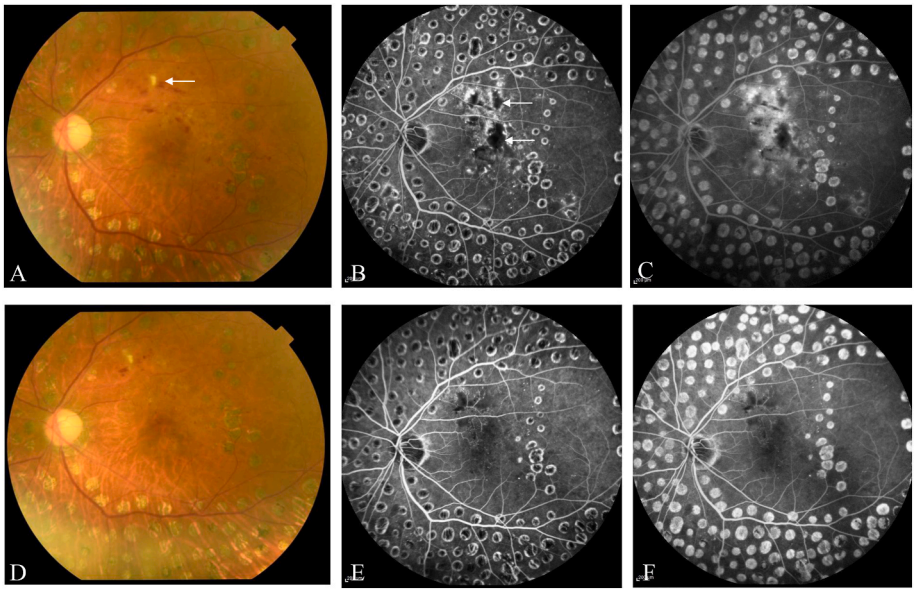

Fig. 5. Case 2. (A) Color fundus photography at baseline showing retinal hemorrhage and cotton wool spots (arrow). At baseline, the early (B: 58 s) and late phase (C: 11 min 1 s) of fluorescein angiography (FA) showing retinal leakage and areas of retinal capillary non-perfusion (arrows). (D) Color fundus photography after the loading phase (at 4 months) showing decreased retinal hemorrhage and the remaining cotton wool spot in the macular area. (E, F) The early (E: 1 min 1 s) and late phase (F: 10 min 16 s) of FA showing the resolution of retinal leakage and stability in areas of retinal capillary non-perfusion. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

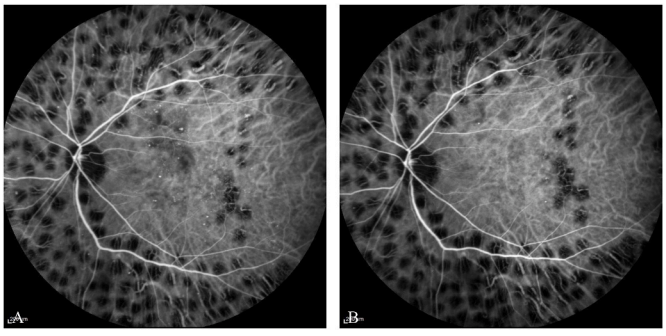

Fig. 6. Case 2. (A) The middle phase of indocyanine angiography (IA) (5 min 25 s) at baseline showing numerous microaneurysms, predominantly superior in the macular area. (B) The middle phase of IA (5 min 47 s) after the loading phase showing reduction of microaneurysms in the macular area.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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