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Faricimab as Treatment for Sarcoid Uveitis With Refractory Cystoid Macular Edema

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Abstract

Purpose: To describe the first use of the bispecific monoclonal antibody faricimab for sarcoid uveitis with refractory cystoid macular edema (CME). **Methods:** A single case was evaluated. **Results:** An 82-year-old woman presented with blurred vision and signs of sarcoid uveitis bilaterally, including swollen optic discs with disc nodules, CME with chorioretinal peripheral lesions in the right eye and segmental periphlebitis in the left eye. Treatment with intravitreal faricimab was initiated after systemic and topical prednisolone and oral ibuprofen failed. Significant improvement in the patient's best-corrected visual acuity and central subfield thickness was seen after 2 faricimab injections. Optical coherence tomography showed resolution of the intraretinal cyst and CME. Color fundus photography also showed improvement in the optic disc swelling and resolution of the retinal macroaneurysm. **Conclusions:** Faricimab can be a promising treatment for refractory CME in patients with sarcoid uveitis.

Keywords

faricimab, sarcoid uveitis, sarcoidosis, panuveitis, cystoid macular edema

Introduction

Sarcoidosis is a granulomatous systemic inflammatory disease characterized by the formation of noncaseating granulomas in organs including the lungs, lymph nodes, skin, and eyes. Ocular symptoms of sarcoidosis, often preceding other systemic presentations by months, represent a leading cause of low visual acuity (VA) and blindness in affected patients.[1]

The most common ocular manifestation of sarcoidosis is uveitis, which is the presenting feature in 60% to 80% of cases.[2] Sarcoid uveitis is characterized by panuveitis, a generalized inflammation of all uveal layers, including the iris, ciliary body, and choroid. Common signs include multiple chorioretinal peripheral lesions, nodular or segmental periphlebitis (with or without candle-wax drippings) or retinal macroaneurysm, optic disc nodules, and solitary choroidal nodules.[3,4] Because more than three quarters of cases manifest solely as uveitis,[5] a diagnosis of sarcoidosis is often overlooked and is considered only when subjects present with other systemic manifestations.[6]

Cystoid macular edema (CME) is a leading cause of vision loss in uveitis.[7] The release of vascular endothelial growth factor (VEGF) and other inflammatory mediators contributes to the pathogenesis of ME in uveitis.[8] Leakage from the retinal capillaries caused by the disruption of the blood–retinal barrier leads to thickening of the macular region. Current treatment options for uveitis and its related complications involve corticosteroids, nonsteroidal anti-inflammatory drugs, and anti-VEGF injections.[9,10] In some patients, however, the disease appears refractory to all treatments. Therefore, additional options for disease management are needed.

Faricimab (Vabysmo, Roche/Genentech) was recently developed for the treatment of neovascular age-related macular degeneration and diabetic ME.[11] It is a bispecific monoclonal antibody with a dual mechanism of action, simultaneously targeting VEGF and angiopoietin 2 (Ang2). Previous studies establishing connections between VEGF, Ang2, and inflamed vasculatures[12–14] underscore the dual therapeutic roles of faricimab as a potential resolution for refractory retinal and choroidal inflammation.

Case Report

An 82-year-old woman presented with a 3-month history of blurred vision. Her medical history included hypertension and

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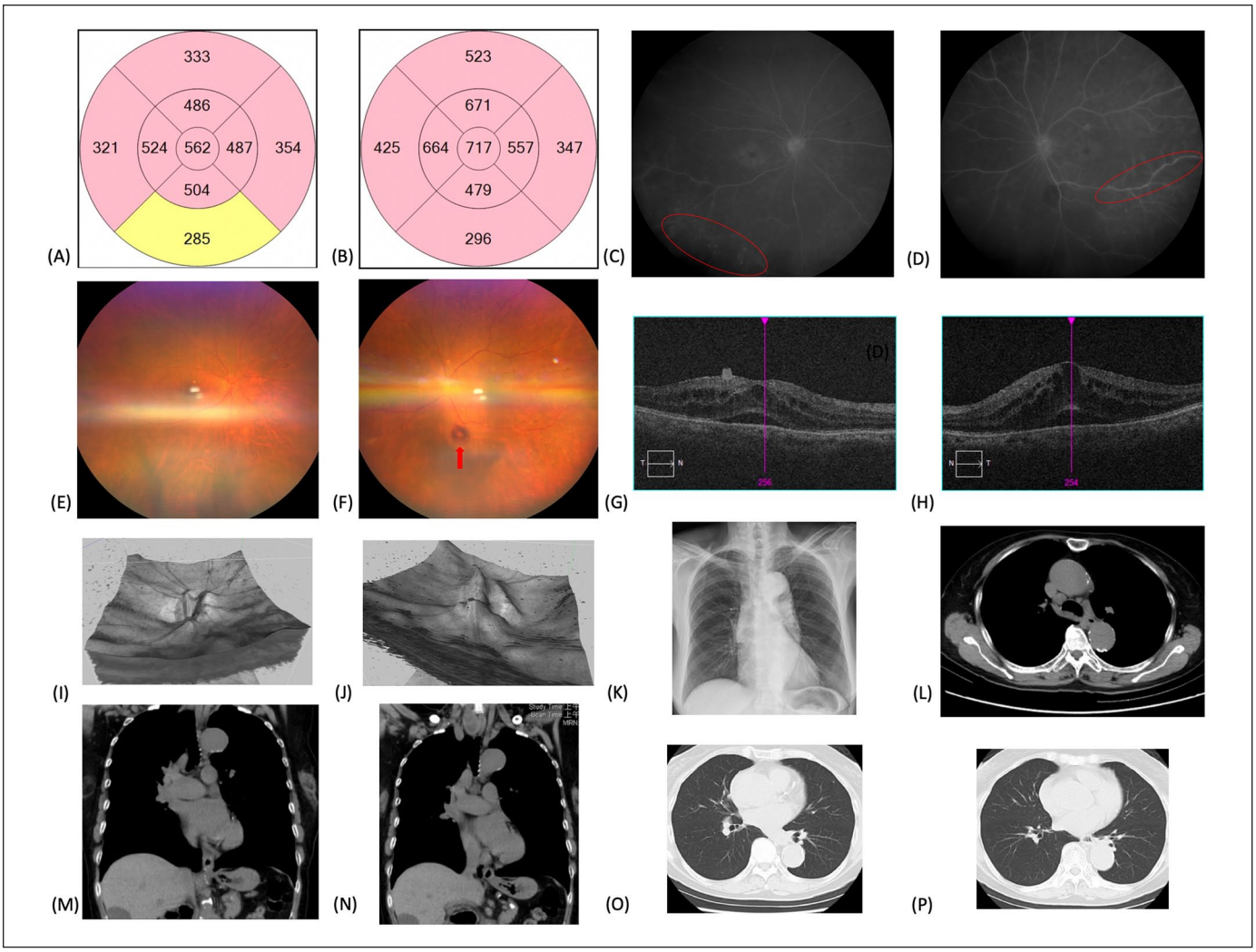

Figure 1. Initial findings in an 82-year-old woman presenting with blurred vision. Central subfield thickness was measured on optical coherence tomography (OCT) using a macular cube for (A) the right eye and (B) the left eye by evaluating the distance between the internal limiting membrane and retinal pigment epithelium. (C) Fluorescein angiography indicates mild capillary dilation and petaloid leakage in the foveal region with chorioretinal peripheral lesions (red circle) in the right eye, and (D) a similar pattern with segmental periphlebitis (red circle) is seen in the left eye. (E) Color fundus photography shows whitish retinal lesions in the midperiphery and swollen optic discs bilaterally, possibly attributable to granulomatous formation in the right eye. (F) A similar pattern with a macroaneurysm (red arrow) is seen in the left eye. (G) OCT scan of the right macula shows findings suggestive of subretinal fluid accumulation as well as intraretinal cysts, which were even more apparent in (H) the left eye. A 3-dimensional visualization of the optic disc cube shows nodules on the optic discs in (I) the right eye and (J) the left eye. (K) Increased lung markings are shown bilaterally on chest x-ray. (L and M) Chest computed tomography shows enlarged lymph nodes in the right paratracheal subaortic region and right hilar region. (N) A 2.7 cm lymph node is located in the right lower paratracheal region and a 4.5 cm heterogeneous mass in the right thyroid, with indentation on the trachea. In addition, tiny ground-glass opacities and nodules are observed in (O) the left lung and (P) the right lung.

dyslipidemia, which was reported to be under regular control. She denied any history of ocular surgery.

At presentation, the patient's best-corrected visual acuity (BCVA) was 20/50 OD and 20/100 OS. The intraocular pressures (IOP) were slightly increased in both eyes (22 mm Hg). Anterior chamber cell grading was 2+ bilaterally. There was no evidence of tuberculosis or syphilis on infection screening.

The central subfield thickness (CST) of the maculas was 562 µm OD (Figure 1A) and 717 µm OS (Figure 1B). Fluorescein angiography of both eyes showed capillary dilation and petaloid leakage in the fovea, with chorioretinal peripheral lesions in the right eye (Figure 1C) and segmental periphlebitis in the left eye (Figure 1D). Color fundus photography showed midperipheral whitish lesions and swollen optic discs bilaterally, accompanied by a macroaneurysm in the left eye (Figure 1, E and F). Optical coherence tomography (OCT) showed intraretinal cysts and subretinal fluid in both maculas (Figure 1, G and H). Three-dimensional visualization of the optic disc cube showed optic disc nodules in both eyes (Figure 1, I and J).

Mild neutrophilia and lymphopenia were seen on the patient's white blood cell count. A chest x-ray showed increased lung markings bilaterally (Figure 1K). Computed tomography

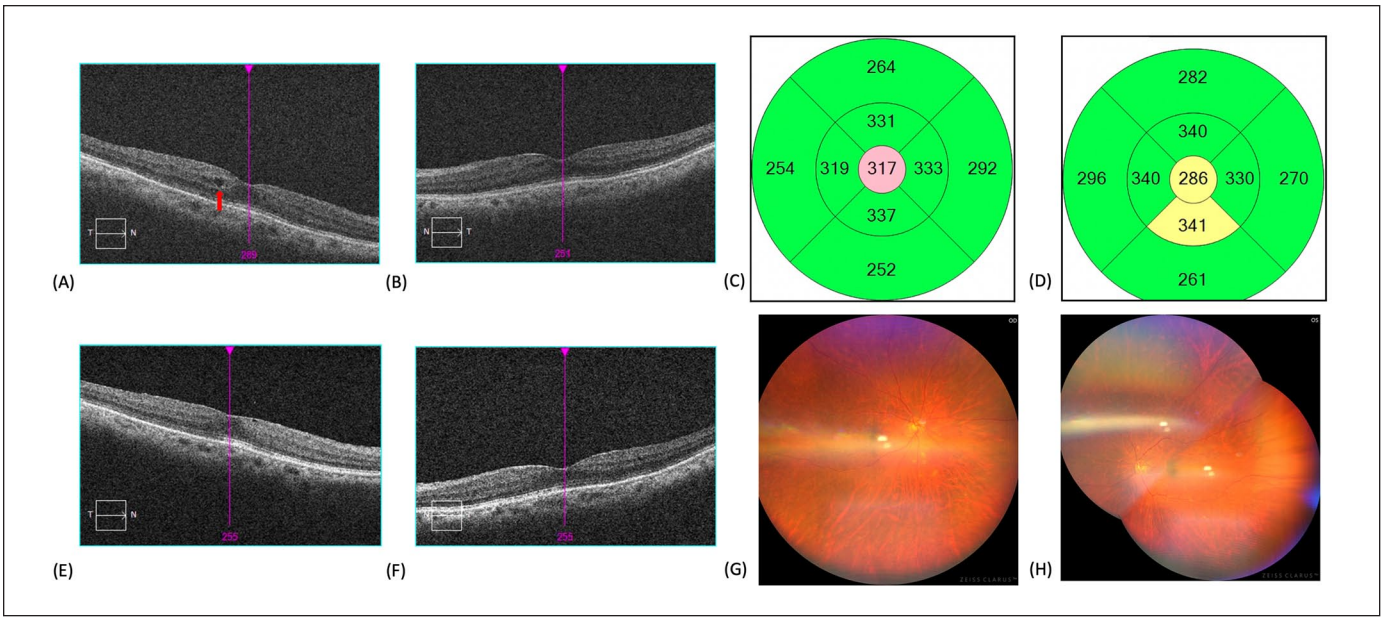

Figure 2. Follow-up fundal examinations. Optical coherence tomography (OCT) scans of both maculas were performed 1 month after the first intravitreal injection of faricimab, showing that (A) the right eye still had a single intraretinal cyst (red arrow), while (B) the left eye had residual swelling. Central subfield thickness was measured on a follow-up OCT scan using a macular cube for (C) the right eye and (D) the left eye. (E) OCT shows resolution of the intraretinal cyst in the right macula, while (F) the cystoid macular edema in both eyes was almost completely resolved. (G–H) Color fundus photography shows improvement in the swelling of the discs in both eyes and resolution of the macroaneurysm in the left eye.

of the chest (Figure 1, L–P) showed mediastinal lymphadenopathy in the right lung (Figure 1, L and M) and a 4.5 cm mass in the right thyroid (Figure 1N). A lymph node and thyroid biopsy were declined by the patient.

Initial treatment for the patient included prednisolone eyedrops, ibuprofen tablets (1200 mg/day), and oral prednisolone (10 mg/day), with carteolol solution for management of IOP.

One month after presentation, the patient's BCVA deteriorated to 20/100 OD (CST, 684 μm) and 20/200 OS (CST, 687 μm). She received sub-Tenon triamcinolone injections (20 mg) bilaterally, as well as ibuprofen tablets and prednisone tablets for 1 month. Because the anterior chamber was shallow and IOP was elevated, we decided not to administer an intraocular steroid. By the end of the first month, the patient's BCVA worsened to 20/200 OD and 20/400 OS; therefore, intravitreal (IVT) faricimab injections were initiated in the second month of treatment.

One month after the patient's first faricimab injection, the BCVA improved to 20/66 OD and 20/100 OS. Follow-up OCT scans showed that while a single intraretinal cyst was still present in the right eye (Figure 2A), remission of intraretinal and subretinal fluid was clearly evident in both eyes (Figure 2, A and B).

A second dose of faricimab was administered 3 months later. Subsequently, the patient's BCVA improved to 20/50 OD and 20/63 OS. Compared with the initial findings, the CST improved from 562 μm to 371 μm OD and from 717 μm to 286 μm OS (Figure 2, C and D). An OCT scan showed resolution of the intraretinal cyst in the right eye, with almost complete resolution of CME bilaterally (Figure 2, E and F). Color fundus photography showed improvement in the optic disc swelling and resolution of the retinal macroaneurysm (Figure 2, G and H). The sequence of treatments and clinical response based on measurements of the BCVA is shown in Figure 3.

Conclusions

A literature search of PubMed, Google Scholar, and Cochrane Library using the keywords "sarcoid uveitis", "sarcoidosis", "uveitis", and "faricimab" did not identify any previous reports of faricimab as a successful treatment for sarcoid uveitis. The diagnosis of probable ocular sarcoidosis in this patient was based on the International Workshop on Ocular Sarcoidosis revised criteria because a biopsy was not performed and only evidence of unilateral hilar lymphadenopathy was seen. In addition, 3 intraocular signs and 2 systemic investigations with relevant findings (negative interferon-gamma releasing assay and lymphopenia) matched the criteria.

Conventional therapy in this patient was unsuccessful for 2 possible reasons. First, because it was combined with a sub-Tenon triamcinolone injection, the steroid was not administered at the maximal dosage of 1 mg/kg. Given the fact that the patient had increased IOP and cataracts, increasing the steroid dosage or repeating the sub-Tenon injection might have worsened her condition. Second, despite our efforts, the patient did not show optimal compliance and thus we could not confirm whether the administered drugs had been taken regularly.

The therapeutic effects lasted for at least 3 months, and no ME or intraretinal fluid was observed. However, the patient was lost to follow-up for almost half a year, and her next return to our outpatient department was 9 months after her latest injection. In this return visit, the CST was 347 μm OD and 386 μm OS. In

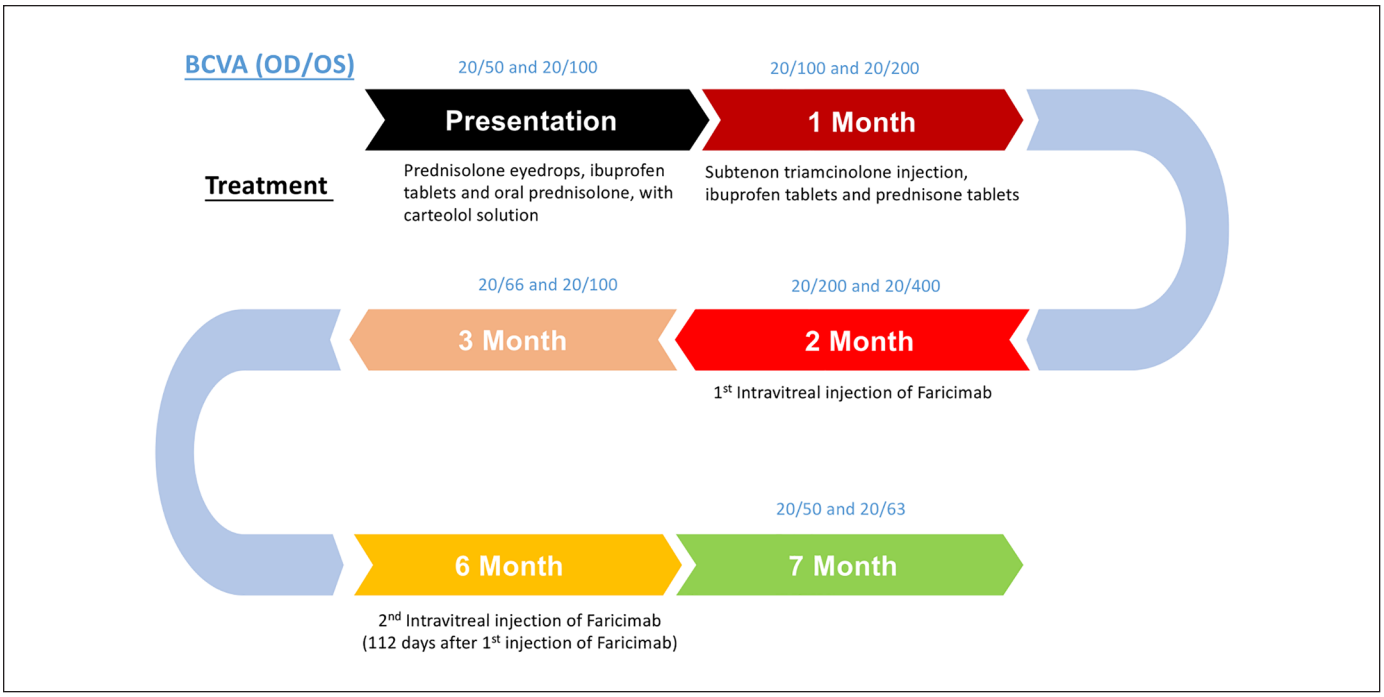

Figure 3. Timeline of treatments and clinical response according to measurements of the patient's best-corrected visual acuity.

addition, CME had recurred, and midperipheral retinal hemorrhages were present. The patient's BCVA was 20/50 OD and 20/200 OS. Given her health status before the initiation of faricimab, her condition at the time of her return was not significantly poor; therefore, maintenance therapy was advised. The continuation of systemic anti-inflammatory and immunomodulatory therapies might also be required because of the recurring inflammatory nature of sarcoid uveitis. Further IVT injections were scheduled, but the patient was lost to follow-up.

Dexamethasone implants, immunomodulatory drugs, and anti-VEGF agents[15] have shown promise as treatment for ME in uveitis.[16] VEGF has been reported to have a key role in the pathogenesis of uveitis.[17] In addition, through the Ang/Tie signaling pathway, Ang2 antagonizes its anti-inflammatory counterpart, Ang-1, on the endothelium,[12] and was shown to induce production of the proinflammatory cytokine interleukin-6,[18] whose role in autoimmune uveitis has been reported.[19] The inhibition of VEGF and Ang2 by faricimab reduces the permeability and inflammation of the retinal vasculature while restoring its stability. The administration of a VEGF-/Ang2-bispecific antibody led to desirable results in a preclinical study of mice with endotoxin-induced uveitis.[13] In another recent study,[20] the protein levels of VEGF-A and Ang2 were found to be significantly higher in vitreous samples from patients with uveitis, and measurement of retinochoroidal messenger RNA in mice with experimental autoimmune uveitis showed that the levels of VEGF-A and Ang2 messenger RNA were significantly upregulated.

There are certain limitations to this study. Because this is a case report, selection bias related to the patient population may exist. Furthermore, the safety of faricimab remains to be investigated, as 1 study reported that uveitis developed after a patient received faricimab.[21] More case reports with different demographic settings are required to further establish the efficacy and safety of faricimab for the treatment of sarcoid uveitis. In addition, because faricimab is a relatively new treatment, whether the inhibition of VEGF and Ang2 embodies the complete action of faricimab on sarcoid uveitis remains to be seen.

Faricimab shows promise as a treatment for refractory CME in patients with sarcoid uveitis. Further studies are needed.

Ethical Approval

This study was conducted in accordance with the Declaration of Helsinki. The collection and evaluation of all protected health information were performed in a US Health Insurance Portability and Accountability Act–compliant manner.

Statement of Informed Consent

Informed consent was obtained before all evaluations and imaging reported herein, as well as before treatments such as intravitreal injection.

Declaration of Conflicting Interest

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