

Case Report

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# Choroidal Effusion following Intravitreal Brolucizumab Injection: A Case Report

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## Keywords

Age-related macular degeneration · Choroidal effusion · Intravitreal brolucizumab injection

## Abstract

This report describes a case of choroidal effusion after intravitreal brolucizumab injection for wet age-related macular degeneration (AMD). A 71-year-old Korean man with a history of wet AMD visited our clinic. On examination, the best-corrected distance visual acuity (BCVA) was 20/200 in the right eye. Fundus photography and optical coherence tomography showed wet AMD in the right eye. The patient showed no improvement while undergoing treatment with anti-vascular endothelial growth factor therapy (aflibercept, 6 times; ranibizumab, 5 times; and bevacizumab 3 times). We administered intravitreal brolucizumab injections in the right eye of the patient. After first brolucizumab injection, the BCVA improved from 20/200 to 20/63 in the right eye. Two months after the intravitreal brolucizumab injection, recurrence of wet AMD and deterioration of the BCVA to 20/200 was observed on the right eye. The patient underwent a second intravitreal brolucizumab injection in the right eye in the same manner. Three days after the second brolucizumab injection, choroidal effusion was observed in the right eye. The choroidal effusion resolved completely 12 days after the injection, without any additional treatment. Intravitreal brolucizumab injection may provoke choroidal effusion. Although it may resolve promptly, short-term follow-up fundus examinations may be necessary for the early diagnosis and treatment of this complication.

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## Introduction

Age-related macular degeneration (AMD), if left untreated, is a major cause of severe visual loss in older adults [1]. With the increase in the number of elderly individuals, the prevalence of AMD may increase as well [2]. Vascular endothelial growth factor (VEGF) is a key regulator of angiogenesis and vascular permeability and plays a crucial role in AMD pathogenesis by promoting choroidal neovascularization [3].

Anti-VEGF therapy using intravitreal anti-VEGF antibody injection is currently widely used for the treatment of exudative AMD [4]. Brolucizumab (RTH258, formerly ESBA1008) is a humanized single-chain antibody fragment that inhibits all isoforms of VEGF-A. It is the smallest of the anti-VEGF antibodies, with a molecular weight of 26 kDa, compared with 48 kDa for ranibizumab, 115 kDa for aflibercept, and 149 kDa for bevacizumab [5]. Although most of the ocular safety profile of brolucizumab seems to be similar to that of the other approved anti-VEGF agents administered by intravitreal injection, some unanticipated adverse events have been observed. Since the approval of brolucizumab for clinical use, several post-marketing cases of severe visual acuity loss associated with retinal vasculitis and retinal artery occlusion have been reported [6, 7]. The adverse effects of the injection should be carefully considered; thus, the need for studies on the adverse effects of the injection is increasing among ophthalmologists.

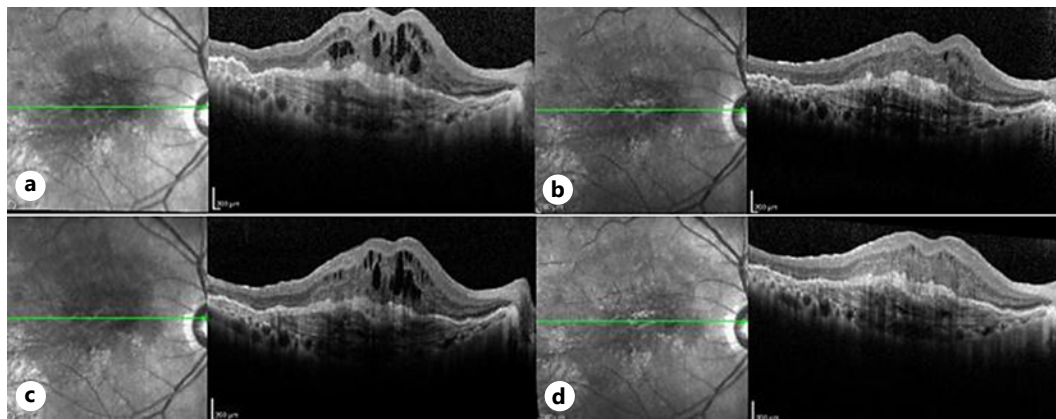
In the present case, the authors experienced an unusual complication after intravitreal brolucizumab injection. Here, we report a case of choroidal effusion following intravitreal brolucizumab injection in a patient with wet AMD.

## Case Presentation

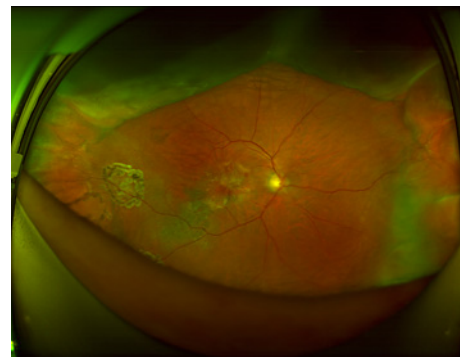
A 71-year-old Korean man with a history of wet AMD in the right eye visited our clinic. The patient had been receiving intravitreal anti-VEGF therapy (aflibercept, 6 times; ranibizumab, 5 times; and bevacizumab 3 times) in the right eye over the past 5 years. The patient underwent pars plana vitrectomy and cataract surgery for vitreous hemorrhage due to wet AMD in the right eye 2 years ago. The patient showed no improvement while undergoing treatment with anti-VEGF (aflibercept, ranibizumab, and bevacizumab) therapy. On examination, the best-corrected distance visual acuity (BCVA) was 20/200 in the right eye. On slit-lamp examination, the cornea and conjunctiva were unremarkable, and there was no evidence of active inflammation in the anterior chamber or neovascularization in the iris. Fundus photography and optical coherence tomography revealed wet AMD in the right eye (shown in Fig. 1).

We administered intravitreal brolucizumab injections in the right eye. Intravitreal injection was performed inferotemporally, 3.5 mm from the limbus. One month after the intravitreal injection, a decrease in the intraretinal fluid and an improvement in BCVA to 20/63 was observed on examination of the right eye.

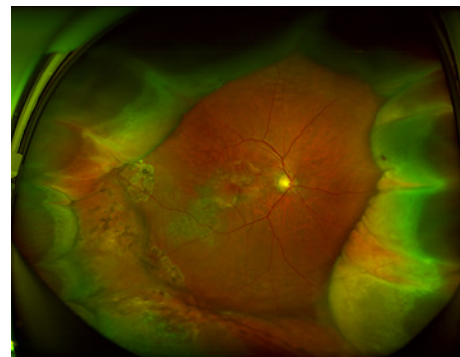
Two months after the intravitreal brolucizumab injection, recurrence of wet AMD and deterioration of the BCVA to 20/200 was observed on the right eye. Therefore, we administered a second intravitreal brolucizumab injection in the right eye in the same manner. On slit-lamp examination performed 1 day after the second injection, moderate flares and 2+ cells were observed in the anterior chamber. The patient was prescribed topical 0.1% fluorometholone acetate eye drops (Flarex®; Alcon Laboratories, Inc., Fort Worth, TX, USA) 4 times a day in the right eye. Three days after the second injection, on fundus examination, we observed choroidal effusion in the right eye (shown in Fig. 2). There were no changes in the anterior chamber depth. Two days after the treatment, the choroidal effusion worsened



**Fig. 1.** Time course of OCT images for wet AMD in the right eye. **a** OCT image for wet AMD in the right eye before first intravitreal brolucizumab injection. **b** OCT image for improved wet AMD in the right eye at 1 month after first intravitreal brolucizumab injection. **c** OCT image for recurred wet AMD in the right eye 2 months after first intravitreal brolucizumab injection. **d** OCT image for wet AMD in the right eye 1 month after second intravitreal brolucizumab injection. OCT, optical coherence tomography.

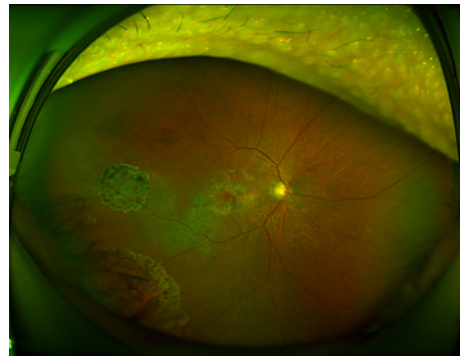


**Fig. 2.** Fundus photography image of choroidal effusion in the right eye at 3 days after intravitreal brolucizumab injection.



**Fig. 3.** Fundus photography image of worsened choroidal effusion in the right eye at 5 days after intravitreal brolucizumab injection.

(shown in Fig. 3). We considered systemic corticosteroid treatment, but the patient had diabetes; thus, we decided to observe the patient for a week. One week after the last visit, on fundus examination, choroidal effusion in the right eye resolved without additional treatment (shown in Fig. 4). One month after the second injection, a decrease in the intraretinal fluid, resolved choroidal effusion, and an improvement in the BCVA to 20/63 were observed on right eye examination.



**Fig. 4.** Fundus photography image of resolved choroidal effusion in the right eye at 12 days after intravitreal brolucizumab injection.

### Discussion and Conclusions

The HAWK and HARRIER phase 3 clinical trials showed that when used for the treatment of wet AMD, brolucizumab 6 mg/0.05 mL dosed at 8 or 12 weeks was noninferior to aflibercept 2 mg/0.05 mL dosed at 8 weeks in improving BCVA at 48 weeks [8]. The overall ocular and nonocular adverse event rates of brolucizumab were similar to those of aflibercept. In the patients treated with brolucizumab in the HAWK and HARRIER trials, the incidence of intraocular inflammation was reported to be 4%. In both trials, adverse events with brolucizumab 6 mg included uveitis and iritis (2.2% each). For aflibercept, uveitis and iritis were at 0.3% and 0% in the HAWK trial. Approximately 90% of the uveitis and iritis cases were mild to moderate, and were treated with a course of topical corticosteroids or antibiotics, and most resolved with no sequelae [8]. Hypersensitivity reactions after anti-VEGF therapy mostly involve type I hypersensitivity reactions due to substances used during intravitreal injection [9]. In our case, 1 day after the second injection, flares and 2+ cells were observed in the anterior chamber.

Retinal vasculitis and intraocular inflammation are severe adverse events associated with brolucizumab that may lead to visual loss [10]. Iyer et al. [10] reported occurrence of ocular inflammation and retinal vasculitis following brolucizumab injection, which improved with prednisolone eye drops and was exacerbated after ranibizumab retreatment. They described that brolucizumab may be more immunogenic than other anti-VEGF agents because of its relatively small molecular size and consequent ability to unfold, which exposes epitopes that may not be recognized by the immune system [11]. The brolucizumab molecule (26 kDa) is substantially smaller than ranibizumab (48 kDa) and aflibercept (115 kDa). Theoretically, because of its small size, brolucizumab should have better target tissue penetration compared with aflibercept and ranibizumab [12, 13]. Alternatively, during the post-translational modification process of protein fragments, such as brolucizumab, structural changes in the protein may result in the creation of new protein epitopes [14]. These new protein structures could lead to the formation of aggregates, which can significantly enhance immunogenicity [14]. Bakir et al. [15] reported that inflammation can also cause effusion. In our patient, inflammation due to immune response may have been one of the causes of choroidal effusion, and the improvement with fluorometholone eye drop alone supports this hypothesis. Our patient had no previous medical history such as diabetes and hypertension. Moreover, he had no past history of uveitis or any medications which may provoke ocular inflammation or choroidal effusion. Despite the previous 14 times of anti-VEGF injections (aflibercept, 6 times; ranibizumab, 5 times; and bevacizumab 3 times), he did not experience any ocular inflammation nor choroidal effusion.

Using pharmacokinetic modeling, Eissing et al. [16] described that the vitreous half-life of brolucizumab was 5.1 days. In our patient, choroidal effusion peaked at 5 days after the injection. This suggests that the concentration of intravitreal brolucizumab may be correlated with choroidal effusion. In our case, the absence of the vitreous due to vitrectomy may have triggered choroidal effusion. The vitreous is made of gel-like materials that are highly viscous. In an eye with previous history of vitrectomy, the vitreous would have been removed and less viscous liquid would currently be filling the vitreous cavity [17]. The authors believe that the vitrectomized eye would be more vulnerable to the choroidal effusion because the viscous gel-type vitreous body is more likely to suppress the choroidal effusion than the less viscous liquid of the vitreous cavity. Arpa et al. [18] reported that the moderate choroidal effusion (20%) occurred after Ahmed valve implantation in vitrectomized eyes. Furino et al. [19] described the concerns of hypotony after intravitreal injections in vitrectomized eyes. Although hypotony may be one of the causes of the choroidal effusion, the intraocular pressure of our patient was 18 mm Hg in the right eye on a day after brolucizumab injection. Consequently, the choroidal effusion was observed 3 days after brolucizumab injection. In conclusion, the combined effects of intraocular inflammation, hypotony, and the absence of the vitreous body are thought to influence the development of the choroidal effusion.

The limitation of this report is that the B mode echo for the choroidal effusion could not be conducted. However, considering the fundus photograph and the resolving time as well as its aspects, the choroidal effusion is seems to be the serous type.

In conclusion, to the best of our knowledge, this is the first reported case of choroidal effusion following intravitreal brolucizumab injection. Intravitreal brolucizumab injection may provoke choroidal effusion. Although it may resolve promptly, short-term follow-up may be necessary for early diagnosis and treatment of this complication, especially in vitrectomized eyes.

## Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. This retrospective review of patient data did not require ethical approval in accordance with local guidelines. All procedures followed were in accordance with ethical standards and the Helsinki Declaration.

## Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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## Author Contributions

Substantial contributions to the conception or design of the work: K.J.S., H.J.H. Acquisition of data for the work: H.J.H. Drafting the work: S.H.E., H.J.H.

## Data Availability Statement

All data generated or analyzed during this study are included in this article, and further inquiries can be directed to the corresponding author.

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