


CASE REPORT

Open Access



Swept-source optical coherence tomography angiography of retinal occlusive vasculitis following brolocizumab administration: a case report

Eun Kyoung Lee* , Baek-Lok Oh, Chang Ki Yoon and Un Chul Park

Abstract

Background: We present a case of retinal occlusive vasculitis following brolocizumab administration and the first report of optical coherence tomography angiography (OCTA) findings after treatment.

Case presentation: A 71-year-old man complained of vision loss in the left eye 6 weeks after brolocizumab injection. His visual acuity was counting fingers, and examination revealed 1 + anterior chamber cells with 2 + vitreous cells. Fundus examination demonstrated vitreous haze, retinal whitening, and vascular sheathing. Fluorescein angiography revealed filling defects in the retinal arteries and veins, and OCTA showed extensive capillary nonperfusion. Under the diagnosis of brolocizumab-associated intraocular inflammation (IOI) and retinal occlusive vasculitis, topical, sub-Tenon, and systemic corticosteroids were administered. After the treatment, visual acuity improved to 20/200, and OCTA revealed gradual improvement in capillary dropout; however, with the limited improvement of reperfusion in the perifoveal areas.

Conclusions: Prompt evaluation and intensive corticosteroid treatments are required for brolocizumab-associated IOI. OCTA imaging provides detailed information on microvascular changes in the retinal vascular plexuses in brolocizumab-associated retinal occlusive vasculitis.

Keywords: Age-related macular degeneration, Brolocizumab, Intraocular inflammation, Retinal occlusive vasculitis, Swept-source optical coherence tomography angiography

Background

Brolocizumab, a humanized, single-chain variable fragment that inhibits vascular endothelial growth factor (VEGF)-A was approved by the US Food and Drug Administration for treatment of neovascular age-related macular degeneration (AMD) on October 7, 2019 [1]. The phase 3 data from two pivotal clinical trials, HAWK

(NCT02307682) and HARRIER (NCT02434328), demonstrated non-inferiority in best-corrected visual acuity (BCVA) with brolocizumab (6 mg/0.05 mL dosed at every 8 or 12 weeks) compared to aflibercept (2 mg/0.05 mL dosed at every 8 weeks) [2, 3]. Increased molar concentration combined with a high binding affinity for VEGF have been postulated to account for its potential for increased durability [4].

In terms of safety, HAWK and HARRIER studies found that the incidence of intraocular inflammation (IOI) was higher with brolocizumab having 4% compared to aflibercept's 1%, and most of these cases were reported as mild to moderate [5, 6]. However, since the approval

*Correspondence: righthanded8282@gmail.com

Department of Ophthalmology, Seoul National University College of Medicine, Seoul National University Hospital, #101, Daehak-ro, Jongno-gu, Seoul, Republic of Korea



© The Author(s) 2022. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

of brolocizumab, there were reports of severe visual acuity loss associated with retinal vasculitis and/or retinal artery occlusion accompanied by IOI following treatment with brolocizumab [7–10]. Novartis announced that the incidence rate of retinal vasculitis and/or retinal vascular occlusion was estimated to be 15.5 per 10,000 injections on post-marketing reports [11]. To further clarify the incidence of these events, Novartis commissioned an external Safety Review Committee (SRC) [11, 12]. The SRC conducted a post hoc unmasked analysis of the images from cases in HAWK and HARRIER that were reported as having IOI. They concluded that the incidence of IOI was 4.6% (IOI+retinal vasculitis, 3.3%; IOI+retinal vasculitis+retinal vascular occlusion, 2.1%), and the overall incidence of at least moderate vision loss associated with IOI was 0.74% [12].

Little is known about the mechanism of IOI and patient characterization and approaches to reduce these adverse events have not yet been clearly established. Given that the number of reported case series of retinal occlusive vasculitis is highly limited, a better understanding of this condition requires more information. Furthermore, to our knowledge, optical coherence tomography angiography (OCTA) in patients with retinal occlusive vasculitis associated with brolocizumab injection has not yet been reported. Herein, we report a case of retinal occlusive vasculitis after intravitreal brolocizumab administration and present the OCTA findings after treatment.

Case presentation

A 71-year-old man with active neovascular AMD in the left eye returned to the clinic owing to a significantly

decreased vision in the left eye (OS). The patient was systemically healthy and did not report a history of diabetes or hypertension. Surgical history was significant only for cataract extraction with a posterior chamber intraocular lens in OS. He had been treated with six intravitreal ranibizumab injections and 25 intravitreal aflibercept injections since 2014 for typical AMD in OS. There was persistent subretinal fluid (SRF) despite multiple injections of ranibizumab and aflibercept. He had never experienced any IOI with either medication. The decision to switch to brolocizumab was made given the persistent SRF in the OS.

On examination before brolocizumab injection, his BCVA was 20/20 in the right eye (OD) and 20/100 in the OS. Fundus examination revealed choroidal neovascularization (CNV) with serous detachment in the OS (Fig. 1A). Optical coherence tomography (OCT) showed foveal SRF with pigment epithelial detachment (PED) (Fig. 1E). The swept-source OCTA device (PLEX Elite 9000; Carl Zeiss Meditec, Inc., Dublin, CA) was used to evaluate the neovascular networks in terms of their location, shape, size, and extent. OCTA revealed no specific vascular network changes at the level of both the superficial and deep capillary plexus and detects CNV by the presence of an abnormal pattern of vascular flow in the outer retina to the choriocapillaris (ORCC) slab (Fig. 2A, E, I, and M). Two weeks after the first brolocizumab injection, BCVA was 20/125 and intraocular pressure (IOP) was within normal limits in OS. Slit-lamp examination was normal, and ultra-wide-field fundus photography revealed nonspecific findings (Fig. 3A).

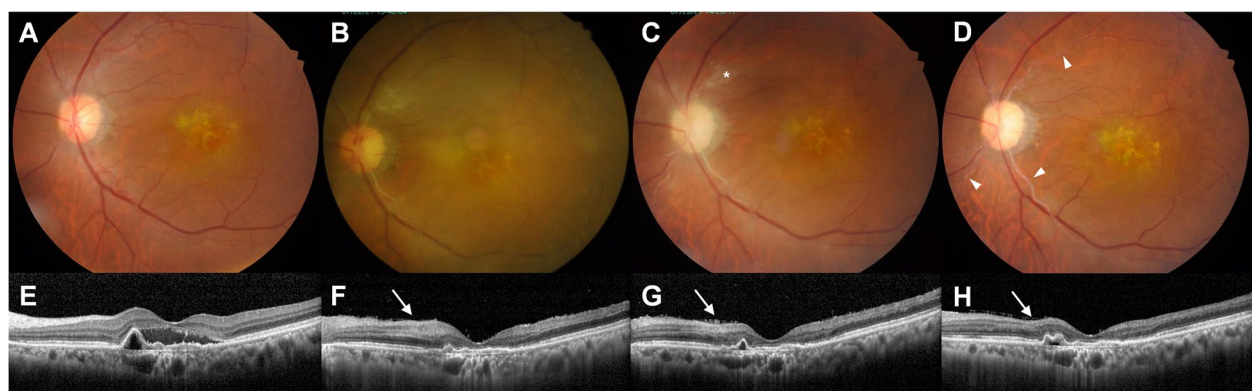


Fig. 1 Fundus photographs (A–D) and cross-sectional horizontal optical coherence tomography (OCT) B-scan images (E–H). All images are arranged from the leftmost column in the order of before (A, E), 6 weeks (B, F)-development of intraocular inflammation (IOI)-, 7 weeks (C, G), and 12 weeks (D, H) after the brolocizumab administration. After the development of IOI and retinal occlusive vasculitis, cotton-wool patches (white asterisk) suggesting precapillary retinal arteriolar occlusion and retinal whitening gradually decreased over time; however, Kyrieleis plaques (white arrowheads) remained. On OCT images, a hyperreflective band consistent with paracentral acute middle maculopathy (white arrows) suggesting inner nuclear layer ischemia decreased and pigment epithelial detachment increased over time

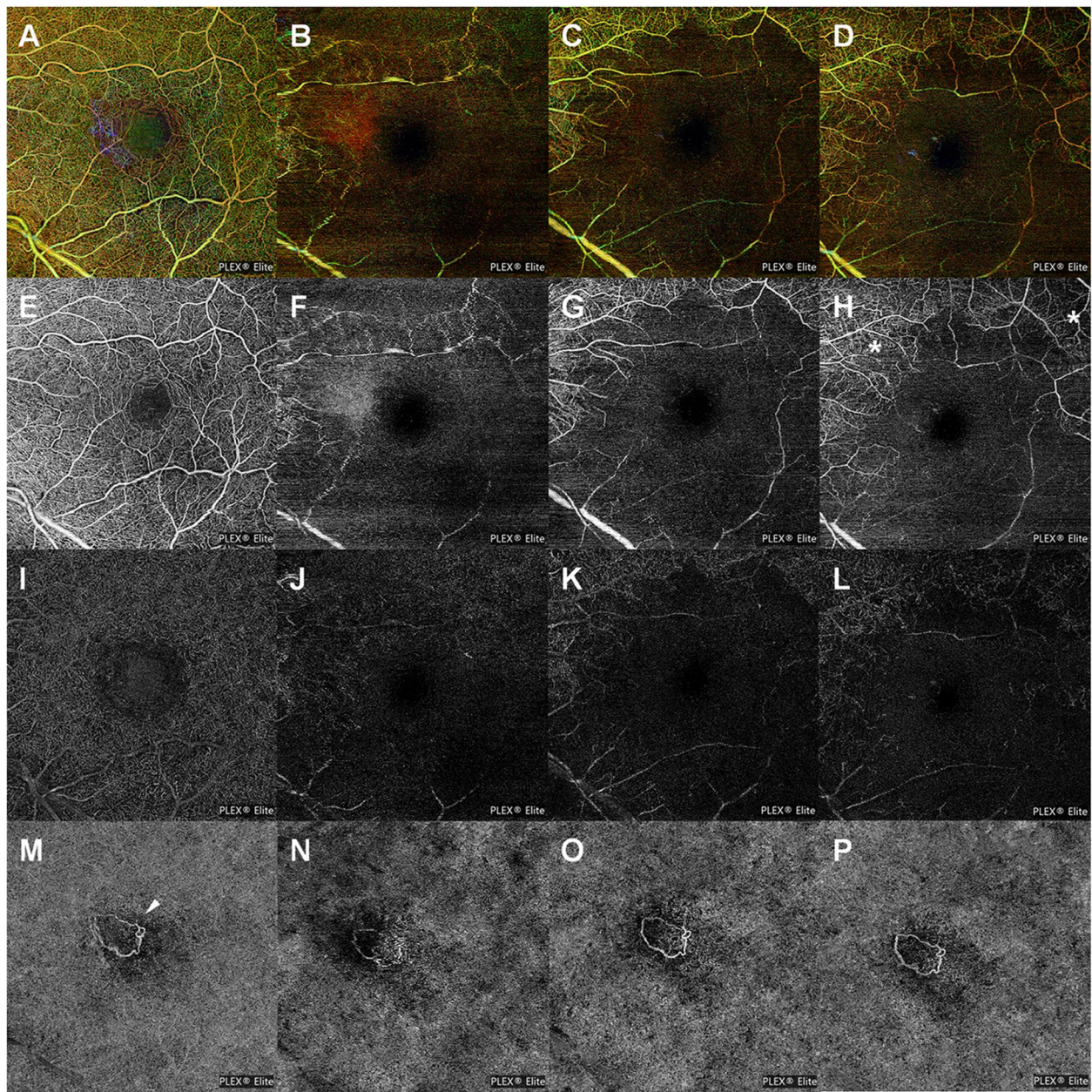


Fig. 2 Swept-source optical coherence tomography angiography (OCTA) images that correspond to the retina depth-encoded (A-D), superficial capillary plexus (SCP) (E-H), deep capillary plexus (DCP) (I-L), and outer retina to choriocapillaris (ORCC) slab (M-P). All images are arranged from the leftmost column in the order of before (A, E, I, M), 6 weeks (B, F, J, N)-development of intraocular inflammation (IOI)-, 7 weeks (C, G, K, O), and 12 weeks (D, H, L, P) after the brolucizumab administration. On OCTA images, extensive non-perfusion areas with capillary dropout were apparent in SCP and DCP. Following the treatment, recanalized capillaries (white asterisks) are shown; however, with persistent perfoveal nonperfusion. The shape and size of choroidal neovascularization (white arrowhead) reveal no specific changes in ORCC slabs

Six weeks after the brolucizumab injection, the patient experienced visual deterioration, which started 3 days back. On clinical examination, his BCVA was counting fingers, and the IOP was 13 mmHg in OS. Slit-lamp examination showed anterior chamber cells (1+) with fine keratic precipitates and vitreous cells (2+); however,

no hypopyon. Fundus examination showed vitreous haze, retinal whitening, cotton-wool patches, and vascular sheathing involving the major retinal arteries, all of which were suggestive of IOI (Fig. 1B). On OCT imaging, SRF and PED were decreased; however, inner retinal edema was observed (Fig. 1F). OCTA showed extensive

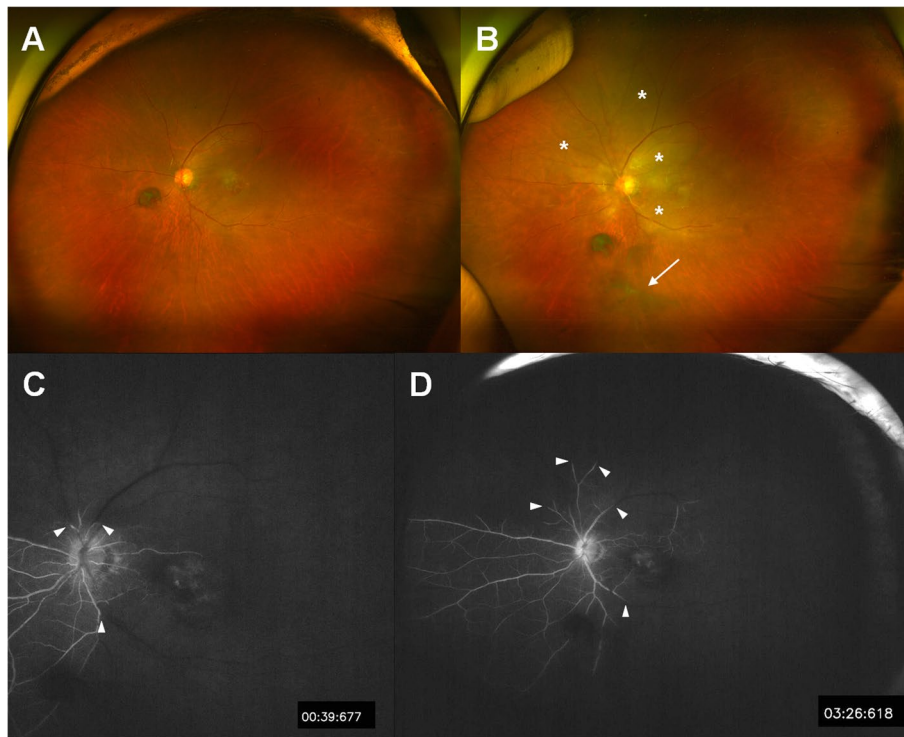


Fig. 3 Ultra-widefield fundus photography (**A, B**) and ultra-widefield fluorescein angiography (**C, D**) recorded 2 weeks (**A**) and 6 weeks (**B-D**) after the brolocizumab administration. **A** No intraocular inflammation is reported. **B** Vitreous opacity (white arrow), retinal whitening (white asterisks) suggestive of associated ischemia in this area are shown. **C, D** Fluorescein angiography demonstrating arterial and venous filling defects (white arrowheads), which persisted into the late phase and involved the macula

non-perfusion areas in the superficial capillary plexus, as well as diffuse capillary network attenuation and disorganization in the deep capillary plexus (Fig. 2B, E, J, N). Ultra-widefield fundus photography revealed vitreous opacity, vascular sheathing, and retinal whitening, particularly in the superotemporal, superonasal, and inferotemporal quadrants (Fig. 3B). Ultra-widefield fluorescein angiography (FA) showed filling defects in the larger retinal arteries and veins proximal to the optic nerve, which remained until late-phase FA, as well as optic disc staining (Fig. 3C, D).

Based on the clinical features and history of brolocizumab, a diagnosis of brolocizumab-associated IOI and retinal occlusive vasculitis was made. The patient was treated with oral prednisolone 30 mg daily and topical prednisolone acetate 1.0% (Pred-forte®) every 2 h. Four days later, he was administered an additional sub-Tenon triamcinolone acetonide injection. One week after the diagnosis of retinal occlusive vasculitis, his BCVA was 20/400 and IOP was 14 mmHg in OS. Slit-lamp examination showed anterior chamber cells (trace) and vitreous cells (1+); however, no keratic precipitates. Fundus examination showed decreased vitreous haze (Fig. 1C),

and OCT revealed decreased inner retinal edema (Fig. 1G). OCTA demonstrated a slight improvement in areas of capillary nonperfusion in both superficial and deep capillary plexuses and no obvious changes in CNV in the ORCC slab (Fig. 2C, G, K, O). Aspirin 100 mg/day and clopidogrel 75 mg/day were additionally prescribed for the patient.

Three weeks after the diagnosis of retinal occlusive vasculitis, his BCVA was 20/200, and the IOP was 14 mmHg. Slit-lamp examination revealed anterior chamber cells (trace) and vitreous cells (trace). Fundus examination revealed that vitreous haze, cotton-wool patches, and retinal whitening decreased more; however, vascular sheathing involving the retinal arteries remained and optic disc pallor was noted (Fig. 1D). On OCT imaging, inner retinal edema decreased further, and there was no recurrence of SRF; however, PED gradually increased (Fig. 1H). OCTA showed gradual improvement in capillary dropout in both superficial and deep capillary plexuses and no obvious changes in CNV in the ORCC slab (Fig. 2D, H, L, P). However, the perifoveal areas revealed no apparent reperfusion and limited improvement throughout the follow-up period. The dose of oral prednisolone was tapered gradually

by 2.5–5 mg every 1–2 weeks. Thereafter, the patient received an additional intravitreal aflibercept injection.

Discussion and conclusion

This is the first report of brolocizumab-associated retinal occlusive vasculitis in Korean patients. In Korea, brolocizumab was approved by the Korean Ministry of Food and Drug Safety on June 15, 2020, and has been commercially available since April 1, 2021. Although the period of experiencing brolocizumab in Korea is still short, clinical data are accumulating, and there are still concerns regarding brolocizumab-associated IOI. We present a case of neovascular AMD in a 71-year-old man who developed IOI and retinal occlusive vasculitis after intravitreal brolocizumab using OCTA images. To the best of our knowledge, this is the first study to demonstrate the findings of OCTA in brolocizumab-associated retinal occlusive vasculitis.

Brolocizumab (~ 26 kDa) is the smallest of the anti-VEGF antibodies, significantly smaller than bevacizumab (149 kDa), aflibercept (97–115 kDa), and ranibizumab (48 kDa) [1]. Such a size difference gives brolocizumab theoretically better target-tissue penetration and therefore a higher concentration that allows up to 6 mg of brolocizumab in a single 50- μ L intravitreal injection, resulting in an anti-VEGF binding capacity 11 and 22 times greater than that of aflibercept and ranibizumab, respectively [1]. The mechanism of retinal occlusive vasculitis and IOI after brolocizumab injection is still not clear; however, several hypotheses have been proposed. Some authors postulated that owing to its more potent anti-VEGF effect, brolocizumab may have a sufficiently high anti-VEGF effect to cause retinal arteriolar constriction and occlusive vasculopathy compared with other anti-VEGF agents [9]. Additionally, relatively late onset of IOI suggests that delayed hypersensitivity against the drug itself or impurities in the product may have been involved with brolocizumab-associated IOI [7, 13]. The European Medicines Agency's suggestion that serum antibodies to the drug did correlate with IOI in the clinical trials also support that local antibodies to the drug may be associated with IOI development [14]. Local antibodies may form immune complexes leading to vasculitis through a mechanism of delayed hypersensitivity [7, 8, 10, 15]. Other suggested causes include the use of previous anti-VEGF therapy, previous IOI events, human leukocyte antigens, and comorbidities [7–10].

MERLIN study investigated the safety and efficacy of brolocizumab at 4 weekly intervals and observed that IOI was higher with brolocizumab (9.3%) compared to aflibercept (4.5%) [16]. Furthermore, proportion of patients with visual loss was also significantly higher with brolocizumab having 4.8% compared to aflibercept's

1.7%. These results suggest that frequent exposure leads to higher immunogenicity. Sharma et al. [17] hypothesized that free brolocizumab molecules would likely accumulate in the vitreous if the injection frequency was less than a month, and that a significant amount could escape into the systemic circulation, leading to the formation of more anti-drug antibodies, thereby enhancing immunogenicity.

The management of brolocizumab-associated IOI in the HAWK and HARRIER trials generally included topical corticosteroids, and systemic and/or intraocular corticosteroids use was infrequent. However, the management approach in the recent literatures recommends more intensive corticosteroid treatment administered by a variety of methods including topical, sub-Tenon, oral, intravitreal, or a combination thereof [7, 9, 10, 18]. Based on the expert panel's recommendations, the eight-step "A BRAVE SAVE" protocol has been suggested [19]. This protocol recommends that intensive treatment of patients with brolocizumab-associated IOI should be started with potent topical corticosteroids. In patients with more severe IOI, intravitreal steroid injections along with systemic corticosteroid therapy should be considered. There have been post-marketing case reports in which brolocizumab-associated adverse events present as a spectrum in which IOI was the initial presentation and retinal vasculitis and/or retinal vascular occlusion developed subsequently in a delayed manner [7, 10]. Therefore, adequate inflammation control with potent corticosteroids may reduce the risk of progression to a more serious spectrum of IOI-related adverse events. Additionally, this intensive treatment could also minimize the risk of secondary ischemic changes after retinal vascular occlusive events [20].

OCTA can provide high-resolution images of individual vascular plexuses in different retinal layers in a noninvasive manner. Previous studies have shown that OCTA plays an important role in the diagnosis and treatment of uveitis [21–24]. OCTA appears to be particularly useful for a detailed evaluation of retinal nonperfusion as well as improvement of retinal ischemia after treatment. The changes observed in the present study support the observations of previous studies in that OCTA is useful in evaluating retinal nonperfusion and confirms that it provides exceptionally detailed images of microvascular flow changes in the retinal vascular plexuses in patients with brolocizumab-associated IOI and retinal occlusive vasculitis.

Although the patient in the current study was treated using intensive corticosteroids, visual acuity demonstrated limited improvement and complete reperfusion was not achieved on OCTA images at the latest follow-up. Although the patient was sufficiently educated

about symptoms associated with IOI in advance, he visited the hospital with retinal vascular occlusion on the third day after symptom onset, which eventually resulted in irreversible visual acuity deterioration. Approximately 75% of the brolocizumab-associated IOI events were first observed within 6 months after initiation of brolocizumab, although some occurred between 12 and 18 months after the injection [12]. Therefore, after the first injection of brolocizumab, clinicians must be aware of the maximum inflammation risk soon after treatment. In particular, even if there is no evidence of inflammation 2 weeks after the first injection of brolocizumab, as in this patient, it is still not reassuring, and the patient must be followed-up for a shorter period after that. It is important to educate patients to visit the hospital as soon as they experience symptoms such as floaters, light sensitivity, or decreased vision. Ultra-widefield imaging techniques are also required to identify retinal vasculitis or retinal vascular occlusion.

In conclusion, a high index of suspicion is required when a patient presents with visual symptoms following brolocizumab treatment. Urgent and continued evaluation is necessary for patients with brolocizumab-associated IOI as occlusive vasculitis may develop subsequently. OCTA imaging is useful for the detailed evaluation of retinal nonperfusion in patients with brolocizumab-associated retinal occlusive vasculitis. Prompt and intensive treatment with topical, intraocular, and/or systemic corticosteroids to control inflammation may prevent further visual deterioration and may allow some improvement of vision in these patients.

Abbreviations

VEGF: Vascular endothelial growth factor; AMD: Age-related macular degeneration; BCVA: Best-corrected visual acuity; IOI: Intraocular inflammation; SRC: Safety Review Committee; OCTA: Optical coherence tomography angiography; OS: Oculus sinister; SRF: Subretinal fluid; OD: Oculus dextrus; CNV: Choroidal neovascularization; OCT: Optical coherence tomography; PED: Pigment epithelial detachment; ORCC: Outer retina to the choriocapillaris; IOP: Intraocular pressure; FA: Fluorescein angiography.

Acknowledgements

Not applicable.

Authors' contributions

All authors have made substantive intellectual contributions to this manuscript. EKL acquired data and wrote the manuscript. BLO, CKY, and UCP participated in the analysis and interpretation of inspection results. All authors read and approved the final manuscript.

Funding

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science and ICT (Information and Communication Technology, NRF-2021R1F1A1045417). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

This case was approved by the Institutional Review Board of Seoul National University Hospital (IRB approval number: 2019–101-1255).

Consent for publication

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

Received: 31 December 2021 Accepted: 24 May 2022

Published online: 03 June 2022

References

- Holz FG, Dugel PU, Weissgerber G, et al. Single-chain antibody fragment vegf inhibitor rth258 for neovascular age-related macular degeneration: a randomized controlled study. *Ophthalmology*. 2016;123:1080–9.
- Dugel PU, Jaffe GJ, Sallstig P, et al. Brolocizumab versus aflibercept in participants with neovascular age-related macular degeneration: a randomized trial. *Ophthalmology*. 2017;124:1296–304.
- Dugel PU, Koh A, Ogura Y, et al. HAWK and HARRIER: phase 3, multicenter, randomized, double-masked trials of brolocizumab for neovascular age-related macular degeneration. *Ophthalmology*. 2020;127:72–84.
- Nguyen QD, Das A, Do DV, et al. Brolocizumab: evolution through preclinical and clinical studies and the implications for the management of neovascular age-related macular degeneration. *Ophthalmology*. 2020;127:963–76.
- Dugel PU, Singh RP, Koh A, et al. HAWK and HARRIER: ninety-six-week outcomes from the phase 3 trials of brolocizumab for neovascular age-related macular degeneration. *Ophthalmology*. 2021;128:89–99.
- Beovu® [US prescribing information] East Hanover NN. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761125s000lbl.pdf. Last accessed on September 1, 2021.
- Baumal CR, Spaide RF, Vajzovic L, et al. Retinal vasculitis and intraocular inflammation after intravitreal injection of brolocizumab. *Ophthalmology*. 2020;127:1345–59.
- Jain A, Chea S, Matsumiya W, et al. Severe vision loss secondary to retinal arteriolar occlusions after multiple intravitreal brolocizumab administrations. *Am J Ophthalmol Case Rep*. 2020;18:100687.
- Witkin AJ, Hahn P, Murray TG, et al. Occlusive retinal vasculitis following intravitreal brolocizumab. *J Vitreoretin Dis*. 2020;4:269–79.
- Haug SJ, Hien DL, Uludag G, et al. Retinal arterial occlusive vasculitis following intravitreal brolocizumab administration. *Am J Ophthalmol Case Rep*. 2020;18:100680.
- Safety of Beovu® (brolocizumab). <https://www.brolocizumab.info/>. Last accessed on September 1, 2021.
- Mones J, Srivastava SK, Jaffe GJ, et al. Risk of inflammation, retinal vasculitis, and retinal occlusion-related events with brolocizumab: post hoc review of HAWK and HARRIER. *Ophthalmology*. 2021;128:1050–9.
- Witkin AJ, Shah AR, Engstrom RE, et al. Postoperative hemorrhagic occlusive retinal vasculitis: expanding the clinical spectrum and possible association with vancomycin. *Ophthalmology*. 2015;122:1438–51.
- European Medicines Agency Committee for Medicinal Products for Human Use (CHMP). European Medicines Agency assessment report EMA/23630/2020. https://www.ema.europa.eu/en/documents/assessment-report/beovu-epar-public-assessment-report_en.pdf. Last accessed on September 1, 2021.
- Sharma A, Kumar N, Parachuri N, et al. Understanding Retinal Vasculitis associated with Brolocizumab: complex Pathophysiology or Occam's Razor? *Ocul Immunol Inflamm*. 2021;20:1–3.

16. Study of safety and efficacy of brolocizumab 6 mg dosed every 4 weeks compared to aflibercept 2 mg dosed every 4 weeks in patients with retinal fluid despite frequent anti-VEGF injections (MERLIN). <https://www.clinicaltrials.gov/ct2/show/NCT03710564>.
17. Sharma A, Kumar N, Parachuri N, et al. Brolocizumab horizontal line termination of 4 weekly trials horizontal line rebalancing the immunogenicity risk. *Expert Opin Biol Ther*. 2022;22:441–3.
18. Kondapalli SSA. Retinal vasculitis after administration of brolocizumab resulting in severe loss of visual acuity. *JAMA Ophthalmol*. 2020;138:1103–4.
19. Sharma A, Kumar N, Parachuri N, et al. Brolocizumab-foreseeable workflow in the current scenario. *Eye (Lond)*. 2021;35:1548–50.
20. Flaxel CJ, Adelman RA, Bailey ST, et al. Retinal and ophthalmic artery occlusions preferred practice pattern(R). *Ophthalmology*. 2020;127:P259–87.
21. Dingerkus VLS, Munk MR, Brinkmann MP, et al. Optical coherence tomography angiography (OCTA) as a new diagnostic tool in uveitis. *J Ophthalmic Inflamm Infect*. 2019;9:10.
22. Marchese A, Agarwal A, Moretti AG, et al. Advances in imaging of uveitis. *Ther Adv Ophthalmol*. 2020;12:2515841420917781.
23. Park JH, Lee SY, Lee EK. Morphological characteristics of ocular toxoplasmosis and its regression pattern on swept-source optical coherence tomography angiography: a case report. *BMC Ophthalmol*. 2019;19:199.
24. Agarwal A, Bhatt S, Keshari S, et al. Retinal microvascular alterations in patients with Quiescent Posterior and Panuveitis using optical coherence Tomography Angiography. *Ocul Immunol Inflamm*. 2021;21:1–7.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

