Case Reports in Ophthalmology

Case Rep Ophthalmol 2022;13:736–743
DOI: 10.1159/000526568
Received: June 17, 2022
Accepted: August 6, 2022
Published online: September 30, 2022

Case Report

Intravitreal Brolucizumab for Neovascular Age-Related Macular Degeneration in a Vitrectomized Eye

Emilia Maggio Alessandro Alfano Maurizio Mete Grazia Pertile

IRCCS Sacro Cuore Don Calabria Hospital, Negrar, Italy

Keywords
Age-related macular degeneration · Anti-VEGF · Brolucizumab · Vitrectomized eye

Abstract
The efficacy of intravitreal anti-VEGF may be reduced in vitrectomized eyes due to accelerated drug clearance. Given its longer durability, brolucizumab may represent a suitable therapeutic option. However, its efficacy in vitrectomized eyes remains to be explored. Herein, we describe the management of a macular neovascularization (MNV) in a vitrectomized eye with brolucizumab after unsuccessful treatment with other anti-VEGF. A 68-year-old male was treated with pars plana vitrectomy for epiretinal membrane in his left eye (LE) in 2018. After surgery, best corrected visual acuity (BCVA) improved to 20/20 with a remarkable reduction of metamorphopsia. After 3 years, the patient returned, presenting visual loss in the LE due to MNV. He was treated with intravitreal bevacizumab injections. However, after the loading phase, an increased lesion size and exudation with worsening BCVA were detected. Therefore, the treatment was switched to aflibercept. However, after three monthly intravitreal injections, further worsening was recorded. Treatment was then switched to brolucizumab. Anatomical and functional improvement was noticed 1 month after the first brolucizumab injection. Two additional injections were performed, and further improvement was recorded with BCVA recovery to 20/20. At the last follow-up visit 2 months after the third injection, no recurrence was detected. In conclusion, determining whether anti-VEGF injections are efficacious for vitrectomized eyes would be helpful for ophthalmologists managing such patients, as well as when considering pars plana vitrectomy in eyes at risk of MNV. In our case, brolucizumab was found to be effective after unsuccessful treatment with other anti-VEGF. Additional studies are required to evaluate the safety and efficacy of brolucizumab for MNV in vitrectomized eyes.

Correspondence to:
Emilia Maggio, emi_maggio@yahoo.it

Case Rep Ophthalmol 2022;13:736–743
DOI: 10.1159/000526568

Introduction

Intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections are the gold standard for the treatment of neovascular age-related macular degeneration (nAMD). Since the widespread adoption of this treatment, the blindness related to nAMD has been decreased by 50–72% [1]. However, these therapeutic results may be reduced in vitrectomized eyes. Although definitive evidence is still lacking, it has been hypothesized that vitreous removal may affect the pharmacokinetics of intravitreally injected drugs [2], accelerating intraocular clearance and reducing the concentrations accordingly. This could result in limited anatomic and visual improvement and the need for more frequent injections.

However, several concerns remain since previous studies on animal models reported controversial findings [3–5], and all clinical trials excluded vitrectomized eyes. Moreover, real-life clinical studies on the effect of anti-VEGF treatment in vitrectomized eyes were either small case series [6], did not include a nonvitrectomized eyes control group [7], or evaluated eyes with disease other than nAMD, such as diabetic macular edema [8].

The novel anti-VEGF brolucizumab was approved in 2019 by the US Food and Drug Administration (FDA). It also recently received approval by the European Medical Agency for the management of nAMD. Data from phase III HAWK and HARRIER trials [9] have revealed longer durability and improved visual outcomes compared to the standard of care by adopting a quarterly rather than bimonthly regimen. Based on these characteristics, brolucizumab may be a suitable therapeutic option for vitrectomized eyes. However, its efficacy in vitrectomized eyes remains to be explored. Here, we describe a case of a vitrectomized eye affected by nAMD and treated with brolucizumab after unsuccessful treatment with other anti-VEGF injections.

Case Presentation

A 68-year-old Caucasian male was referred to our tertiary center for vitreo-retinal surgery with a diagnosis of epiretinal membrane (ERM) in his left eye (LE). The patient complained of progressive vision loss and increasing metamorphopsia in the LE for the last 2 years. His previous ophthalmologic and medical history was unremarkable. On examination, his best corrected visual acuity (BCVA) was 20/20 in the right eye and 20/32 in the LE. Slit-lamp biomiscroscopy showed a slight nuclear cataract in both eyes. Dilated fundus examination and OCT scans revealed ERM with a wrinkling of the retinal surface and vitreous floaters in the LE, and macular drusen were detected in both eyes (Fig. 1a–c). The patient was treated with pars plana vitrectomy with ERM and ILM peeling and cataract extraction in the LE. After surgery, BCVA improved to 20/20 with a remarkable reduction in metamorphopsia (Fig. 1d).

After 3 years, the patient returned, complaining of acute metamorphopsia and visual loss in the LE. Clinical examination and OCT scans demonstrated the presence of an extrafoveal type 2 macular neovascularization (MNV) superiorly to the foveal area, with intra- and subretinal fluid (Fig. 2). BCVA was 20/25. To protect the BCVA, the LE was immediately treated with three monthly intravitreal injections of bevacizumab. However, the examination performed after the loading phase showed worsening in the MNV exudation, increased lesion size, and a BCVA reduction to 20/32 (Fig. 3b). Therefore, the treatment was switched to aflibercept. Nevertheless, after 3 monthly intravitreal injections, further anatomic and functional worsening was detected, with intra- and subretinal fluid reaching the foveal area (Fig 3c, 4e). We thus decided to treat with brolucizumab. Before treatment,

Case Rep Ophthalmol 2022;13:736–743
DOI: 10.1159/000526568

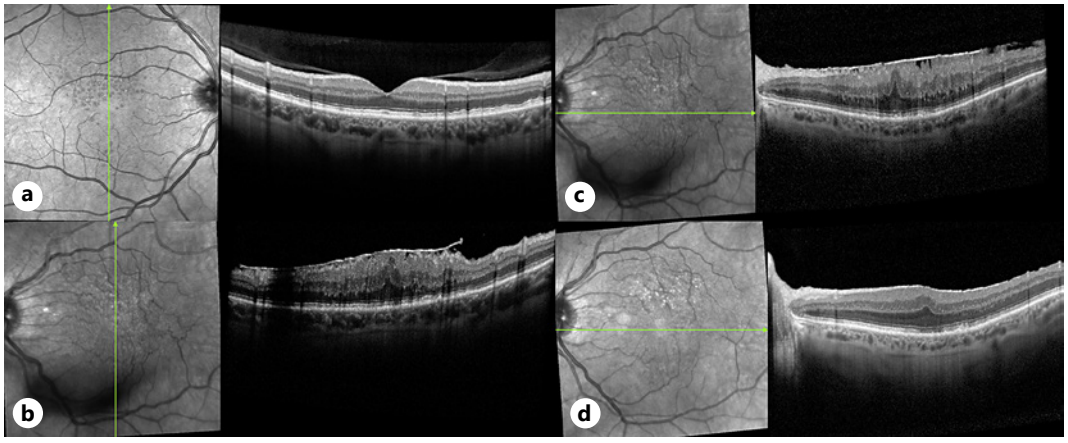

Fig. 1. a OCT scan of RE from the first examination, showing macular drusen. **b**, **c** OCT scan of LE performed before vitrectomy, showing epiretinal membrane, floaters, macular drusen. **d** OCT scan of LE after vitrectomy.

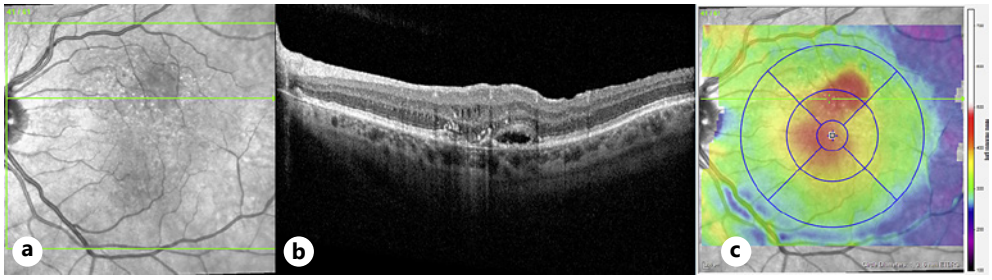

Fig. 2. OCT scan showing MNV in LE.

central and peripheral fluorescein angiography and indocyanine green angiography were performed, confirming the MNV activity and excluding any inflammatory condition (Fig. 4). One month after the first brolucizumab injection, an anatomical and functional improvement was noticed with a reduction in intra- and subretinal fluid, and BCVA improved to 20/25 (Fig. 3d, 5b). No subfoveal fluid was detected. Two additional injections were performed, at monthly intervals, and further anatomic and visual improvement was recorded with a BCVA of 20/20. At the last follow-up visit, 2 months after the third injection, no recurrence was found (Fig. 6).

Discussion and Conclusion

Although clinical trials and real-life studies [9–12] have reported the efficacy of brolucizumab in nAMD management, response to the treatment in vitrectomized eyes remains to be explored. Barchichat et al. [13] described a case of very severe adverse event after bilateral same-day brolucizumab injections, with progression to blindness. Incidentally, one eye had previously undergone vitrectomy.

To the best of our knowledge, there is no other reported case describing response to treatment with brolucizumab for nAMD in a vitrectomized eye. In our case, it proved efficacious and safe, with good and sustained outcomes.

Case Rep Ophthalmol 2022;13:736–743
DOI: 10.1159/000526568

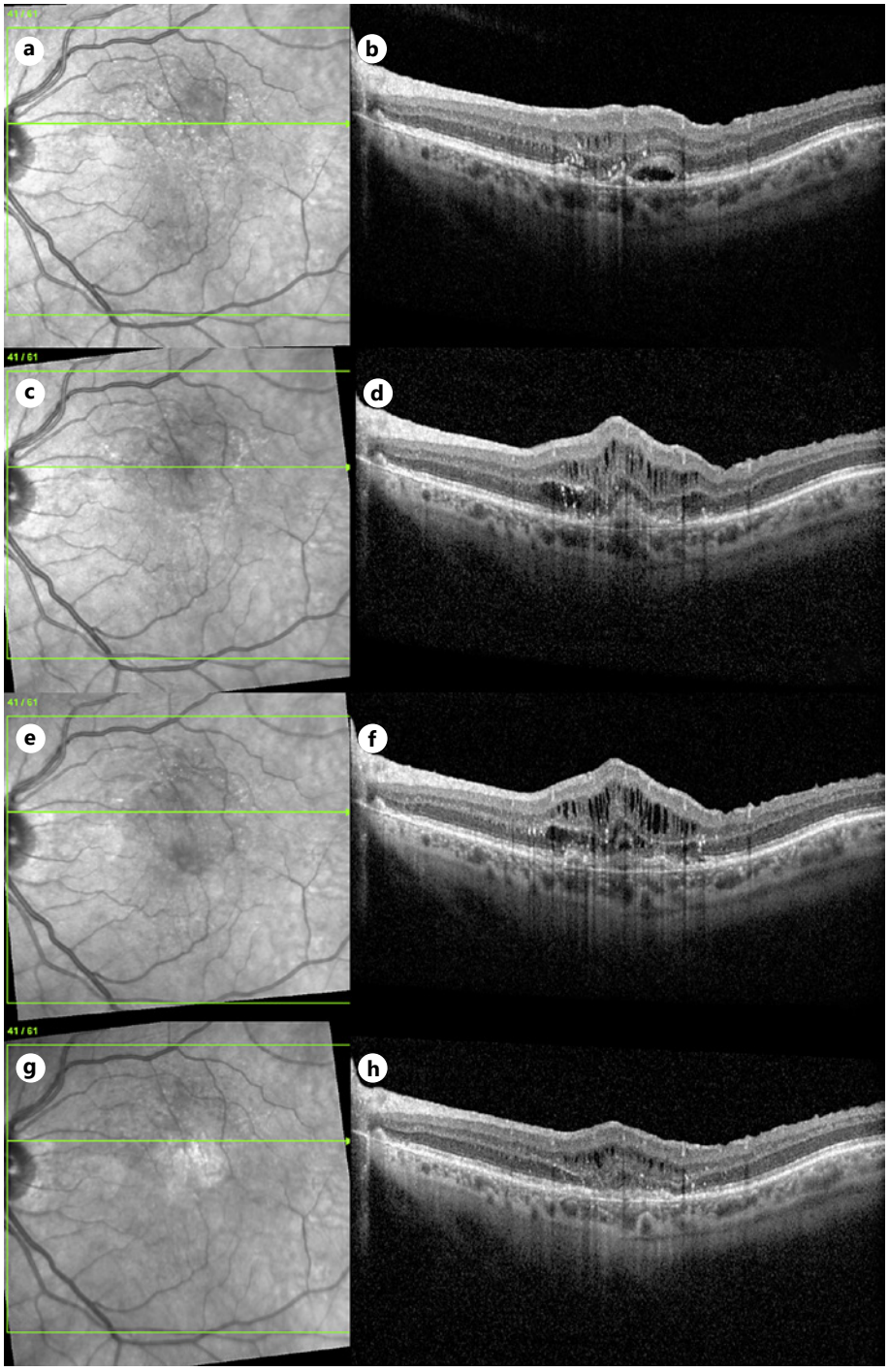

Fig. 3. a OCT scan crossing the lesion before anti-VEGF treatment. **b** After three intravitreal bevacizumab injections, an increase in lesion size and intraretinal fluid were detected. **c** After three intravitreal aflibercept injections, further worsening in lesion size and exudation are visible. **d** After one intravitreal brolucizumab injection.

Our patient was offered brolucizumab after the unsuccessful treatment with other anti-VEGF. Bevacizumab and aflibercept are commonly used to manage nAMD with excellent results, though our patients did not benefit from these treatments. Despite the immediate therapy with three monthly injections, no improvement was recorded; on the contrary, there

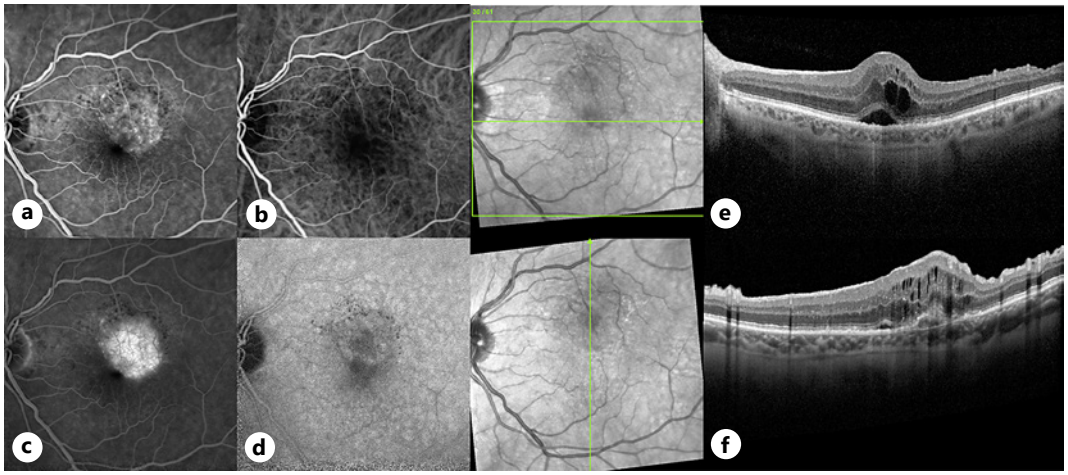

Fig. 4. Imaging performed before brolucizumab injections. **a**, **c** Fluorescein angiography (early and late phase). **b**, **d** Indocyanine green angiography (early and late phase). **e** OCT scan crossing the foveal area. **f** OCT scan crossing the lesion.

was an increase in exudation and visual worsening. Although we cannot exclude the possibility of a nonresponder eye, this result is likely related to the faster drug wash out, due to the absence of the vitreous. The durability of brolucizumab may have obviated this, explaining the prompt and sustained improvement after this treatment.

Changes in anti-VEGF efficacy in vitrectomized human eyes are still not entirely understood. Although reduced efficacy and the need for more frequent injections may be expected, secondarily to an increased intraocular clearance, firm evidence of this is lacking. Animal studies have shown controversial results [3–5]. Vitreous removal has even been proposed to favorably reduce the intravitreal VEGF level, according to research on rabbit eyes [4]. However, given the different volumes of vitreous, potential differences should be considered when translating animal study results to the human context.

Despite the limited evidence, many previous authors have suggested utilizing an agent with a higher binding affinity and consistent treatment intervals to manage vitrectomized eyes [14]. Considering these reflections, brolucizumab may be a suitable option in light of its characteristics. It is composed of a humanized scFv structure that inhibits all the isoforms of VEGF-A and maintains high bioavailability due to its small molecular size and lack of a fragment crystallizable domain. In vitro studies have reported better penetration of the tissues, resulting in increased local efficacy and longer action duration. Moreover, brolucizumab injections contain a higher dose of antibodies; thus, the higher final concentration may affect the durability [15].

In our patient, who had undergone vitrectomy for ERM, the treatment with brolucizumab was found to be safe. However, the safety of brolucizumab in vitrectomized eyes should be further investigated. Considering the possible side effects, brolucizumab should be avoided in patients that underwent vitrectomy for uveitis complications.

In conclusion, determining whether anti-VEGF injections may be efficacious for vitrectomized eyes would be helpful to ophthalmologists managing such patients, as well as when considering vitrectomy in eyes at risk of nAMD. Given its longer durability, brolucizumab may be a suitable therapeutic option for these eyes where a faster clearance of intravitreally injected drugs is expected. In our case, it was found to be effective after unsuccessful treatment with other anti-VEGF. Additional studies are required to evaluate the safety and efficacy of brolucizumab for nAMD in vitrectomized eyes.

Case Rep Ophthalmol 2022;13:736–743
DOI: 10.1159/000526568

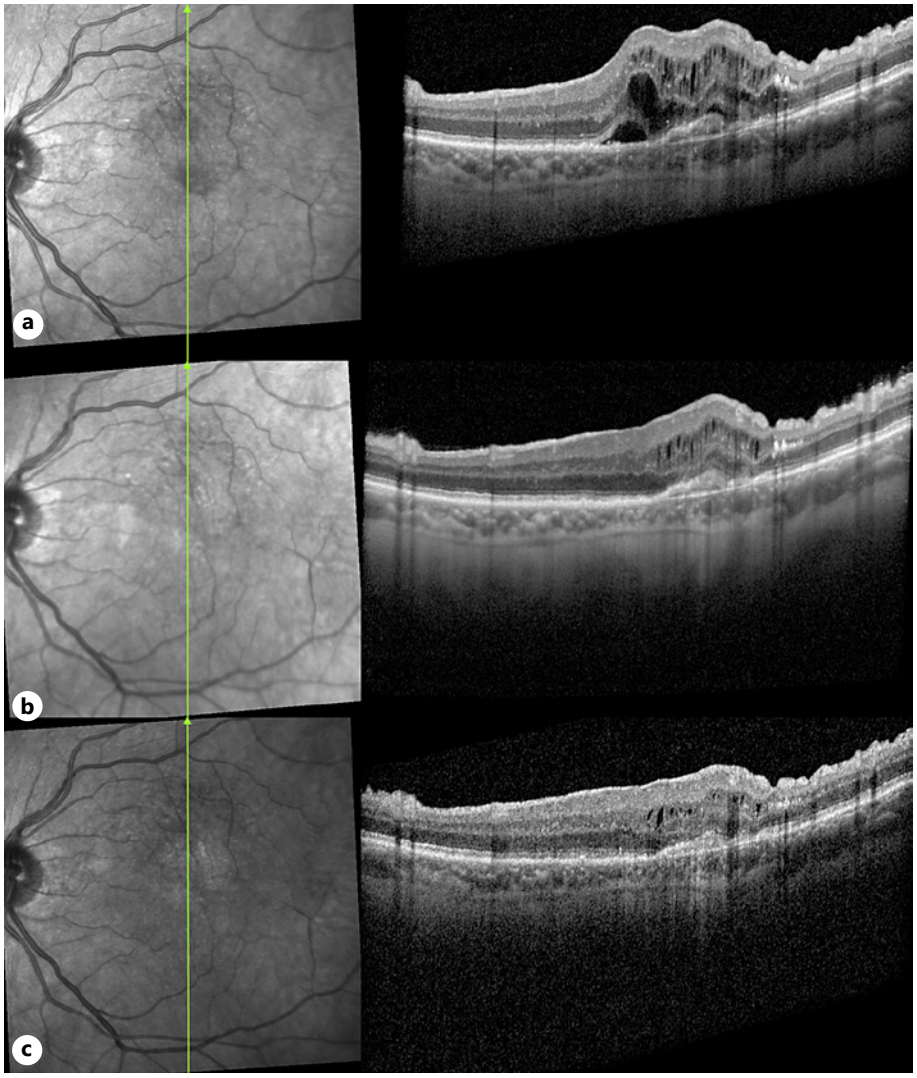

Fig. 5. OCT scans crossing the lesion performed before and after brolucizumab treatment. **a** Before brolucizumab treatment. **b** After one brolucizumab injection. **c** After three brolucizumab injections.

Statement of Ethics

The study was conducted in accordance with the Declaration of Helsinki. The IRCCS Sacro Cuore Hospital Institutional Review Board ruled out need for IRB approval for case reports. This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors declare that they have no financial disclosures.

Case Rep Ophthalmol 2022;13:736–743
DOI: 10.1159/000526568

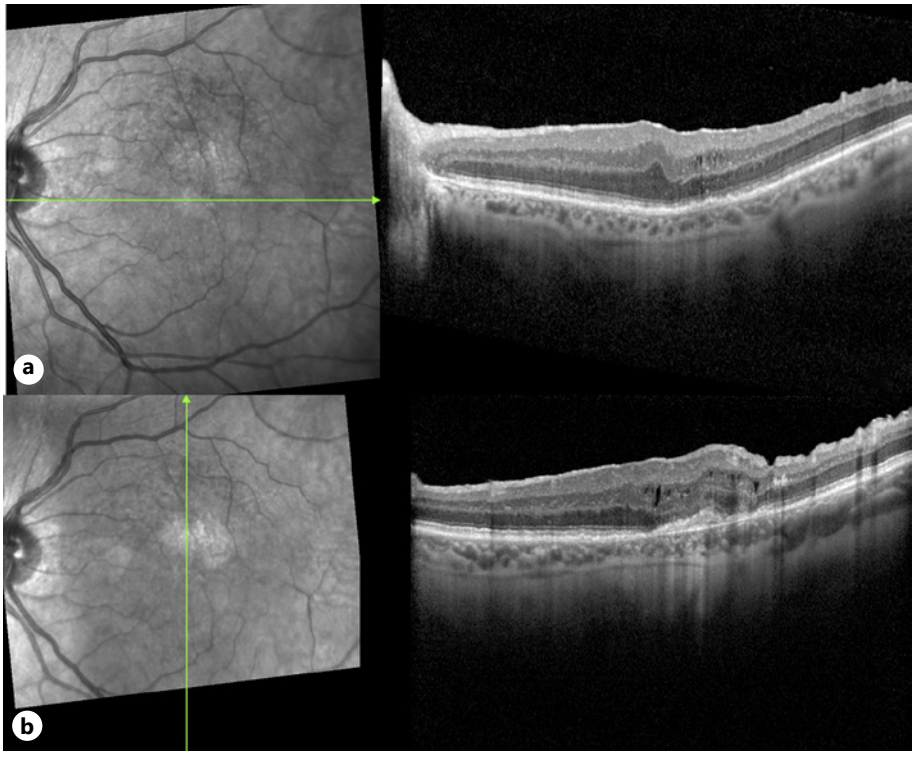

Fig. 6. OCT scans performed at the last follow-up visit. **a** OCT scan crossing the foveal area. **b** OCT scan crossing the lesion.

Funding Sources

No funding was received.

Author Contributions

Emilia Maggio conceived and designed the study; participated in the acquisition, analysis, and interpretation of data; wrote the manuscript; and read and approved the final manuscript. Alessandro Alfano participated in the acquisition, analysis, and interpretation of data; critically revised the manuscript; and read and approved the final manuscript. Maurizio Mete participated in the analysis of data, critically revised the manuscript, and read and approved the final manuscript. Grazia Pertile participated in the design and coordination of the study, gave contribution in the analysis and interpretation of data, critically revised the manuscript, and read and approved the final manuscript.

Data Availability Statement

All data and material are included in the manuscript and the figures. Further inquiries can be directed to the corresponding author.

References

1 Bloch SB, Larsen M, Munch IC. Incidence of legal blindness from age-related macular degeneration in Denmark: year 2000–2010. Am J Ophthalmol. 2012;153(2):209–13.e2.
2 Meyer CH, Holz FG. Preclinical aspects of anti-VEGF agents for the treatment of wet AMD: ranibizumab and bevacizumab. Eye. 2011 Jun;25(6):661–72.
3 Ahn J, Kim H, Woo SJ, Park JH, Park S, Hwang DJ, et al. Pharmacokinetics of intravitreally injected bevacizumab in vitrectomized eyes. J Ocul Pharmacol Ther. 2013;29(7):612–8.
4 Lee SS, Ghosn C, Yu Z, Zacharias LC, Kao H, Lanni C, et al. Vitreous VEGF clearance is increased after vitrectomy. Invest Ophthalmol Vis Sci. 2010;51(4):2135–8.
5 Ahn SJ, Ahn J, Park S, Kim H, Hwang DJ, Park JH, et al. Intraocular pharmacokinetics of ranibizumab in vitrectomized versus nonvitrectomized eyes. Invest Ophthalmol Vis Sci. 2014 Jan 29;55(1):567–73.
6 Jung JJ, Hoang QV, Arain MZY, Chang S. Aflibercept anti-vascular endothelial growth factor therapy in vitrectomized eyes with neovascular age-related macular degeneration. Acta Ophthalmol. 2016 May;94(3):e249–50.
7 Mun Y, Park KH, Park SJ, Woo SJ. Efficacy of anti-vascular endothelial growth factor agents for treating neovascular age-related macular degeneration in vitrectomized eyes. PLoS One. 2021 Jun 10;16(6):e0252006.
8 Tran THC, Verdun S, Le Rouic JF, Uzzan J, Milazzo S, Kodjikian L, et al. Two-year outcome of aflibercept intravitreal injection in vitrectomized eyes with diabetic macular edema. Clin Ophthalmol. 2022 Mar 7;16:603–9.
9 Dugel PU, Koh A, Ogura Y, Jaffe GJ, Schmidt-Erfurth U, Brown DM, et al. HAWK and HARRIER: phase 3, multicenter, randomized, double-masked trials of brolucizumab for neovascular age-related macular degeneration. Ophthalmology. 2020;127(1):72–84.
10 Rübsam A, Rau S, Pilger D, Zeitz O, Joussen AM. Early OCT angiography changes of macular neovascularization in patients with exudative AMD treated with brolucizumab in a real-world setting. J Ophthalmol. 2022 Mar 25; 2022:2659714.
11 Boltz A, Radunsky K, Weingessel B, Vécsei-Marlovits VP. Brolucizumab for pre-treated patients with choroidal neovascularization and signs of tachyphylaxis to aflibercept and bevacizumab. Graefes Arch Clin Exp Ophthalmol. 2022 Mar 29;260(8):2561–6.
12 Musiał-Kopiejka M, Polanowska K, Dobrowolski D, Krysik K, Wylęgała E, Grabarek BO, et al. The effectiveness of brolucizumab and aflibercept in patients with neovascular age-related macular degeneration. Int J Environ Res Public Health. 2022 Feb 17;19(4):2303.
13 Barchichat I, Thiel M, Job O, Schmid M. Bilateral blindness after uneventful brolucizumab injection for macular degeneration. BMC Ophthalmol. 2022 Feb 16;22(1):80.
14 Edington M, Connolly J, Chong NV. Pharmacokinetics of intravitreal anti-VEGF drugs in vitrectomized versus non-vitrectomized eyes. Expert Opin Drug Metab Toxicol. 2017 Dec;13(12):1217–24.
15 Meyer CH, Krohne TU, Holz FG. Intraocular pharmacokinetics after a single intravitreal injection of 1.5 mg versus 3.0 mg of bevacizumab in humans. Retina. 2011 Oct;31(9):1877–84.