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Response of extra-large pigment epithelial detachment to intravitreal brolucizumab injection

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ABSTRACT

Purpose: To determine the role of intravitreal injection (IVI) of brolucizumab for extra-large pigment epithelial detachment (PED) secondary to macular neovascularization (MNV).

Observations: A prospective, non-randomized, uncontrolled case series of three eyes of three patients with extra-large PED (maximum height >350 μm) due to untreated MNV was undertaken at a single center. All three eyes showed significant improvement in the PED height by week 4, with complete resolution by week 8 in two of the three. The third patient who received the second dose is scheduled for a follow-up. Simultaneous notable visual improvement was also observed in all of the eyes. Furthermore, there were no ocular or systemic safety concerns in any of the cases.

Conclusions and Importance: Our real-world case series indicates that intravitreal brolucizumab is efficacious and safe for the management of extra-large PEDs in treatment-naïve MNV eyes. To better understand brolucizumab's mechanism of action, particularly at the sub-RPE and choroidal levels, and the underlying functional principle for the PED response, more study of the drug's pharmacotherapeutics is warranted.

1. Introduction

Macular neovascularization (MNV) is the most common cause of irreversible visual loss in the aged population globally.[1] Pigment epithelial detachment (PED) is one of the earliest biomarkers of MNV and one of the many imaging characteristics of the disease.[2] Sub-retinal pigment epithelial (sub-RPE) fluid, sub-retinal fluid (SRF), intra-retinal fluid (IRF), and hemorrhage can all develop in the presence of PED, serving as additional biomarkers of disease activity.[3] Also, the change from the quiescent form of MNV to the exudative form is linked to the rise in PED height.[4] One year after diagnosis, approximately half of the patients with newly diagnosed PED experience a severe reduction in visual acuity (>3 lines) if they are not treated.[2,5,6] Moreover, it has been widely reported that sub-RPE fluid persists longer than SRF or IRF.[2,7,8]

Anti-vascular endothelial growth factor (anti-VEGF) therapy remains the standard of care for MNV management, but it has yielded suboptimal outcomes in terms of PED morphology.[8,9] Brolucizumab (Beovu®; Novartis, Basel, Switzerland), approved recently in 2019, has shown excellent efficacy for MNV, including in refractory cases.[11,12] In the phase III HAWK and HARRIER trials, brolucizumab outperformed aflibercept in resolving sub-RPE fluid.[13] Here, we describe the role of brolucizumab in the management of extra-large PED (>350 μm) in three eyes with treatment-naïve MNV.

Three eyes of three patients with extra-large PED secondary to treatment-naïve MNV who received intravitreal injection (IVI) brolucizumab were included in this prospective, non-randomized, uncontrolled case study performed at a single tertiary center in India. Extra-large PEDs were defined as PEDs with a maximal height exceeding 350 μm.[14] The study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board and the Ethical Committee of the Retina Institute of Bengal, India. Written informed consent was obtained from each patient. The procedure of IVI brolucizumab (6 mg/0.05 ml) was performed in an operating room under aseptic precautions. Topical moxifloxacin 0.5% was advised post-injection for seven days. The patients were reviewed on day 2, week 4, and subsequently 4 weekly after the baseline injection. The clinical evaluation at each visit included best-corrected visual acuity (BCVA) testing using a Snellen chart, intraocular pressure measurements using a Goldmann applanation tonometer, and anterior and posterior segment examinations. Spectral-domain optical coherence was also performed at all visits. Using the built-in calipers, a masked observer (S.C.) measured the PED's maximum height (S.C.). Three monthly loading

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dose regimen was employed for the patients.

2. Findings

2.1. Case 1

An 81-year-old one-eyed male presented with decreased vision in the left eye (OS) for 15 months. His best-corrected visual acuity (BCVA) was 20/125 in the OS. The patient had an active MNV in the OS with an extra-large PED (Fig. 1a and1b). The patient was administered three monthly IV brolucizumab in the OS. At weeks 4 and 8, his BCVA improved to 20/120, with further improvement to 20/80 at week 12. The PED height also dramatically decreased after 4 weeks (Fig. 1c), resolved entirely after 8 weeks (Fig. 1d), and did not recur after 12 weeks (Fig. 1e). No adverse events were noted during any visit.

2.2. Case 2

A 70-year-old female patient developed a sudden onset of decreased vision in the right eye (OD) for 10 days. Her BCVA was 20/120 in the OD, while it was no PL in the OS. The patient was diagnosed with active MNV with subfoveal bleed and an extra-large PED in the OD (Fig. 2a and b). Following the first dose of IVI brolucizumab, the patient's BCVA improved to 20/32 in the OD, with significant resolution of PED, subretinal fluid (SRF), and subfoveal bleed (Fig. 2c and d) at 4 weeks. Four weeks after the second dose, her BCVA remained stable at 20/32, with complete resolution of the PED, SRF, and subfoveal bleed (Fig. 2e and f). The patient received the third loading dose of IVI brolucizumab and is scheduled for a follow-up. There were no safety concerns with the brolucizumab injection during any of the visits.

2.3. Case 3

A 77-year-old female patient presenting with OS decreased vision and metamorphopsia was diagnosed with active MNV with an extra-large PED (Fig. 3a and b). Her BCVA was 20/20 in the OD and 20/80 in the OS. The patient had bilateral pseudophakia for 10 years. The patient was advised three loading doses of brolucizumab and underwent the first dose in July 2022. At 4 weeks, her BVCA improved to 20/60 with a near-total resolution of the PED (c). No ocular or systemic adverse events were noted. The patient is scheduled for the second dose of brolucizumab.

3. Discussion

In our real-world case series, we show that brolucizumab is effective at improving the morphology of the PED in eyes with MNV. The PED resolution was accompanied by an improvement in vision in all three eyes without any safety concerns.

PED is a hallmark feature of MNV.[2] It denoted the separation between the inner collagenous layer of the Bruch's membrane and the basal lamina of the RPE.[15] There is still much uncertainty about the specific pathophysiology of PED. It is believed that Bruch's membrane degeneration, which is an indispensable component of the progression of MNV disease, plays a significant role.[15,16] PED arises when fluid or blood leaks into the sub-RPE compartments due to the proliferation of MNV.[15,16] It can be encountered in anywhere between 30 and 80% of patients who have MNV.[15] These PEDs can cause progressive vision deterioration if not adequately treated.[17,18] In addition, complications, including RPE rips and bleeding, may result in an acute loss of vision.[17,18] Serra et al.[4] investigated the natural history of quiescent MNVs and found that an increase in PED height (>140 μm) is a key indicator of the transformation from the quiescent stage to the exudative form. The PED height was also a significant predictive factor for the visual outcome.[4] Taller PEDs may therefore indicate a more aggressive type of the disease with a higher probability of adverse visual outcomes.[4] Additionally, they are more resistant to anti-VEGF therapy, which is an important cause of suboptimal visual outcomes.[8,9] To learn more about and explore this aspect, the authors enrolled eyes with extra-large PEDs that were at least 350 μm high in the study and investigated how they responded to treatment with brolucizumab.

Currently, the management of PED is complex due to its relative unresponsiveness to anti-VEGF therapy. Previously, aflibercept has shown a good response in treatment-resistant PEDs.[19] In the phase III HAWK and HARRIER trials, visual outcomes at 96 weeks showed that brolucizumab was non-inferior to aflibercept.[13] Furthermore, brolucizumab was more effective than aflibercept in decreasing retinal thickness and clearing fluid from the sub-RPE, subretinal, and intraretinal regions.[13] In a retrospective comparative study, it was demonstrated that brolucizumab was superior to aflibercept in achieving faster resolution of PED, noted as early as 1 month.[20] Similarly, in all three eyes of our study, the PED showed excellent early response, resolving almost completely within four weeks. Additionally, in two of the three eyes, complete resolution was seen within 8 weeks, which was prior to the completion of the three loading doses. Although faster PED resolution has been linked to an increased risk of RPE rip,[20] none of the three eyes in our series showed any signs of this complication, even when the PEDs were extra-large. Due to the small sample size and brief follow-up period

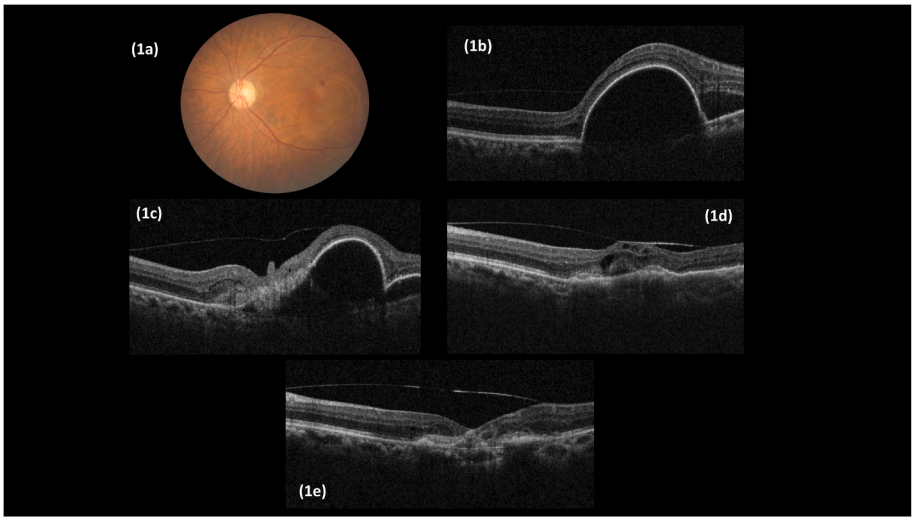

Fig. 1. Case 1 – (a) Color fundus photography showing the extra-large pigment epithelial detachment (PED) with hemorrhage in the left eye (OS). (b) Spectral-domain optical coherence tomography (SD-OCT) confirmed the presence of the PED with intraretinal fluid (IRF). Post three loading doses of intravitreal brolucizumab injection, the sequential SD-OCT illustrated a significant reduction in PED at week 4 (c), which resolved completely by 8 weeks (d), with no recurrence at week 12 (e). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

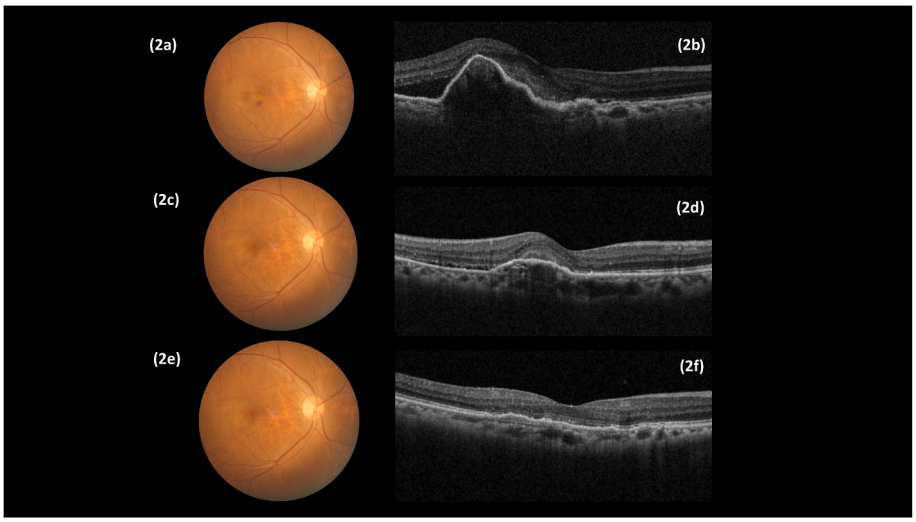

Fig. 2. Case 2 - Color fundus photograph (a) and spectral-domain optical coherence tomography (SD-OCT) (b) of the right eye (OD) showed the presence of an extra-large pigment epithelial detachment (PED) with subfoveal hemorrhage. After brolucizumab therapy, the PED and the subfoveal bleed resolved significantly at week 4 (c, e), and completely by 8 weeks (d, f). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

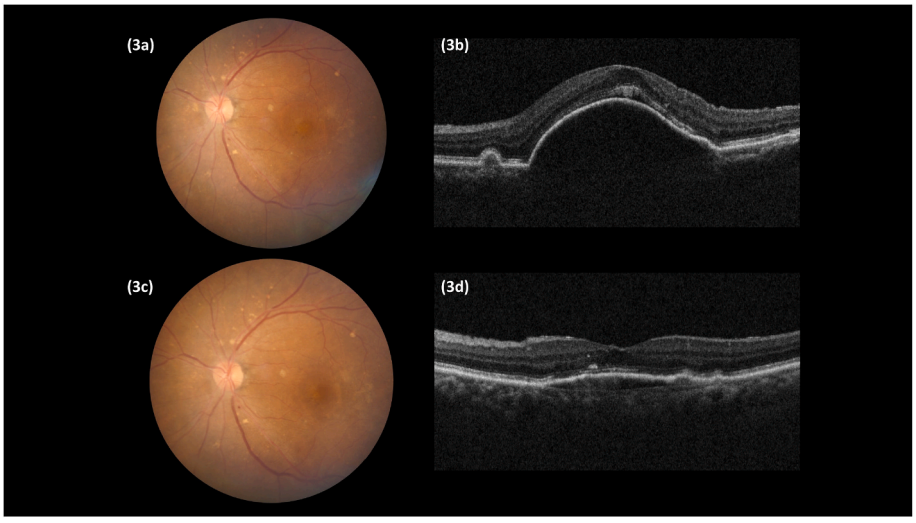

Fig. 3. Case 3 - Color fundus photograph of the left eye (OS) (a) shows the presence of an extra-large pigment epithelial detachment (PED) that was confirmed on the spectral-domain optical coherence tomography (SD-OCT) (b). Following a single dose of intravitreal injection (IVI) of brolucizumab, there was a near-total resolution of the PED (c,d). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

in our study, more research is required in this aspect.

Brolucizumab's superior outcomes can be attributed to its molecular properties, such as its smaller size of 26 kDa, which enables better penetration across the retinal layers, including the RPE.[12,21] Also, it helps deliver a higher molar dose of the drug with its ability to bind in a 2:1 ratio with VEGF-A.[12,21] This allows for greater efficacy as well as durability of the agent when injected into the eye.[12,21] Tamashiro T et al.[22] have demonstrated that brolucizumab therapy induces considerable alterations in choroidal morphology, which may be greater than those documented previously for other anti-VEGF drugs. Brolucizumab outperformed all anti-VEGF molecules, including the recently FDA-approved faricimab, in terms of BCVA gains and reduction in retinal thickness, in a systematic review and network meta-analysis of anti-VEGF medicines in nAMD.[23] As a result of its greater efficacy compared to other anti-VEGF medications, brolucizumab therapy was initiated in all of our cases, despite the fact that they were all treatment-naive. Indeed, the excellent response of PED observed in our series calls for additional molecular and immunological research to better understand the pharmacodynamics and pharmacokinetics of brolucizumab at the sub-RPE and choroidal levels.

Intraocular inflammation (IOI) remains a major concern with the use of brolucizumab. The rate of IOI in the landmark HAWK and HARRIER studies was around 4.4%.[13] However, in the real world, there have been reports of significant variations, ranging from 0% in the BRAILLE study to 12.4% in the SWIFT study.[12,24] In two large real-world datasets, the IRIS Registry (10,654 eyes) and the Komodo Healthcare Map (11,161 eyes), the rate of IOI was approximately 2.4%.[25] The BRAILLE study is the first real-world data from India to evaluate the safety and effectiveness of brolucizumab in nAMD eyes.[26,27] In the short-term results, no occurrences of IOI were seen, however in the 52-week data, the incidence was 3.66%.[26,27] Here, all three patients had mild IOI that resolved completely with topical therapy.[27] The authors suggest looking into how race and genetics may contribute to or protect against brolucizumab-related IOIs.[26,27] Therefore, taking into consideration the somewhat improved safety profile of brolucizumab in Indian eyes, with the episodes of IOI being restricted to milder episodes, the authors had

no reservations in starting all patients on brolucizumab therapy. Even though we did not observe any adverse events, our series was too small, and the follow-up period was too short, to draw any meaningful conclusions.

We have limited evidence on the safety and efficacy of brolucizumab in MNV eyes with extra-large PEDs based on only three cases. To get a better understanding of the role that brolucizumab plays in the eyes of this particular subset of MNV patients, additional research with larger sample sizes and longer follow-ups are required.

4. Conclusion

In this real-world case series, we demonstrate the short-term efficacy of brolucizumab for the management of extra-large PED in treatment-naïve MNV eyes. Further research on the pharmacotherapeutics of brolucizumab is required to better understand its mechanism of action, particularly at the sub-RPE and choroidal levels, and the underlying functional principle for the PED response.

Patient consent

Written informed consent was obtained from patients for publication of these case reports and any accompanying images.

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Authorship

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

Declaration of competing interest

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References

1. Thomas CJ, Mirza RG, Gill MK. Age-related macular degeneration. *Med Clin.* 2021 May;105(3):473–491.
2. Cheong KX, Teo KYC, Cheung CMG. Influence of pigment epithelial detachment on visual acuity in neovascular age-related macular degeneration. *Surv Ophthalmol.* 2021;66(1):68–97.
3. Mukai R, Matsumoto H, Nagai K, Akiyama H. Comparison of the regressive effects of aflibercept and brolucizumab on pigment epithelial detachment. *BMC Ophthalmol.* 2022;22(1):387. Published 2022 Sep. 29.
4. Serra R, Coscas F, Boulet JF, et al. Predictive activation biomarkers of treatment-naive asymptomatic choroidal neovascularization in age-related macular degeneration. *Retina.* 2020;40(7):1224–1233.
5. Patel KH, Chow CC, Rathod R, et al. Rapid response of retinal pigment epithelial detachments to intravitreal aflibercept in neovascular age-related macular degeneration refractory to bevacizumab and ranibizumab. *Eye.* 2013;27(5):663–668.
6. Pauleikhoff D, Löffert D, Spital G, et al. Pigment epithelial detachment in the elderly. Clinical differentiation, natural course and pathogenetic implications. *Graefes Arch Clin Exp Ophthalmol.* 2002;240(7):533–538.
7. Schmidt-Erfurth U, Waldstein SM, Deak GG, Kundi M, Simader C. Pigment epithelial detachment followed by retinal cystoid degeneration leads to vision loss in treatment of neovascular age-related macular degeneration. *Ophthalmology.* 2015;122(4):822–832.
8. Sharma S, Toth CA, Daniel E, et al. Macular morphology and visual acuity in the second year of the comparison of age-related macular degeneration treatments trials. *Ophthalmology.* 2016;123(4):865–875.
9. Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group, Martin DF, Maguire MG, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology.* 2012;119(7):1388–1398.
11. Dugel PU, Jaffe GJ, Sallstig P, et al. Brolucizumab versus aflibercept in participants with neovascular age-related macular degeneration: a randomized trial. *Ophthalmology.* 2017;124(9):1296–1304.
12. Chakraborty D, Maiti A, Sheth JU, et al. Brolucizumab in neovascular age-related macular degeneration - Indian real-world experience: the BRAILLE study. *Clin Ophthalmol.* 2021;15:3787–3795.
13. Dugel PU, Singh RP, Koh A, et al. HAWK and HARRIER: ninety-six-week outcomes from the phase 3 trials of brolucizumab for neovascular age-related macular degeneration. *Ophthalmology.* 2021 Jan;128(1):89–99.
14. Sarraf D, London NJ, Khurana RN, et al. Ranibizumab treatment for pigment epithelial detachment secondary to neovascular age-related macular degeneration: post hoc analysis of the HARBOR study. *Ophthalmology.* 2016;123(10):2213–2224.
15. Zayit-Soudry S, Moroz I, Loewenstein A. Retinal pigment epithelial detachment. *Surv Ophthalmol.* 2007;52(3):227–243.
16. Tan ACS, Simhaee D, Balaratnasingam C, Dansingani KK, Yannuzzi LA. A perspective on the nature and frequency of pigment epithelial detachments. *Am J Ophthalmol.* 2016;172:13–27.
17. Hoerster R, Muether PS, Sitnilska V, Kirchhof B, Fauser S. Fibrovascular pigment epithelial detachment is a risk factor for long-term visual decay in neovascular age-related macular degeneretion. *Retina.* 2014;34(9):1767–1773.
18. Poliner LS, Olk RJ, Burgess D, Gordon ME. Natural history of retinal pigment epithelial detachments in age-related macular degeneration. *Ophthalmology.* 1986;93(5):543–551.
19. He L, Silva RA, Moshfeghi DM, Blumenkranz MS, Leng T. Aflibercept for the treatment of retinal pigment epithelial detachments. *Retina.* 2016;36(3):492–498.
20. Mukai R, Matsumoto H, Nagai K, Akiyama H. Comparison of the regressive effects of aflibercept and brolucizumab on pigment epithelial detachment. *BMC Ophthalmol.* 2022;22(1):387. Published 2022 Sep. 29.
21. Chakraborty D, Sheth JU, Boral S, Sinha TK. Off-label intravitreal brolucizumab for recalcitrant diabetic macular edema: a real-world case series. *Am J Ophthalmol Case Rep.* 2021;24, 101197.
22. Tamashiro T, Tanaka K, Itagaki K, et al. Subfoveal choroidal thickness after brolucizumab therapy for neovascular age-related macular degeneration: a short-term multicenter study. *Graefes Arch Clin Exp Ophthalmol.* 2022;260(6):1857–1865.
23. Finger RP, Dennis N, Freitas R, et al. Comparative efficacy of brolucizumab in the treatment of neovascular age-related macular degeneration: a systematic literature review and network meta-analysis. *Adv Ther.* 2022;39(8):3425–3448.
24. Bulirsch LM, Saßmannshausen M, Nadal J, Liegl R, Thiele S, Golz FG. Short-term real- world outcomes following intravitreal brolucizumab for neovascular AMD: SHIFT study. *Br J Ophthalmol.* 2021;106:1288–1294.
25. Khanani AM, Zarbin MA, Barakat MR, et al. Safety outcomes of brolucizumab in neovascular age-related macular degeneration: results from the IRIS Registry and Komodo Healthcare Map. *JAMA Ophthalmol.* 2022;140(1):20–28.
26. Chakraborty D, Maiti A, Sheth JU, et al. Brolucizumab in neovascular age-related macular degeneration - Indian real-world experience: the BRAILLE study. *Clin Ophthalmol.* 2021;15:3787–3795.
27. Chakraborty D, Maiti A, Sheth JU, et al. Brolucizumab in neovascular age-related macular degeneration - Indian real-world experience: the BRAILLE study - fifty-two-week outcomes. *Clin Ophthalmol.* 2022;16:4303–4313.