Intravitreal Injection of Brolucizumab for Recalcitrant Macular Edema due to Central Retinal Vein Occlusion: A Small Case Series

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Keywords
Brolucizumab · Central retinal vein occlusion · Recalcitrant macular edema

Abstract
This was a single center, prospective uncontrolled nonrandomized case series. Two eyes with recalcitrant ME secondary to CRVO, who have received a minimum of ten intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections, underwent IVI brolucizumab (BRZ). Patients underwent best corrected visual acuity (BCVA) testing, ophthalmic examination, and optical coherence tomography at baseline and follow-up visits (weeks 4, 8, 12, and 16). Both patients demonstrated notable improvement in BCVA and reduction of fluid on SD-OCT lasting up to week 12. At week 16, though both the eyes maintained the visual acuity gains, early increase in fluid was noted in both cases, for which second dose of IVI BRZ was given. No ocular or systemic adverse events were noted in these 2 cases.

Introduction
Intravitreal anti-vascular endothelial growth factor (anti-VEGF) injection is today the gold standard for management of chorioretinal vascular diseases, including age-related macular degeneration (AMD), diabetic macular edema (DME), and retinal vein occlusion (RVO) [1]. Four anti-VEGF molecules have been approved by the US Food and Drug Administration (FDA) for intraocular use, including pegaptanib sodium (Macugen®; Eyetech/OSI
Pharmaceuticals, New York, NY, USA), ranibizumab (Lucentis®; Genentech, S. San Francisco, CA/Roche, Basel, Switzerland), aflibercept (Eylea®; Regeneron, Tarrytown, NY, USA), and brolucizumab (BRZ) (Beovu®; Novartis, Basel, Switzerland) [2–4]. Of these agents, BRZ is the latest to receive approval in 2019 for the treatment of neovascular AMD (nAMD). In India, the drug was launched in October 2020 as Pagenax® (Novartis India Ltd, Mumbai, India)

The 96-week results from the phase 3 clinical trials, HAWK and HARRIER, have demonstrated the noninferiority of BRZ to aflibercept in visual outcomes while achieving superior anatomical outcomes with quarterly (q12-week) dosing in the management of nAMD [5]. Likewise, two phase 3 clinical trials, KESTREL and KITE, evaluated the noninferiority of BRZ 6 mg to aflibercept 2 mg in terms of functional and morphological improvement for management of DME [6]. BRZ showed robust visual gains and anatomical improvements with an overall favorable benefit/risk profile in patients with DME [7]. The results of this trial subsequently lead to approval of BRZ by US FDA for DME in June 2022 [8]. Here we describe the safety and efficacy of IVI BRZ in two eyes with recalcitrant macular edema (ME) following central RVO (CRVO) over 16 weeks in a real-world scenario. Both eyes had undergone multiple intravitreal injections (IVIs) of anti-VEGF were switched to IVI BRZ. Both patients had also received dexamethasone implant with subsequent rise of intraocular pressure (IOP). Written informed consent was obtained from each patient. Injections were performed in an operating theater under sterile technique. Povidone-iodine 5% was applied to eyes both immediately before and after each injection, preoperative antibiotic eye drops were not given, but topical moxifloxacin 0.5% was administered postoperatively for 1 week. The patients were followed up on the second day after injection and at weeks 1, 4, 8, 12, and 16, respectively. At all visits, a detailed history was taken by the treating physician regarding the occurrence of any ocular and systemic adverse event. Additionally, at each follow-up visit, the patients underwent a detailed clinical examination by a retina specialist including best corrected visual acuity (BCVA) assessment using the Snellen’s visual acuity chart, IOP measurement by Goldmann applanation tonometer, anterior segment evaluation using slit-lamp biomicroscopy, and fundus examination with both slit-lamp biomicroscopy (+90D lens) and indirect ophthalmoscopy (+20D lens). Spectral-domain optical coherence tomography (SD-OCT) was performed at all visits from week 4 to week 16. Repeat IVI BRZ was planned based on pro re nata (PRN) regimen.

Findings

Case 1

A 51-year-old male with a history of hypertension since 15 years had CRVO with ME in the right eye (Fig. 1a). He had undergone 14 intravitreal anti-VEGF injections (10 IVI ranibizumab,

Fig. 1. Optos fundus image of case 1.
2 IVI bevacizumab, 2 IVI aflibercept) and one dose of dexamethasone implant over 4 years. Raised IOP was noted after the dexamethasone implant, which was controlled with topical antiglaucoma medications. His last injection (IVI aflibercept) was given with minimal response, 3 months prior to receiving intravitreal BRZ. His BCVA was 20/100 with a CMT of 826 µm on SD-OCT (Fig. 2a). He was administered IV BRZ in the right eye. Subsequently, his BCVA improved to 20/80 at week 4 and 20/63 at weeks 8, 12, and 16, respectively. The SD-OCT showed significant reduction of fluid till week 12 (Fig. 2b–d). However, at 16 weeks, the BCVA was 20/100, and there was an increase in the intraretinal fluid (Fig. 2e) for which the patient received second dose of IVI BRZ. Following the second IVI BRZ, the patient was reviewed after 1 week, 4 weeks, and also 8 weeks. There was no recurrence of fluid noted till last follow-up at 8 weeks following 2nd IVI BRZ. The IOP was normal at all visits, and no intraocular inflammation (IOI) was noted.
Case 2
A 48-year-old male with hypertension having CRVO with ME in the left eye (Fig. 3) had received 12 IVI ranibizumab and 3 aflibercept and 2 dexamethasone over 3 years. He had a history of raised IOP following the second dexamethasone implant which was controlled with antiglaucoma medications. The last injection of aflibercept was given 2 months prior to receiving IVI BRZ. There was minimal response to the last dose of IVI aflibercept, with his BCVA being 20/120 and CMT 811 µm on SD-OCT. The SD-OCT showed presence of gross edema (Fig. 4a). The patient was shifted to IVI BRZ. Consecutively, his BCVA improved and was maintained at 20/80 over 16 weeks. Simultaneously, we noted complete resolution of fluid on SD-OCT at all the visit through 12 weeks (Fig. 4b–d) with a notable reduction in the CMT. Early recurrence of intraretinal fluid was seen at week 16 (Fig. 4e) for which the patient was advised the second IVI BRZ. The patient received the 2nd injection of IVI BRZ and subsequently came for checkup at 1 week and 4 weeks. There was no recurrence of fluid noted on SD-OCT at last follow-up. The patient did not show any evidence of IOI till last follow-up.

Discussion
In our real-world case series, we demonstrate that IVI BRZ is efficacious in improving and maintaining the visual acuity through week 16 for recalcitrant ME secondary to CRVO. Excellent anatomical response was noted on SD-OCT lasting up to 12 weeks with a single dose of BRZ in both cases. However, early recurrence of fluid was seen at week 16 in both eyes for which the second dose of injection was injected. We did not note any ocular or systemic adverse events in these 2 patients.

CRVO is a global health concern. It is estimated to affect 2.5 million people worldwide; its age- and sex-standardized prevalence is 0.8 per 1,000 people [9]. Notably, VEGF levels observed in CRVO cases are among the highest in all retinal disorders, and ME is the most frequent cause of vision loss in those who have the disease [10, 11]. Anti-VEGF treatment is effective for treating ME secondary to CRVO. However, despite aggressive treatment with anti-VEGF agents, a subset of ME patients continue to exhibit suboptimal visual and anatomical response. Such nonresponders or poor responders having recalcitrant ME may benefit by switching to an alternative anti-VEGF agent or corticosteroids [10, 11]. Many of these patients need frequent and repeated IVIs, leading to the burden of frequent clinic visits for IVIs – which is both stressful and inconvenient [12]. BRZ prolonged suppression of VEGF may ensure...
extension of treatment intervals in many patients to 12 weeks or more without compromising the VA gains.

The new anti-VEGF agent BRZ is yet to be evaluated for nonresponsive cases of ME secondary to CRVO, but data from the literature have supported its role as an effective anti-VEGF agent for poorly responsive nAMD and DME [5–7]. A possible reason for this could be related to its higher molar dose and/or causing inhibition of both VEGFR1 and VEGFR2 (ranibizumab causes inhibition of only VEGFR2) [5–8]. Based on these factors and its evolving role as an effective agent for switching anti-VEGF therapy in nonresponsive nAMD, we utilized and performed an initial analysis of the role of IVI BRZ in recalcitrant ME secondary to CRVO.

BRZ is a humanized single chain antibody fragment weighing just 26 kDa. Due to its smaller size, it binds to VEGF-A in 2:1 ratio initially, which may reduce to 1:1 with decreased concentration of the drug [13–15]. However, even at 1:1 ratio, a complete blockage of VEGF-A is maintained by BRZ [15]. Additionally, with a low-molecular weight of BRZ, which is 4 times lower than aflibercept and 1.8 times lower than ranibizumab, it is possible to deliver a 12-fold higher molar dose as compared to aflibercept and 22-fold higher molar dose as compared

Fig. 4. Case 2 – a Spectral domain optical coherence tomography (SD-OCT) image at baseline showing significant intraretinal fluid (IRF) with subretinal fluid (SRF). After undergoing intravitreal injection (IVI) BRZ treatment, there was complete resolution of SRF with notable reduction in IRF on SD-OCT at week 4 (b), week 8 (c), and week 12 (d). At week 16, the SD-OCT showed early recurrence of SRF with minimal increase in IRF (e).
with ranibizumab [15–17]. With these molecular characteristics, BRZ has been shown to have longer durability in the initial trials on nAMD. In the first trial in humans, SEE study, the median time for repeat injection was 30 days longer with 3 mg and 6 mg of BRZ as compared to ranibizumab [17]. In the phase II OSPREY trial, approximately 50% of eyes treated with BRZ maintained stable visual acuity with q12w dosing schedule [18]. Likewise, in the phase 3 HAWK and HARRIER trials, around 50% of patients were maintained on q12w dosing up to 48 weeks [5, 16]. Of these eyes, around 75% continued successfully on q12w injection interval up to 96 weeks [5]. Although a 12-weekly regimen of IVI BRZ would have been ideal in our series, the patients were offered PRN regimen, considering their socioeconomic profile and affordability.

Both cases demonstrated encouraging visual acuity improvement that was maintained up to 12 weeks after a single dose of IVI BRZ. In addition, reduction in the CMT and fluid was observed in both cases over 12 weeks. The significant anatomical and tomographic response of these recalcitrant ME eyes to a single dose of IVI BRZ could be due to distinct pharmacokinetics and pharmacodynamics of the BRZ molecule and tachyphylaxis to the previous molecule due to neutralizing antibodies, altered surface receptor expression, macrophage mediated upregulation of VEGF, and/or altered pharmacokinetics [5, 16, 17]. Further molecular and immunological studies are warranted to rationalize the mechanism of action and validate the encouraging therapeutic response seen after switching to IVI BRZ in recalcitrant DME. IVI BRZ has been associated with IO. The incidence of IOI in the HAWK and HARRIER studies was 4% for BRZ as compared to 1% for aflibercept [5]. The American Society of Retinal Specialists had issued an alert in February 2020 after 14 cases of retinal vasculitis, of which 11 were occlusive vasculitis, were reported after use of IVI BRZ [19]. The “IRIS Registry and Komodo Healthcare Map” data published recently are the largest data so far, on safety of IVI BRZ, in real-world nAMD. They noted an IOI rate of 2.9% in eyes with nAMD [20].

Our group published data on use of BRZ in wet AMD and recalcitrant DME in Indian eyes where we did not find any inflammation with the use of BRZ [21–23]. Recently, Novartis terminated the RAPTOR for branch RVO and RAVEN for CRVO trials in which BRZ was dosed at 4-weekly interval due to high incidence of IOI in both groups, in the interest of patient safety [24]. Novartis has further emphasized that after three loading doses given at 4 weekly intervals, the subsequent doses of BRZ should not be given with less than 8-week interval [25]. The FALCON study which is underway may help us understand whether a 12-week extension from the initiation will be of some help in reducing the immunogenic potential of this efficacious molecule [26].

In the current real-world series of two eyes with recalcitrant CRVO, we have followed a PRN regimen with IVI BRZ. While the efficacy in controlling edema was noted, we did not observe any incident of anterior or posterior segment inflammation during the follow-up period. Additionally, no patients reported any systemic adverse event. However, our series is too small with a short follow-up. And hence, it is insufficiently powered to determine the risks of systemic adverse events. The major limitations of this study include the small number of cases and brief follow-up period.

**Conclusion**

In our real-world case series, we noted an improvement in visual acuity and resolution of fluid in eyes with recalcitrant CRVO with IVI BRZ. The anatomical improvement persists up to 12 weeks after a single dose, with early recurrence of fluid noted at 16 weeks allowing for a PRN regimen in these eyes. The results of these 2 cases, however, need to be validated by larger prospective studies, and BRZ should remain a drug of last resort for eye with recalcitrant CRVO in the current scenario of heightened safety concerns.
Statement of Ethics

The case report is reviewed and approved by the Central Ethics Committee of Disha Eye Hospitals, Kolkata (Number ECR/846/Inst/WB/2016/RR-19: EC-CT-2022-138) and follows Declaration of Helsinki. The study subjects have given their written informed consent to publish their case (including publication of images). Information revealing the subject's identity has been carefully avoided.

Conflict of Interest Statement

Dr. Debdulal Chakraborty, Dr. Soumen Mondal, Dr. Subhendu Boral, and Dr. Arnab Das have no conflicts of interest to declare.

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Author Contributions

Dr. Debdulal Chakraborty (corresponding author): the conception and design of the work, data acquisition, and manuscript writing. Dr. Soumen Mondal: initial drafting of manuscript, image arrangement, and revising manuscript. Dr. Subhendu Boral: literature search and drafting of manuscript. Dr. Arnab Das: defining intellectual content and revision of manuscript. Dr. Debdulal Chakraborty, Dr. Soumen Mondal, Dr. Subhendu Boral, and Dr. Arnab Das attest that they meet the current ICMJE criteria for authorship.

Data Availability Statement

All data generated or analyzed during this case series are included in this article. Further inquiries can be directed to the corresponding author.

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