Intravitreal injection of brolucizumab for recalcitrant macular edema due to central retinal vein occlusion; a small case series

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Abstract

Purpose: To report the efficacy of intravitreal injection (IVI) of brolucizumab for recalcitrant macular edema (ME)due to central retinal vein occlusion (CRVO) in a real-world setting. **Observations:** This was a single-center, prospective uncontrolled non-randomized 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 and were followed-up for minimum of 16 weeks. Patients underwent best-corrected visual acuity (BCVA) testing, ophthalmic examination, and optical coherence tomography at baseline and all the scheduled follow-up visits (Weeks 4, 8, 12, and 16). Both patients demonstrated notable improvement in BCVA and reduction in the fluid on SD-OCT lasting up to week 12. At week 16, both the eyes maintained the visual acuity gains. However, early increase in fluid was noted in both cases, for which second dose of IVI brolucizumab was planned. No ocular or systemic adverse events were noted in any of the cases. **Conclusions:** In this real-world case series, treatment with IVI brolucizumab exhibited excellent visual acuity outcomes lasting up to 16 weeks for the treatment of recalcitrantME secondary to CRVO. Single dose IVI brolucizumab achieves good anatomical improvement based on SD-OCT persisting up to 12 weeks, followed by early recurrence of fluid at week 16. The results did not show any ocular or systemic safety concerns for IVI brolucizumab.

Intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections is 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), and brolucizumab (Beovu®; Novartis, Basel, Switzerland)[2-4]. Of these agents, Brolucizumab is the latest to receive approval in 2019 for the treatment of neovascular age-related macular degeneration (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 non-inferiority of brolucizumab 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, are underway at 200 sites in 36 countries to evaluate the non-inferiority of Brolucizumab 6 mg to Aflibercept 2 mg in terms of functional and morphological improvement for management of DME over 2 years[6]. The interim results of these trials have shown encouraging visual acuity and anatomical outcomes at the end of one year[7,8]. However there is no data available on the use of these agents in retinal vein occlusion. Here we describe the safety and efficacy of IVI brolucizumab in two eyes with recalcitrant ME following central retinal vein occlusion (CRVO) over 16 weeks in a real-world scenario.

Material and Method:

Both eyes had undergone 12 or more intravitreal injections (IVI) of anti-VEGF, were switched to IVI brolucizumab. Written informed consent was obtained from each patient. Injections were performed in an operating theatre under sterile technique. Povidone-iodine 5% was applied to eyes both immediately before and after each injection, pre-operative antibiotic eye drops were not given, but topical moxifloxacin 0.5% was administered post-operatively for one week. The patients were followed-up on the second day after injection, and at weeks 4, 8, 12, and 16,

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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, intraocular pressure (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 Brolucizumab was offered 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 (OD) (Fig 1). He had undergone 14 intravitreal anti-VEGF

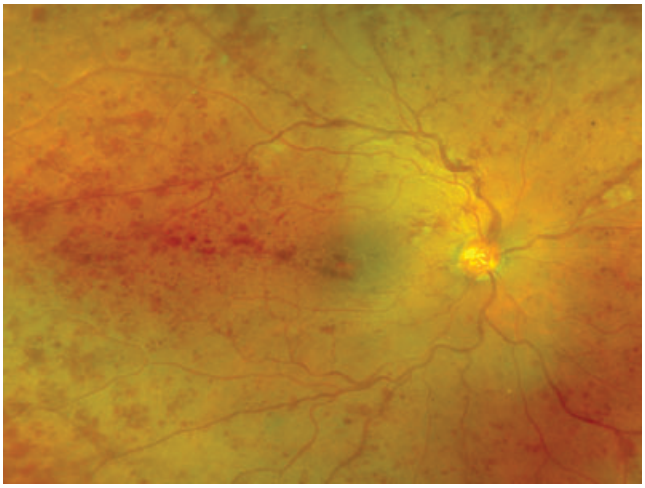

Fig 1: Optos fundus image of case 1

injections (10 IVI Ranibizumab, 2 IVI Bevacizumab, 2 IVI Aflibercept) and one dose of Dexamethasone implant over 6 years. Raised intraocular pressure (IOP) was noted after the Dexamethasone implant, which was controlled with topical anti-glaucoma medications (AGM). His last injection (IV Aflibercept) was given with minimal response. His BCVA was 20/100 with a CMT of 826¼m on SD-OCT (Fig. 2a). In February 2021, he received IVI Brolucizumab. 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

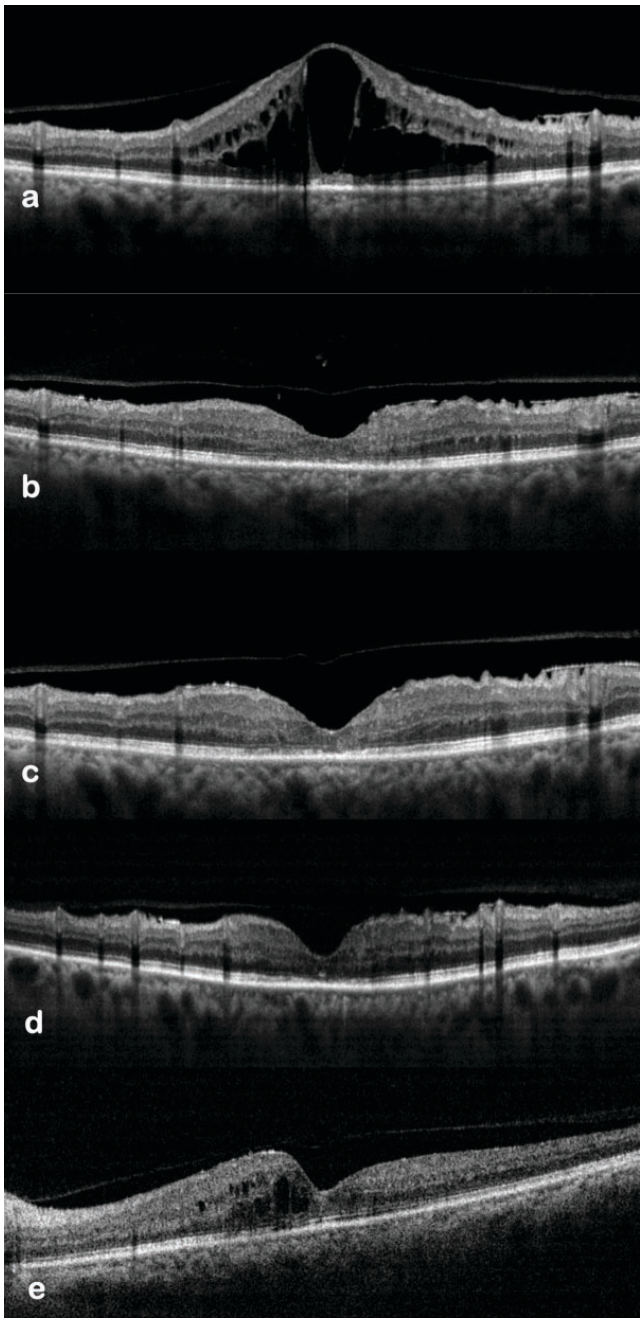

Fig 2: Case 1 - a. Spectral domain optical coherence tomography (SD-OCT) image at baseline. After undergoing intravitreal injection (IVI) Brolucizumab treatment, the patient demonstrated considerable reduction in edema on SD-OCT at week 4 (b), week 8 (c) and week 12 (d).

2 b,c,d). However, at 16 weeks, the BCVA was 20/100, and there was an increase in the intra retinal fluid (IRF)(Fig 2e)for which the patient received second dose of IVI Brolucizumab. The intraocular pressure (IOP) was normal

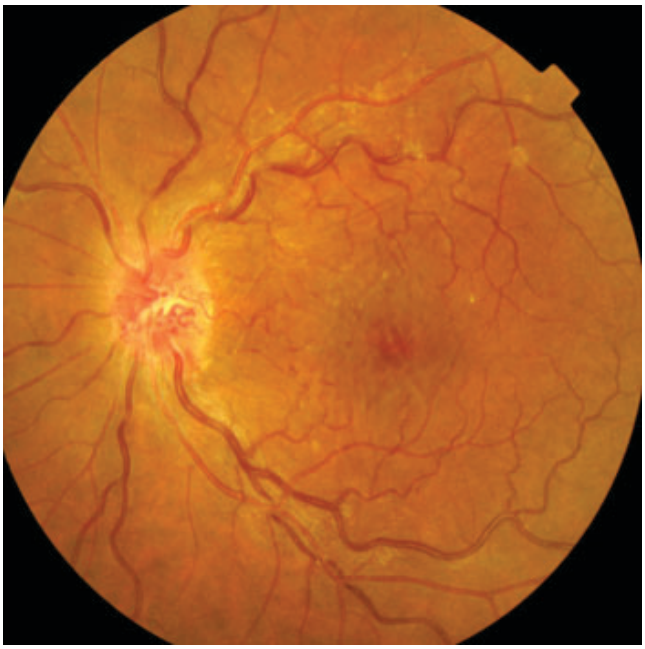

Fig 3: Fundus image of Case 2

at all visits with absence of any side adverse reaction.

Case 2 : A 48-year-old male with hypertension having CRVO with ME in the left eye (OS)(Fig 3) had received 12 IVI Ranibizumab over 6 years, with last injection given in February 2021. There was minimal response to the last dose of IVI Ranibizumab, with his BCVA being 20/120 and CMT 811¼m on SD-OCT . The SD-OCT showed presence of gross edema (Fig. 4a). The patient was shifted to IVI Brolucizumab. 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 4 b,c,d) with a notable reduction in the CMT. Early recurrence of IRF was seen at week 16 (Fig 4e) for which the patient was advised the second injection of Brolucizumab.

Discussion:

In our real-world case series, we demonstrate that IVI brolucizumab 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 brolucizumab in both cases. However, early recurrence of fluid was seen at week 16 in both eyes for which the second dose of injection was planned. We did not note any ocular or systemic adverse events in our series.

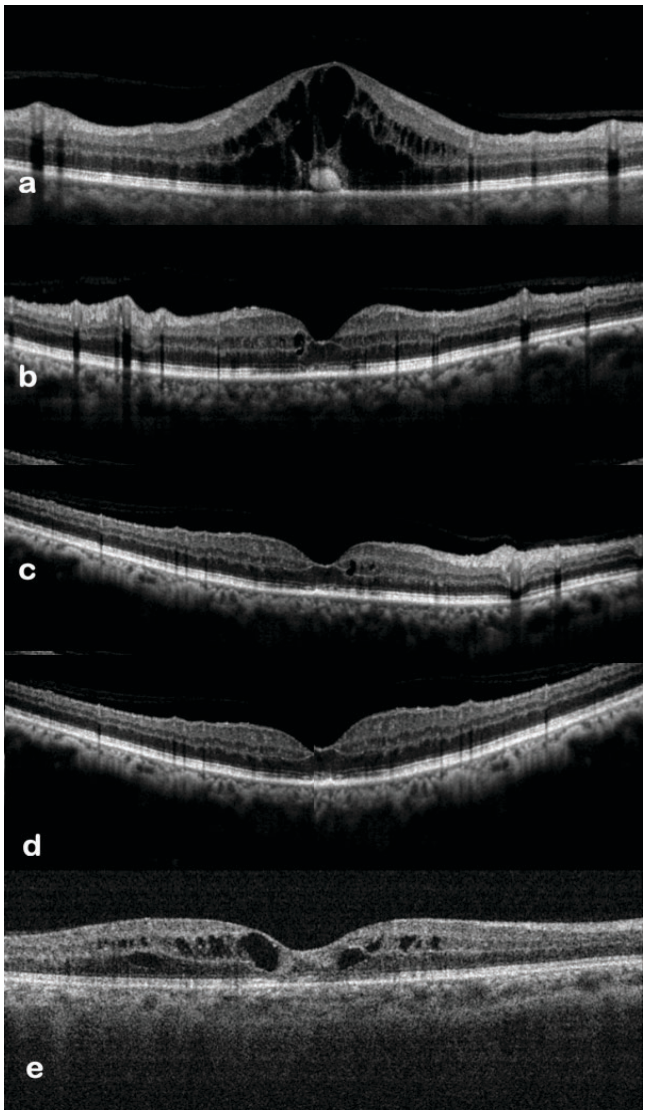

Fig 4: Case 2 - a. Spectral domain optical coherence tomography (SD-OCT) image at baseline showing significant intraretinal fluid (IRF) with subretinal fluid (SRF). After undergoing intravitreal injection (IVI) Brolucizumab treatment, there was complete resolution of SRF with notable reduction in IRF 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).

Central retinal vein occlusion (CRVO) is a global health concern. It's 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[10] and ME is the most frequent cause of vision loss in those who have the disease[11].

When treating ocular diseases, we want to improve

patients' visual and anatomic outcomes with the minimum amount of injection burden. Anti-VEGF treatment is effective for treating ME secondary to CRVO, but the burden can be treatment-associated adverse events or the hassle of frequent clinic visits for intravitreal injections – both stressful and inconvenient.

Brolucizumab's prolonged suppression of VEGF means that treatment intervals can be extended in many patients to 12 weeks or more without compromising the VA gains

Over the past 16 years, the management of ME secondary to retinal vascular disease has been revolutionized by widespread adoption of IVI of anti-VEGF agents[10,11]. However, despite aggressive treatment with these anti-VEGF agents, a subset of ME patients continue to exhibit suboptimal visual and anatomical response. Such non-responders having recalcitrant ME may benefit by switching to an alternative anti-VEGF agent or corticosteroids.

The newer anti-VEGF agent brolucizumab is yet to be evaluated for non-responsive cases of ME secondary to CRVO, but data from the literature has supported its role as an effective anti-VEGF agent for poorly responsive nAMD agents[13,14]. A possible reason for this could be related to the autoantibodies developed to the prior anti-VEGF agent, its higher molar dose, and/or causing inhibition of both VEGFR1 and VEGFR2 (Ranibizumab causes inhibition of only VEGFR2)[13,14]. Based on these factors and its evolving role as an effective agent for switching anti-VEGF therapy in non-responsive nAMD, we utilized and performed an initial analysis of the role of IVI Brolucizumab in recalcitrant ME secondary to CRVO.

Brolucizumab is a humanized single chain antibody fragment weighing just 26kDa[15]. 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[15]. However, even at 1:1 ratio, a complete blockage of VEGF-A is maintained by brolucizumab[15]. Additionally, with a low molecular weight of brolucizumab, that 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 with ranibizumab[15,16]. With these molecular characteristics, brolucizumab has been shown to have longer durability in the initial trials on nAMD. The first trial in humans, SEE study, the median time for repeat injection was 30 days longer with 3mg and 6mg of brolucizumab as compared to ranibizumab[17]. In the phase II OSPREY trial, approximately 50% of eyes treated with brolucizumab 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[16]. Of these eyes, around 75% continued successfully on q12w injection interval up to 96 weeks[5]. Although a 12-weekly regimen of IVI brolucizumab 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 brolucizumab. 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 brolucizumab could be due to distinct pharmacokinetics and pharmacodynamics of the brolucizumab molecule and tachyphylaxis to the previous molecule due to neutralizing antibodies, altered surface receptor expression, macrophage mediated up-regulation of VEGF and/or altered pharmacokinetics[9,12]. Further molecular and immunological studies are warranted to rationalize the mechanism of action and validate the encouraging therapeutic response seen after switching to IVI brolucizumab in recalcitrant DME. IVI brolucizumab has been associated with intraocular inflammation (IOI). The incidence of IOI in the HAWK and HARRIER studies was 4% for brolucizumab as compare to 1% for aflibercept[5]. The American Society of Retinal Specialists (ASRS) 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 brolucizumab[19]. The incidence of Retinal vasculitis +/retinal vascular occlusion in the post-marketing surveillance was 15.31 per 10,000 injections (till February 12, 2021)[20]. However, our group published data on use of brolucizumab in wet AMD and DME where we did not find any inflammation with the use of brolucizumab[20-22].

In the two eyes also we did not observe any incident of anterior or posterior segment inflammation during the 16 weeks follow-up period. Additionally, no patients reported any systemic adverse event. However, our series is too small with a short follow-up of 16 weeks. 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 without any safety concerns amongst both the eyes with CRVO up to 16 weeks.The concurrent anatomical improvement persists up to 12 weeks after a single dose, with early recurrence of fluid noted at 16 weeks. The results of these two cases however need to be validated by larger prospective studies.

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

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

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