Management of Submacular Hemorrhage Using Intravitreal Brolucizumab with Pneumatic Displacement: A Case Series

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Keywords
Brolucizumab · Macular neovascularization · Anti-vascular endothelial growth factor · Age-related macular degeneration · Polypoidal choroidal vasculopathy

Abstract
The management of submacular hemorrhage (SMH) necessitates rapid clearing of the bleed for optimal visual outcomes. We present a series of 3 cases with large fresh SMH (≤7 days) secondary to MNV that were treated with intravitreal injection (IVI) of brolucizumab along with SF6 gas injection. A face-down position was recommended for 5 days after the injection, with follow-up visits at regular intervals. All eyes demonstrated notable improvement in visual acuity with complete resolution of SMH lasting up to 6 months. There were no ocular or systemic side effects. Thus, IVI brolucizumab with SF6 gas injection is efficacious and safe for the management of large SMH secondary to MNV.

Introduction
Submacular hemorrhage (SMH) is a potentially blinding complication of macular neovascular (MNV) diseases such as neovascular age-related macular degeneration (nAMD) and polypoidal choroidal vasculopathy (PCV) [1]. The retinal pigment epithelial and the neurosensory retina, particularly the photoreceptor layer, can be severely compromised by the deposited blood [2]. Thus, it is imperative to rapidly clear the hemorrhage in such cases.
Intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy remains the gold standard for the management of MNV and is greatly beneficial for clearing smaller SMH [3]. However, in the presence of large SMH, anti-VEGF monotherapy has inferior treatment outcomes. To overcome this, the use of additional agents such as intravitreal gas injection and intravitreal recombinant tissue plasminogen activator (rtPA) has been utilized successfully [4] in combination with anti-VEGF therapy. Additionally, for extensive SMH cases, even pars plana vitrectomy with/without subretinal rtPA has been employed [5].

Bevacizumab (AVASTIN, Genentech, Inc.), ranibizumab (Lucentis®; Genentech, S. San Francisco, CA/Roche, Basel, Switzerland), aflibercept (Eylea®; Regeneron, Tarrytown, NY, USA), and brolucizumab (Beovu®; Novartis, Basel, Switzerland) are the anti-VEGF agents that have been used successfully to treat SMH [6–8]. Amongst them, there has been a single case series where brolucizumab was administered along with rtPA and C3F8 gas for large SMH secondary to nAMD [8]. We herein report a novel case series in which patients with large SMH (>4-disc diopters and a thickness of >100 μm on the spectral-domain optical coherence tomography [SD-OCT]) were managed with a combination of intravitreal injection (IVI) of brolucizumab and SF6 gas. Repeat IVI brolucizumab was offered on a pro re nata basis. This retrospective chart analysis 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.

**Case 1**

A 53-year-old female with treatment-naïve MNV in the left eye (OS) presented with a sudden onset of decreased vision for 2 days. Her best-corrected visual acuity (BCVA) was 20/125 in the OS. Fundus examination showed the presence of a large SMH (Fig. 1a).

![Fig. 1. a Color fundus photograph (CFP) of case 1 illustrating the presence of a large submacular hemorrhage (SMH) in the left eye (OS) at baseline. b The spectral-domain optical coherence tomography (SD-OCT) demonstrated the presence of subretinal fluid (SRF) and a large pigment epithelial detachment (PED). Two months after treatment with intravitreal injection (IVI) brolucizumab + 0.3 cc SF6 gas injection, the SMH had considerably reduced (c) with a dry macula on SD-OCT (d). The SMH gradually disappeared over the follow-up visits at months 3 (e) and 6 (g) with absence of fluid on SD-OCT (3 months: (f), 6 months: (h)).](image)
On the SD-OCT, there was the presence of significant subretinal fluid (SRF) and a large pigment epithelial detachment (PED) (Fig. 1b). A provisional diagnosis of MNV secondary to PCV was made and the patient was treated with IVI brolucizumab (6 mg in 0.05 mL) + 0.3 mL of 100% SF6 gas injection. Postinjection, the patient was advised to remain in a prone position for 5 days. Post the therapy, the patient was lost to follow-up due to COVID-19 lockdown. When the patient presented after 2 months, her BCVA had improved to 20/80 with a significant resolution of the SMH (Fig. 1c). On SD-OCT, the macula was dry with the persistence of the PED (Fig. 1d). After observation, the PED completely resolved at 3 months (Fig. 1f), with a further clearing of the SMH (Figure E) and improvement in the BCVA to 20/60. At 6 months, the BCVA was maintained at 20/60, with complete clearing of the SMH (Fig. 1g) and a dry macula on the SD-OCT (Fig. 1h). There were no safety concerns at any of the visits.

**Case 2**

A 74-year-old male developed a sudden onset of decreased vision in the OS for 7 days. His BCVA was 20/120 in OS while it was 20/400 in OD. The fundus examination revealed the presence of a massive SMH extending beyond the inferior arcade (Fig. 2a) in OS, while OD showed the presence of scarred MNV. On SD-OCT, there was the presence of thick SMH with multiple thumb-like PEDs suggestive of MNV secondary to PCV (Fig. 2b). IVI brolucizumab (6 mg in 0.05 mL) + 0.3 mL of 100 percent SF6 gas injection was used to treat the patient, and subsequently, a face-down position was advised for 5 days. At 1 month, the BCVA was reduced to 20/400 with the presence of breakthrough vitreous hemorrhage. Since there was the presence of significant yellowish blood with a dramatic decrease in the BCVA and also since the patient was one-eyed, the patient underwent pars plana vitrectomy with a...
second dose of IVI brolucizumab. At 2 months, his BCVA improved to 20/100 with a significant reduction in the SMH (Fig. 2c) and the presence of trace SRF on SD-OCT (Fig. 2d). The PEDs had completely resolved on the SD-OCT at this visit. The patient was advised to receive additional injections, but he refused owing to financial restrictions. At 3 months, the SMH gradually reduced (Fig. 2e) with the BCVA improving up to 20/80 and a dry macula on SD-OCT (Fig. 2f). The SMH completely disappeared by the end of 6 months (Fig. 2g). However, the SD-OCT demonstrated early recurrence of intraretinal fluid, SRF, and the PED (Fig. 2h). The third dose of IVI brolucizumab was administered to the patient at this stage, and the patient is scheduled for a follow-up visit. There were no major adverse effects reported during any of the visits.

Case 3

A 70-year-old male had a sudden onset of decreased vision in the OS for 7 days. His BCVA was 20/200 in OS. There was the presence of a large SMH in the OS on fundus evaluation (Fig. 3a), which was confirmed on the SD-OCT (Fig. 3b). Additionally, the SD-OCT also showed significant SRF and large PEDs (Fig. 3b). The authors performed IVI brolucizumab (6 mg in 0.05 mL) + 0.3 mL of 100 percent SF6 gas injection and the patient was advised to remain in a prone position for 5 days. After 1 month, the BCVA improved significantly to 20/60 with a gradual reduction in the SMH (Fig. 3c). The SMH completely disappeared by the end of 6 months (Fig. 3g). During the follow-up visits at months 3 (e) and 6 (g), the SMH gradually disappeared, with no fluid on SD-OCT (3 months: (f), 6 months: (h)).
Discussion

In our case series, we demonstrate the efficacy of the brolucizumab agent in combination with SF6 gas in the management of large SMH. Our results also show the use of this novel combination in PCV management. Furthermore, no ocular or systemic side effects were noted in our study.

SMH is a rare but catastrophic complication of MNVs, especially nAMD and PCV [1, 2]. It must be promptly treated to avoid permanent vision loss. Although anti-VEGF therapy is the cornerstone of addressing the underlying disease, the use of adjunctive agents such as rtPA and gas is vital to manually iron out the bleeding from the macular region, especially the fovea. In a literature review of five publications involving 681 eyes, Stanescu-Segall D et al. [4] have noted the displacement rate of SMH to be 76%. They looked at the data on several combination therapies for SMH and found that visual improvement was seen in all of them, with the best improvement noted with a combination of anti-VEGF therapy along with rtPA and gas [4]. Thus, choosing the best combination therapy for SMH is vital to avoid overtreating the patients. The duration of the bleeding is the most crucial factor in determining the best therapy for large SMH. Patients who are treated early, i.e., ≤14 days of bleeding, have the best visual outcomes [9]. All 3 patients in our study were treated within the first week of bleeding, allowing us to obtain good visual and anatomical outcomes. Nonetheless, long-term prospective studies are warranted to compare the different management strategies to better understand the optimal management of SMH.

The use of rtPA, which is an efficient fibrinolytic agent, has revolutionized the management of SMH [10]. This is especially true for patients with older bleeds, where the use of rtPA is critical to lyse the blood clots, which can then be easily displaced by the gas bubble [10]. For eyes with relatively recent SMH, gas injection alone may be adequate to displace the relatively fresh clots [10]. Fang IM et al. [10] evaluated 53 eyes with SMH, of which 25 eyes received intravitreal gas injection alone and 28 eyes received intravitreal tPA and gas injection. The authors concluded that intravitreal t-PA was beneficial for SMH only in eyes with a hemorrhage duration of more than 14 days [10]. Thus, based on the literature, rtPA was not deemed necessary in our series because all patients had relatively fresh SMH (≤7 days). Moreover, the aflibercept molecule has been shown to be cleaved by rtPA when combined with plasmin [11]. This impacts its ability to bind to the VEGF molecule, thereby reducing its efficacy [11]. Brolucizumab, the newer agent, is a single-chain humanized antibody fragment with a weight of only 26 kDa [12]. It should potentially penetrate the retina tissue more effectively than aflibercept because it has a lower molecular weight (1/4th) and a greater molar dose (12 times) than aflibercept. Although no in-vitro studies have been conducted to determine the effect of the brolucizumab molecule in the presence of rtPA with/without plasmin, the authors hypothesize that the brolucizumab molecule, like the aflibercept molecule, is most likely to be cleaved by rtPA in the subretinal space. From this perspective, along with the fresh nature of the SMH, all three eyes in our series were treated with only brolucizumab and SF6 gas, and rtPA was avoided. Nonetheless, in-vitro studies are warranted to better understand the compatibility of the brolucizumab molecule with rtPA in the presence of plasmin.

IVI brolucizumab has been linked to episodes of intraocular inflammation, with a reported incidence of roughly 4% in the HAWK and HARRIER studies [13]. However, in the recently published Indian real-world data (BRAILLE Study) on the safety and efficacy of IVI brolucizumab in nAMD, the authors did not report any incidence of intraocular inflammations among 126 injections [14]. Similarly, no ocular or systemic adverse effects were observed in our series, although it was not powered for safety analysis.

In conclusion, this is the first reported series demonstrating the role of intravitreal brolucizumab injection in combination with SF6 gas for the management of large SMH secondary
to MNV. To corroborate our findings, additional prospective studies with larger sample sizes and different therapeutic regimens are needed.

**Statement of Ethics**

This study protocol and retrospective review of patient data were reviewed, and the need for approval was waived by the Retina Institute of Bengal Ethics Board. Written informed consent was obtained from the patients for the publication of this case series and any accompanying images.

**Conflicts of Interest Statement**

None of the authors has any conflicts of interest or disclosures to declare.

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**Author Contributions**

Somnath Chakraborty is the principal investigator who assisted with data acquisition, data analysis, interpretation, and critical review of the manuscript. Jay Umed Sheth conducted the literature review and wrote the manuscript. Jay Umed Sheth conducted the literature review and wrote the manuscript.

**Data Availability Statement**

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

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