Brolucizumab: What's new and newer about it?

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ABSTRACT

Brolucizumab is the newest anti-vascular endothelial growth factor (anti-VEGF) drug approved for use. The aim of this review is to review the HAWK/HARRIER clinical trials, examine post-marketing experience with the drug, and evaluate the packaging/procedural differences with brolucizumab. Brolucizumab is a more potent and longer lasting anti-VEGF agent, and is an important agent that may be used in the treatment of neovascular age-related macular degeneration. Retinal vasculitis is a rare but very serious complication of brolucizumab that the patient and physician must be aware of.

Key Words: Brolucizumab, VEGF

INTRODUCTION

The introduction of intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents in ophthalmology has sparked a tremendous paradigm shift in the management of numerous retinal disorders. The most common retinal pathologies in which VEGF plays an important role include neovascular age related macular degeneration (AMD), diabetic retinopathy and retinal vein occlusion. The medical literature on the development of anti-VEGF therapies, clinical trials leading to their approval, and post-marketing experience with the drug are all essential information for the clinician to review. The most recent anti-VEGF agent approved in the United States is brolucizumab (Beovu, Novartis, Basel, Switzerland) which was approved for use in neovascular AMD in October 2019[1]. The purpose of this review is to examine the clinical trials leading to its approval, to review post-marketing experience, as well as evaluate packaging and procedural differences in preparing this agent for administration. Recently, there has also been a recommendation by American Society of Retina Specialists (ASRS) to consider withholding or limiting its use due to higher risk of intraocular inflammation compared to other anti-VEGF agents.

What is Brolucizumab?

Brolucizumab is a single chain antibody fragment that binds to VEGFR1 and VEGFR2, inhibiting the production of VEGF-A[1]. One of the ways brolucizumab differs from other anti-VEGF agents is its small molecular size (26kDa), which allows for increased tissue penetrance of the drug. The small molecular size also allows for a higher molar concentration of drug per injection (6mg dose). The combination of the increased penetrance and high molar concentration of brolucizumab allow it to have increased stability and a more potent intraocular effect. Brolucizumab is also the first anti-VEGF agent that has been approved to be administered at an increased interval length of 8-12 weeks after the loading dose (three doses spaced one month apart)[1].

Clinical Trials Leading to Brolucizumab

FDA requires two separate multicenter double blind randomized clinical trials revealing the same outcome for an agent's approval. In the case of brolucizumab, those were the HAWK and HARRIER trials. Both trials showed that 6mg/0.05ml brolucizumab was non-inferior to 2mg/0.05ml aflibercept in regard to visual acuity at 48 weeks for neovascular AMD (Table 1). Patients who received aflibercept were treated at 8-week intervals after

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Received: 08.10.2020
Accepted: 25.11.2020
Ret-Vit 2020; 29: 287-291
DOİ:10.37845/ret.vit.2020.29.52

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Table 1. *Mean change in BCVA at 48 weeks.*

	Brolucizumab	Aflibercept
HAWK	+6.6 letters (n=360) (56% of patients on q12weeks)	+6.8 letters (n=360) (All patients on q8weeks)
HARRIER	+6.9 letters (n=370) (51% of patients on q12weeks)	+6.8 letters (n=370) (All patients on q8weeks)

the loading dose. Patients who received brolucizumab were treated at either 8- or 12-week intervals after the loading dose. More than 50% of eyes treated with 6 mg brolucizumab were maintained on 12-week dosing throughout the study period (48 weeks). Brolucizumab also showed improved anatomic outcomes across the board when compared to aflibercept in both trials (Table 2). There was a statistical difference favoring brolucizumab when evaluating for central subfield thickness reduction, as well as the presence of intraretinal, subretinal fluid, and sub-RPE fluid. Finally, the overall rates of adverse events were similar between brolucizumab and aflibercept, however rates of intraocular inflammation were higher with brolucizumab (4.4%) compared to aflibercept (0.8%).

Post-marketing Experience with Brolucizumab

There is limited post-marketing data given brolucizumab's recent release in October 2019, however some initial investigations with brolucizumab have shown improvement in subretinal fluid (SRF) and central macular thickness (CMT) in recalcitrant chronic neovascular AMD. Although, even with improvement in SRF there was no statistically significant improvement in final visual acuity[2].

Several studies with brolucizumab since its release have centered around the topic of post-injection inflammation, specifically regarding retinal vasculitis. To date the largest case series of retinal vasculitis after brolucizumab reviewed 26 eyes from 25 patients that were reported to the ASRS Research and Safety in Therapeutics Committee[3]. In this study 22 of the 25 patients were female, which may suggest an auto-immune etiology. There is limited data at the present time to establish this correlation. In this study the average time of presentation was 25 days (range 3-63 days) after the most recent brolucizumab injection. Of those affected, 46% of eyes had a decrease of 3 lines or more at last follow up visit[3].

Novartis has performed a cumulative review of post-marketing data with a data lock point of August 28th, 2020 which showed a rate of retinal vasculitis and/or retinal vascular occlusion at 10.67 per 10,000 injections[4].

ASRS Warnings on Brolucizumab Use

In February 2020, the ASRS issued a member alert after 14 cases of vasculitis following injection of brolucizumab were reported. Subsequently, Novartis created an external safety review committee (SRC) and launched an internal review of the data for the HAWK and HARRIER trials. In the report it was found that the rate of retinal vasculitis occurred at 3.3%[5]. Occlusive retinal vasculitis occurred in 2.1% of patients. Of those patients with retinal vasculitis, 22% experienced 3 or more lines of vision loss. However, it is important to note that even when considering vision loss related to retinal vasculitis, the overall rates of at least moderate vision loss (>15 ETDRS letter loss) in the study population were similar between brolucizumab (7.4%) and aflibercept (7.7%)[5].

Perspective and Recommendation from Novartis

To date, the safety data continue to support a favorable benefit-risk profile for Beovu. As with all medicines, adverse events can occur, which is why we continuously monitor the safety of our products for the occurrence of such events. The prescribing information leaflet for Beovu in the US states a 4% rate of intraocular inflammation and a 1% rate of retinal artery occlusion. We believe the incidence of these events remains consistent with or below the package insert. In the registration trials, the incidence

Table 2. *Central thickness reduction in OCT at 48 weeks.*

	Brolucizumab	Aflibercept
HAWK	-172.8µ (n=360) (56% of patients on q12weeks)	-143.7µ (n=360) (All patients on q8weeks)
HARRIER	-193.8µ (n=370) (51% of patients on q12weeks)	-143.9µ (n=370) (All patients on q8weeks)

of vision loss was comparable at all letter intervals across Beovu and aflibercept. Physicians are also reminded to act promptly when symptoms are reported by patients, and if clinical signs of intraocular inflammation or changes in vision after Beovu injection are observed, withhold Beovu, perform the appropriate diagnostic evaluation and treat the symptoms or intraocular inflammation as per good medical practice[6].

Novartis has been completely transparent throughout the process of investigating intraocular inflammation related to brolucizumab. The company commissioned a safety review committee to have complete access to the HAWK/HARRIER trials to conduct a third-party review of the data independent and autonomous to Novartis oversight. Novartis is continuing to work towards identifying patients at risk for severe inflammatory vasculitis events.

Preparation and Administration Differences in Clinical Practice

Brolucizumab is provided in a single dose glass vial along with a filter needle for drawing the medication (Figure 1). A total of 0.09-0.10ml of medication is provided in the glass vial and 0.05ml is the dose used for injection (Figure 2). The physician must be cautious to not waste drug in the preparation process, or there is a risk of having an insufficient amount for injection. After withdrawing the drug from the vial, the filter needle is exchanged for a short needle for injection (usually 30 gauge). Currently there is no option to obtain brolucizumab in a prefilled syringe.

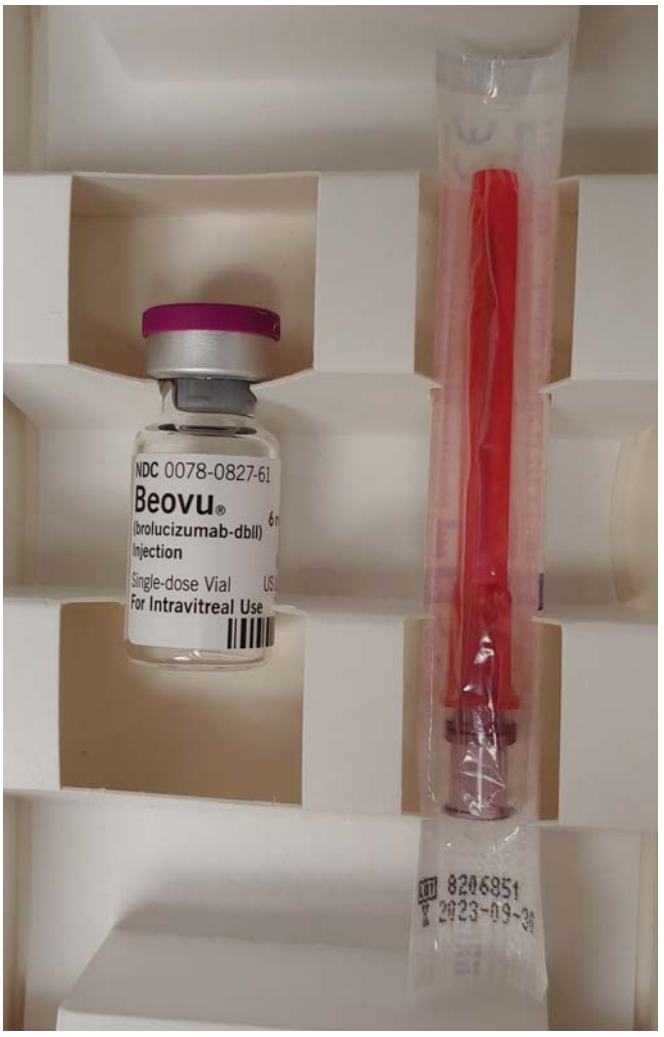

Figure 1. *Contents of brolucizumab package: The vial and a filter needle.*

Case Example

The following is a case example of where brolucizumab may play a role in recalcitrant AMD. Patient is a 76-year-old female who presented initially in January 2018 (Figure 3) with a best corrected visual acuity (BCVA) of 20/200 and was diagnosed with neovascular AMD. The patient was subsequently started on aflibercept injections on a treat and extend regimen. By December 2019, after 17

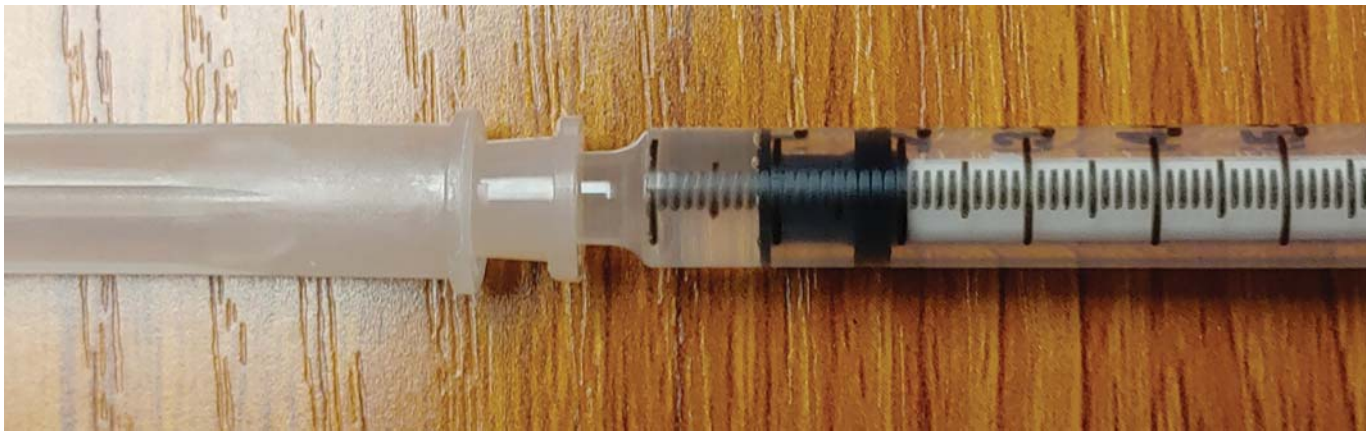

Figure 2. *Total amount of the medicine the vial has in it has been drawn into a syringe. Note that approximately 0.09 ml was provided in the vial. The amount to be injected needs to be 0.05 ml after squirting out the excess amount before brolucizumab is ready for injection).*

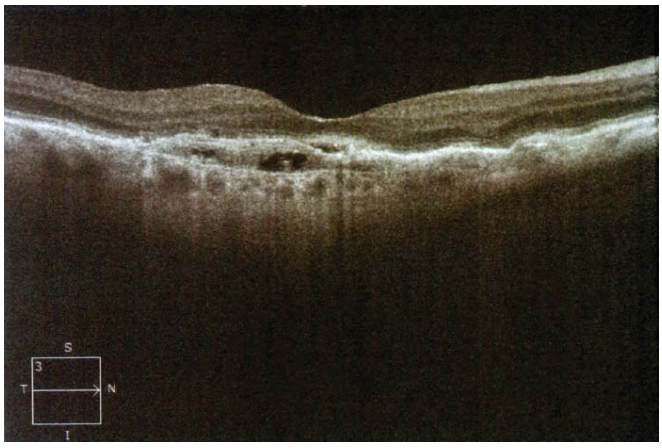

Figure 3. *OCT scan of the CNVM secondary to AMD and the retinal edema prior to starting aflibercept. Visual acuity was 20/200 at this initial visit.*

aflibercept injections (Figure 4), the patient's BCVA had improved to 20/40. At that visit she received her 18th injection, and 6 weeks later retinal edema and subretinal fluid persisted. (Figure 5). After discussing risks and benefits with the patient, the clinical decision was made to switch to brolucizumab in January 2020 due to persistent subretinal fluid with aflibercept. On the subsequent follow up visit in February 2020 the patients subretinal fluid had completely resolved (Figure 6). However, the patient's BCVA decreased to 20/60 in conjunction with resolution of subretinal fluid. The patient had no observed intraocular inflammation or adverse reaction to brolucizumab noted on exam.

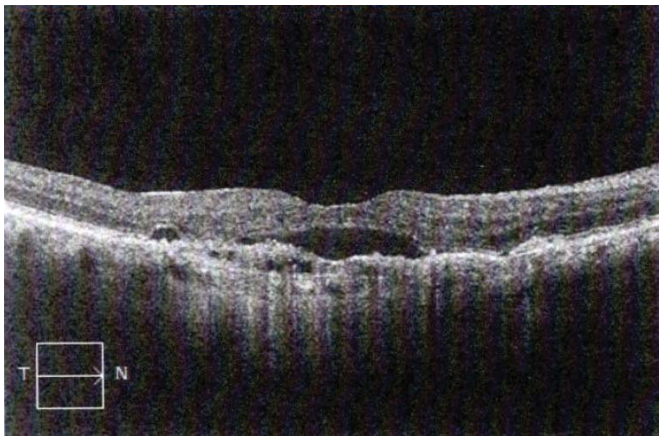

Figure 4. *Subretinal fluid/retinal edema remains after 17 injections of aflibercept.*

This case highlights brolucizumab's potential for drying the retina compared to previous anti-VEGF agents at the same injection interval, especially in recalcitrant cases. In this specific case it resulted in an interval decrease in BCVA, which could be due to a variety of factors. Subretinal fluid has been shown in previous studies to coincide with better visual acuity and preserved retinal function unlike intraretinal edema in nAMD patients[7-9]. It is also possible that the progression of AMD/retinal atrophy coincided with the drying of the retina. Additionally, there could have been an unexpected adverse effect of brolucizumab despite no clinically apparent inflammation. Anatomic outcomes provide detailed indicators of disease burden, yet it is important to note that this is not always correlated to clinical outcomes. While the HAWK/HARRIER trials which showed that brolucizumab was superior in central subfield thickness and anatomic outcomes, BCVA outcomes were similar compared to aflibercept.

The MERLIN trial is an ongoing prospective trial aimed to assess brolucizumab in the setting of recalcitrant AMD cases. This trial will compare brolucizumab dosed every 4 weeks compared to aflibercept dosed every 4 weeks in patients with persistent retinal fluid despite frequent anti-VEGF injections. Observations from the HAWK/HARRIER trials indicated that brolucizumab achieved better retinal fluid resolution, and the MERLIN trial will

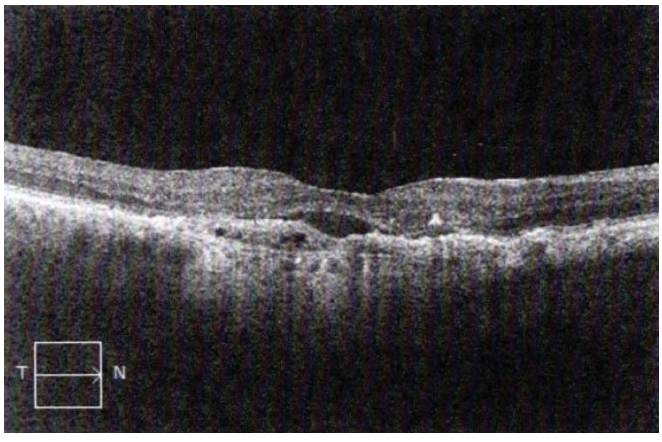

Figure 5. *Persistent subretinal fluid with aflibercept after the 18th injection, the previous one being 6 weeks ago. Visual acuity was 20/40 at this visit.*

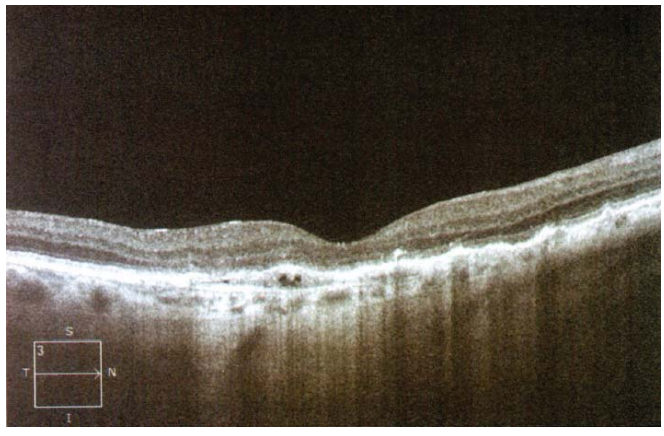

Figure 6. *Six weeks after the brolucizumab injection, retinal edema and the subretinal fluid was totally resorbed. Visual acuity was 20/60 at this visit.*

be helpful in evaluating the use of brolucizumab in cases of persistent retinal fluid.

Other approaches to recalcitrant AMD include the addition of dorzolamide-timolol (Cosopt®) topical drops to patients receiving intravitreal anti-VEGF[10]. Hsu et al showed a significant improvement in central subfield thickness in nAMD patients with recalcitrant subretinal fluid who received Cosopt compared to placebo. The mechanism of this effect could be explained by decreased aqueous humor production leading to reduced clearance of anti-VEGF and a prolonged effect of anti-VEGF[11,12]. Further, the beta blocker may act in conjunction to benefit the effects of anti-VEGF at the receptor level. Another approach is increasing the frequency of injection in identified "non-responders" who may show improvement with more frequent injections[13].

CONCLUSION

Brolucizumab, a more potent and longer acting anti-VEGF agent, is an important addition to the armamentarium against neovascular AMD. Likely, this agent will soon get approved for other indications as well. It is not uncommon in medicine to have rare, severe adverse events with therapeutic agents. In regard to brolucizumab, the ASRS was very prompt in recognizing the potential for severe vision loss due to occlusive retinal vasculitis associated with brolucizumab. Novartis has been transparent with their clinical data and the incidence of this complication was noted to be 3.3% in the ASRS committee review of the HAWK/HARRIER trial data. The overall incidence is likely lower given the number of reported cases to date, Novartis has reported incidence of 10.67 per 10,000 injections in post marketing reports to date, however the exact incidence is unknown given the bias to under-reporting. While the incidence of retinal vasculitis associated with brolucizumab in the HAWK/HARRIER trials raises concern, it is also important to note that the overall rate of all-cause moderate vision loss (>15 ETDRS letter loss) was similar between aflibercept and brolucizumab groups[5]. Although retinal vasculitis is a rare complication of intravitreal brolucizumab, it is our responsibility to consider safer medications when available. If the clinical scenario supports the use of brolucizumab, we must clearly discuss the potential for vision loss secondary to retinal vasculitis, making sure that the patient fully comprehends and participates in the decision-making process.

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