

# Anatomical and functional responses to single brolocizumab injection in neovascular age-related macular degeneration patients not responding to antiangiogenics: a case series

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## ABSTRACT

**Introduction:** Neovascular age-related macular degeneration (nAMD) is treated with antivasular endothelial growth factor (anti-VEGF) drugs. However, resistance to anti-VEGF therapy is observed in some patients. Brolocizumab is a new-generation anti-VEGF drug for the treatment of nAMD, with proven efficacy in fluid resolution and long-lasting effects.

**Methods:** We report here a case series of nAMD patients not responding to previous anti-VEGF therapy showing anatomical and functional response to a single intravitreal injection of brolocizumab.

**Results:** Nine patients with nAMD, undergoing treatment with anti-VEGF therapy (aflibercept, bevacizumab, or ranibizumab) but with either fluid persistence or frequent fluid recurrences in retinal compartments, were switched to intravitreal brolocizumab and examined 4 weeks postinjection. No signs of active disease were observed in all but one patient, with complete retinal fluid resolution in seven patients. Central macular thickness and visual acuity significantly improved, and changes were sustained for up to 12 weeks in a subset of three patients. No adverse reactions were observed.

**Conclusions:** This new anti-VEGF drug showed great efficacy since the first week from the injection with a significant reduction of subretinal fluid and rapid improvement of visual acuity. In conclusion, brolocizumab administered intravitreally appears to be an effective treatment in nAMD patients, leading to both early anatomical and functional improvements.

**Keywords:** Anti-VEGF, Brolocizumab, Case series, Neovascular age-related macular degeneration (nAMD)

## Introduction

Neovascular age-related macular degeneration (nAMD) is a chronic degenerative disease characterized by the pathological growth of vessels, which leak blood and fluids in the various retinal compartments, leading to loss of visual acuity (VA) (1,2). Fluids accumulating in retinal compartments

(i.e., intraretinal fluid [IRF], subretinal fluid [SRF], or fluid accumulating in the subretinal pigment epithelium [sub-RPE] space) are used as biomarkers for disease activity. Treatment of nAMD is based on the use of antivasular endothelial growth factor (anti-VEGF) drugs, with the objective of controlling the exudation from the vessels to minimize disease activity and consequently avoid VA loss (3,4). Appropriate treatment intervals maintain and sometimes improve patients' vision in the long term (3,5-9).

Macular neovascularization secondary to nAMD requires continuous treatment because it remains active for years (10). Randomized controlled trials showed that SRF and/or IRF is still present after two years of treatment in around 40%-50% of patients (3,11,12). Long-term retrospective observational studies have also reported around 40% of patients with detectable active disease at the end of the study, after 3 and 10 years, respectively (9,13). The activity pattern of nAMD is often unpredictable and patients must be continuously monitored and treated to avoid permanent VA loss

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(14-16), thus representing an important burden for both patients and clinicians (4,17).

In clinical practice, patients are treated in a personalized way with the aim of controlling recurrences, but over time anti-VEGF therapies may experience reduced effectiveness: after 5 and 10 years of treatment, 41% and 42% of patients, respectively, made at least one switch to other anti-VEGFs (9,18). The poor response (with either fluid persistence or recurrences) may be due to tachyphylaxis, changes in the neovascular membrane characteristics (e.g., increased fibrosis acting like a resorption barrier), chronic changes in vessel walls, changes in the type of lesion evolving over time, or an inadequate treatment frequency (19,20). As a consequence, switching treatment becomes necessary and it is important to re-establish control of the disease. While VA is not usually regained, treatment switch is consistently associated with anatomical improvement (20,21). In patients showing fluid persistence despite at least three-monthly injections with bevacizumab, switching to either aflibercept or ranibizumab showed comparable efficacy, with anatomical improvement noticeable after a single injection (22).

Brolucizumab 6 mg (Beovu<sup>®</sup>, Novartis AG, Basel, Switzerland), a monoclonal single-chain variable domain antibody fragment, is a new-generation anti-VEGF drug approved for the treatment of nAMD, with proven efficacy in fluid resolution and long-lasting effects (23). Brolucizumab shows great promise in reducing the risk of undertreatment and permanent VA loss. Results from the HAWK and HARRIER studies (24) showed that patients treated with brolucizumab (administered at 8- and 12-week intervals after three-monthly loading doses) had a significantly higher reduction in retinal central subfield thickness (CST) and absence of SRF/IRF at 48 and 95 weeks postinjection, compared with those treated with aflibercept (23). These data also showed that disease activity was controlled in a shorter timeframe after diagnosis when using brolucizumab compared with aflibercept (24). The use of brolucizumab in patients showing no response to other anti-VEGFs offers a valuable therapeutic option to maintain disease control and VA while reducing treatment burden.

Preliminary observations on patients switched to brolucizumab have recently been published (25,26), confirming its efficacy in controlling fluid accumulation. However, more data are needed to further characterize brolucizumab efficacy and rapidity in obtaining complete fluid resolution and the impact on functional outcomes.

We report here the anatomical and functional responses observed in a group of nAMD patients with persistent or recurrent fluids 1 month after a single injection of brolucizumab, as assessed retrospectively in a center in Italy.

## Materials and methods

### Study design

We retrospectively analyzed data from nine patients with nAMD who were switched to brolucizumab 6 mg because they were not responsive to other anti-VEGFs. All recruited patients were followed and treated at Villa Donatello Hospital, Florence, Italy. The use of brolucizumab for treating

nAMD was officially introduced in October 2020. Patient demographic and clinical information collected at baseline (i.e., before the brolucizumab injection) included: age; gender; treatment prior to brolucizumab injection (anti-VEGF used, treatment duration, number of injections, last interval between injections, time from last injection to the first brolucizumab injection); VA; CST; type of lesion; and the presence of IRF, SRF, or sub-RPE fluid, fibrosis, subretinal fibrosis, and subretinal hyperreflective material (SHRM).

Following the first brolucizumab injection, patients were examined at two time points ( $T_1 = 1 \pm 1$  weeks and  $T_2 = 4 \pm 1$  weeks) to determine the presence of anatomical and functional changes using slit-lamp ophthalmoscopy, spectral domain optical coherence tomography (SD-OCT), fundus examination, and VA assessment (ETDRS scoring). Three patients had further assessments at a longer follow-up.

Due to the possibility of intraocular inflammation (IOI), vasculitis, or retinal vascular occlusion, all patients were informed and instructed to report, within 24 hours of the injection, any of the following symptoms: redness, reduction of viscous, floaters, eye pain or pressure, scotoma, or blurred vision. A notification letter was sent to the local Ethical Committee, according to Italian regulations. All patients provided written informed consent prior to receiving the brolucizumab injection.

### Patient inclusion and exclusion criteria

The study only included patients with nAMD not responsive anymore to other anti-VEGFs (i.e., showing either fluid persistence or frequent fluid recurrences), who were first injected with brolucizumab by December 2020, and had a visit 1 month ( $T_2$  range  $4 \pm 1$  weeks) after the injection. Patients with a maculopathy other than nAMD or who received brolucizumab injection after December 2020 were excluded.

### Study outcomes

The main outcome measured was the proportion of patients without SRF and IRF 1 month after brolucizumab injection. Secondary outcomes were the proportion of patients with reduced (or absent) SRF/IRF 1 month after injection, the proportion of sub-RPE fluid resolution 1 month after injection in patients with sub-RPE fluid at baseline, the proportion of patients without active disease 1 month after injection, the mean time to first disease inactivation, and the mean difference of CST and VA between baseline and 1-month postinjection.

### Statistical analysis

Descriptive statistics were used to summarize demographic and clinical data at baseline and successive time points, as appropriate. Continuous data were described using the mean, standard deviation (SD), and range, while categorical data were expressed as percentages. The difference in CST and VA between baseline and the assessment at 1 month was tested using the nonparametric Wilcoxon



signed-rank test, with statistical significance set at  $p < 0.05$ . The time to first disease inactivation was determined using Kaplan-Meier survival analysis using the two available observation time points,  $T_1$  and  $T_2$ . Analyses were performed using IBM® SPSS® version 26.

## Results

### Patient characteristics at baseline

A total of nine patients were eligible and included in the study. None of the patients had signs of IOI at baseline or study end. Patient demographics and clinical and treatment history at baseline are summarized in Table I.

Before switching to brolocuzumab, six patients were treated with a single anti-VEGF: aflibercept ( $n = 2$ ) or bevacizumab ( $n = 2$ ) or ranibizumab ( $n = 2$ ). The remaining patients switched from aflibercept to bevacizumab ( $n = 1$ ), from

bevacizumab to aflibercept ( $n = 1$ ), and from bevacizumab to ranibizumab to aflibercept ( $n = 1$ ).

### Anatomical and functional outcomes at 1-month postinjection

Patients were assessed within 1 week and 1 month (mean  $29.1 \pm 4.6$  days, range 24-35) after the first brolocuzumab injection. No signs of active disease were observed in eight (88.9%) patients: in seven patients (77.8%) SRF and IRF were absent, while in one patient (11.1%) fluid was only partially reabsorbed. All three patients presenting with sub-RPE fluid at baseline showed complete resolution.

The CST showed a significant reduction from  $398.4$  (97.5 SD)  $\mu\text{m}$  at baseline to  $258.3$  (32.4 SD)  $\mu\text{m}$  at 1 month postinjection (mean difference  $131.1$   $\mu\text{m}$ , 95% confidence interval [CI] 46.4-215.8; related-samples Wilcoxon signed-rank test  $p = 0.007$ ).

In parallel, VA improved significantly from  $54.4$  (20.1 SD) letters at baseline to  $72.8$  (16 SD) letters at 1 month postinjection (mean difference 18.3 letters, 95% CI 6.64-30.02; related-samples Wilcoxon signed-rank test  $p = 0.011$ ).

The estimated mean and median time to disease inactivation were 14.2 (range 5-23.4) days and 3 (range 2.03-3.97) days, respectively (shown in Fig. 1).

In the three patients who were further examined at 60, 62, and 92 days, respectively, from the injection, no sign of disease reactivation or fluid recurrence was observed, and the VA remained stable; thus, there was no need for additional injections. As a case example, the retinal SD-OCT B-scans of one of the patients at different time points following brolocuzumab injection are shown in Figure 2.

IOI, vasculitis, or retinal vascular occlusion was not reported for any patient in the follow-up period under consideration.

## Discussion

Significant anatomical improvements were observed in patients switching to brolocuzumab, as expected according to the available data (25,27,28). These included a significant reduction in CST and almost complete resolution of fluids in most patients.

Although the most frequent timepoint used to evaluate the postinjection anatomical response is approximately 1 month, in the case of no response it would be useful to have an earlier assessment since there is a correlation between CST reduction and the time passed from the last injection (29,30). In the group of patients we described, the response to brolocuzumab treatment was rapid according to anatomical improvement, which occurred on average 2 weeks after the injection.

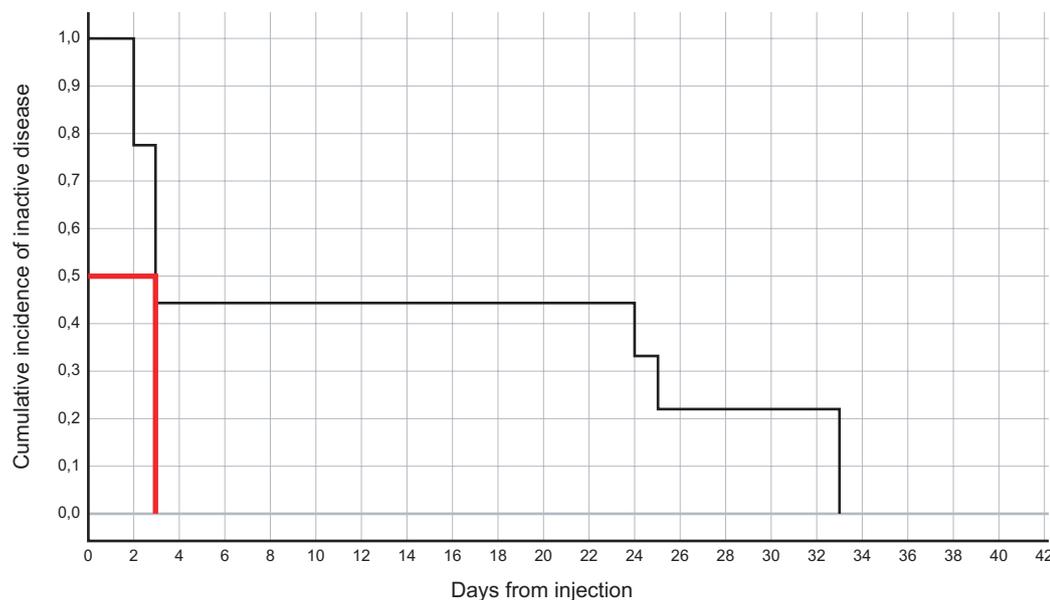
Furthermore, in the subgroup of patients followed for more than 4 weeks, the improvements were stable for at least 8 to 12 weeks after injection. Despite these results being obtained in non-treatment-naïve patients, they seem to be in line with those from the HAWK and HARRIER studies, which showed that nAMD was controlled for at least 12 weeks in more than 50% of naïve patients injected with brolocuzumab (24). Such long-term effects suggest patients may be stabilized with an interval of 12 weeks between injections, thus

TABLE I - Baseline characteristics

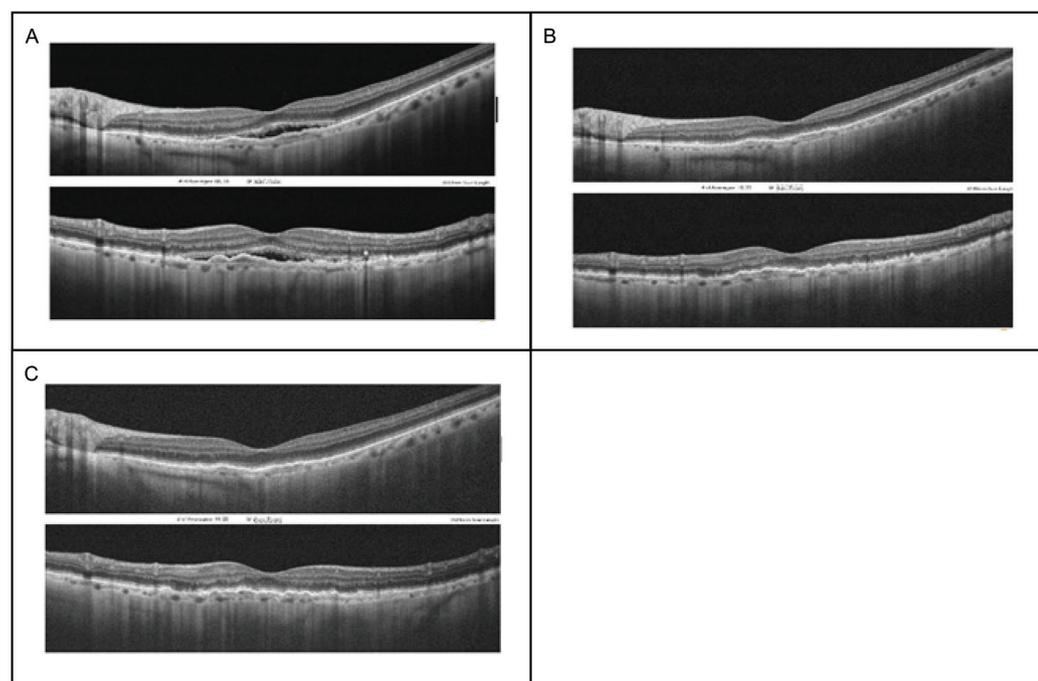
Characteristic	Data
Age (years), mean (SD; range)	77.2 (11.6; 58-90)
Female gender, no. (%)	7 (77.8)
<i>Clinical profile, mean (SD)</i>	
VA (letters)	54.4 (20.1)
CST ( $\mu\text{m}$ )	386.4 (97.5)
<i>Angiographic lesion type, no. (%)</i>	
1	4 (44.4)
2	5 (55.6)
With IRF	6 (66.7)
With SRF	7 (77.8)
With sub-RPE fluid	3 (33.3)
With fibrosis	3 (33.3)
With subretinal fibrosis	1 (11.1)
With SHRM	1 (11.1)
<i>Anti-VEGF treatment prior to brolocuzumab injection, mean (SD; min-max)</i>	
Treatment length (months)	9.9 (5.8; 3-18)
No. of injections	5.7 (3.5; 2-12)
Last administration interval (months)	2 (0.7; 1-3)
Months from last injection to brolocuzumab switch	3.1 (1.2; 2-6)
<i>Reason for switching to brolocuzumab, no. (%)</i>	
Fluid persistence	4 (44.4)
Frequent fluid recurrences	5 (55.6)

$\mu\text{m}$  = micrometers; CST = retinal central subfield thickness; IRF = intraretinal fluid; max = maximum; min = minimum; no. = number; RPE = retinal pigment epithelium; SD = standard deviation; SHRM = subretinal hyperreflective material; SRF = subretinal fluid; VA = visual acuity; VEGF = vascular endothelial growth factor.





**Fig. 1** - Kaplan-Meier plot for time to disease inactivation in the nine patients. The median (50th percentile) is indicated in red.



**Fig. 2** - Representative case of a woman, 90 years old, treated with three intravitreal injections of aflibercept during the previous 9 months. Spectral domain optical coherence tomography (SD-OCT) B-scans at different time points: A) Baseline (before brolocizumab injection). B) Follow-up 1 month after injection. C) Follow-up 2 months after injection.

constituting a significant improvement of treatment burden. This is also clearer considering that retinal fluid was not successfully controlled with injections every 8 weeks before the switch to brolocizumab.

In our group of patients, we also observed a significant improvement in terms of VA. This appears to contradict a recent case series of six patients who did not show any increase in VA (26), and a retrospective analysis of 172 eyes, in which there was no improvement in VA after one to three brolocizumab injections (28). There are two possible explanations for our observation: the low number of cases in this case series, and the fact that our patients were treated for a shorter

follow-up compared with the other studies (9.9 months and at least 2 years, respectively).

No inflammatory adverse events were reported in our patients, which may also be due to the small sample size and short follow-up. An independent Safety Review Committee, analyzing inflammatory ocular adverse events in the HAWK and HARRIER trials, observed an incidence of retinal vasculitis and retinal vascular occlusion of 3% and 2%, respectively, with a risk of severe visual loss in approximately 1 in every 200 patients (31).

In this context, it is important to consider the balance between the risk of adverse events and the benefits. In our case

series, the decision to initiate brolocizumab treatment was made for patients who were not responding anymore to other anti-VEGFs despite regular treatment. Notwithstanding, close contact with the patient is needed during follow-up, as it is expected that adverse inflammatory events can be successfully managed if they are recognized and treated promptly.

This retrospective case series has some limitations. Despite the important improvements observed, the sample size was small, and the measured changes had wide ranges. To better characterize the long-term efficacy and safety profile of brolocizumab in clinical practice, patients undergoing a treatment switch to brolocizumab should be followed for longer. Furthermore, naïve patients not undergoing treatment with other anti-VEGFs should be recruited to verify the anatomical superiority of brolocizumab and to optimize the treatment of nAMD by reducing the treatment burden for both patients and clinicians (24,25).

## Conclusion

In conclusion, a single injection of brolocizumab was shown to be rapid and effective in fluid resolution, thus representing a valuable therapeutic option for controlling disease activity in nAMD patients. Indeed, the first month after the injection was shown to be very important to predict the response to the anti-VEGF drug of the single patient and brolocizumab showed a rapid and intense response.

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## Disclosures

Statement of ethics: This retrospective study was conducted in accordance with the ethical standards set forth in the 1964 Declaration of Helsinki and its subsequent amendments. A notification letter was sent to the local Ethical Committee (Comitato Etico Area Vasta Centro at the Careggi University Hospital, Florence, Italy), as required by Italian regulations. Written informed consent for both medical treatment and publications of their data was obtained from all participants.

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