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BRIEF REPORT

Two-Years Real-World Experience of a Tertiary Center with Intravitreal Brolucizumab Switch for Treatment of Exudative Neovascular Age-Related Macular Degeneration

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ABSTRACT

***Introduction*:** To analyze visual and anatomical outcomes in patients switched to brolucizumab and previously treated with other intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents for exudative neovascular age-related macular degeneration (nAMD). These outcomes were was assessed in the real-world setting of a tertiary center with a follow-up period of 2 years.

***Methods*:** This retrospective longitudinal study included 29 eyes of 24 patients with exudative nAMD previously treated with at least three injections of another intravitreal anti-VEGF molecule. The eyes were then treated with brolucizumab for at least 24 months following the switch. A pro re nata ("as needed") therapeutic regimen was followed in our clinic between January 2021 and June 2024, during which time clinical and anatomical parameters were evaluated, and possible adverse events were recorded.

***Results*:** After 24 months of treatment with brolucizumab, patients showed a significant reduction in central macular thickness ($P=0.001$) and choroidal thickness ($P<0.001$). Visual acuity remained stable during the follow-up period. "Poor responders" had longer disease duration and had received more injections before the switch than "good responders." Adverse events included one subretinal hemorrhage and one intraocular inflammation across 302 injections.

***Conclusions*:** Treatment with brolucizumab is effective in patients previously treated with other therapeutic molecules. The best outcomes were achieved in patients who switched therapy to brolucizumab early in their disease. Treatment with brolucizumab in this population demonstrated an acceptable risk profile, with only one intraocular inflammatory event out of 302 intravitreal injections.

PLAIN LANGUAGE SUMMARY

This study looks at switching to brolucizumab for patients with neovascular age-related macular degeneration (nAMD) who had previously

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been administered other treatments. 39 eyes of 32 patients were evaluated, of which 29 eyes of 24 patients were tracked for 2 years, checking vision, retinal swelling, and side effects. Patients who switched early in their disease had better results. Overall, retinal swelling decreased, and vision remained stable. Patients who had longer disease duration and who had received relatively more injections before switching responded less well to brolucizumab. Across a total of 302 injections administered during the study period, there was one case of eye inflammation and one case of bleeding. Overall, brolucizumab was effective and safe, especially for those who switched early.

Keywords: Age-related macular degeneration; Anti-vascular endothelial growth factor; Brolucizumab; Fluid analysis; Intraocular inflammation; Switch therapy

Key Summary Points
Why carry out this study?
Anti-vascular endothelial growth factor (anti-VEGF) agents are standard treatments for neovascular age-related macular degeneration (nAMD) but sometimes require frequent dosing.
Bolucizumab showed efficacy in trials, but real-world long-term data are limited and safety concerns include intraocular inflammation and retinal vasculitis were present.
What was learned from the study?
Brolucizumab significantly reduced macular and choroidal thickness while maintaining visual stability in 2-year follow-up in real-world setting.
Early switching led to better outcomes, while longer disease duration predicted poorer response.
The rate of adverse events in the patient cohort was at an acceptable level, with a low incidence of adverse events.

INTRODUCTION

Intravitreal anti-vascular endothelial growth factor (anti-VEGF) drugs have gained a pivotal role in the treatment of exudative neovascular age-related macular degeneration (nAMD) [1]. However, the duration of the effect is limited, and frequent administrations and follow-up visits are required, increasing the burden on clinicians, patients, and healthcare systems [2]. Real-world evidence indicates that the administration of these therapies is often inadequate, leading to less-than-optimal visual outcomes [3]. Given the aim to minimize disease activity in nAMD [4], longer-acting agents are necessary to enhance patient care and visual results [5].

Brolucizumab, a new humanized, single-chain variable fragment antibody, inhibits VEGF-A, and its 26-kDa molecular mass allows the administration of higher molar dosing than is allowed with aflibercept and ranibizumab [5]. The ocular and non-ocular side effects of brolucizumab were comparable in the brolucizumab and aflibercept arms during the HAWK and HARRIER phase 3 trials [6]. However, post-marketing results revealed increased rates of intraocular inflammation (IOI) and retinal occlusive vasculitis in patients treated with brolucizumab, resulting in severe vision loss in 12.3% of eyes that showed any IOI, retinal vasculitis (RV), and retinal vascular occlusion (RO) event (3.4% of total injections analyzed) [7]. The subsequent MERLIN phase 3a trial also noted significantly higher rates of IOI, including RV and RO [8]. Notably, real-world data on patients undergoing brolucizumab switch therapy for at least 2 years are limited [9].

The aim of this study was to assess the efficacy and safety of switching eyes with exudative nAMD that had been previously treated with multiple intravitreal injections (IVIs) of other anti-VEGF agents to therapy with intravitreal brolucizumab, in a real-world tertiary center, over a 24-month follow-up.

METHODS

This is a retrospective, observational, longitudinal investigation. This study adhered to the

tenets of the Declaration of Helsinki (1964) and its later amendments. Ethical approval was waived due to the retrospective nature of the study and because all of the procedures are part of routine clinical care. As no additional interventions were performed and all data were anonymized; informed consent was not required according to local regulations.

Patients with nAMD were switched to intravitreal brolucizumab therapy after multiple IVIs of at least one anti-VEGF agent, including ranibizumab, aflibercept, and bevacizumab. All brolucizumab injections were administrated between January 2021 and February 2024 at San Raffaele Hospital (Milan, Italy).

Inclusion criteria were age > 50 years; nAMD with previous treatment of at least three IVIs of ranibizumab, aflibercept, or bevacizumab; shift to brolucizumab within 2 months from the last anti-VEGF injection; persistent retinal fluid despite prior frequent IVIs; best-corrected visual acuity (BCVA) between 20/200 and 20/25 Snellen; and at least 24 months of follow-up from the switch to Brolucizumab.

Exclusion criteria were macular scarring impeding visual function change; concomitant diseases affecting visual acuity; and intraocular surgery within the first year of brolucizumab treatment.

The presence and type of macular neovascularization (MNV) were determined using dye angiography or optical coherence tomography angiography (OCTA), following the criteria proposed by Spaide et al. [10]. The evaluation was independently performed by two experienced retina specialists (RS and FB) with 100% agreement.

Enrolled patients were treated with brolucizumab according to a Pro Re Nata regimen, after a loading phase of three injections every 6 weeks, based on the presence of fluid on optical coherence tomography (OCT).

Clinical data were collected at baseline, after 12 months and after 24 months after the first brolucizumab injection.

Demographic and clinical data, including age, sex, duration of the disease, and number and type of intravitreal treatments previously used prior to the switch to brolucizumab were recorded. Ophthalmic evaluations, including BCVA, applanation tonometry, slit-lamp biomicroscopy, fundus biomicroscopy, and structural OCT (Spectralis®; Heidelberg Engineering, Heidelberg, Germany), were conducted throughout the study. Patients were educated about IOI symptoms and advised to report adverse events promptly.

The main outcome measures included BCVA, which was measured using the Snellen decimal scale and then converted to LogMAR for analysis. Central macular thickness (CMT) was assessed using spectral domain OCT (SD-OCT) and defined as the mean retinal thickness (in microns) between the internal limiting membrane and Bruch's basement membrane within the central 1 mm of the fovea. CMT measurements were automatically obtained through 19 horizontal scan lines covering a 6 × 6-mm area centered on the fovea, each consisting of nine averaged OCT B-scans with 1024 A-scans per line at 240-µm intervals. In cases where automatic segmentation was inaccurate, manual segmentation was performed. Subfoveal choroidal thickness (ChT) was manually measured by a trained grader (FB) using the built-in caliper tool and expressed in microns, referring to the reference line passing through the fovea in the OCT scan. The presence of intraretinal fluid (IRF), subretinal fluid (SRF), and pigment epithelium detachment (PED) was recorded on OCT scans both at baseline and during follow-up visits. The presence of geographic atrophy (GA) at baseline was assessed, defined as the presence of complete outer retinal and retinal pigment epithelium atrophy (cRORA) on structural OCT [11], as well as subretinal fibrosis, defined on structural OCT as highly hyperreflective, well-demarcated material located subretinally or sub-RPE, often disrupting adjacent retinal layers [12].

Statistical Analysis

Statistical analysis was performed using SPSS ver. 29 (SPSS IBM Corp., Armonk, NY, USA). All quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as counts and percentages. Comparison of quantitative variables among the three different time-points (i.e. baseline,

and 1- and 2-year follow-ups) were performed using analysis of variance (ANOVA) for repeated measures with Bonferroni correction for post hoc analysis. Chi-squared test or Fisher's exact test was performed for the comparisons between subgroups in the evaluation of qualitative variables. Results were considered statistically significant if the *P* value was < 0.05.

RESULTS

A total of 39 eyes of 32 patients were evaluated. Of these, 29 eyes from 24 patients (12 men, 12 women; mean [± SD] age 77.6 ± 8.5 years) previously treated with other anti-VEGF agents and then switched to brolucizumab and followed up at San Raffaele Hospital for at least 24 months were included in the analysis. The total number of injections across these patients was considered to be 302.

Regarding the ten eyes that were not included in the statistical analyses, seven were switched back to another drug due to a poor response, defined as the persistence of SRF or IRF, or the need for intravitreal treatment with a dosing interval of < 8 weeks, which is not allowed with brolucizumab as per the product information. One patient discontinued treatment after the second intravitreal injection of brolucizumab due to the onset of a systemic hypertensive crisis, with a reported systolic peak of 200 mmHg. The patient had a history of systemic hypertension under treatment, and during the visit, her blood pressure was measured at 160/90 mmHg. As a precaution, the patient was switched to another drug, remains under treatment, and has not reported any long-term side effects. One patient developed a subretinal hemorrhage within the neovascular lesion following the first intravitreal injection of brolucizumab, which had not been present at the previous follow-up visit. As a result, the patient was switched back to another drug. One patient developed an episode of hypertensive intraocular inflammation after receiving five intravitreal injections of brolucizumab. This patient was receiving treatment at our center but resided in another city. The diagnostic and therapeutic pathway was reconstructed using the available medical reports. Ten days after the last injection, the patient presented to the emergency department of his local hospital, complaining of blurred vision and mild periorbital pain. Examination revealed the presence of anterior chamber cells (2+), corneal edema, and an intraocular pressure of 32 mmHg. Topical therapy with apraclonidine, tobramycin, and dexamethasone, along with systemic therapy with acetazolamide, was initiated, resulting in good symptom control and normalization of intraocular pressure. Subsequently, a tapering systemic therapy with prednisone was started. The patient showed no signs of vasculitis and did not report any permanent visual damage. At the follow-up visit at out center, the patient showed no signs of active intraocular inflammation, and a switch to a different therapeutic agent was advised.

Regarding the 29 eyes with 24 months of follow-up, the mean (± SD) age of the patients was 78 ± 9 years, and the average duration of the disease was 50 ± 28 months. The mean number of pre-treatment injections was 24 ± 14. Baseline disease activity in these patients included SRF (10 patients), IRF (11 patients), and concomitant SRF and IRF (8 patients). At baseline, four patients showed signs of atrophy and 25 showed no signs of atrophy, and nine patients showed signs of fibrosis and 20 showed no signs of fibrosis.

Over the 2 years of follow-up, the total number of brolucizumab injections per patient was on average 8.575 ± 2.69. The average number of injections during the first year and second year of treatment was 5.2 ± 1.54, and 3.55 ± 2.02, respectively.

The analysis of BCVA showed a *P* value of 0.706, indicating that there were no statistically significant differences between the BCVA at baseline and the BCVA at the 2-year follow-up. The mean BCVA values (expressed in LogMar) were 0.51 ± 0.40 at baseline, 0.54 ± 0.64 after the first year, and 0.47 ± 0.42 after the second year (Table 1).

The CMT analysis revealed a statistically significant *P* value of 0.001 when baseline CMT was compared with the CMT in the second year of follow-up. At baseline, the mean CMT was 436 ± 140 µm. After the first year, the mean

Table 1 Comparisons of anatomical and functional variables at baseline and at the 1- and 2-year follow-ups after the switch to brolucizumab in the total study population

Anatomical and functional variables	Baseline		1-Year follow-up		2-Year follow-up		
	Mean ± SD	*P* value[a]	Mean ± SD	*P* value[b]	Mean ± SD	*P* value[b]	*P* value[c]
BCVA, LogMAR	0.51 ± 0.40	0.706	0.54 ± 0.64	1.000	0.47 ± 0.42	1.000	1.000
CMT, µm	436 ± 140	0.001*	343 ± 113	0.001*	354 ± 151	0.001*	1.000
Subfoveal ChT, µm	235 ± 102	< 0.001*	214 ± 96	0.031*	203 ± 95	< 0.01*	0.295

BCVA Best-corrected visual acuity, *ChT* choroidal thickness, *CMT* central macular thickness, *SD* standard deviation

*Significant difference at $P < 0.05$

[a]Analysis of variance (ANOVA) for paired samples

[b]Comparison with baseline values using analysis of variance (ANOVA) for paired samples with Bonferroni post-hoc analysis

[c]Comparison with values at the 1-year follow-up using ANOVA for paired samples with Bonferroni post-hoc analysis

CMT decreased to 343 ± 113 µm, and after the second year, it remained stable at 354 ± 151 µm (Table 1).

Analysis of subfoveal ChT revealed a *P* value < 0.001, indicating significant differences between the value recorded at baseline and the value measured after 2 years of follow-up. At baseline, the mean choroidal thickness was 235 ± 102 µm. After the first year, the mean choroidal thickness dropped to 214 ± 96 µm, and after the second year, it further decreased to 203 ± 95 µm (Table 1).

Following analysis based on the total patient population, patients were divided into the subcategories "good responders" and "poor responders" based on their response to treatment. The criterion for this division was an improvement of at least 5 letters in the Snellen chart after 2 years of treatment [14]. Demographics and baseline characteristics of the total population, good responders, and poor responders are summarized in Table 2. In total, 16 out of 29 eyes were included in the "good responders" category. The mean age of "poor responders" (76 ± 10 years) was on average younger than that of "good responders" (79 ± 6 years), without a statistically significant difference ($P = 0.141$). Additionally, "poor responders" had a longer mean (± SD) disease duration than "good responders" (59 ± 30 vs. 40 ± 22 months; $P = 0.034$). The number of pre-treatment injections was also higher in the "poor responders" than in the "good responders (29 ± 13 vs. 19 ± 15; $P = 0.044$). The total number of brolucizumab injections required was equivalent in "poor responders" and "good responders" (mean ± SD: 8.8 ± 3.0 vs. 8.7 ± 2.3, respectively). No other differences emerged between "poor responders" and "good responders".

Finally, a contingency analysis was conducted to examine additional parameters. No statistically significant correlation was found between treatment response and the presence of SRF, IRF, geographic atrophy, or baseline fibrosis. However, the distribution of the type of MNV showed a non-significant trend, with a predominance of type 1 in "good responders" compared to "poor responders" (11 patients vs. 9, respectively).

DISCUSSION

This study provides valuable insights into the long-term efficacy and safety of brolucizumab in patients with nAMD who were previously treated with other anti-VEGF agents. The findings contribute to the growing body of evidence on the role of brolucizumab in managing nAMD in real-world clinical practice, highlighting its capacity to achieve significant anatomical improvements while maintaining visual stability (Figs. 1, 2).

The significant reduction in CMT and subfoveal ChT observed in this cohort underscores brolucizumab's potent anti-VEGF effects. These

Table 2 Demographics and main clinical features of the total study population and of the "good responder" and 'poor responder" groups at baseline

Demographics and main clinical features	Total study population	Good responder group	Poor responder group	*P* value
Eyes, *n*	29	13	16	–
Age, years	77.6 ± 9	79.5 ± 5	76.1 ± 10	0.141
BCVA, LogMAR	0.51 ± 0.40	0.51 ± 0.40	0.51 ± 0.41	0.476
CMT, μm	453 ± 140	407 ± 89	459 ± 170	0.152
Subfoveal ChT, μm	235 ± 102	237 ± 120	232 ± 88	0.455
SRF, *n*	18	9	9	0.372
IRF, *n*	19	8	11	0.493
GA, *n*	4	2	2	0.617
Fibrosis, *n*	9	3	6	0.336
MNV, *n*				0.438
- Type 1	20	9	11	
- Type 2	5	3	2	
- Type 3	4	3	1	

Values in table are presented as the mean ± standard deviation or as the number of eyes, as appropriate

BCVA Best-corrected visual acuity, *ChT* choroidal thickness, *CMT* central macular thickness, *GA* geographic atrophy, *IRF* intraretinal fluid, *MNV* macula neovascularization, *SRF* subretinal fluid

results align with the results of previously reported clinical trials, such as the HAWK and HARRIER trials, as well with the findings of real-world studies that have highlighted brolucizumab's ability to reduce retinal fluid and disease activity [5, 6, 9, 13]. Importantly, these anatomical improvements were achieved with a relatively low injection burden, particularly in the second year of follow-up, during which time the average number of injections decreased. This reduced treatment frequency highlights the durability of brolucizumab's effects and its potential to alleviate the treatment burden associated with other anti-VEGF therapies, which often require more frequent injections to maintain disease control [2, 3, 13].

Although anatomical outcomes were significantly improved, BCVA remained stable over the 2-year follow-up period. This finding is consistent with other real-world data, indicating that patients with advanced disease or long treatment histories may experience limited functional gains due to cumulative retinal damage or irreversible structural changes [9, 14]. Nevertheless, maintaining visual stability is a clinically meaningful outcome, particularly in patients who might otherwise experience disease progression. Future studies should explore whether earlier intervention with brolucizumab, either in treatment-naïve patients or those with shorter disease duration, might yield more substantial functional improvements.

The differentiation between "good responders" and "poor responders" offers important insights into patient-specific factors that may influence treatment outcomes. Poor responders were characterized only by a longer disease duration and a larger pre-treatment injection burden. The data indicate that the two groups under comparison are homogenous in most baseline characteristics, ensuring that differences in outcomes are likely attributable to the differences previously stated.

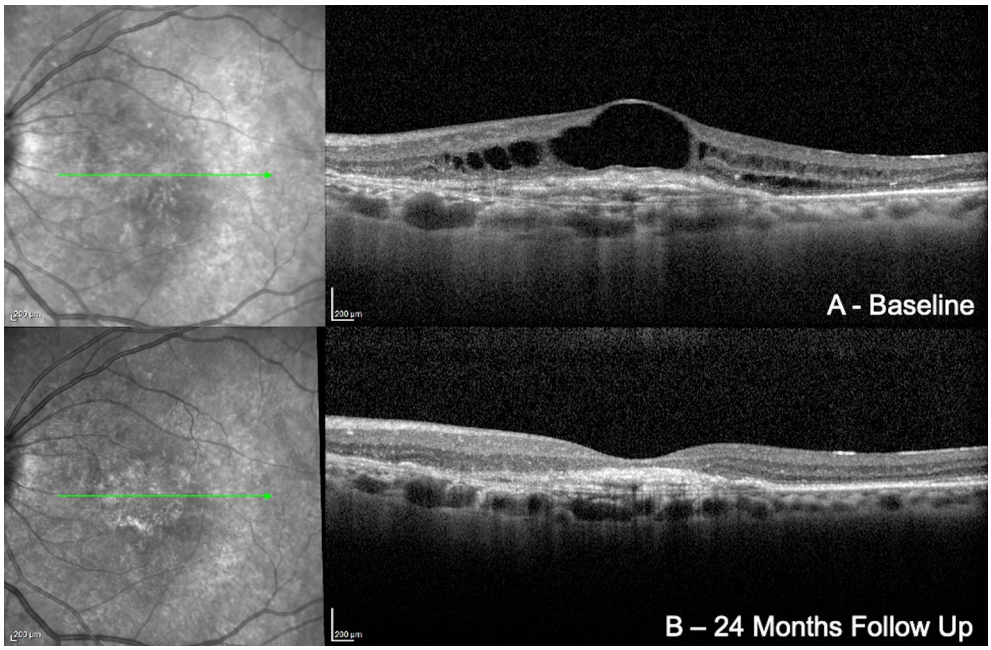

Fig. 1 Combined infrared reflectance and structural B-scan optical coherence tomography showing a type 1 exudative neovascular age-related macular degeneration. At baseline (**a**), intraretinal fluid (IRF) and an elevated retinal pigmented epithelium (RPE) with a double layer sign (DLS) are present, suggesting the presence of a neovascular membrane. At the 24-month follow-up visit (**b**)—after 7 brolucizumab intravitreal injections— it is noted that there is complete reabsorption of IRF and a reduction of the dimensions of the RPE. To note, the best-corrected visual acuity of the patient has not changed, remaining stable at 1 LogMAR. Despite the short duration of the disease (7 months) and the small number of intravitreal injections received at baseline (3), we noted that complete disruption of the external limiting membrane and ellipsoid zone were already present at baseline, possibly explaining the absence of visual improvement

This finding highlights the need for early and effective intervention in patients with shorter disease duration and fewer prior treatments. Tailored strategies should be considered for patients with prolonged disease to optimize outcomes.

The safety profile of brolucizumab observed in this study aligns with previous findings, including those from systematic reviews and meta-analyses of real-world data [6, 8, 14]. The low incidence of adverse events, including IOI, is reassuring, particularly given the initial safety concerns raised in the MERLIN trial [8]. However, the cases of hypertensive IOI and systemic hypertensive crisis observed in this study underscore the importance of pre-treatment risk assessment and ongoing monitoring. Educating patients to recognize early symptoms of IOI remains essential to minimize the risk of severe complications. These findings are consistent with the conclusions drawn by Baumal et al. [15], who emphasized the importance of early detection and prompt management of adverse events to ensure patient safety.

Notably, the results of the present study highlight the benefits of an early switching to brolucizumab therapy. Patients who underwent the switch earlier in their disease course achieved better anatomical and functional outcomes, reinforcing the importance of timely therapeutic adjustments. These findings align with those reported by Yoshida et al. [13], who observed superior outcomes in patients treated earlier in their disease progression using a treat-and-extend protocol. Delaying the switch to brolucizumab may allow irreversible damage to accumulate, limiting the potential for recovery. Clinicians should, therefore, consider transitioning patients with persistent disease activity to

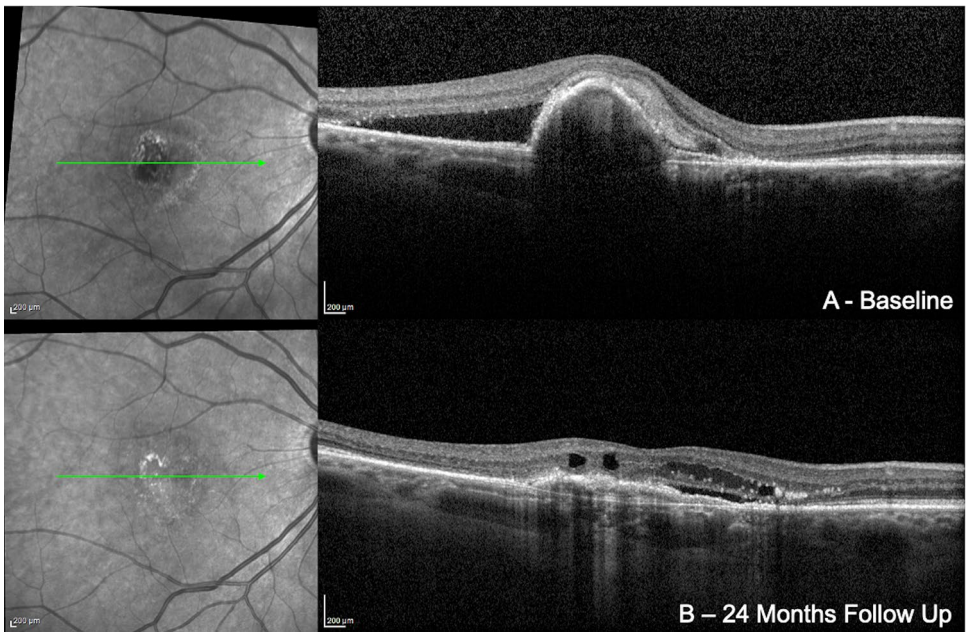

Fig. 2 Combined infrared reflectance and structural B-scan optical coherence tomography showing a type 1 exudative neovascular age-related macular degeneration. At the baseline (**a**), a siero-vascular pigmented epithelium detachment (PED) with subretinal fluid (SRF) and subretinal hyperreflective material (SHRM) is present. At the 24-month follow-up visit (**b**)—after 11 brolucizumab intravitreal injections— we achieved only partial response with a notable anatomic improvement, namely resolution of the PED, but the SRF persisted, and intraretinal fluid (IRF) appeared. The presence of multiple hyperreflective foci nasal to the fovea can be expression of the activation of the Müeller cells and of the neurodegenerative process, with the loss of retinal fluids stability and the appearance of IRF. Visual acuity remained stable over this 24-month period at 0.7 LogMAR

brolucizumab sooner rather than later, particularly those who require frequent injections with other anti-VEGF agents.

It is important to highlight that our study population consisted exclusively of patients previously treated with other anti-VEGF agents. Other real-life studies have included patients treated with brolucizumab as a first-line therapy, then comparing the two groups. According to Rossi et al., who evaluated the improvement in visual acuity and the reduction in central retinal thickness after 1 year of treatment in a real-life setting in patients with nAMD, there was no statistically significant difference between patients treated with brolucizumab as a first-line therapy and those who underwent a therapeutic switch [16].

Faraldi et al. compared the efficacy of brolucizumab treatment in patients with nAMD by analyzing anatomical and functional parameters in both treatment-naïve patients and those who switched after 1 year of treatment [17]. In the treatment-naïve group, the reduction in subfoveal choroidal thickness and the increase in visual acuity were statistically significant, whereas in the group that switched therapy to brolucizumab, these parameters remained stable. Interestingly, 55% of the treatment-naïve patients achieved a 12-week dosing interval (q12), compared to 33.5% in the group that switched therapy [17]. These findings are consistent with our results in terms of underlying the importance of an early switch.

While these findings are encouraging, several limitations to our study must be acknowledged. This study was retrospective, with potential biases, including selection bias and incomplete data. The relatively small sample size and the exclusion of patients who discontinued brolucizumab early may limit the generalizability of

the results. The statistical power of the analysis could be limited by the sample size. Additional limitations are the inclusion of patients who had undergone at least three injections, corresponding to the loading phase, of another anti-VEGF drug, and not considering the category of "late responder" patients, and add a potential selection bias to our sample. The classification of patients as "poor" or "good" responders was performed arbitrarily, using an improvement of 5 letters on the Snellen chart as the criterion. This may have introduced a bias, considering the different LogMAR equivalents in patients with low visual acuity compared to those with good visual acuity. This approach was necessary as the data were derived from clinical practice. Additionally, quality-of-life measures and patient-reported outcomes were not assessed, leaving an important aspect of treatment efficacy unexplored. Recently, new anti-VEGF agents, such as aricimab and aflibercept 8 mg, have been introduced into clinical practice. Despite the good safety profile demonstrated in registration studies, some adverse events have been reported in real-world use [18–20]. Further studies are needed to compare the efficacy and safety of brolucizumab against these new anti-VEGF agents in the treatment of non-naïve nAMD patients. Future prospective studies with larger cohorts are needed to validate these results, further elucidate predictive factors for response, and evaluate the long-term safety and efficacy of brolucizumab.

CONCLUSION

Brolucizumab is an effective therapeutic option for patients with nAMD previously treated with other anti-VEGF agents, with brolucizumab therapy resulting in significant anatomical improvements and visual stability over 24 months. The best outcomes were observed in patients who switched to brolucizumab relatively earlier in their disease course, underscoring the importance of timely intervention. The safety profile observed in this study, consistent those reported in the broader literature [6, 8, 13–15], supports the use of brolucizumab in real-world settings if patients are appropriately selected and monitored. Future research should focus on optimizing patient selection, identifying predictive biomarkers, and evaluating strategies to further enhance treatment outcomes.

Author Contributions. Federico Beretta, Ilaria Zucchiatti, Riccardo Sacconi, Federico Fantaguzzi, Stefano Lingardo, Francesco Bandello, and Giuseppe Querques contributed to the study conception and design. Material preparation, data collection, and data analysis were performed by Federico Beretta, Stefano Lingardo, Ilaria Zucchiatti, and Federico Fantaguzzi. The first draft of the manuscript was written by Federico Beretta and Ilaria Zucchiatti, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. The author(s) declare the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article. Federico Beretta, Ilaria Zucchiatti, Federico Fantaguzzi, and Stefano Lingardo declare that they have no competing interests. Riccardo Sacconi is a consultant for AbbVie, Bayer Shering-Pharma, Carl Zeiss Meditec, Hoffmann-La-Roche, and Novartis. Francesco Bandello is a consultant for AbbVie, Alcon, Alimera Sciences, Farmila-Thea, Bayer Shering-Pharma, Bausch and Lomb, Genentech, Hoffmann-La-Roche, NovagaliPharma, Novartis, Sanofi-Aventis, Thrombogenics, and Zeiss. Giuseppe Querques is a consultant for AbbVie, Alimera Sciences, Amgen, Heidelberg Engineering, KBH, LEH Pharma, Lumithera, Novartis, Bayer Shering-Pharma, Sandoz, Sifi, Soof-Fidia, and Zeiss.

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Ethical Approval. This is a retrospective, observational, longitudinal investigation. This study adhered to the tenets of the Declaration of Helsinki (1964) and its later ammendments. Ethical approval was waived due to the retrospective nature of the study and because all of the procedures are part of routine clinical care. As no additional interventions were performed and all data were anonymized, informed consent was not required according to local regulations. No identifying information is included in the manuscript.

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