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Research article

Real-world evidence for brolucizumab efficacy in age-related macular degeneration and central serous chorioretinopathy patients

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A R T I C L E   I N F O

A B S T R A C T

Real-world studies concerning different populations are valuable and bring new information regarding different regimens of Brolucizumab injections and their adverse reactions. The present study investigates the efficacy of a pro-re-nata regimen (PRN) for neovascular Age-related Macular Degeneration (nAMD). Separate from the main statistics we report the use of Brolucizumab in central serous chorioretinopathy (CSC).

A retrospective observational single-center study was conducted on 82 eyes treated with Brolucizumab between 2021 and 2023, for nAMD. Patients were injected at intervals of at least 2 months after the loading phase. In 9 (3–20) months follow-up, only 0.26 % adverse reactions were noticed, with good resolution of retinal fluid (significant reduction of CST on SD-OCT, -72.50μ, $p < 0.05$), especially for subretinal fluid. 54 % of the eyes remained fluid-free. The interval of injection (INTOI, a parameter calculated by averaging the results of the division of the follow-up period to the number of injections received by each patient) was 2.68 (corresponding to an injection interval of 11 weeks). This could become an important parameter for the characterization of Brolucizumab and any other anti-VEGF therapy and could provide a more precise interval of injection in the future.

Four patients also received Brolucizumab for the treatment of chronic CSC (3 doses each). All showed good response, 3 of them remaining fluid-free.

1. Introduction

Age-related macular degeneration (AMD) is the main cause of loss of vision in the developed world [1]. As a sign of aging, drusen accumulate in the macula of most people over 50 years (some studies [2,3] suggest a prevalence of more than 90 %). These can progress towards a debilitating disease, in about 10 % of cases [4]. AMD has 2 forms of aggressive disease: dry and wet/neovascular AMD. With no efficient prophylaxis, other than UV-light protection, dietary changes (yellow vegetables and greens) and lutein supplementation, the management of AMD has been focused on the treatment for the neovascular form of the disease (nAMD), in the past 20 years [5].

Brolucizumab, a single-chain antibody fragment, was FDA-approved for nAMD in 2019. It is a small molecule, with a molecular

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weight of 26 kDa. HAWK and HARRIER [6], double-masked, multicenter phase 3 trials, assessed the safety and efficacy of Brolucizumab intravitreal injections for the treatment of nAMD, compared with Aflibercept. Besides the 3 monthly loading doses (6 mg, 0.05 ml solution), 2 regimes were advised: q8 (1 injection every 8 weeks) and q12 (1 injection every 12 weeks). Compared to Aflibercept (q8 administration after 3 monthly loading doses), Brolucizumab showed clinical noninferiority at long-term follow-up. Over 50 % of patients treated with Brolucizumab were maintained on an exclusive q12w dosing interval immediately following the loading phase to Week 48. However, the number of adverse reactions was much higher (>5 %) compared to Aflibercept. Intraocular inflammation (IOI) (4 %, uveitis, keratitis, etc.), and retinal vascular occlusions (RO) and vasculitis (RV) (>1 %) were the main concerns. IRIS [7] and KOMODO [8] retrospective cohort studies followed Brolucizumab patients in the real-world and found 2.4 % IOI and 0.55 % retinal vasculopathies. Patient selection was advised, avoiding cases with a prior history of IOI, RV, or RO. Following MERLIN [9] trial, in 2022, Brolucizumab was indicated only in regimens at intervals greater than 2 months, after the loading phase.

Real-world studies concerning different populations are valuable and could add information regarding different regimens of Brolucizumab injections and adverse reactions. The present study is one of the first conducted on Brolucizumab in Romania and investigates the efficacy of a pro-re-nata regimen (PRN). This type of regimen usually tends to undertreat. However, we hypothesize that with more efficient molecules, a regimen individualized to the patient's need could lower the burden of frequent injections and may lower the incidence of complications. Brolucizumab could better fit PRN regimens compared to previous treatments.

Separate from the main statistics, this study reports the use of Brolucizumab in central serous chorioretinopathy (CSC). Anti-VEGF use in this disease was previously reported, but Brolucizumab was not indicated for CSC, so far. To our knowledge, there is only one study investigating Brolucizumab on CSC, published recently in 2024 [10].

2. Material and method

A retrospective observational single-center study was conducted for the period 2021–2023 in the Ophthalmology Clinic Vedis in Cluj. Consecutive patients with Brolucizumab treatment indication were enrolled, in accordance with the tenets of the Declaration of Helsinki. Inclusion criteria were as follows: patients receiving Brolucizumab intravitreal treatment, at least 1 dose; diagnostic of nAMD; minimum follow-up of 3 months after the first injection (enough for the assessment of short-term efficiency and injection-related complications); complete observation files. OCTs and fundus photographs were reexamined and the diagnosis of nAMD was reconfirmed.

Best corrected visual acuities (BCVA) had been measured on Snellen charts. BCVA before treatment varied from 0.04 to 0.8 (mean 0.23, median 0.2). We also converted Snellen visual acuity in logarithm of the minimum angle of resolution (LogMAR) units for statistical calculations, using available calculators [11].

Fluid location inside the retina was evaluated on SD-OCT: sub-Retinal Pigment Epithelial fluid (SRPEF, accumulated under RPE), sub-neuroretinal fluid (SRF, accumulated between RPE and the outer segment layer of the retina), and intraretinal fluid (IRF, above the outer segment layer of the retina). Macular central thickness (defined as the distance between the internal limiting membrane and Bruch's membrane) was automatically measured in the 9 ETDRS macular sectors, but the statistics were performed only for the central 0.6 mm ETDRS sector, measuring central subfield thickness (CST). Automatic segmentation was always verified by both retina specialists (SL and SO).

To better understand the need for injection, the Interval of injection (INTOI), a relationship between the number of doses and the follow-up period was calculated by the formula:

$$Interval\ of\ injection\ (INTOI) = \frac{1}{n} \sum_{1}^{n} \left(follow-up\ period\ (months) \middle/ number\ of\ injections \right)$$

A monthly injection would result in an INTOI of 1 month. A q8 protocol would result in an INTOI of 2 months.

2.1. Injection protocols

Brolucizumab injection was performed under topical anesthesia in the operating theatre, by the same surgeon (SL). Short-term antibiotic drops were indicated after each injection (for 5 days, q.i.d.). The loading dose consisted of three-monthly injections, 0.05 ml each. Patients were followed 1 month after the last dose, and then every 2 months if the fluid was absent. At each follow-up visit, visual acuity (Snellen chart), macular OCT (Central macular thickness, SD-OCT), and fundus examinations (Fundus camera) were performed. Pro-re-nata protocols were applied and re-injection was performed when the fluid reappeared (however, at intervals no smaller than 2 months, as indicated following MERLIN trials [9]).

Patients with previous ocular inflammation and retinal vascular occlusions were not injected, in accordance with Brolucizumab recommendations [7,8]. Low vision cases were accepted if the fluid was present in the retina, making potential visual improvement possible (macular inactive scars were this way excluded).

2.2. Patients

Demographic distribution is presented in Table 1. In total, 82 eyes from 69 nAMD patients were treated between 2021 and 2023. Brolucizumab was indicated in the following situations: patients with poor response to other anti-VEGF therapies (however, the full previous history of each patient was not available for this study), and cases with large accumulation of fluids (in these cases, the retina

specialist considered that the patient could benefit from the newest drug). A precise definition of a large accumulation of fluid was not considered (the decision being subjective). Therefore, this study describes the first clinical experience with Brolucizumab.

Mean age was 76.14 (in the interval 51–92 years). Patients with bilateral indication (13 patients, 8 women, and 5 men) had the injections administered on different days for each eye. Most patients had previous anti-VEGF treatment (61 eyes, 75 %).

Apart from the main study, 4 cases with CSC were also injected and followed. Chronic CSC was diagnosed based on clinical (absence of drusen on retinal examination, fluid persistence for more than 6 months – fundus photographs were available for reexamination) and OCT findings (fluid under neuroepithelium, no macular neovascular membrane), and the absence of macular neovascularization on OCT angiography (OCTA).

2.3. Statistics

Variable analysis was performed in Excel. Statistical analysis and graphics were performed in IBM SPSS statistics Version 26: correlation and regression analysis, and mean comparison. Normal distribution was verified for each variable, with the Kolmogorov-Smirnov test. For ordinal and continuous variables, Spearman's correlation has been conducted. Wilcoxon signed-ranked test for non-parametric evaluation and the Kruskal Wallis H test, an alternative for one-way ANOVA in case of assumptions violation, were used for data comparison. The Mann-Whitney *U* test compared non-normal distributed continuous data. Significance was set at a *p-value* of 0.05. 95 % Confidence interval (CI) was calculated.

3. Results

In total, between 2021 and 2023, 376 Brolucizumab doses were administered for different eye pathologies: nAMD, diabetic macular edema, and central serous chorioretinopathy. From these, 330 Brolucizumab doses were administered in 82 eyes with nAMD, an average of 4 injections per patient. Most eyes received at least the loading dose (71 eyes, at least 3 injections). In the same period, the clinic administered 1222 doses of other anti-VEGF molecules (Brolucizumab injections accounting for 23 % of the total anti-VEGF treatments).

The follow-up period ranged from 3 to 20 months, with a mean of 9 months (median 8 months). The maximum number of injections per eye was 8, in 13 months of follow-up. The individual Interval of injection (follow-up period/number of injections), for each case, ranged between 1 (3/3) and 20 (20/1) months. Averaging these results for 82 eyes (n = 82) resulted in a calculated INTOI±SD, of 2.68 ± 2.58 months.

13 eyes (16 %) were injected every 2 months, corresponding to a q8 interval, and 18 eyes (22 %) every 3 months, corresponding to a q12 interval. 34 eyes (42 %) were injected at irregular intervals (2–6 months). 6 eyes (7 %) remained fluid-free for more than 6 months, and no further injection was needed at the last follow-up. The average time without macular fluid was 4 months (ranging between 0 and 20 months).

The macular OCT (CST) was significantly reduced, from 317.13 ± 106 μm preinjection to 246.14 ± 78 μm postinjection (normal distribution parameters – Kolmogorov-Smirnov, paired sample *t*-test, $p = 0.000$, 95 % CI [46.68–97.01]; the reduction in CST was 72.50 ± 103 μm). These results are reported at the 3-month follow-up visit, meaning after the loading phase.

Best corrected visual acuity also improved, from median 0.2 to 0.3 (mean: 0.23 to 0.36) at the end of follow-up, a variation of 0.1 (equivalent to at least 1 Snellen line improvement). In LogMAR units, vision significantly improved from 0.8 to 0.66 (non-normal distribution - Kolmogorov-Smirnov; Wilcoxon test, $p = 0.000$, 95 % CI [0.079–0.192]). The evolution of visual acuity didn't have a significant correlation with OCT variation (a small negative correlation of −0.205 on the Spearman nonparametric correlation test, $p = 0.038$). However, an increase in OCT central thickness meant a decrease in vision.

The individual Interval of injection, as defined here, did not significantly influence the visual outcome or the OCT variation.

At baseline, 19 (23.2 %) eyes presented only IRF, 5 (6.1 %) only SRPEF, 10 (12.2 %) only SRF, and 48 (58.5 %) multiple locations: SRPEF + SRF + IRF 13 (15.8 %), SRPEF + SRF 8 (9.7 %), SRPEF + IRF 17 (20.7 %), SRF + IRF 10 (12.3 %). After Brolucizumab, the liquid subsided in 44 cases (53.7 %). 10 eyes (12.2 %) remained with SRPEF, 12 (14.6 %) remained with IRF, 6 (7.3 %) with SRF, 4 (4.9 %) with SRPEF + SRF + IRF, and 6 (7.3 %) with SRPE + IRF. If only the locations are considered, with no consideration to mixed fluids, the results could be presented as follows: at baseline, 59 (72 %) had IRF, 41 (50 %) SRF, and 43 (52 %) SRPEF; after the injection, 22 (27 %) remained with IRF, 10 (12 %) with SRF, and 20 (24 %) with SRPEF (Table 2). That means that IRF was totally resolved in 63 % of the cases, SRF in 76 %, and SRPEF in 54 %.

On the Kruskal Wallis test, the location of retinal fluid (IRF, SRF, SRPEF, or mixt) did not influence the BCVA evolution ($p = 0.109$) but influenced the reduction of macular thickness on OCT ($p = 0.016$). The presence of fluid under the neuroepithelium (SRF) influenced the most reduction in OCT thickness, compared to the presence of IRF or SRPEF (however, there is not sufficient data to perform a valid statistical test on this issue). The location of the fluid did not influence the number of injections or the intervals of injection (there was no difference between q8, q12, and irregular administration when the location of the fluid before the treatment

Table 1
Demographic characteristics for the patients admitted to the study.

	Patients/eyes	Age (mean ± SD)	Age interval	Patients/eyes with no previous anti-VEGF
Female	23/31	75.96 (±7.27)	63–85	5/7
Male	46/51	76.27 (±8.33)	51–92	12/14

Table 2

Location of the retinal fluid: number and percent of eyes before and after treatment.

	SRPEF	IRF	SRF	SRPEF + SRF + IRF	SRPEF + SRF	SRF + IRF	SRPE + IRF
Pretreatment:							
- overlapping	43 (52 %)	59 (72 %)	41 (50 %)				
- no overlapping	5 (6.1 %)	19 (23.2 %)	10 (12.2 %)	13 (15.8 %)	8 (9.7 %)	10 (12.3 %)	17 (20.7 %)
Posttreatment:							
- overlapping	20 (24 %)	22 (27 %)	10 (12 %)				
- no overlapping	10 (12.2 %)	12 (14.6 %)	6 (7.3 %)	4 (4.9 %)	0	0	6 (7.3 %)

SRPEF – sub retinal pigment epithelium fluid; IRF – intra retinal fluid; SRF – sub retinal fluid.

was considered).

Most patients had a history of previous injections. 27 eyes (32.9 %) had a history of Aflibercept and Bevacizumab injections, 5 eyes (6 %) had a history of Aflibercept injections, and 29 eyes (35.4 %) had a history of Bevacizumab injections. 21 eyes (25.6 %) were naïve (7 eyes of 5 females, and 14 eyes of 12 males).

The preexistent treatment did not significantly influence the OCT variation (U Mann Whitney, $p = 0.65$) (Fig. 1) or visual acuity evolution.

In total, 11 patients discontinued the treatment but still presented to follow-up visits. There was one complication after the first dose of Brolucizumab received by a male patient, 69 years old, for nAMD. The vision dropped from 0.1 to 0.04 after the injection. The eye inflammation, with conjunctival congestion and corneal edema, with normal intraocular pressure, persisted for 5 days and subsided without any consequences under local anti-inflammatory drops. The vision was restored to pretreatment value, and the patient was switched to other available anti-VEGF subsequently.

Other 2 patients interrupted Brolucizumab after an initial drop in vision (0.5–0.4, and 0.1 to 0.04), without signs of adverse reactions, after dose 1 and dose 2, respectively. They were considered non-responsive and were successfully continued with alternative anti-VEGF therapies.

One patient received 1 dose of Brolucizumab and remained fluid-free for 20 months, refusing further injections. The remaining 7 patients refused further treatment after subjective vision improvement.

3.1. CSC patients

Four cases with CSC received Brolucizumab and showed a good response. These were not included in the main statistics. Table 3 presents the main characteristics of the CSC patients. All presented chronic CSC disease. Three of them had prior treatment (including anti-VEGF and spot laser) with no benefit. Fluid resolution was achieved in 3 cases after the loading dose (3 injections) and the vision also improved (Table 3, Fig. 2). One case (Patient 4) had partial fluid resolution with stationary vision. The patient was highly myopic with no macular neovascularization on OCTA.
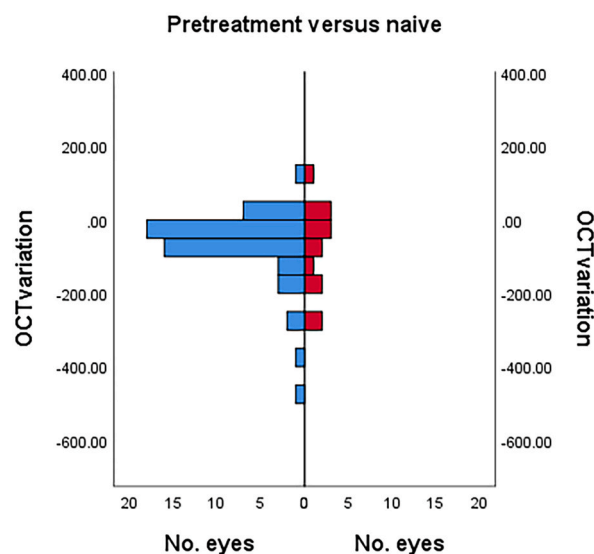

Fig. 1. Pretreatment (blue) versus naïve (red): OCT variation. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Follow-up ranged from 4 to 17 months after the first injection. Recurrence was observed in patient 1, but promptly resolved after 1 injection (a pro-re-nata regimen was then followed).

4. Discussions

Brolucizumab is a new treatment for nAMD patients, designed to extend the intervals between injections. In our study, it was well tolerated, with only 1 adverse reaction, in the category of IOI. Reported to all nAMD doses this accounts for 0.3 % complications. Reported to the total number of doses administered in the 3-year period, this accounts for 0.26 % complications. No RV or RO was observed. The numbers are much lower than in the HAWK and HARRIER [6] studies (4.6 %) or the real-life studies IRIS and KOMODO [7,8] (2.4 %). This suggests that patient selection (only cases with no prior IOI or retinal vascular incidents) and PRN regimen (in our case an INTOI of 2.68 months) are efficient in lowering the incidence of adverse reactions. Lowering INTOI may lead to an increase in adverse reactions, as was seen in the MERLIN [9] study (monthly injections, translated into INTOI = 1), terminated abruptly after a very high incidence of IOI, 9.3 %, including RV and RO. On the contrary, the PRN regimen in the small PROBE [12] study reported no adverse reactions in 27 patients, with an average of 2.2 injections in 11 months (INTOI = 5 months, approximately). It is also possible that the low number of females in our study (37 % of cases) could partially explain the low incidence of IOI. Mean follow-up was 9 months, enough for most AE to appear, knowing from previous studies [6,8] that most AE appear in the first 6 months after injection.

Defining INTOI was considered necessary, in consideration that the mean interval between injections could be calculated in several ways. For example, the mean period of follow-up (9 months) divided by the mean number of injections (4) would result in a 2.25 months mean interval of injection. Considering the non-normal distribution of these parameters, the median should be used in statistical calculations, resulting in further differences. Comparison of such ill-defined parameters between studies could account for inconsistent results. Throughout the text, we used the familiar notation q8 and q12 for the notation of 2-month and 3-month intervals. However, the actual injection intervals were usually slightly more, between 8 and 9 weeks, and 12–13 weeks, respectively, due to the constraints of patient workflow.

No patient received monthly injections after the loading phase. 16 % remained stable on q8, 22 % remained stable at q12, and 42 % were injected as needed, at 2–6 months intervals (one patient remaining fluid free for 20 months after only the first injection). It may be that the interval for injection for Brolucizumab is 2.68 months (as calculated with the INTOI formula), or approximately 11 weeks. When talking about efficiency, higher injection frequency (equivalent to a lower INTOI number) may be associated with better visual function [13]. Increasing the average yearly injection frequency of unspecified Anti-VEGF from 5 to 8 yielded better visual outcomes in a report from 2019. A balance between efficacy and adverse reactions must always be considered. The INTOI could become an interesting parameter for future comparison of anti-VEGF drugs. Future studies with larger numbers of treated patients on PRN regimens, and longer follow-up intervals, could refine this parameter for Brolucizumab and practitioners could inject at the specific interval to achieve maximum efficiency with the lowest dosing in most patients.

Subcentral macular thickness on OCT greatly improved, but this was not correlated well with vision improvement. The treatment had the most efficacy on the fluid located under the neuroepithelium (SRF), which subsided in 76 % of cases. At least 54 % of the eyes remained fluid-free, 7 % for periods longer than 6 months. These numbers are comparable to other studies [14], also considering that most of our patients (75 %) were previously treated with other anti-VEGF. Naïve patients are considered better candidates for Brolucizumab therapies. However, in our series, preexistent treatment did not negatively influence the results of the OCT or BCVA. Larger cohorts could statistically change these results.

Only one previous study evaluated the efficiency of Brolucizumab in CSC: a recent study from 2024 [10] showed a faster reduction of retinal fluid in CSC injected with Brolucizumab. At the 2-month follow-up, Brolucizumab outperformed PDT or Aflibercept (77 % resolution, versus 72 %, and 33 %, respectively). In our 4 patients, Brolucizumab has proved effective. 3 eyes had total resolution of the fluid and one had partial resolution. PRN regimens were initially indicated in all 4, and fluid recurrence was seen in only 1 patient, with prompt resolution after 1 injection.

5. Limitations

The Brolucizumab experience presented in this study is the result of a cautious transition from previous, to new anti-VEGF molecules (one reason for the cautionary approach being the high IOI previously reported). That means that most of the patients were

Table 3
Patients with CSC, treated with brolucizumab injections.

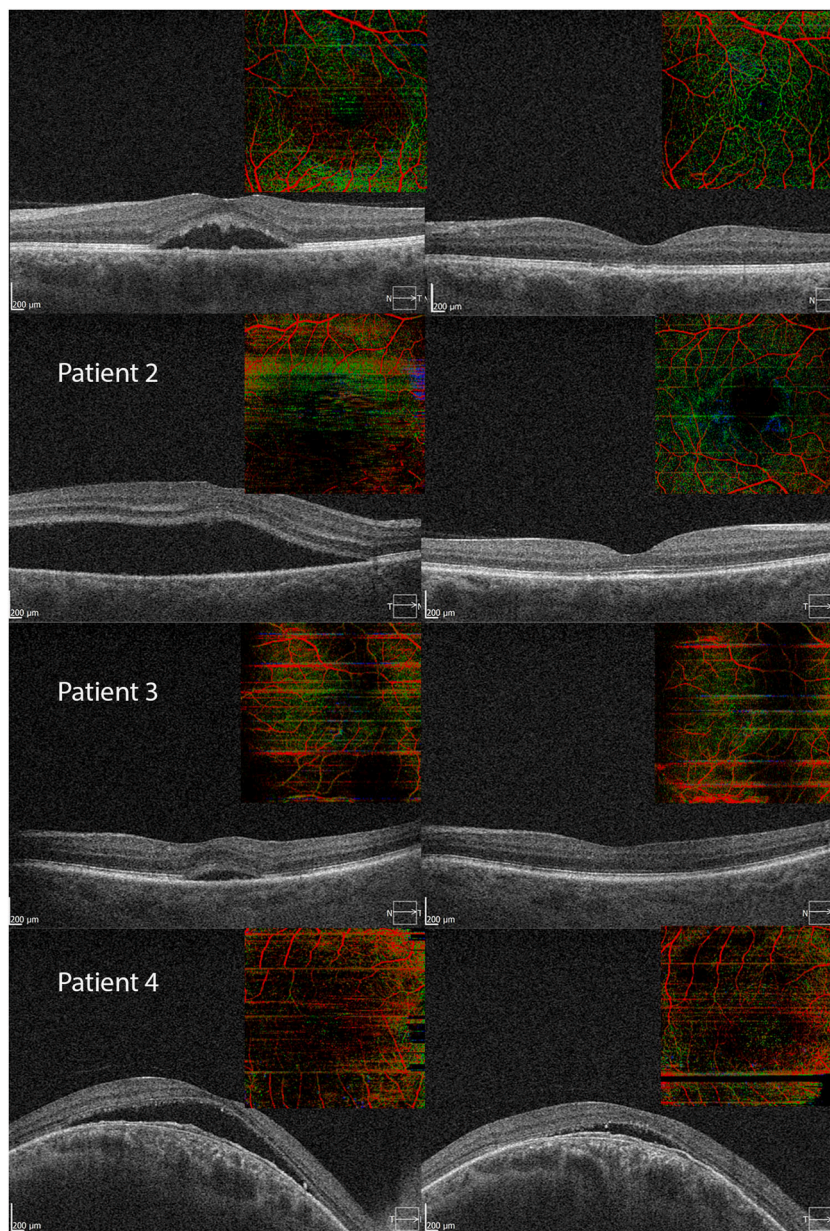| No.	Sex	Age	Doses	Prior treatment	BCVA initial	BCVA post treatment	OCT CST variation	Fluid resolution	Follow-up (months)
Patient 1	male	39	4	Bevacizumab Aflibercept Laser	0.7	1	−224μ	yes	17
Patient 2	male	42	3	Bevacizumab Aflibercept	0.8	1	−289μ	yes	7
Patient 3	female	70	3	Bevacizumab Aflibercept	0.5	0.8	−35μ	yes	4
Patient 4	female	50	3	None	0.1	0.1	−88μ	partial	8

Fig. 2. Four patients with chronic CSC, before (left) and after (right) injection with Brolucizumab (OCT and OCTA images).

enrolled with poor vision and a lack of results from previous treatments. 75 % of the patients had already received other anti-VEGF. The conclusions presented here could change after the inclusion of more suitable patients (or naïve).

Another limitation is the low number of patients and short follow-up duration. This is especially valid for the CSC report, where only 4 patients were injected. Furthermore, the accuracy of CSC diagnostic could always be contested, considering that indocyanine green angiography was not available and the absence of macular neovascularization was assessed only on OCT angiography. The older age of Patient 3 from the CSC group (70 years) is also an issue, considering the usual presentation under 50 years of age. However, all the CSC patients met the diagnostic criteria, and during the follow up there was no suspicion of drusen formation.

One further limitation is the retrospective nature of the study. The lack of randomization protocols for anti-VEGF treatments prevents any efficient comparison between different injected molecules. The familiar anti-VEGF drugs (e.g. Aflibercept) were considered safer and used in most cases, while the new Brolucizumab was reserved in cases subjectively considered difficult.

6. Conclusions

Brolucizumab was safe and efficient in nAMD, even in cases where other anti-VEGF were previously used. The Interval of injection was calculated and could become a parameter to consider when comparing anti-VEGF drugs and regimens. PRN regimen with an Interval of injection 2.68 months (11 weeks, approximatively) showed good resolution of macular fluid and a very low incidence of adverse reactions. Chronic CSC patients could also benefit from Brolucizumab intravitreal injections.

Ethics approval and written informed consent

All procedures involving human participants were in accordance with the ethical standards of the institutional research comity of the University of Medicine and Pharmacy Iuliu Hatieganu Cluj-Napoca (DEP49) and with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from all participants.

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Not applicable.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Samoila Lacramioara: Writing – review & editing, Writing – original draft, Investigation, Data curation, Conceptualization. **Samoila Ovidiu:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Clichici Simona:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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