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Long-Term Follow-Up of Brolucizumab in Macular Neovascularization

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Keywords
Spectral-domain optical coherence tomography · Optical coherence tomography angiography · Macular neovascularization · Anti-vascular endothelial growth factor · Brolucizumab

Abstract
Introduction: The aim of the study was to evaluate functional and anatomical changes in type 1 and type 2 naïve macular neovascularization (MNV) patients treated with brolucizumab injections up to 1 year of treatment (week 48). ***Methods:*** Thirty-eight eyes of 38 patients with active MNV were enrolled at the Ophthalmology Clinic of the University "G. d'Annunzio," Chieti-Pescara, Italy. All patients were scheduled for brolucizumab intravitreal injections as per label, according to the standard HAWK and HARRIER trials guidelines. Enrolled patients underwent complete ophthalmic evaluation, including optical coherence tomography (OCT) and OCT angiography. All measurements were evaluated at baseline and then monthly up to week 48. The main outcome measures were changes in best-corrected visual acuity (BCVA); central macular thickness (CMT); subfoveal choroidal thickness (SCT); pigment epithelial detachment presence and maximum height (PEDMH); intraretinal fluid (IRF) presence, subfoveal subretinal fluid (SSRF) presence and maximum height, macular atrophy area, and neovascular membrane flow area in the slab extending from the outer retina to choriocapillaris (ORCC flow). ***Results:*** CMT and BCVA significantly changed in both groups over time. ORCC flow and SCT significantly reduced in both groups over time. Atrophy areas increased from 0 to 0.17 mm^2 and from 0 to 0.23 mm^2 in type 1 MNV and type 2 MNV patients, respectively. PEDMH reduced in type 1 MNV from 138 µm at T0 to 96 µm at T5. Changes in fluids were noted, with SSRF thickness reduction and IRF changes in both groups. ***Conclusion:*** Our one-year results of treatment confirm brolucizumab to be efficient and safe in both type 1 and type 2 MNV patients, proposing novel OCT parameters as possible biomarkers of treatment.

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Introduction

Neovascular age-related macular degeneration (nAMD) is one of the leading causes of irreversible blindness in the developed world, affecting approximately 10% of elderly patients over 65 years old [1]. Different pathogenic factors are reported to be involved in disease development and progression. Among all, a central role is covered by vascular endothelial growth factor (VEGF), whose expression causes the growth of new pathologic vessels, the hallmark of the disease [2].

Other reported findings are subretinal exudates, hemorrhage, pigment epithelium detachments (PEDs), and the presence of sub/intraretinal and/or subretinal pigment epithelium (RPE) fluid due to chronic vessel exudation. The final stage of this pathologic process is macular atrophy (MA), fibrosis, and scarring, which is known to adversely affect visual function [3].

The introduction of optical coherence tomography (OCT) and OCT angiography (OCT-A) has permitted a better comprehension of disease; thus, basing on OCT findings, nAMD has been classified into type 1, type 2, and type 3 neovascularization (NV) according to the severity of the clinical picture on OCT scans as described by a recent consensus document [4]. The aim of AMD treatment is to reduce vision loss and optimize vision-related quality of life; therefore, anti-VEGF intravitreal treatment has widely been accepted as the first-line therapy for patients with macular NV (MNV) [5]. Different anti-VEGF drugs have been used in order to antagonize the role of the VEGF and reduce exudation caused by MNV [6–8]. Among all, it is relevant the role of a relatively new anti-VEGF agent, brolucizumab (Beovu; Novartis, East Hanover, NJ, USA), whose efficacy in nAMD has yet to be demonstrated in HAWK and HARRIER phase 3 clinical trials and different real-world studies [9, 10].

According to the previous, brolucizumab seems to be noninferior to fixed dose aflibercept in best-corrected visual acuity (BCVA) changes. In addition, the anti-VEGF agent has proved to be efficient in prolonging the resolution of MNV activity biomarkers, including PEDs and fluids [9, 10].

Mehta et al. [11] found intravitreal brolucizumab (IVBr) to be well tolerated and associated with improvements in macular fluids, BCVA stabilization, and/or increased intravitreal treatment interval by studying non-naïve eyes with nAMD treated with IVBr alone or in combination with aflibercept. William et al. [12] compared changes occurring in naïve eyes treated with IVBr compared with non-naïve eyes, finding improved BCVA in only naïve eyes, in contrast with foveal central thickness (FCT), which was found to be reduced in both groups.

In our previous study, we assessed the functional and anatomical changes in MNV type 1 naïve patients in the loading phase up to week 16 after IVBr treatment administered as per label finding improved the anatomical and functional parameters [13]. The aim of the present study was to evaluate functional and anatomical changes occurring in patients with type 1 and type 2 naïve MNV treated with IVBr injections up to week 48.

Materials and Methods

In this prospective observational study, a total of 40 eyes of 40 patients with active MNV were enrolled at the Ophthalmology Clinic of University "G. d'Annunzio," Chieti-Pescara, Italy, from January 2021 to January 2022. 24 eyes of 24 subjects had a definite diagnosis of active naïve type 1 MNV (G1) and 16 eyes of 16 subjects were diagnosed for active naïve type 2 MNV (G2) according to the consensus classification. Two patients were lost at follow-up examinations; thus, 38 eyes of 38 patients were analyzed. Excluding criteria were previous treatments for MNV such as photodynamic therapy and intravitreal injections of other anti-VEGF drugs, concomitant ophthalmological diseases or autoimmune general conditions, media opacities hypersensitivity to the drug or its excipient.

The study observed the tenets of the Declaration of Helsinki and was approved by an Institutional Review Board of the University "G. d'Annunzio" of Chieti-Pescara. Patients provided informed consent for participation in the study.

Patients were treated with IVBr as per label (q12/q8 dosing regimen), and according to the standard HAWK and HARRIER trials guidelines, all patients received a single dose of 6-mg IVBr (0.05 mL solution) injections. The protocol included three initial monthly doses of brolucizumab, and then at week 16, a disease activity assessment was performed and patients were shifted to a 12-week interval (q12w) or to a 8-week interval (q8w) based on the anatomical and functional criteria in accordance with the registration trials (CST reduction, presence of IRF and/or SRF, presence of disease activity). Treatment was repeated over time, following the same scheme of treatment.

All patients underwent a complete ophthalmic examination at baseline (T0) and then monthly up to week 48 (T5). Examination included BCVA evaluation using Early Treatment Diabetic Retinopathy Study (ETDRS) chart, Goldmann applanation tonometry, slit-lamp biomicroscopy, and indirect fundus ophthalmoscopy. In addition, all patients underwent fundus fluorescein angiography, indocyanine green angiography, fundus autofluorescence (FAF), SD-OCT using Spectralis® HRA+OCT (Heidelberg Engineering; Heidelberg, Germany), and OCTA using the RTVue XR Avanti® OCT-A system (AngioVue system, Optovue Inc., Fremont, CA, USA) (Fig. 1).

The main outcome measures from baseline to each follow-up were changes in BCVA; central macular thickness (CMT); subfoveal choroidal thickness (SCT); PEDs presence and maximum

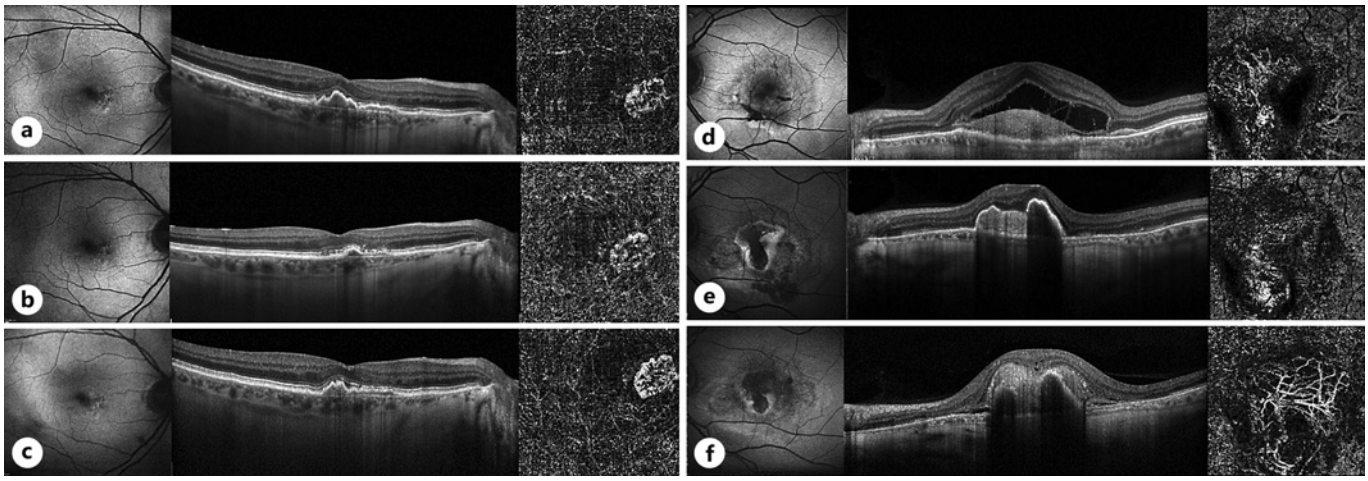

Fig. 1. Autofluorescence, OCT, and ORCC OCT-A images of G1 at T0 (**a**), T4 (**b**), and T5 (**c**) and G2 at T0 (**d**), T4 (**e**), and T5 (**f**).

height (PEDMH); intraretinal fluid (IRF) presence, subfoveal subretinal fluid (SSRF) presence and maximum height (SSRFT), and MA. Neovascular membrane flow area was evaluated as well.

Va Assessment

BCVA was measured using the logarithm of the minimum angle of the resolution system.

SD-OCT Analysis

The acquisition protocol for SD-OCT included 49 horizontal raster dense linear B-scans centered on the fovea. Moreover, horizontal and vertical B-scans centered on the fovea with enhanced depth imaging mode were acquired in all patients.

All acquisitions following baseline visit were acquired using the follow-up function. CMT was measured using the central 1-mm-diameter circle of the ETDRS thickness map.

SSRFT, defined as the vertical distance between the end of the outer segment and the RPE at the foveal center, was measured using the inbuilt manual caliper. PED was defined as the separation between the basal lamina of RPE and the inner collagenous layers of Bruch's membrane and was manually measured in its maximum height (PEDMH) using the caliper tool using the scan revealing the most prominent lesion site within the central 6-mm-diameter circle of the ETDRS grid.

SCT, measured vertically from the outer border of the RPE to the inner border of the sclera, was evaluated using the inbuilt manual caliper on enhanced depth imaging OCT scans. IRF and SRF in the central 6-mm-diameter circle of the ETDRS grid were defined as present, absent, or unreadable.

If present, the maximum height of SRF was measured in the foveal central area. MA was defined as an area at least 175 mm in linear diameter identified as a circumscribed hyper-reflective zone with baring of the choroidal vessels at IR with corresponding RPE and outer retinal loss and corresponding choroidal signal enhancement at SD-OCT [14, 15].

FAF was the method of choice to measure MA characterized by an area of hypoautofluorescence corresponding to the IR images into the macular area. The area of atrophy was manually determined by the measuring tool on the Heidelberg Explorer software using the FAF images. Every SD-OCT scan image was reviewed to ensure that the area of atrophy measured with FAF corresponded to atrophy seen on SD-OCT using the aforementioned definition of MA.

Images with poor signal strength (<25) were excluded and thus repeated. All measurements were performed by two independent experienced readers and then compared.

OCTA Analysis

MNV flow area was calculated in all cases. Analyses were performed on an outer retina to choriocapillaris (ORCC) slab. The ORCC slab was set manually, with a slab extended from the outer boundary of the outer plexiform layer to 8 μm beneath Bruch's membrane.

Images were exported as JPEG files and then analyzed with ImageJ software version 1.52° (National Institutes of Health, Bethesda, MD, USA; available at http://rsb.info.nih.gov/jj/index.html). The NV lesions were manually circumscribed by two independent retinal specialists and the flow within was calculated as the number of pixels over a nonperfusion threshold, and then converted in a comparable mm^2 area value. In cases of hyporeflective PED not permitting MNV evaluation, it was considered a "0" value.

Statistical Analysis

Descriptive statistics included frequencies and proportions for categorical variables and mean and standard deviation or median and interquartile range for continuous variables following their distribution. Differences between the two groups were tested by the Student's t test and Pearson's χ^2 test for continuous and categorical variables, respectively. A two-way mixed ANOVA was applied to compare G1 and G2 (between-subject effect) over time (within-subject effect). All statistical tests were two sided, with a significance level set at $p < 0.05$. Analyses were performed using the R software environment for statistical computing and graphics (version 3.4.1; http://www.r-project.org/).

Table 1. Patients' baseline characteristics expressed as median (q1 = first quartile; q3 = third quartile) for continuous variables and as absolute frequency (percentage) for categorical variables

Baseline characteristics	G1	G2	*p* value
	N = 22	*N* = 16	
Age, years	78.00 (71.00; 84.00)	83.00 (80.50; 86.20)	0.099
Gender, %, male/female	45.5/54.5	75.0/25.0	0.100
BCVA, logMar	0.70 (0.32; 1.00)	1.30 (0.92; 2.00)	0.017
CMT, μm	430.00 (393.00; 517.00)	592.00 (530.00; 657.00)	0.066
SCT, μm	210.00 (166.00; 234.00)	162.00 (130.00; 183.00)	0.078
ORCC flow, mm^2	0.17 (0.13; 0.23)	0.32 (0.27; 0.37)	0.001
MA, mm^2	0.40 (0.22; 1.44)	2.17 (1.87; 2.59)	0.271
SSRF, *n* (%)			0.417
Absence	9 (40.9)	10 (62.5)	
Presence	13 (59.1)	6 (37.5)	
IRF, *n* (%)			0.004
Absence	13 (59.1)	0 (0.00)	
Presence	9 (40.9)	16 (100)	

BCVA, best corrected visual acuity; CMT, central macular thickness; SCT, subfoveal choroidal thickness; ORCC, outer retina to choriocapillaris; MA, macular atrophy; SSRF, subfoveal subretinal fluid; IRF, intraretinal fluid.

Results

A total of 38 eyes of 38 patients with AMD and active MNV were included in this study. 22 eyes were diagnosed with active G1, whereas 16 eyes were diagnosed with G2.

The mean age was 78.0 years in G1 (ranging from 71.0 to 84.0), 10 (45.5%) out of 22 patients were men, 9 (40.9%) were left eyes, and 13 were right eyes. In G2, the mean age was 83.0 years (ranging from 80.5 to 86.2), 12 (75.0%) out of 16 were men, 10 (62.5%) were left eyes, and 6 were right eyes (Table 1 reporting baseline characteristics).

SD-OCT and OCT-A images were acceptable for all eyes, and qualitative and quantitative parameters were achieved in all cases. BCVA improved significantly differently over time from T0 to T5 in both groups (from 0.65 to 0.20 and from 0.61 to 0.30 for G1 and G2, respectively, $p < 0.001$) (Table 2), with no significant interaction between groups ($p = 0.508$).

CMT showed a significant reduction over time in both groups (430 at T0 to 247 at T5 for G1 and 592 at T0 to 194 at T5 for G2; $p < 0.001$) with significant interaction ($p < 0.001$). SCT significantly reduced over time in both groups (210 at T0 to 147 at T5 for G1 and 162 at T0 to 109 at T5 for G2; $p = 0.001$); however, no significant interaction between groups was found ($p = 0.739$), i.e., the groups change over time in the same way.

No significant differences were found during follow-ups in ORCC flow in both groups, although ORCC changes over time ($p = 0.045$) but in a similar way in both groups ($p = 0.401$). Atrophy areas significantly changed over time in groups ranging from 0 in G1 and G2 to 0.17 in G1 and 0.23 in G2 ($p < 0.001$). Moreover, PEDMH changed over time in G1 from 138 at T0 to 96 at T5.

SSRF reduced in both groups, ranging from 38.2% at T0 to 11.8% at T5 in G1 and 30% at T0 to 10.0% at T5 in G2 (Fig. 2), whereas changes in IRF presence were found in both groups, ranging from 6.8% at T0 to 3.0% at T5 in G1 and from 16.7% at T0 to 10.4% at T5 in G2 (Fig. 3). 17 eyes over 22 in G1 (77%) and 6 eyes over 16 (37%) in G2 were in the q12 interval when evaluated at week 48. Besides, 5 eyes over 22 (23%) in G1 and 10 over 16 eyes (63%) in G2 were in the q8 interval. Brolucizumab showed an overall well-tolerated safety profile, and no ocular adverse events were observed.

Discussion

nAMD is one of the main ocular diseases affecting elderly patients causing reduced visual acuity, metamorphopsia, and low quality of life. Anti-VEGF treatment has overall changed the disease story, giving affected patients a suitable therapy in order to stabilize the disease. Over time, different anti-VEGF agents have been

Table 2. Over time, descriptive statistics are expressed as median (q1 = first quartile; q3 = third quartile); the *p* values derived from two-way mixed ANOVA reporting the main effect (group and time) and interaction

Group	Variables	T0	T1	T2	T3	T4	T5	Group[a]	Time[b]	Interaction[c]
G1	BCVA, logMar	0.65 (0.33; 1.00)	0.61 (0.23; 0.93)	0.40 (0.20; 0.70)	0.30 (0.20; 0.65)	0.20 (0.11; 0.40)	0.20 (0.10; 0.38)	0.205	<0.001	0.508
G2		0.61 (0.48; 0.78)	0.85 (0.65; 1.00)	0.56 (0.45; 0.70)	0.46 (0.28; 0.70)	0.35 (0.30; 0.55)	0.30 (0.28; 0.53)			
G1	CMT, μm	430.00 (393.00; 517.00)	326.00 (277.00; 411.00)	310.00 (250.00; 362.00)	262.00 (215.00; 314.00)	288.00 (256.00; 340.00)	247.00 (212.00; 391.00)	0.088	<0.001	<0.001
G2		592.00 (530.00; 657.00)	537.00 (515.00; 580.00)	399.00 (335.00; 459.00)	275.00 (210.00; 349.00)	234.00 (186.00; 373.00)	194.00 (159.00; 322.00)			
G1	SCT, μm	210.00 (166.00; 234.00)	182.00 (143.00; 219.00)	139.00 (120.00; 202.00)	128.00 (106.00; 214.00)	139.00 (98.30; 181.00)	147.00 (101.00; 222.00)	0.146	0.001	0.739
G2		162.00 (130.00; 183.00)	154.00 (126.00; 168.00)	135.00 (124.00; 147.00)	131.00 (123.00; 142.00)	109.00 (91.50; 124.00)	109.00 (92.00; 129.00)			
G1	ORCC flow, mm^2	0.17 (0.13; 0.23)	0.19 (0.14; 0.22)	0.16 (0.11; 0.19)	0.16 (0.11; 0.21)	0.15 (0.10; 0.23)	0.13 (0.02; 0.21)	0.005	0.045	0.401
G2		0.32 (0.28; 0.37)	0.34 (0.30; 0.42)	0.28 (0.16; 0.45)	0.22 (0.15; 0.39)	0.17 (0.10; 0.33)	0.21 (0.12; 0.34)			
G1	MA, mm^2	0.00 (0.00; 0.05)	0.00 (0.00; 0.08)	0.00 (0.00; 0.14)	0.00 (0.00; 0.14)	0.08 (0.00; 0.21)	0.17 (0.11; 0.50)	0.924	<0.001	0.044
G2		0.00 (0.00; 0.00)	0.00 (0.00; 0.10)	0.00 (0.00; 0.51)	0.21 (0.00; 0.76)	0.22 (0.00; 1.43)	0.23 (0.00; 1.31)			
G1	PEDMH, μm	138.00 (104.00; 194.00)	113.00 (93.30; 176.00)	98.50 (69.00; 141.00)	103.00 (72.80; 126.00)	114.00 (62.30; 164.00)	96.00 (58.30; 148.00)	/	0.065	/
G2		/	/	/	/	/	/			

[a]Probability that the effect of treatment on the variable was influenced by groups. [b]Probability that the effect of the group on the addressed variable was influenced by time; for each variable, the differences between the means of each period of the two groups were tested. [c]Probability that the effect of time was greater in one of the groups (interaction time × group). Dunn's post-hoc test with Bonferroni correction to express the effect of the group at each time point.

proposed to downregulate VEGF, which is responsible for the growth of the new vessels. Among all, brolucizumab, a relatively new anti-VEGF, has demonstrated efficacy in nAMD patients in terms of functional and anatomical outcomes.

In our previous work, brolucizumab demonstrated to be efficient in a 16-week interval in patients with naïve G1 in reducing OCT and OCT-A biomarkers mirror of the disease activity and improving visual acuity with overall patient satisfaction [13]. The aim of our new study was to analyze structural and morphofunctional changes occurring in naïve eyes with G1 and G2 treated with brolucizumab in a 1-year interval.

Consistent with our previous results, the 1-year follow-up confirmed the efficacy of brolucizumab in patients with G1 by observing improved BCVA and reduction of CMT and SCT [13]. CMT has been considered a validated biomarker of activity and final endpoint for different studies [16, 17].

Abdin et al. [18] in their first-year real life experience with brolucizumab for refractory active nAMD by analyzing structural and functional parameters observed a decrease in CMT at week 16, which remained so even afterward. They attributed this result to the long story of nAMD with chronic IRF, SRF, and PED in their enrolled patients, leaving permanent structural changes that limited the functional recover. In our study, a reduction in CMT was observed in both G1 and G2 patients, with significant improvements in BCVA.

A reduction in SFCT was observed as well from baseline to 1 year follow-up in both groups of patients. Choroidal thickness has a key role in the pathogenesis of

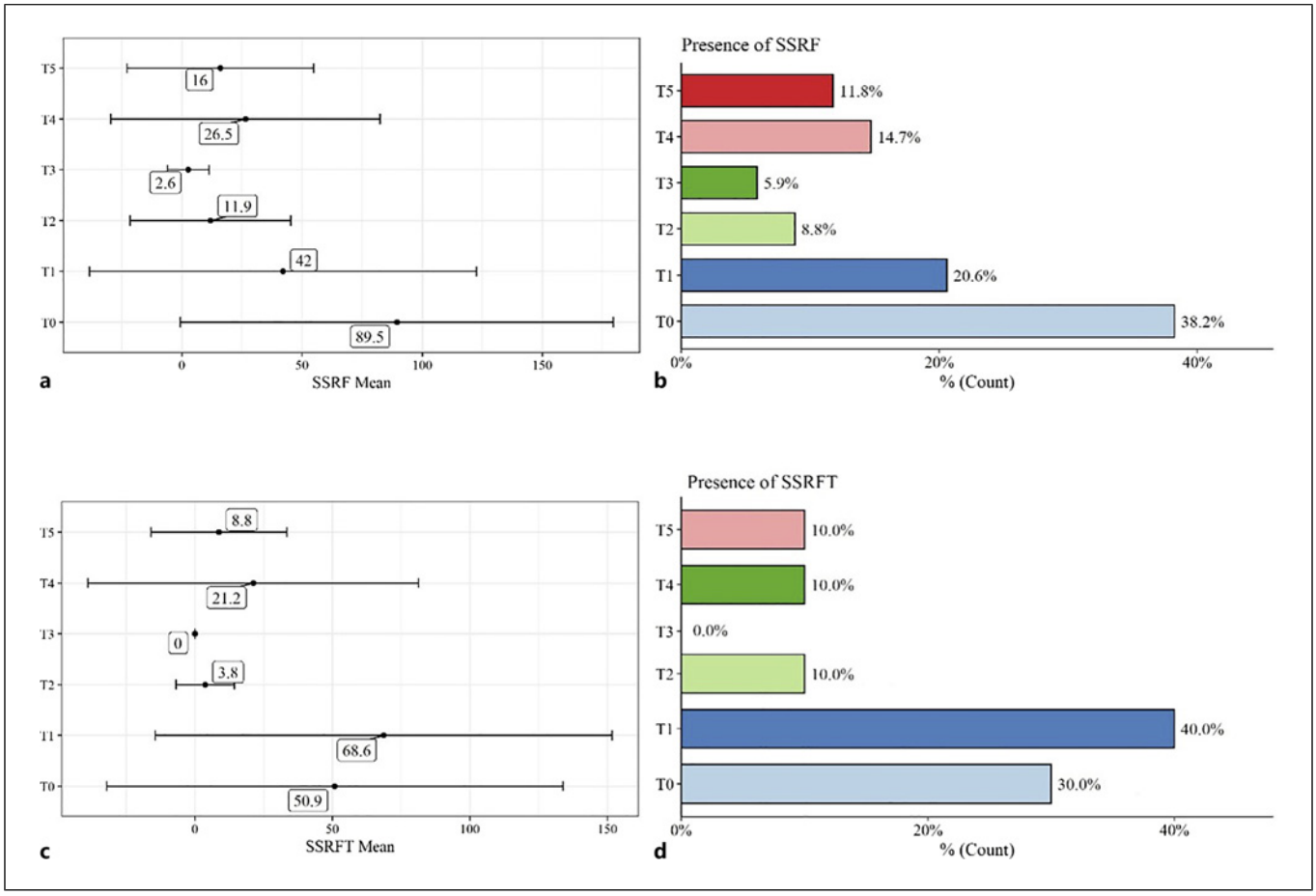

Fig. 2. Mean ± SD and presence of SSRFT expressed as a percentage (absolute frequency) for group 1 (**a**, **b**) and group 2 (**c**, **d**).

different ocular diseases, including nAMD. In fact, SFCT reduces according to AMD severity. Particularly, studies have demonstrated SFCT to be reduced in eyes with reticular pseudodrusen and geographic atrophy; nevertheless, SFCT has shown to reduce after anti-VEGF treatment [19, 20]. Therefore, these considerations have made SFCT a suitable biomarker to follow the disease activity in patients with nAMD. Changes in SSRF and IRF as well were found in both groups. Consistent with our results, the BEL study observed changes in SRF and IRF over time in their patients with nAMD [21].

OCT-A changes have been proposed over time as a marker of disease in patients with active MNV due to the ability of visualizing flow in different slabs [22, 23]. Thus, despite its variability, OCT-A has been proposed as a potential biomarker to evaluate changes occurring in eyes treated with IVBr by Rispoli et al. [24]. In this study, a significant decrease of ORCC flow was found during follow-up with no significant differences between the two groups.

Recently, authors have focused on the role of atrophy in MNV patients [25–30]. Particularly, the latest publications have considered G1 patients to be more resistant to atrophy development, and this is in line with the better long-term functional outcomes. Cabral et al. [25] in their manuscript reported the presence of an immature blood flow pattern on OCT-A to be associated with a lower progression rate of MA in G1 patients during long-term anti-VEGF treatment. Xu et al. [26], in their retrospective study, observed treatment naïve G1 patients to be less likely to develop geographic atrophy when compared to G2, G3, and mixed MNV. In fact, in their study, the overall annualized rate of atrophy progression was 0.58 mm^2 per year; however, the progression rate per type was reported to be 0.17 mm^2 for G1, 1.36 mm^2 for G2, 0.55 mm^2 for G3, and 1.22 mm^2 for mixed MNV per year. They retained that eyes with different neovascular types at baseline have different risks of developing GA; therefore, the anatomical classification has important

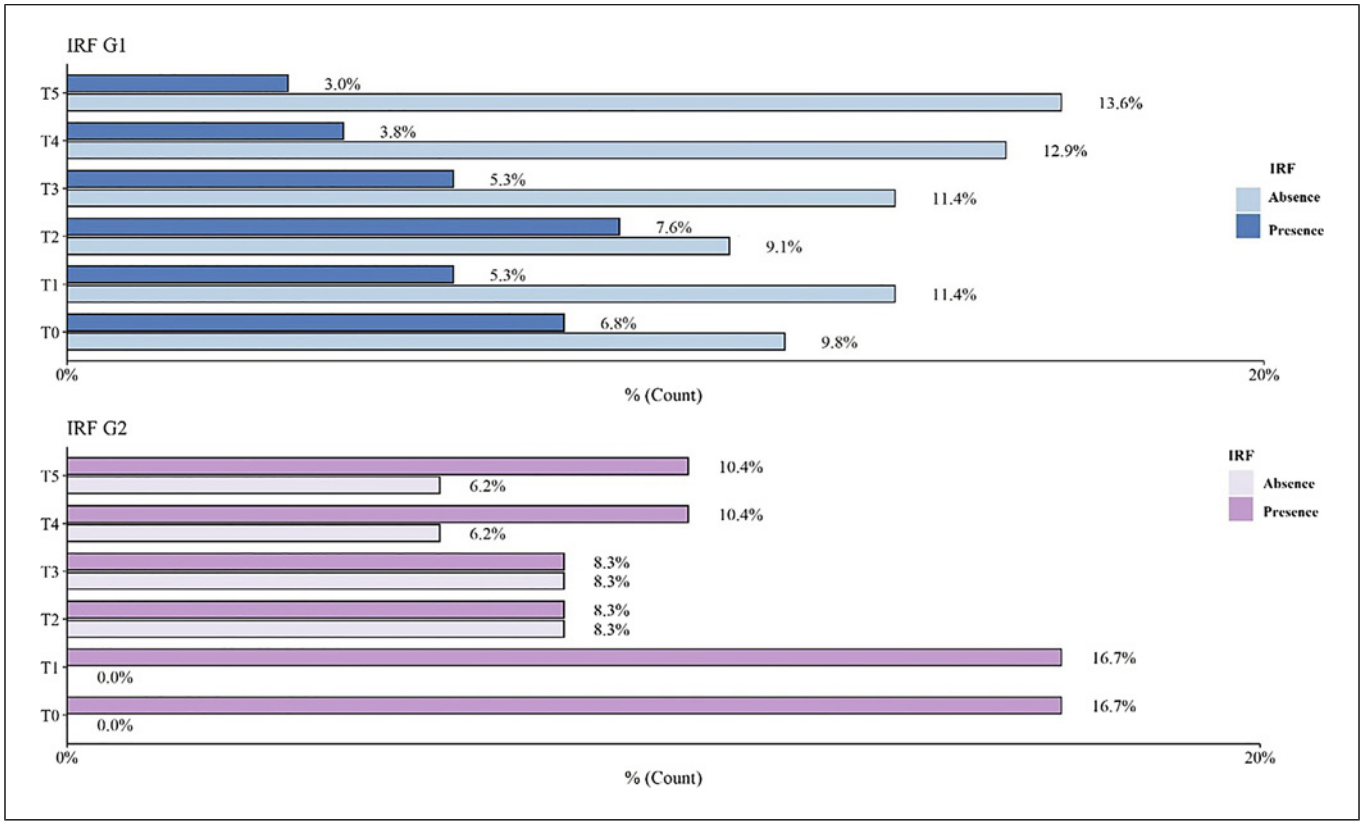

Fig. 3. Absence and presence of IRF in group 1 (IRF G1) and group 2 (IRF G2) expressed as percentages.

prognostic value in stratifying the risk of developing atrophy [26].

In our study, we found different baseline atrophy parameters in G1 and G2 MNV patients; in fact, it was found to be more present in the latter, although possibly attributable to higher values at baseline. These differences between the two groups were maintained until 1-year treatment follow-up, although not significant. In line with the literature, our results enhance the efficiency of brolucizumab in nAMD patients.

Similarly, Pece et al. [27] recently reported a short-term experience in nonresponder patients with G1 treated with brolucizumab observing improved anatomical outcomes and reduction of structural activity biomarkers, thus enhancing the efficiency of brolucizumab treatment. Besides, Viggiano et al. [28] defined brolucizumab as a valid option with significant morphofunctional impact on enrolled eyes with G1 already treated with other anti-VEGF molecules.

Besides, functional and anatomical outcomes improved in G2 enrolled patients. In fact, BCVA improved significantly from baseline to 1-year follow-up, CMT and SFCT reduced, and SSRF and IRF changes were found over time. To our knowledge, no data are present in the literature regarding patients with G2 treated with IVBr.

Brolucizumab demonstrated overall safety and efficacy more, and when evaluated at 1 year follow-up, the majority of patients were in their q12 interval, thus enhancing the efficacy of brolucizumab in maintaining beneficial effect over time with the possibility of delaying injections, thus reducing the socio-economic burden. However, it must be assessed that when evaluated at 1-year follow-up, the majority of G2 patients were in their q8 interval in contrast with G1 patients who had longer interval of treatment (q12). The efficacy of treat-and-extend regimen has already been validated in the literature, with the strength of being as effective as the fixed regimen with fewer injections, thus it is widely recommended [29–31]. Matsumoto et al. [32] in their study reported the average intended injection interval at the last visit to be 14 ± 2.9 weeks in treatment-I G1 patients treated with IVBr over 1 year. Conversely, no data regarding G2 patients treated with brolucizumab are present in the literature to our knowledge. We hypothesized the different timing of injection in

the two groups to be attributable to a different baseline vascular flow area. In fact, the longer injection interval in G2 patients may be explained by higher area values at baseline. However, due to the low number of cases, further studies are suggested to confirm and thus investigate the trend of injection.

Conclusions

To our knowledge, this is the first article reporting 1-year result of treatment with brolucizumab in both G1 and G2. We acknowledge that the small sample of patients may be a limitation for our study; thus, further studies are required to confirm our result in a higher number of patients. Our 1-year results of treatment confirm brolucizumab to be efficient and safe in both G1 and G2, with novel OCT parameters as the possible biomarkers of treatment to be considered over time.

Statement of Ethics

The study observed the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the University "G. d'Annunzio" of Chieti-Pescara (2/2021). Patients provided written informed consent for participation in the study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conceptualization, visualization, and writing – review and editing, Lisa Toto; methodology, Rossella D'Aloisio and Chiara de Nicola; software, Patrizio Venturoni, Matteo Gironi, and Alberto Quarta; validation, Lisa Toto and Maria Ludovica Ruggeri; formal analysis, Raffaella Aloia and Emanuele Doronzo; investigation, resources, and writing – original draft preparation, Maria Ludovica Ruggeri; data curation, Marta Di Nicola; data analysis, Annamaria Porreca; supervision and project administration, Rodolfo Mastropasqua. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

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

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