Ophthalmic Research

Research Article

Ophthalmic Res 2023;66:218–227
DOI: 10.1159/000526851

Received: April 26, 2022
Accepted: July 31, 2022
Published online: September 26, 2022

Brolucizumab Intravitreal Injection in Macular Neovascularization Type 1: VA, SD-OCT, and OCTA Parameter Changes during a 16-Week Follow-Up

Lisa Toto[a] Maria Ludovica Ruggeri[a] Rossella D'Aloisio[a]
Chiara De Nicola[a] Chiara Trivigno[a] Luca Cerino[a] Guido Di Marzio[a]
Marta Di Nicola[b] Annamaria Porreca[b] Rodolfo Mastropasqua[c]

[a]Ophthalmology Clinic, Department of Medicine and Science of Ageing, University G. D'Annunzio Chieti-Pescara, Chieti, Italy; [b]Department of Medical, Oral and Biotechnological Sciences, Laboratory of Biostatistics, University "G. D'Annunzio" Chieti-Pescara, Chieti, Italy; [c]Ophthalmology Clinic, Department of Neurosciences, Imaging and Clinical Science, University G. D'Annunzio Chieti-Pescara, Chieti, Italy

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

Abstract
Introduction: The aim of this study was to assess early anatomical and functional changes after brolucizumab intravitreal injection (BIVI) in patients with age-related macular degeneration (AMD) and macular neovascularization type 1 (MNV1). ***Methods:*** A total of 24 eyes of 24 patients suffering from naïve AMD with MNV1 candidates to BIVI as per label with q12/q8 dosing regimen after the loading dose were enrolled in this prospective study. Main outcome measures during a 16-week follow-up period included changes in best corrected visual acuity (BCVA), central macular thickness (CMT), subfoveal subretinal fluid (SSRF) thickness (SSRFT), subfoveal sub-retinal pigment epithelium (RPE) fluid thickness (SSRPEFT), subfoveal choroidal thickness (SFCT), and pigment epithelial detachment (PED) maximum height (PED-MH). In addition, MNV1 flow area; percentages of eyes with intraretinal fluid (IRF), subretinal fluid, and sub-RPE fluid at different time points; and percentages of eyes candidates to a q8 or q12 injection interval after disease activity assessment at week 16 were evaluated. ***Results:*** BCVA improved significantly from baseline (T0) to week 12 (T3) (p = 0.028). CMT showed a significant reduction from 456 ± 123 µm at T0 to 265 ± 85 µm at T3 ($p < 0.001$). SSRFT and SSRPEFT reduced significantly as well ($p < 0.001$ and $p = 0.049$, respectively). PED-MH and SFCT reduced significantly at the different time points ($p = 0.020$; $p = 0.006$, respectively). IRF presence changed significantly from 41.7% of eyes at T0 to 20.8% at T3 ($p = 0.045$). SSRF reduced significantly during follow-up, being present in 62.5% of eyes at T0 and 4.2% of eyes at T3 ($p < 0.001$). Subfoveal sub-RPE fluid decreased significantly during time, being present in 20.8% of eyes at T0 and 0% at T3 ($p = 0.013$). Most of the eyes (18 eyes, 75%) at week 16 after disease activity assessment were shifted in the q12 interval, and only a minority of eyes shifted in a q8 interval (6 eyes, 25%). ***Conclusion:*** Brolucizumab is efficient in AMD patients with MNV1 by reducing all retinal fluids during the

Lisa Toto and Maria Ludovica Ruggeri contributed equally to this work.

Karger@karger.com
www.karger.com/ore

Correspondence to:
Rossella D'Aloisio, ross.daloisio@gmail.com

loading phase and shows reduction of macular thickness, choroidal thickness, and PED height. Most eyes at disease activity assessment (75%) fall into 12-week interval and the minority (25%) into the 8-week interval.

Introduction

Neovascular age-related macular degeneration (nAMD) is a chronic and progressive disease characterized by the presence of pathological choroidal neovascularization related to the overexpression of vascular endothelial growth factor (VEGF) [1, 2]. The chronic exudation from new vessels causing sub/intraretinal and/or sub-retinal pigment epithelium (RPE) fluid formation results in metamorphopsia and visual impairment. Macular atrophy and scarring are the late-stage complications of the disease, leading to irreversible visual loss [1–8].

The use of multimodal retinal imaging and ultimately optical coherence tomography angiography (OCTA) provides an assessment of retinal and choroidal vasculature [9], leading to precise diagnosis and monitoring of the disease status during treatment. Anti-VEGF intravitreal treatment is an established first-line therapy for patients with nAMD [10–14].

Recently, HAWK and HARRIER phase 3 clinical trials approved brolucizumab, a new anti-VEGF agent for the treatment of MNV [15, 16]. Brolucizumab is a novel anti-VEGF humanized single-chain antibody fragment with a molecular weight of 26 kDa binding with high affinity to all VEGF-A isoforms [17]. The proposed protocol with q12/q8 dosing intervals showed efficacy in improving and maintaining visual acuity up to 96 weeks in patients with a diagnosis of nAMD, demonstrating the noninferiority compared to aflibercept and superior reductions in central subfield thickness up to 96 weeks [15, 18].

Some real-world studies confirmed the efficacy and safety of brolucizumab in nAMD, both in naïve and previously treated patients [19–22]. Our study aimed to report early functional and anatomical changes in age-related macular degeneration (AMD) patients with active naïve macular neovascularization type 1 (MNV1) in the loading phase up to week 16 after intravitreal brolucizumab treatment administered as per label and to assess percentages of patients at week 16 candidate to a q12 or q8 interval.

Materials and Methods

In this prospective observational study, 24 eyes of 24 subjects with AMD and active naïve MNV1 with foveal involvement candidates for intravitreal treatment with brolucizumab as per label with a q12/q8 dosing regimen after the loading dose were enrolled at the Ophthalmology Clinic of University G. d'Annunzio, Chieti-Pescara, Italy, from January to August 2021. Exclusion criteria were previous treatments for MNV such as photodynamic therapy and intravitreal injections of anti-VEGF, the presence of concomitant ophthalmological diseases, pachychoroid diseases, autoimmune general conditions, and media opacities.

This study complied with 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 informed consent for participation in the study.

Brolucizumab 6 mg (0.05 mL solution) intravitreal injections were administered according to the standard guidelines according to the HAWK and HARRIER trials [15, 16]. Treatment-naïve type 1 MNV eyes received three initial monthly doses of brolucizumab and then, at week 16, a disease activity assessment was performed, and patients were shifted to the 12-week interval (q12w) or to the 8-week interval (q8w) based on anatomical and functional criteria in accordance with the registration trials.

All patients underwent a complete ophthalmic examination, including best corrected visual acuity (BCVA) evaluation using Early Treatment Diabetic Retinopathy Study (ETDRS) chart (logarithm of the minimum angle of resolution system), Goldmann applanation tonometry, slit-lamp biomicroscopy, and indirect fundus ophthalmoscopy. In addition, fundus fluorescein angiography, and indocyanine green angiography, spectral-domain OCT (SD-OCT) were performed using Spectralis® HRA+OCT (Heidelberg Engineering; Heidelberg, Germany). OCTA was performed in all patients using the RTVue XR Avanti® OCT-A system (AngioVue system; Optovue Inc., Fremont, CA, USA). BCVA, anterior segment biomicroscopy, intraocular pressure, indirect fundus exam, SD-OCT, and OCTA were performed at baseline (T0) and then monthly up to week 16 (T1–T4). Fundus fluorescein angiography and indocyanine green angiography were performed at baseline.

Main outcome measures were BCVA; central macular thickness (CMT); subfoveal choroidal thickness (SFCT); pigment epithelial detachment (PED) maximum height (PED-MH); intraretinal fluid (IRF) presence, subfoveal subretinal fluid (SSRF) presence and thickness (SSRFT), and subfoveal sub-RPE fluid (SSRPEF) presence and thickness (SSRPEFT); MNV flow area. In addition, percentages of patient candidates to a q8 or q12 injection interval after disease activity assessment at week 16 were reported.

SD-OCT Analysis

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

All acquisitions following the 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. SSRPEFT was defined as the vertical

Table 1. Mean and standard deviation (SD) of functional and anatomical parameters reported at each time point

	T0	T1	T2	T3	*p* value[a]	T4	*p* value[b]
BCVA (logMAR)	0.61 (0.37)	0.56 (0.33)	0.48 (0.29)	0.36 (0.24)	**0.028**	0.33 (0.21)	0.721
CMT, µm	456.0 (123.0)	370.0 (105.0)	318.0 (85.3)	265.0 (85.0)	**<0.001**	293.0 (61.0)	0.282
SSRFT, µm	105.0 (102.0)	43.5 (83.7)	12.2 (33.3)	1.4 (6.1)	**<0.001**	17.5 (52.6)	0.260
SSRPEFT, µm	64.0 (107.0)	31.3 (52.9)	26.0 (51.2)	4.9 (21.0)	**0.049**	39.6 (79.6)	0.121
PED-MH, µm	162.0 (110.0)	139.0 (84.9)	102.0 (48.7)	94.1 (38.9)	**0.020**	115.0 (66.4)	0.290
SFCT, µm	203.0 (56.9)	186.0 (55.0)	155.0 (55.9)	146.0 (64.2)	**0.006**	149.0 (51.7)	0.902
CC flow, mm^2	0.31 (0.27)	0.23 (0.16)	0.20 (0.13)	0.22 (0.13)	0.208	0.21 (0.05)	0.815
ORCC flow, mm^2	0.22 (0.11)	0.19 (0.08)	0.18 (0.08)	0.20 (0.12)	0.147	0.19 (0.09)	0.185
FDSCP	20.2 (9.2)	21.6 (12.5)	20.2 (11.7)	20.1 (14.2)	0.974	19.7 (11.5)	0.924
FDDCP	37.8 (11.7)	34.9 (9.5)	30.1 (10.1)	32.2 (14.8)	0.174	28.2 (9.0)	0.386
PDSCP	41.5 (8.5)	38.0 (7.6)	40.7 (6.6)	38.6 (9.2)	0.492	38.8 (6.9)	0.960
PDDCP	47.2 (6.3)	46.5 (7.2)	47.7 (7.5)	46.1 (7.8)	0.917	46.9 (7.0)	0.788

BCVA, best corrected visual acuity; CMT, central macular thickness; SSRFT, subfoveal subretinal fluid thickness; SSRPEFT, subfoveal sub-RPE fluid thickness; PED-MH, pigment epithelial detachment maximum high; FDSCP, foveal density of superficial capillary plexus; FDDCP, foveal density of deep capillary plexus; PDSCP, parafoveal density of superficial capillary plexus; PDDCP, parafoveal density of deep capillary plexus; ORCC, outer retina to choriocapillaris; CC, choriocapillaris. [a] *p* value derived from one-way repeated measures ANOVA models for repeated measures. [b] *p* value derived from paired *t* test for T3 versus T4.

distance between the end of the hyperreflective tissue beneath the RPE related to type 1 NV and the inner collagenous layers of Bruch's membrane at the foveal center and was manually measured using the inbuilt manual caliper.

PED was defined as the separation between the RPE and Bruch's membrane and was manually measured at its maximum height (PED-MH) using the caliper tool using the scan revealing the most prominent lesion site within the central 6-mm-diameter circle of the ETDRS grid. SFCT, measured vertically from the outer border of the RPE to the inner border of the sclera, at the foveal center was measured using the inbuilt manual caliper on enhanced depth imaging OCT scans.

Images with poor signal strength (<25) were excluded and thus repeated. IRF, SSRF, and SSRPEF were defined as present, absent, or unreadable. All measurements were performed by two independent, experienced readers.

OCTA Analysis

All patients underwent OCTA imaging using SD-OCTA using RTVue XR Avanti SD-OCT device with AngioVue software (version 2018.1.0.43; Optovue, Inc., Freemont, CA, USA), which is based on a split spectrum amplitude decorrelation angiography algorithm. In all cases, 3 × 3-mm volume scans were performed in all eyes, and only when the scan did not cover the entire lesion, a 6 × 6-mm scan was acquired.

MNV flow area was calculated in all cases. Fully automated segmentation algorithms and projection artifact removal algorithms were used for the choriocapillaris slab; the outer retina to choriocapillaris slab was set manually, extending from the outer boundary of the outer plexiform layer to 8 µm beneath Bruch's membrane, and projection artifact removal algorithms were also used.

Images were exported as JPEG files and then analyzed with Image J 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 non-perfusion threshold, then converted to a comparable mm^2 area value. NV density was considered as the ratio of pixels occupied by flowing vasculature to all pixels included in the analyzed region, as already described [8, 23].

Statistical Analysis

The sample size was calculated using the *F* test for repeated measures analysis of variance (within factor) with G*Power 3.1.9.2 for Windows software (available at http://www.gpower.hhu.de/en.html). Assuming a medium effect size of $f = 0.25$ for BCVA [24], an α error probability of 0.05, power (1 − β error probability) of 0.80, correlation among repeated measurements of 0.5, and a nonsphericity correction of 1, it was calculated that a total sample size of 24 eyes would be required.

Descriptive analysis was carried out using mean and standard deviation (SD) for the continuous variables and percentage values for the categorical ones. Lin's concordance correlation coefficient (CCC) was applied to evaluate the magnitude of bias between readers with its 95% confidence interval. According to high CCC values, each subject was attributed the mean value between reader 1 and reader 2.

The statistical analysis plan was structured in two phases: (1) one related to data derived from the loading dose period (from T0 to T3) to evaluate the treatment effect and (2) one related to the maintenance period (T3 vs. T4). One-way repeated measures analysis of variance was used to test within-mean differences from T0 to T3. Paired *t* test was used to assess mean differences between T3 and T4. Test for dependent proportions was applied to assess differences in the percentage of unresolved patients, meaning patients with residual intraretinal, subretinal, or sub-RPE fluid [25]. All statistical analyses were performed using R Statistical Software (version 3.5.3; R Foundation for Statistical Computing, Vienna, Austria). All tests were two-tailed, and a statistical significance was defined as p value < 0.05.

Results

Twenty-four patients (24 eyes) with AMD and active naive MNV1 were included in the study and completed the follow-up. The mean age was 77.6 ± 7.6 years (range from 58 to 82 years) and 11 out of 24 patients were men, 14 were right eyes and 10 were left eyes. SD-OCT images were acceptable for all eyes, and qualitative and quantitative parameters were scored in all cases. OCTA images were of unacceptable quality and thus were not analyzed in 3 eyes at baseline, 3 eyes at T1, and 2 eyes at T2, T3, and T4.

Interobserver repeatability of the measures evaluated by CCC shows a high grade of agreement for all considered parameters. BCVA improved significantly from baseline (T0) to week 12 (T3) (p = 0.028) and did not change significantly from T3 to T4 (p = 0.721) (Table 1). No significant differences were found at T4 between patients with fluid presence of any type and patients with resolved fluid (for IRF presence or absence, p = 0.906; for SSRF presence or absence, p = 0.073; for SSRPEF presence or absence, p = 0.605; for at least one of IRF/SSRF/SSRPEF presence, p = 0.631) (Table 1).

CMT showed a significant reduction from 456 ± 123 μm at T0 to 265 ± 85 μm at T3 (p < 0.001). SSRFT and SSRPEFT reduced significantly as well (p < 0.001 and p = 0.049, respectively) (Fig. 1; Table 1).

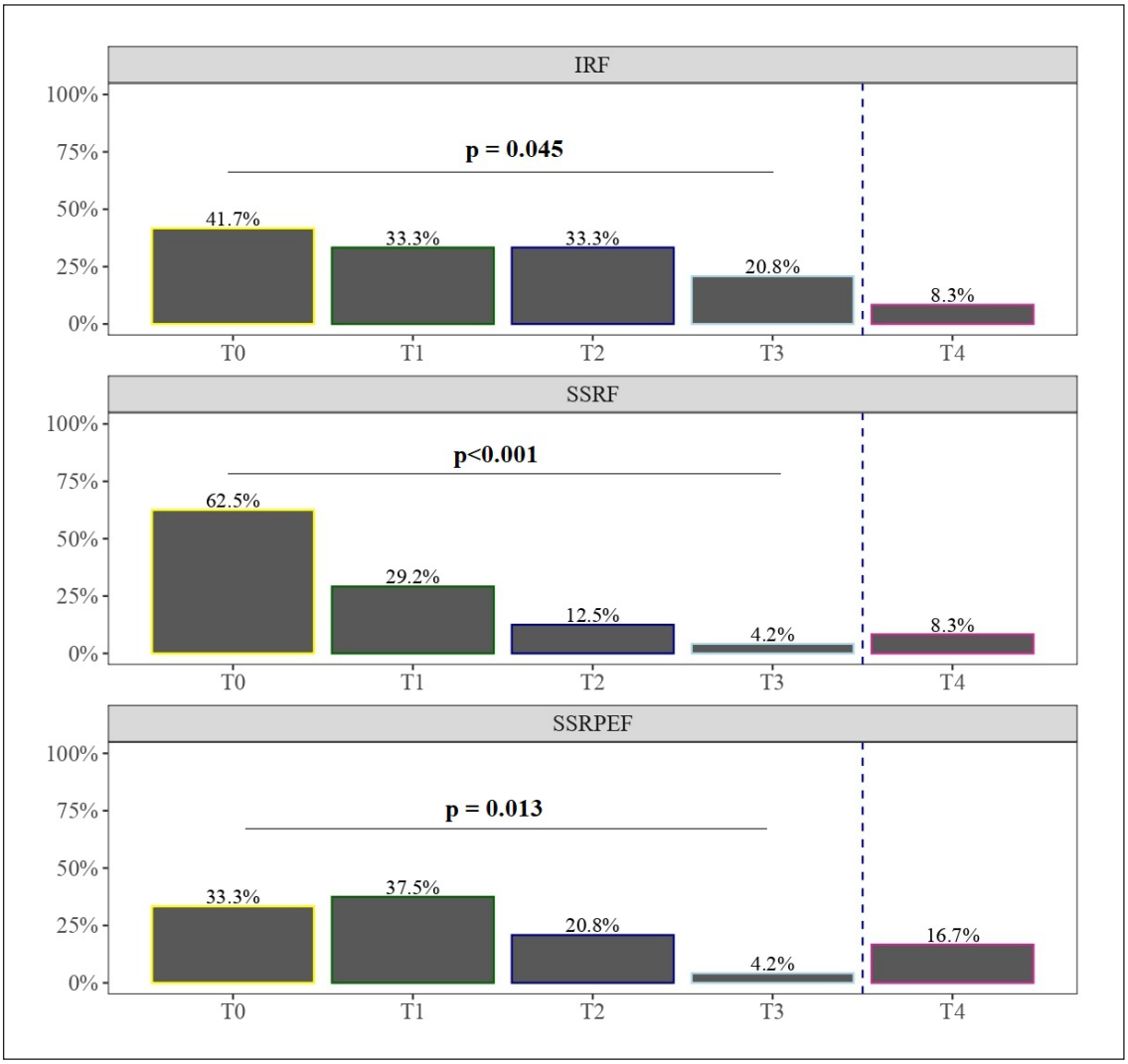


Fig. 1. Percentage of unresolved fluids (IRF, intraretinal fluid; SSRF, subfoveal subretinal fluid; SSRPEF, subfoveal subretinal pigment epithelium fluid) at all assessment times. Significant p values derived from the test for dependent proportions are reported.

PED-MH reduced significantly from 162 ± 110 μm at T0 to 94.1 ± 38.9 μm at T3 (p = 0.020) and SFCT from 20,356.9 μm at T0 to 146.0 ± 64.2 μm at T3 (p = 0.006) (Table 1). Choriocapillaris flow and outer retina to choriocapillaris flow did not show significant differences during follow-up (Fig. 2; Table 1).

IRF changed significantly from 41.7% at T0 to 20.8% at T3 (p = 0.045, Fig. 3; Table 1). SSRF reduced significantly during follow-up, being present in 62.5% of patients at T0 and 4.2% of patients at T3 (p < 0.001, Fig. 3; Table 1). SSRPEF decreased significantly during the time, being 33.3% at T0 and 4.2% at T3 (p = 0.013, Fig. 3; Table 1).

Most eyes (18 eyes, 75%) at week 16 after disease activity assessment were shifted in the q12 interval, and only a minority of eyes shifted in the q8 interval (6 eyes, 25%). Brolucizumab exhibited an overall well-tolerated safety profile with no occurrence of ocular adverse events.

Discussion

This study assessed early anatomical and functional changes after BIVI in patients with AMD and active treatment-naïve MNV1 during a 4-month follow-up.

Brolucizumab IVI was effective, showing recovery of retinal morphology and statistically significant improvement in visual function. CMT and PED-MH showed significant reduction, and all types of fluids such as intraretinal, subretinal, and sub-RPE fluid were significantly reduced during follow-up. Most eyes (18 eyes, 75%) at week 16 after disease activity assessment were shifted in the q12 interval and only a minority of eyes shifted in the q8 interval (6 eyes, 25%).

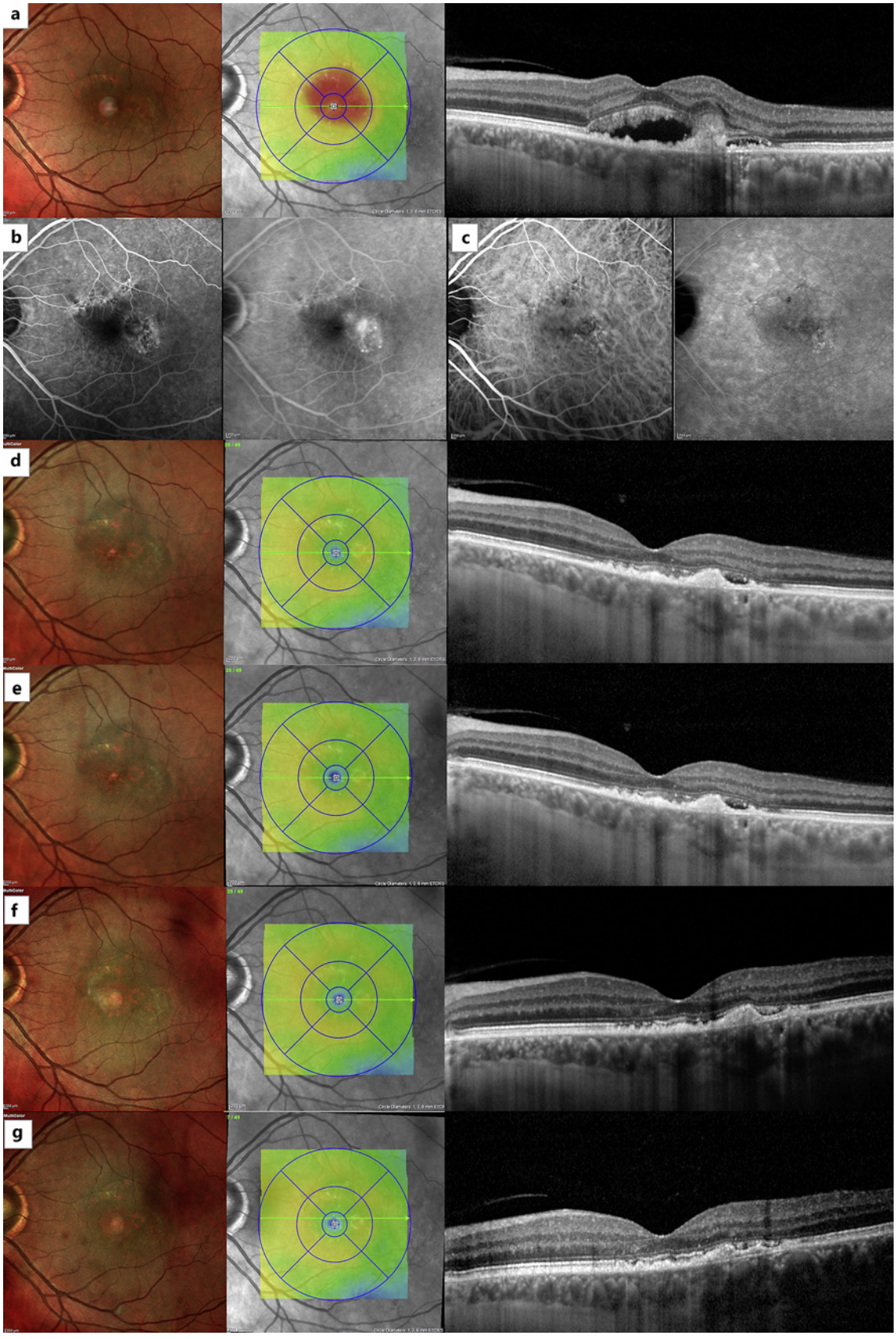
The treatment of nAMD has always been challenging over the years, aiming at improving or maintaining visual acuity. The recent introduction of a novel anti-VEGF agent, brolucizumab, has proven to be a valid therapeutic option for MNV treatment.

HAWK and HARRIER [15, 16] clinical trials showed brolucizumab noninferiority toward aflibercept in a q12/q8 regimen in improving and maintaining visual acuity up to 96 weeks in patients with a diagnosis of nAMD [15, 26]. In addition, superior reductions in central subfield thickness from baseline at week 16 were maintained at week 48 and 96, and a longer durability of brolucizumab was demonstrated with more than 50% of patients treated maintained on a q12w injection interval after the loading phase up to week 48 and over 75% of the eyes completing week 48 on a q12w injection interval continuing successfully until week 96 [16, 18].

Different real-world studies proved brolucizumab's efficacy in improving retinal morphology and visual function in naïve and previously treated nAMD patients [26]. Matsumoto et al. [19] in their study of 42 eyes with treatment-naïve MNV type 1 treated with brolucizumab reported improvement in visual acuity and reduction of exudative changes at the end of the loading dose.

Michalska-Małecka et al. [20] in patients with MNV who underwent brolucizumab intravitreal injections (BIVIs) reported VA improvement, central retinal thickness, and neovascular membrane reduction during 3 months of follow-up. Rispoli et al. [21] in a 1-month follow-up study investigated early changes in the morphology of PEDs and flow area after brolucizumab injection in patients with MNV and fibrovascular PED, demonstrating a decrease in the PED-MH. The Brew study reported significant central retinal thickness reduction, PED decrease, and complete or partial resolution of retinal fluids in the majority of patients with previously treated MNV that underwent intravitreal injection of brolucizumab during a follow-up of 7.2 ± 3.6 weeks [27].

Fig. 2. Multimodal retinal imaging of a 70-year-old man with naïve MNV1 in the left eye at baseline and after BIVI during 16-week follow-up. At baseline, best corrected visual acuity (BCVA) was 0.2 logarithm of the minimum angle of resolution (logMAR). **a** Multicolor fundus image (MCI) (left image) shows retinal pigment epithelium (RPE) degeneration and serous retinal detachment (SRD) at the macular area, volume optical coherence tomography (OCT) map (middle image) shows increased central macular thickness (CMT) of 406 μm, central foveal horizontal OCT scan (right image) shows irregular RPE elevation with medium to high reflectivity and subretinal fluid in the macular area. **b** Fluorescein angiography (FA) images (left images) show ill-defined areas of hyperfluorescence (early phase) with late leakage (late phase). **c** Indocyanine green angiography (ICGA) images (right images) show neovascular network (early phase) with late spot of hypercyanescence (late phase). At 4 weeks after brolucizumab injection, BCVA was 0.1 logMAR. **d** MCI (left image) shows RPE degeneration, volume OCT map shows reduced CMT compared to baseline of 241 μm (central image), central foveal OCT scan (right image) shows almost complete reabsorption of subretinal fluid with persistence of RPE elevation. At 8, BCVA remained stable at 0.1 logMAR. **e** MCI (left image) shows RPE degeneration; volume OCT maps show stable CMT (central image); central foveal OCT scan (right image) shows RPE elevation with unchanged subretinal fluid compared to 4 weeks. At 12 and 16 weeks, BCVA was still at 0.1 logMAR. **f**, **g** MCI images (left images) show RPE degeneration, volume OCT maps show stable CMT (central images), central foveal OCT scan images (right images) show RPE elevation with complete reabsorption of subretinal fluid (right images). *(For figure see next page.)*



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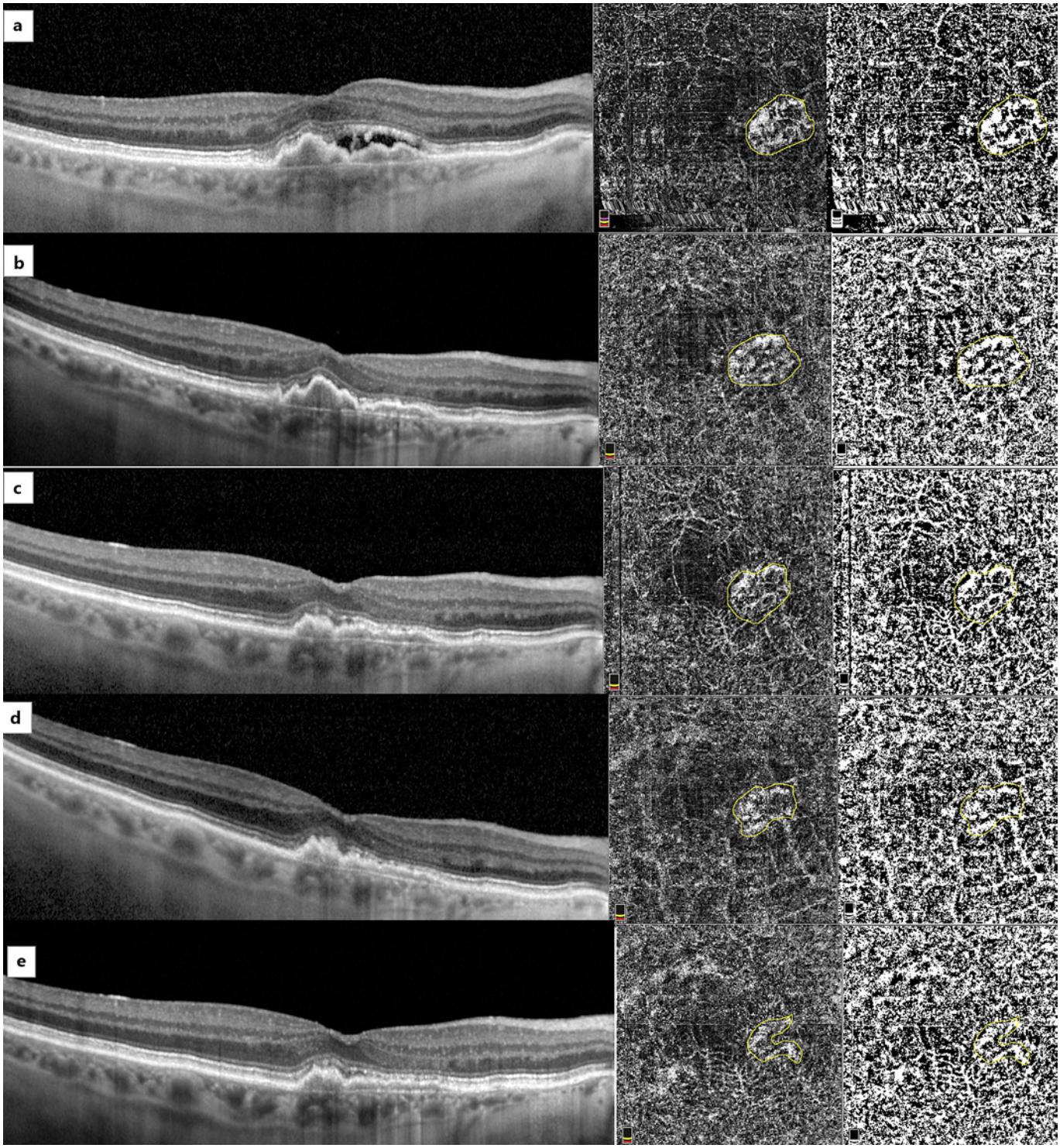

Fig. 3. Multimodal retinal imaging of a 68-year-old man with naïve MNV1 in the right eye at baseline and after BIVI. At baseline, best corrected visual acuity (BCVA) was 0.4 logarithm of the minimum angle of resolution (logMAR). **a** Central foveal horizontal OCT scan (left image) shows irregular RPE elevation with medium reflectivity and subretinal fluid in the macular area; outer retina to choriocapillaris (ORCC) en face image with neovascular (NV) lesion manually delineated (central image) and its binarized image (right image). At 4 weeks, BCVA was 0.3 logMAR. **b** OCT scan (left image) shows resolution of subretinal fluid and slight reduction of RPE elevation, ORCC image and its binarized image shows unmodified lesion size. At 8, 12, and 16 weeks, BCVA was 0.3 logMAR. **c**–**e** OCT scan (left image) shows further reduction of RPE elevation compared to week 4; ORCC image and its binarized image show slightly reduced lesion size.

In our study, we assessed different anatomical SD-OCT and OCTA biomarkers to monitor the efficacy of BIVIs administered as per label in treatment-naïve MNV type 1 patients during a 4-month follow-up. As universally validated, CMT is an important parameter to monitor disease activity, therefore has frequently been analyzed in studies observing anti-VEGF efficacy [28–30]. In our study, CMT was significantly reduced compared to baseline ($p < 0{,}001$), similar to registrative trials and real-world studies using brolucizumab in MNV [20].

In addition, in our study, brolucizumab was also efficacious in reducing PED height that significantly decreased during follow-up ($p = 0.020$), thus confirming the possible role of PED as a biomarker. Different authors found a connection between the growing PED horizontal diameter and the maintenance of a quiescent CNV type, whereas the increase in vertical diameter being related to an exudative state, reinforcing possible use of PED as a biomarker [31, 32].

Brolucizumab has proved to be capable of controlling retinal fluid in MNV in several reports [15, 16, 33–35]. In the Hawk and Harrier registrative trials, the proportions of eyes with IRF and/or SRF at week 96 were lower in the brolucizumab arm compared to the aflibercept arm [15, 16].

Matsumoto et al. [19] reported complete dry macula, meaning absence of intraretinal, subretinal, and sub-RPE fluid in 17 eyes (47.2%) after 1 month of intravitreal brolucizumab, in 31 eyes (86.1%) after 2 months, and in 34 eyes (94.4%) after 3 months. Montesel et al. [36] in a retrospective case series of patients with nAMD treated with a minimum of 2 IVBI with a mean follow-up of 14.4 ± 9.0 weeks reported IRF presence at baseline in 12 eyes (63%) and in three eyes (16%) at the last follow-up and SRF presence at baseline in 17 eyes (89%) and at the last follow-up in three eyes (16%).

In our study, IRF decreased significantly and subfoveal SRF decreased significantly, as shown in other studies ($p = 0.045$ and $p < 0.001$, respectively). The reduction of fluid in the sub-RPE compartment was significant as well ($p = 0.013$). The majority of eyes (18 eyes, 75%) at week 16 after disease activity assessment were shifted in the q12 interval and only a minority of eyes shifted in the q8 interval (6 eyes, 25%). OCTA has proven to be efficient in nAMD to visualize NV in different slabs [37, 38]. Rispoli et al. [21] proposed flow area as a potential biomarker to evaluate changes in eyes treated with brolucizumab, even taking into consideration OCT-A variable sensitivity [21, 39, 40].

Our study observed changes in flow area; however, despite observing a decrease, it was not significant. We never observed a complete regression of the MNV flow area, thus confirming the observation made by Spaide [41] regarding the permanent presence of the main trunk of the new vessel even after anti-VEGF injections. Overall, the literature reports a reduced MNV associated flow area after IV treatment; therefore, the lack of significance might be related to the small number of study participants or to the short follow-up [39, 42].

OCTA has proven to be efficient in nAMD to visualize NV in different slabs [37, 38], although imaging artifacts being one of the major limitations of this technology limit its sensibility and specificity in diseased eyes. OCTA devices have been implemented with modified scanning protocols and eye-tracking systems for motion correction artifacts, as well as manual segmentation editing tools for segmentation artifacts correction and projection-resolved algorithms to address projection artifacts. Low OCT signal artifacts have been addressed with different approaches [43, 44].Previous reports demonstrated how choroidal changes during anti-VEGF intravitreal treatment influence wet AMD course [45–48]. Koizumi et al. [45] well studied the relation between SFCT and BCVA in patients treated with aflibercept, observing visual gain and improved exudative changes in patients with reduced SFCT. They hypothesized that VEGF suppression could cause reduced choroidal thickness by both inhibiting choroidal vascular permeability and through direct or secondary vasoconstriction. Hence, the suppression of persistent or recurrent retinal fluid may result in improved clinical outcomes. The HAWK and HARRIER clinical trials showed greater control of sub-RPE fluid with brolucizumab than with aflibercept and hypothesized that brolucizumab reduces choroidal thickness more effectively than aflibercept, and this could be related to better fluid control [15, 16]. Tamashiro et al. [49] reported a reduction of SFCT after a loading dose of brolucizumab that was greater in naïve eyes compared to previously treated eyes, suggesting a role of brolucizumab in causing significant anatomic changes in the choroid, particularly in treatment-naïve AMD eyes. In line with these results, in our study, we observed a significant SFCT reduction at week 16 compared to baseline that probably influenced the retinal fluid behavior during follow-up, stating the possible role of SFCT as a possible biomarker.

In conclusion, the recent introduction of brolucizumab has given light to the therapeutic possibility of nAMD patients. Brolucizumab is efficient in improving anatomical parameters such as macular thickness, choroidal

thickness, and PED height, which may be predictive factors. The new drug is successful in obtaining a dry macula; however, no OCTA parameters demonstrated a significant reduction. More studies are needed to evidence the relationship between flow and choroidal reduction as well as to better understand PED behavior related to the disease story. A long follow-up is needed to better investigate long-term effects as well as adverse reactions of this new anti-VEGF agent. However, undoubtedly, the introduction of brolucizumab has changed the horizons of treatment for wet AMD.

Statement of Ethics

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

Conflict of Interest Statement

The authors declare no conflicts of interest.

Funding Sources

This research received no external funding.

Author Contributions

Conceptualization, writing – review and editing, and visualization: Lisa Toto; methodology: Rossella D'Aloisio; software: Chiara Trivigno; validation: Lisa Toto, Maria Ludovica Ruggeri, and Chiara Di Nicola; formal analysis: Luca Cerino; investigation and writing – original draft preparation: Maria Ludovica Ruggeri; resources: Guido Di Marzio; data curation: Marta Di Nicola and 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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