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Effect of Pro Re Nata Regimen with Anti-VEGF on Type 3 Macular Neovascularization: Long-Term Outcomes

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Keywords
Type 3 MNV · Pro Re Nata regimen · Macular atrophy

Abstract

Introduction: The purpose of this study was to investigate long-term outcomes of intravitreal injections (IVI) of antivascular endothelial growth factor (VEGF) in neovascular age-related macular degeneration (nAMD) with type 3 macular neovascularization (MNV). ***Methods:*** This retrospective study included 19 eyes of 17 patients with nAMD and type 3 MNV treated with anti-VEGF IVI with a loading dose and a PRN regimen. Best corrected visual acuity (BCVA), central macular thickness (CMT), presence of macular intraretinal fluid (IRF) and subretinal fluid (SRF), flow area (FA), subfoveal choroidal thickness (CT), and macular atrophy (MA) were assessed at baseline (T0) and during follow-up (T1, post-loading phase; T2, 1 year; T3, 2 years; T4 >2 years). The correlations between MA at the last follow-up and standard deviation (SD) values of CMT and CT during follow-up were assessed. The influence of the number of injections on the change in MA over time was also analyzed. MA differences at T4 were assessed for pseudodrusen presence. ***Results:*** BCVA improved significantly during follow-up ($p = 0.013$) particularly increasing from baseline to post-loading phase and then did not modify significantly thereafter. CMT significantly reduced from T0 to T1 and remained stable during follow-up ($p = <0.001$). MNV flow area showed a trend toward an increase in the post-loading phase that was not statistically significant ($p = 0.082$) and CT decreased significantly during follow-up ($p < 0.001$). MA changed significantly during follow-up ($p < 0.001$) with a significant increase from T0 to T3 and from T0 to T4 ($p < 0.010$). A Cochran-Armitage test for trend showed a significant reduction ($p = 0.001$) of macular IRF and SRF during follow-up. MA at T4 showed a significant positive correlation with SD (standard deviation) values of CMT ($p = 0.040$) and CT ($p = 0.020$). Indeed, the number of injections did not influence the change over time of MA ($p = 0.709$). MA at T4 was not statistically significantly different between patients with pseudodrusen at baseline ($p = 0.497$). ***Conclusions:*** Intravitreal anti-

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VEGF injections with PRN regimen in MNV type 3 showed functional and anatomical benefits. Variations of retinal thickness and choroidal thickness during treatment were related to MA modification over time.

Introduction

Originally described in 2001 by Yannuzzi et al. as "retinal angiomatous proliferation," and then renamed by Freund et al., as type 3 macular neovascularization (MNV) is the second most common type of MNV in the context of neovascular age-related macular degeneration (nAMD), representing from 4.5% to 15% of all nAMD cases [1–3]. Antivascular endothelial growth factor (VEGF) intravitreal injection (IVI) has become the gold standard treatment of nAMD, improving its anatomical and functional outcomes as demonstrated in several randomized clinical trials and real-world studies [4]. Nevertheless, some factors may influence the final outcome of patients nAMD treated with IVI of anti-VEGF including long-term complications such as subretinal fibrosis and macular atrophy (MA) [5].

Some studies found that the type of MNV has an impact on the regional retinal atrophy rate [6–10], which could explain variations in the long-term visual function. While eyes with other MNV types gradually improve visual acuity in the long term, type 3 MNV shows lost vision after an early phase of visual recovery. In particular, the CATT trial showed a 1.69 larger risk of MA with type 3 MNV [10]. Patients with type 3 MNV have thin choroid and more compromised choriocapillaris (CC), suggesting that an abnormal VEGF release exists [11].

Considering type 3 MNV as a well-recognized factor for MA, it is not well understood if the amount of atrophy is part of the natural course of MNV type 3, or if it is the result of a chronic suppressive activity against VEGF resulting from aggressive IVI treatment, leading to poor vascular support to the outer retina. In this study, we retrospectively analyzed the long-term outcome of patients with MNV type 3, considering baseline features, anatomical and functional follow-up parameters, treatment regimen, and particularly the number of IVIs and possible long-term complications with special attention to MA occurrence or progression.

Methods

This was a multicenter, retrospective, observational cohort study that adhered to the tenets of the Declaration of Helsinki. Eyes with a definite diagnosis of treatment-naïve type-3 MNV in nAMD patients of different stages according to the classification proposed by Su et al. (intraretinal hyperreflective focus and cystoid macular edema in stage 1; additional external limiting membrane/ellipsoid zone disruption with or without retinal pigment epithelium disruption in stage 2; and all stage 2 alterations with serous pigment epithelial detachment, with or without SRF in stage 3 lesions) [3], treated in the above-mentioned ophthalmology clinics with IVIs of anti-VEGF and a pro re nata (PRN) regimen after a loading dose, were identified and recruited from the clinical practices of LT, MCS, and PV between October 2017 and January 2023.

A minimum of 24 months of total follow-up was required to enter into the study. The baseline-entry point of each eye into the study was selected based on the patient's first visit with LT, MCS, and PV when anti-VEGF therapy was initiated. Inclusion criteria included age greater than 55 years and unilateral or bilateral type 3 MNV determined by multimodal imaging including spectral domain optical coherence tomography (SD-OCT), multicolor color fundus photography, fundus fluorescein angiography, indocyanine green angiography, and optical coherence tomography angiography (OCTA); intravitreal anti-VEGF treatment with a PRN regimen for at least 2 years based on functional and anatomical parameters.

Patients with a history of treatment in the study eye such as laser photocoagulation, intravitreal anti-VEGF, or intravitreal steroids before the baseline entry point, and preexisting retinal pathology other than nAMD were excluded from the study. This study further excluded eyes with any preexisting or coexisting evidence of type 1 or type 2 MNV.

After a loading phase consisting of 3 monthly IVIs, a PRN regimen was adopted. The retreatment criteria during the maintenance phase with a monthly assessment from week 12 were lost five letters from the previous visit in conjunction with intraretinal fluid (IRF) and/or subretinal fluid (SRF); IRF, SRF more than 50 μm, new macular hemorrhage, or new neovascularization. The following parameters were recorded for each patient: demographic features (age, sex), best corrected visual acuity (BCVA) (logMAR), presence of pseudodrusen, and the total number of anti-VEGF IVIs an eye received including the specific anti-VEGF agent used for the entire follow-up period.

In addition, central macular thickness (CMT) at SD OCT; the presence of macular IRF and SRF at SD OCT; subfoveal choroidal thickness (CT) at SD OCT; NV flow area at OCTA; and MA estimated at blue fundus autofluorescence (FAF) confirmed at OCT and infrared reflectance imaging were recorded for each patient. Data were recorded for each patient at baseline (T0), after the loading dose (T1), at 1 year (T2), 2 years (T3), and when available at the last follow-up greater than 2 years and within 5 years (T4), from the initial treatment.

Multimodal Imaging Protocol

Multicolor color fundus photography, SD-OCT, blue FAF, fundus fluorescein angiography, and indocyanine green angiography were imaged using Spectralis HRA + OCT (Heidelberg Engineering, Heidelberg, Germany). OCTA for NV flow area was obtained using RTVue XR Avanti OCT-A system (AngioVue System, version 2018.1.0.43, Optovue® Inc., Fremont, CA, USA).

SD OCT Analysis

OCT maps including 49 horizontal raster dense linear B-scans centered on the fovea at baseline and SD OCT maps acquired with the follow-up function were considered for each patient. A

horizontal B-scan centered on the fovea with enhanced depth imaging mode was acquired in all patients. Each scan was acquired through the tracking function.

CMT was measured using the central 1-mm-diameter circle of the ETDRS thickness map. Subfoveal CT measured vertically from the outer border of the RPE to the inner border of the sclera was measured using the inbuilt manual caliper on enhanced depth imaging OCT scans.

Macular IRF inside the 6-mm-diameter circle of the ETDRS grid and foveal SRF were defined as present, absent, or unreadable. MA was defined as sharp, delineated hypoautofluorescence with corresponding attenuation of the RPE band and loss of overlying ellipsoid zone and external limiting membrane with thinning of the outer nuclear layer, together with enhanced signal transmission into the choroid as evidenced on OCT as previously described [12].

The area of atrophy both incident and preexisting was manually measured using the measuring tool on the Heidelberg Explorer Software using the FAF images within the central 6-mm-diameter circle of the ETDRS grid. The minimal lesion size was defined as an atrophic area measuring 0.02 mm^2, quantified using the measuring tool on Heidelberg Explorer Software. 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. If more than 1 area of atrophy were present, they were measured and summed to generate the total MA area.

The presence of pseudodrusen based on the appearance of reticular patterns was identified by using OCT as previously described [13]. We compared the results obtained by two independent graders who were masked to the data. If there was a difference of less than 20% in the quantitative outcomes between the graders, the results from the individual graders were averaged. In cases where there was a difference of more than 20% among the graders, a third examiner was consulted to establish a consensus.

Subfoveal CT measurement, macular IRF and SRF presence assessment, MA area measurement, and pseudodrusen identification were performed by two independent, experienced readers (LT and MCS). The ETDRS grid was used to assess fluid localization.

OCTA Analysis

In all cases, volume scans measuring 3 × 3 mm were initially conducted for all eyes. If the scan did not fully encompass the lesion, a larger 6 × 6 mm scan was then acquired. NV flow area was calculated in all cases. The most adequate slab to identify type 3 MNV was chosen in each case. The avascular slab and the CC slab were obtained using the default layer segmentation settings of the device; on the contrary, the outer retina to CC segmentation slab was set manually extending from the outer boundary of the outer plexiform layer to 8 μm beneath Bruch's membrane. The projection artifact removal algorithms were 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 (LT and MCS) 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. NV flow area was considered as the ratio of pixels occupied by flowing vasculature to all pixels included in the analyzed region, as already described [14, 15]. For NV flow area for statistical analysis, each subject was attributed the mean value between reader 1 and reader 2.

Main Outcome Measures

BCVA, CMT, IRF and SRF presence, NV flow area, subfoveal CT, and MA were assessed at baseline and during follow-up.

Statistical Analysis

Descriptive statistics are reported as median and quartiles (first = q1; third = q3) for continuous variables, while categorical data were summarized as frequency and percentage. Normal distribution was evaluated for each variable using Shapiro-Wilk's test. To check the differences (Δ) in the change of parameters, the statistical analysis plan was structured in two phases: [1] one related to data derived from the loading dose period (from T0 to T1) to evaluate the treatment effect and [2] one related to the maintenance period (T2 vs. T4). The Friedman test was used to assess changes in overall observer time within groups for continuous variables.

Post hoc analyses were Bonferroni corrected for multiple comparisons (critical $p = 0.005$). Because we are interested in the variability over time, we computed the standard deviation (SD) of repeated CMT and CT measurements for each patient across the entire study duration (from T0 to T4) and used them to investigate the relationship with MA at the last follow-up. The Mann-Whitney U test was used to assess differences in unpaired samples. The Cochran-Armitage test assessed trends in reducing the presence of IRF and SRF. The Spearman rho correlation coefficient was used to assess the relationship between the within-subject variability retinal thickness and CT and the last MA follow-up values. A simple linear regression model assessed how the number of injections influenced the relative change between each parameter's baseline (T0) and the last follow-up (T4). All statistical tests were two-sided, with a significance level set at $p \leq 0.05$. Analyses were performed using the R software environment for statistical computing and graphics (version 3.4.1; http://www.r-project.org/).

Results

The mean and SD follow-up was 36.20 ± 13.04 months. Nineteen eyes of 17 patients (9 males and 8 females) with a mean age of 76.15 ± 19.01 years were included.

In 16 eyes, there was a solitary MNV type 3 lesion and in 3 eyes multifocal MNV type 3 lesions (2 eyes with bifocal lesions and 1 eye with quadrifocal lesion). Considering staging classification among all eyes at baseline, there were 2 MNV type 3 at stage 1, 12 MNV type 3 at stage 2, and 10 MNV type 3 at stage 3.

Table 1. Descriptive statistics expressed as median [q1; q3] and absolute difference (Δ) between T1 = post-loading and T0 = baseline and T4 = 2 years' follow-up and T2

Variables	Baseline (T0)	Post-loading (T1)	Δ (T1 vs. T0)	1-year follow-up (T2)	2 years' follow-up (T3)	Last follow-up (T4)	Δ (T4 vs. T2)
BCVA (EDTRS letters)	50.0 [35.5; 66.0]	65.0 [53.5; 71.0]	13.0 [3.0; 19.5]	65.0 [52.5; 69.0]	60.0 [46.0; 67.0]	58.0 [47.5; 70.0]	0.0 [−6.0; 5.5]
CMT, μm	444.0 [314.0; 535.0]	248.0 [224.0; 270.0]	−122.0 [−225.0; −27.5]	267.0 [231.0; 318.0]	249.0 [214.0; 347.0]	241.0 [214.0; 316.0]	−14.0 [−45.0; 1.50]
CT, μm	149.50 [112.00; 249.00]	125.50 [90.50; 215.00]	−10.00 [−15.50; −2.00]	148.00 [97.00; 202.00]	103.00 [98.00; 165.00]	136.50 [95.00; 200.00]	−7.00 [−17.50; −0.25]
NV flow area, mm^2	0.06 [0.04; 0.17]	0.04 [0.01; 0.07]	−0.02 [−0.04; −0.01]	0.06 [0.02; 0.10]	0.05 [0.02; 0.20]	0.19 [0.04; 0.31]	0.03 [−0.01; 0.22]
MA, mm^2	3.20 [1.15; 6.22]	4.50 [1.70; 7.65]	0.90 [0.40; 1.65]	6.00 [2.45; 8.30]	6.90 [3.85; 9.65]	8.30 [5.50; 11.60]	2.20 [1.80; 5.15]

IRF was present in 19/19 eyes (100%) and SRF was present in 52.6% (10/19) of eyes. Seventeen out of 19 eyes showed MA (extrafoveal in 13 eyes and foveal in 4 eyes) and 10 out of 19 eyes showed reticular pseudodrusen.

All patients performed a loading dose of 3 injection with an anti-VEGF drug; in the post-loading phase, the median number of injections was 9.00 (5.50; 11.50). During loading phase and follow-up period, 3 eyes received only aflibercept, 4 eyes received only ranibizumab, and 12 eyes received a mixed treatment over time with aflibercept and ranibizumab.

Descriptive analysis of all variables at baseline and during follow-up is reported in Table 1. A median variation of BCVA from T1 versus T0 was 13.00 (3.00; 19.50) ETDRS letters and 0.00 (−6.00; 5.50) ETDRS letters from T4 versus T2. A change of CMT was −122.00 (−225.00; −27.50) μm from T1 versus T0 and −14.00 (−45.00; 1.50) μm from T4 versus T2; CT −10.00 μm (−15.50; −2.00) from T1 versus T0 and −7.00 μm (−17.50; −0.25) from T4 versus T2.

NV flow area variation was −0.02 (−0.04; −0.01) mm^2 from T1 versus T0 and 0.03 (−0.01; 0.22) mm^2 from T4 versus T2. The modification of MA was 0.90 (0.40; 1.65) mm^2 from T1 versus T0 and 2.20 (1.80; 5.15) mm^2 from T4 versus T2.

BCVA improved significantly during follow-up (p = 0.013), particularly increasing from T0 to T1 and not modifying thereafter (Fig. 1a). CMT significantly reduced from T0 to T1 and remained stable during follow-up (p = <0.001) (Fig. 1b), and CT decreased significantly during follow-up ($p < 0.001$) (Fig. 1c). NV flow did not modify significantly during follow-up (p = 0.082) (Fig. 1d). MA changed significantly during follow-up ($p < 0.001$) with a significant increase from T0 to T3 and T0 to T4 ($p <$ 0.010) (Figure 1e, Fig. 2). Incident MA developed in 1 out of 2 eyes at T2, not showing MA at baseline.

A Cochran-Armitage test for trend showed a significant reduction (p = 0.001) of macular IRF and SRF during follow-up. IRF reduced from 100% at T0 to 36.8% at T4 (p = 0.001). SRF decreased from 52.6% at T0 to 0% at T4 (Fig. 3).

MA at T4 showed a significant positive correlation with CMT SD values (rho = 0.47, p = 0.040) and CT SD values (rho = 0.61, p = 0.020). The number of injections does not affect the change over time of MA (β1 = 0.251; p = 0.709). Mann-Whitney U test showed that MA at T4 was not statistically significantly different between patients with pseudodrusen at baseline (p = 0.497).

Discussion

This study evaluates the long-term effect of IVI of anti-VEGF therapy with a PRN regimen after the loading dose in patients with type 3 MNV. Anti-VEGF therapy is the gold standard therapy for type 3 MNV as well as other subtypes of nAMD. Different treatment regimens have been used for type 3 MNV to achieve good efficacy and safety [16–18]. In this context, several studies particularly focused on long-term complications during treatment such as MA influencing the final functional outcome of type 3 MNV [12, 19–22].

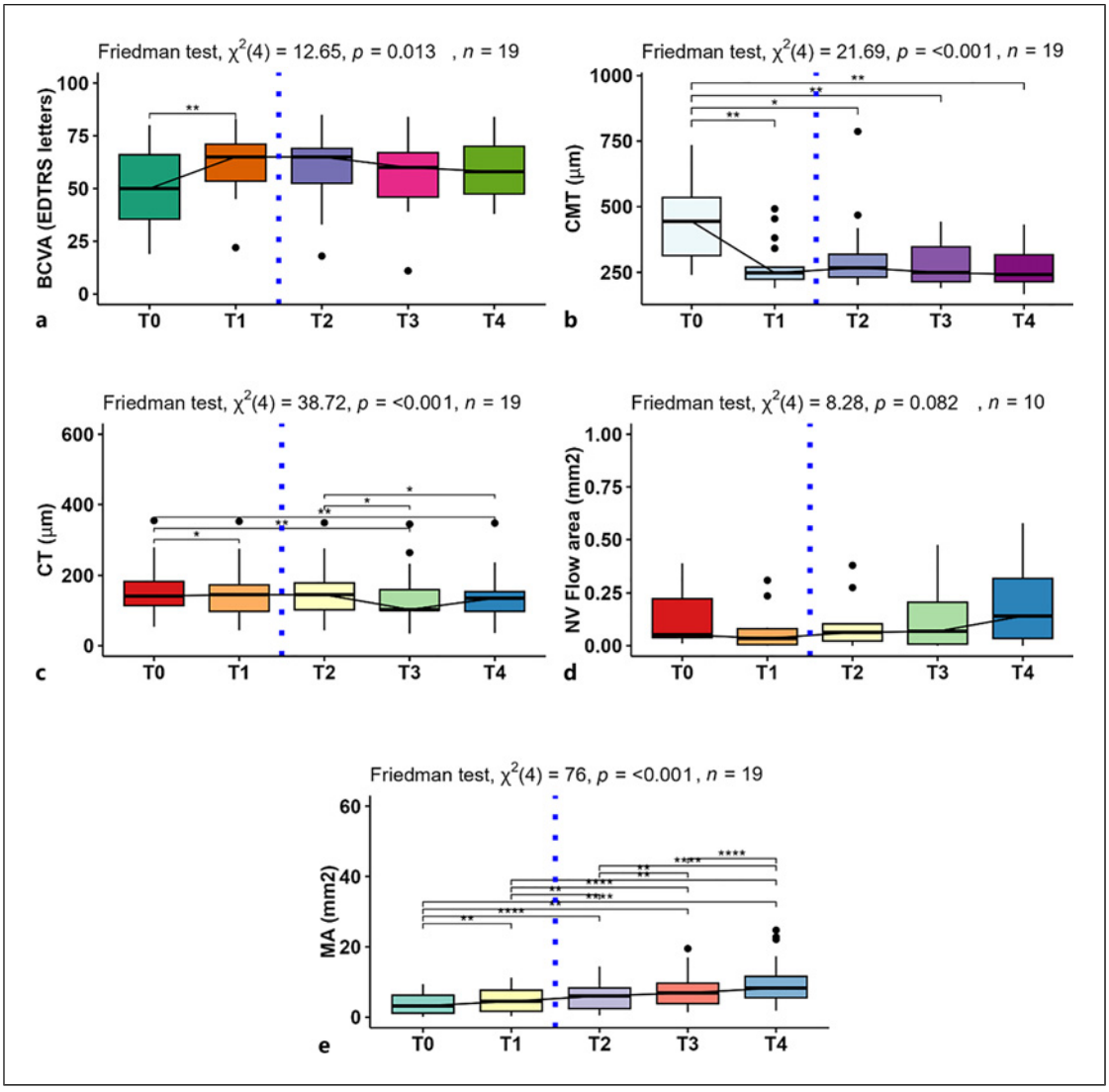

Fig. 1. Boxplot for BCVA (**a**), CMT (**b**), CT (**c**), NV flow area (**d**), and MA (**e**). The Friedman test, χ^2 statistics along with the p value are reported. A significant post hoc code is $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, and $****p < 0.0001$.

In our study, a reduction of CMT related to the resolution of IRF and SRF demonstrated a good response to anti-VEGF treatment with the PRN regimen that was particularly evident after loading dose but remained stable during follow-up. The modification of OCT structural parameters was not associated to a reduction of OCTA parameters such as MNV flow area that did not modify significantly during follow-up. The anatomical results were paralleled by functional results with an improvement of BCVA mainly after the loading phase that slightly not significantly declined thereafter.

Several randomized clinical trials and real-world studies evaluated treatment response to anti VEGF with different regimen in patients with type 3 MNV [10, 12]. In the CATT trial in patients treated with an anti-VEGF and PRN regimen, visual acuity was reported to improve during the loading phase period with stabilization during the first year and modest decline in the second year. One year after treatment, there was a decrease in foveal total thickness observed in 46% of eyes, along with complete resolution of fluid accumulation. Additionally, there was a reduction in the overall size of the choroidal neovascularization (CNV) lesion [10]. In real-world clinical studies, anti-VEGF

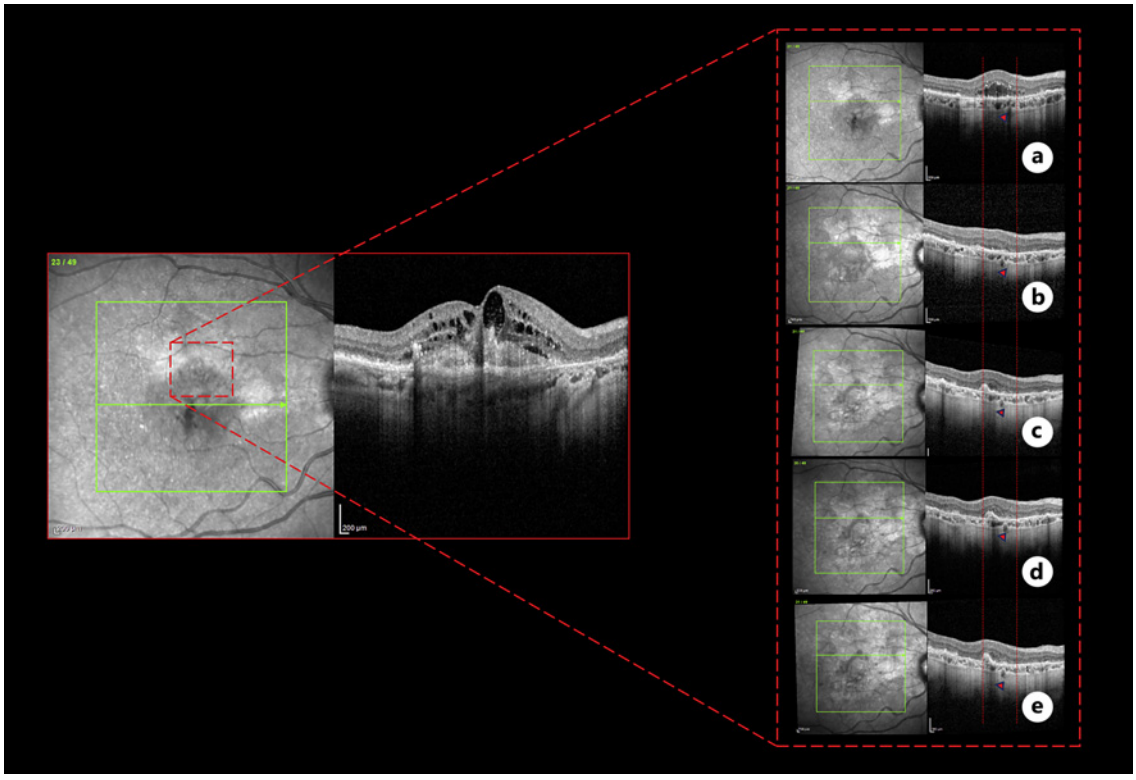

Fig. 2. Infrared reflectance (IR) image and optical coherence tomography (OCT) horizontal B-scan image passing through the fovea of a patient with MNV type 3 (left panel) at baseline and a focus of extrafoveal MA progression (IR image and extrafoveal horizontal OCT B-scan) (right panel) from baseline (**a**) to post-loading (**b**), 1-year follow-up (**c**), 2 years' follow-up (**d**), and more than 2 years' follow-up after IVI of anti-VEGF (**e**). Disappearance of IRF after loading phase with an initial collapse of the outer retinal layers and MA extension during follow-up can be observed.

treatment of type 3 MNV stabilized or improved visual acuity and reduced macular thickness [16–18, 23].

Regardless of the response to treatment, the occurrence of MA and progression of preexisting MA in eyes with MNV and particularly with type 3 MNV are a serious concern as they may worsen vision and they have been extensively investigated relating to baseline features of nAMD eyes such NV area, reticular pseudodrusen presence and CT, type of treatment, and number of IVIs [24–32].

Several clinical trials described the incidence of MA at baseline in patients with all types of MNV associated to wAMD including MNV type 3 and reported its progression or the development of de novo MA as an outcome during treatment with anti-VEGF agents. Percentages of MA at baseline in eyes with MNV have been reported from 9% as evidenced in data from the CATT and IVAN trials to 44% of the MANEX study and 76.9% of the TREX-AMD trial [12, 33, 34].

The progression of MA has also been described in type 3 MNV in variable percentages and growth rate and has been related to several risks factors. In the CATT study including type 1, 2, and 3 neovascularization geographic atrophy developed in 12%, 17%, and 38% of patients at 1, 2, and 5 years; type 3 MNV, monthly regimen and ranibizumab compared to bevacizumab being risk factors [24].

Cho et al. in a cohort of eyes with wAMD and all types of MNV reported incident MA in 26.3% during the first 12 months, 36.2% between the 12 and 24 months, and 37.5% after 24 months. In this study, MNV type 3 showed the highest growth rate of MA of 1.21 mm^2/year for type 3 MNV [35].

The same results were described in the MANEX study with the greatest increase in MA size in type 3 MNV compared to other MNV types ($p = 0.04$) [12]. In our study, a high percentage [89.5%] of patients showed the presence of MA at baseline that was prevalently extrafoveal [76.5%] with a high percentage of patients at initial stages of MNV type 3 [58.3% of patients with stage 1 or 2 MNV type 3 lesions] and de novo MA occurred at 1 year in 1 out of 2 eyes not showing MA at baseline. A significant increase of mean MA area was observed during follow-up particularly at 2 years from baseline and after 2 years up to 5 years. It is

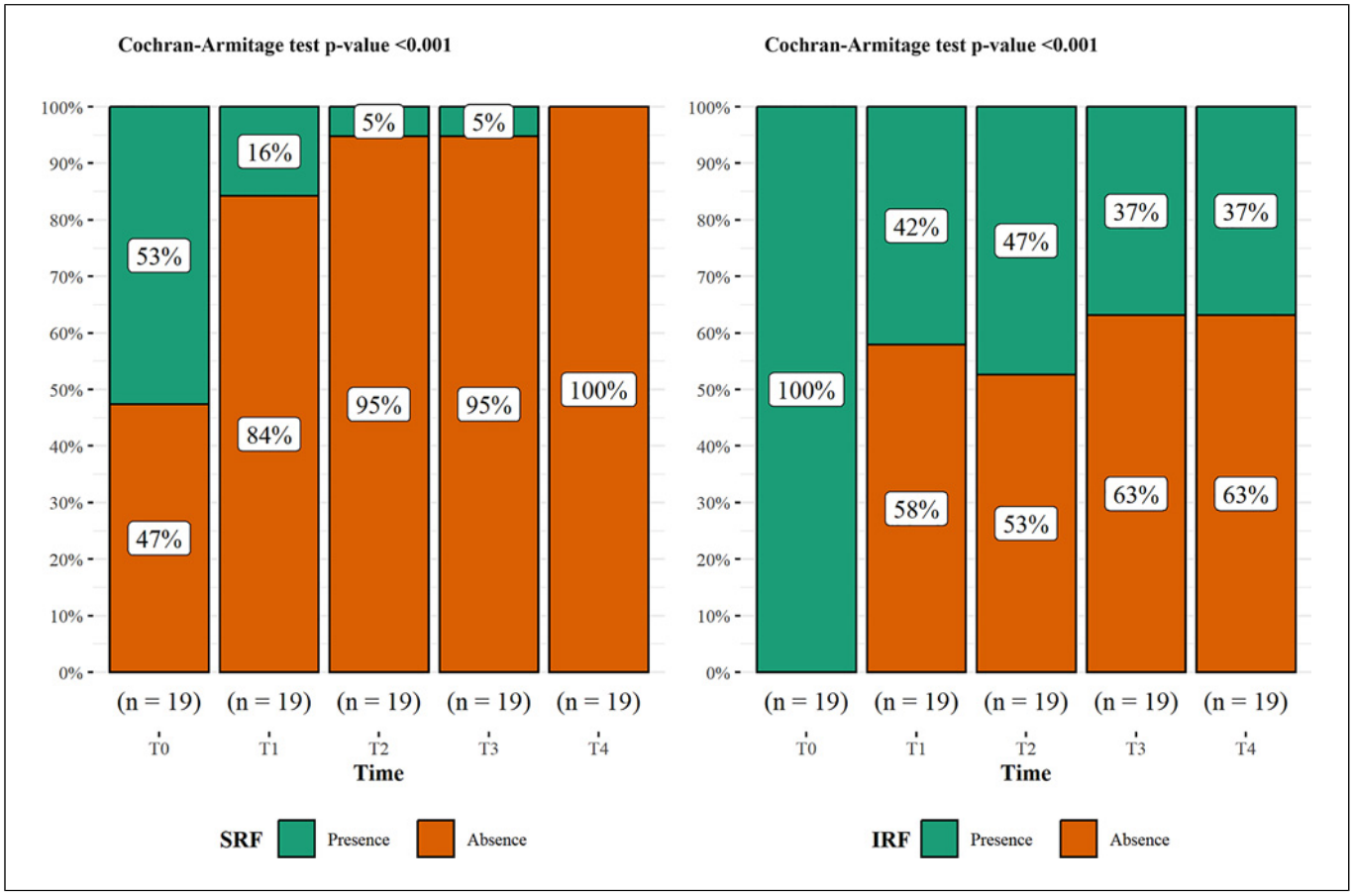

Fig. 3. Bar plot with absolute frequency (*n*) and IRF and SFR resolution percentage. A *p* value is derived from the Cochran-Armitage test for trend.

possible to hypothesize that the higher percentage of MA at baseline compared to other studies could be related to baseline patients' features such as very advanced age, high percentage of pseudodrusen presence, and CT.

There is evidence that in patients with nAMD receiving long-term anti-VEGF treatment, the presence of pseudodrusen is associated with a greater mean area of MA [25]. A thinner choroid and reticular pseudodrusen are characteristic findings in patients with type 3 MNV compared with other nAMD [26, 27, 28].

Cho et al. found that thinning of the subfoveal choroid and presence of reticular pseudodrusen at baseline were identified as significant risk factors for geographic atrophy development in type 3 MNV [13]. In this cohort of patients, a significant correlation was found between MA at the last follow-up and SD values of CT confirming data from the literature concerning the rule of a thin choroid in MA of type 3 MNV. Instead, no relationship was found between MA at the last follow-up and pseudodrusen presence.

There is evidence from the literature that both treat-and-extend and extended PRN approaches may have an impact on MA development and/or progression due to a more sustained VEGF suppression in the first regimen and greater fluid fluctuations related to the recurrence of NV activity in the PRN regimen [22, 28, 29]. In the post hoc analysis of CATT and IVAN trials, incident geographic atrophy was also more likely to occur in eyes with the highest macular thickness fluctuation, meaning that eyes with greater retinal thickness due to IRF or SRF may have lost more neural tissue and thus been more likely to develop features of atrophy [30].

In accordance with data from the literature in our study, MA values at the last follow-up showed a positive correlation with SD values of CMT, indicating a correlation between retinal thickness variations and MA. In our sample, the number of IVIs did not influence the progression of MA during follow-up. Similar results were reported by the MANEX study assessing the progression of MA both incident and preexisting in eyes with MNV of

all types including MNV type 3 treated with both PRN and the treat-and-extend regimen [22].

The majority of comparison studies of anti-VEGF therapies to date have not demonstrated that anyone anti-VEGF drug is more likely to cause MA than another [31, 32]. The CATT study's findings, however, indicated that individuals treated with ranibizumab had a higher risk of developing MA than those treated with bevacizumab [10]. Because ranibizumab, bevacizumab, and aflibercept are thought to permeate the retina differently [36, 37], the effective dose of ranibizumab may have been higher and this may suggest that more intense anti-VEGF therapy could increase the risk of developing MA.

In our study, patients received both ranibizumab and aflibercept or a mixed treatment of both anti-VEGF. The limited sample size of the study and the use of a combination of anti-VEGF in the majority of patients did not allow for establishing differences in MA by anti-VEGF type.

Another limit relies on the lack of analysis regarding macular fibrosis during time, which could impact on final MA. Since the type 3 MNV could also be extramacular as previously described [38], subfoveal CT could be a partial reflector for choroidal changes and should be considered when discussing about the role of the choroid in this context.

In addition, the lack of analysis of MA in the fellow eyes of patients with monolateral MNV type 3 disease did not allow us to exclude a natural progression of MA independently from the MNV type 3 presence. The retrospective, unmasked design and the study's small sample size are its main drawbacks. The inclusion of type 3 MNV that is a relatively rare type of MNV with follow-up visits up greater than 2 years and high-quality imaging could have limited the inclusion of patients.

Conclusion

Type 3 MNV revealed good functional and anatomical response to intravitreal anti-VEGF injections with PRN regimen. MA showed a significant increase during follow-up that was not related to the number of injections. MA increase or occurrence was related to variation of retinal thickness and reduction of CT during follow-up.

Statement of Ethics

This study was approved by the Ethics committee of the Gabriele D'Annunzio University (No. 867-1/23), Catholic University of the Sacred Heart, Roma; and Ophthalmology Clinic, Department of Translational Biomedicine Neuroscience, University of Bari "Aldo Moro," Bari. Patient written consent was not required as this study was based on publicly available data. The need for written informed consent was waived by the Ethics Committee of the Gabriele D'Annunzio University, Chieti-Pescara (No. 867-1/23).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conceptualization: L.T. and P.V.; methodology; L.T. and C.D.N.; formal analysis: A.M.P. and M.D.N.; investigation: M.O.G., G.B., and A.Q.; data curation: A.Q., R.A., and R.D.A.; writing – original draft preparation: L.T. and A.Q.; writing – review and editing: L.T., P.V., and A.Q.; and supervision: F.B., M.S., and R.M. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

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

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