# Fluorescein Leakage and Optical Coherence Tomography Features of Choroidal Neovascularization Secondary to Pathologic Myopia

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**Purpose.** We compare the fluorescein angiography (FA) patterns with morphologic alterations detectable on spectral-domain OCT (SD-OCT) in myopic choroidal neovascularization (mCNV) and evaluate whether they influence the effects of intravitreal ranibizumab (IVRI) in an as-needed (PRN) regimen.

**Methods.** The 49 patients enrolled in this prospective case series underwent a complete ophthalmologic examination, including best-corrected visual acuity (BCVA), FA, and SD-OCT assessment. The main outcome measure was correlation between FA patterns and SD-OCT features. Secondary outcomes were changes in BCVA and central macular thickness (CMT), and characterization of subretinal hyperreflective exudation (SHE).

**Results.** Three main patterns were identified on the FA: no (5%), minimal (35%), and profuse (59%) leakage CNV. Comparison between minimal versus profuse leakage CNV subtypes revealed no difference regarding baseline and final BCVA, CNV area, choroidal thickness, final CMT, and proportion of intraretinal cysts, subretinal fluid, and external limiting membrane (ELM) interruption; however, the minimal leakage CNV subgroup revealed a lower percentage of SHE ($P = 0.0039$), required fewer IVRI ($P = 0.003$), and showed a baseline smaller CMT ($P = 0.004$). Patients presenting with SHE showed a similar baseline BCVA to those without exudation, but displayed greater final BCVA improvement. CMT was greater at the baseline and the reduction also was more marked. CNV area achieved a significant reduction only in eyes with SHE. ELM interruption was present in all cases compared to 86.3% of eyes without SHE. Lastly, the eyes with SHE required more injections ($P = 0.04$).

**Conclusions.** Different patterns of mCNV may be identified in FA and they correlate with specific SD-OCT alterations. Moreover, the type of FA leakage may assist in identifying more active mCNV.

Keywords: fluorescein angiography, spectral-domain OCT, myopic choroidal neovascularization

Assessing the activity of choroidal neovascularization (CNV) secondary to pathologic myopia can prove difficult at baseline diagnosis and also over the posttreatment follow-up. Indeed, many characteristics make it awkward to detect activity, including the usually small size of the myopic CNV (mCNV), limited exudative manifestations, and RPE response.[1–8]

Fluorescein angiography (FA) still can be considered the gold standard for identification of activity based on dye leakage. Several features of optical coherence tomography (OCT) have been described as indirect signs that may reflect CNV activity, including increased central macular thickness (CMT), intraretinal cysts, intraretinal fluid, interruption of the external limiting membrane (ELM), and subretinal hyperreflective exudation (SHE).[7–11] Nevertheless, there is no perfect correspondence between FA leakage and OCT features and, in addition, OCT signs can vary according to mCNV pattern and over follow-up, especially when treated.[4–13]

We compared FA patterns to morphological alterations detectable on spectral-domain optical coherence tomography (SD-OCT) in treatment-naïve subfoveal mCNV and evaluated whether they influence the effects of ranibizumab therapy.

## Methods

Patients consecutively referred to the department of ophthalmology of the Vita-Salute University in Milan for treatment-naïve subfoveal CNV secondary to pathologic myopia from January 2012 to June 2014 were considered prospectively for the study with a planned follow-up of 12 months. Each patient was informed carefully about the purpose of the research and provided signed consent. The research adhered to the tenets of the Declaration of Helsinki and the institutional review board approved the study.

Inclusion criteria were spherical equivalent refractive error of –6.0 diopters (D) or more (an eye that had a spherical equivalent under –6.0 D was eligible if there were chorioretinal abnormalities consistent with PM, such as lacquer cracks, chorioretinal atrophy, and posterior staphyloma, and if the axial

length of the eye was at least 26.5 mm), naïve CNV, and baseline best-corrected visual acuity (BCVA) of at least 20/400.

Exclusion criteria included intraocular surgery of any kind within 6 months of the day of injection; any ocular disease able to confound a proper clinical examination, including vitreoretinal traction and myopic foveoschisis; ocular hypertension or glaucoma; uncontrolled systemic hypertension; peripheral vascular disease; history of thromboembolism; ischemic heart disease or stroke; and pregnancy.

Each patient underwent a complete ophthalmologic examination, including BCVA assessment on Early Treatment of Diabetic Retinopathy Study (ETDRS) charts, slit-lamp examination, tonometry, dilated fundus evaluation, FA, and SD-OCT. The existence of CNV activity was based on the detection of a new choroidal vascular network in the early frames of FA. Three main patterns of CNV were considered, on the strength of the evidence of leakage at 5 minutes: no leakage (characterized by staining without evidence of leakage; Fig. 1, left), minimal leakage (mild dye leakage extending slightly beyond the CNV border; Fig. 1, center), and profuse leakage (intense leakage considerably exceeding the CNV border; Fig. 1, right).

Signs of CNV activity on SD-OCT examination included intraretinal cysts (areas of low reflectivity in the intraretinal space), subretinal fluid (areas of low reflectivity in the subretinal space), interruption of the ELM (lack of visibility of ELM), and subretinal hyperreflective exudation (SHE). As previously stated, SHE was defined as a moderately hyperreflective deposit with fuzzy edges located between the RPE and ellipsoid zone.[7]

FA and OCT were examined with a Spectralis HRA+OCT instrument (Heidelberg Engineering, Heidelberg, Germany). All FA and SD-OCT images were acquired by a single retinal specialist of proven experience and certified by an OCT image reading center (MBP).

Acquisition protocols for SD-OCT analysis were as large as possible to allow inspection of the whole CNV extension by each examiner and included cross-hair scan, 7-line raster scan and a 20° × 20° 49-line high-speed macular cube, with additional horizontal and vertical single lines to cover the entire extension of the lesion. High-resolution scans with 50 to 100 automatic real-time averaging frames were performed. SD-OCT scans were generated at the same location at every visit using the follow-up function. There was no limit to the number of additional high-resolution single scans performed.

The area of the CNV was measured on the angiogram picture taken just before the arteriovenous phase and expressed as square millimeters. CMT was calculated manually, measuring the distance between Bruch's membrane and the internal limiting membrane, centering the examination on the fovea. Central choroidal thickness (CCT) was defined as the distance from the RPE line to the hyperreflective line behind the large vessel layers of the choroid, presumed to be the choroid–sclera interface. If the choroid was tilted, the distance was measured right to the RPE line. CCT was measured manually on the horizontal section, passing directly through the fovea.

FA and all acquired SD-OCT scans were assessed by two different and masked retinal specialists in separate sessions (PI and FB); the examiners were unaware of the purposes of the study and of the clinical data related to the analyzed eyes. Each of them provided a complete report for each of the characteristic signs of CNV activity on SD-OCT and FA. Uncertain cases were judged by a third examiner (FR), unaware of the reports provided by the two previous judges.

The study protocol treatment required a complete ophthalmologic examination, including BCVA assessment, fundus examination, and SD-OCT, to be performed monthly during a planned follow-up of 12 months. FA was not part of the routine examination during follow-up; additional FA was performed when SD-OCT was questionable or symptoms showed discrepancies with exudative manifestations on SD-OCT. For example, increased metamorphopsia or a decline in visual acuity in the absence of signs of CNV activity on SD-OCT required confirmation on FA examination; additional illustrative cases were patients who presented with CNV leakage on FA at the baseline examination with no exudative manifestation on SD-OCT. As per protocol, each patient underwent FA at the end of the planned follow-up of 12 months.

The patients were treated with an initial intravitreal injection of ranibizumab within 1 week from the diagnosis, with a subsequent as-needed (PRN) regimen based on monthly examination. Additional injections were administered if persistent or recurrent exudative manifestations were observed on OCT, a new hemorrhage was observed on the fundus examination, FA showed persistence, or there was recurrent leakage.

The primary outcome measure was correlation between FA patterns and SD-OCT features. Secondary outcome measures included changes in BCVA and CMT during follow-up according to the FA classification in each subgroup, along with the number of injections required for each subgroup. To evaluate the possible influence of the presence of the subretinal hyperreflective material on final visual acuity, the number of injections, CMT, CCT, and the CNV area, the subjects were additionally categorized according to the baseline presence/absence of SHE and regardless of the type of CNV leakage. Lastly, univariate and multivariate regression analysis was performed to examine the effects of the baseline morphologic variables, namely type of leakage, presence/absence of SHE, CMT, CCT, and CNV area, with the final number of injections as the dependent variable representative of the activity of the mCNV.

For statistical analysis, the ETDRS chart scores were converted to logMAR values using the interpolated method, so that 0.02 logMAR units were allocated for each letter correctly identified on the entire chart. The Mann-Whitney $U$ test and Wilcoxon test were performed to evaluate differences in BCVA and CMT. The level of significance was considered $P < 0.05$.

Interrater agreement (κ) analysis was performed to examine the concordance between the two retinal specialists in classifying CNV activity on FA and SD-OCT. The κ-statistic was interpreted according to the classification provided by Landis and Koch,[14] specifically <0, 0 to 20, 0.21 to 0.40, 0.41 to 0.60, 0.61 to 0.80, and >0.80, indicated poor, slight, fair, moderate, substantial, and almost perfect agreement. MedCalc Statistical Software (version 18.2.1, Ostend, Belgium) was used for all analyses.

## Results

A total of 49 patients (51 eyes; mean age ± SD, 56.1 ± 13.7 years; 30 females, 21 males) presenting with naïve mCNV were recruited for the study and completed the 12-month follow-up. Mean duration of CNV based on referred symptoms was 23.9 ± 6.4 days. Baseline mean BCVA was 0.50 ± 0.22 logMAR (approximately corresponding to 20/63 Snellen equivalent), whereas final BCVA was 0.37 ± 0.32 logMAR (approximately corresponding to 20/50 Snellen equivalent; $P = 0.019$). Baseline and final CMT were 295 ± 89 and 235 ± 92 μm, respectively ($P = 0.001$). As per protocol study, three main patterns could be identified based on the FA leakage: no, minimal, and profuse leakage CNV (Fig. 1).

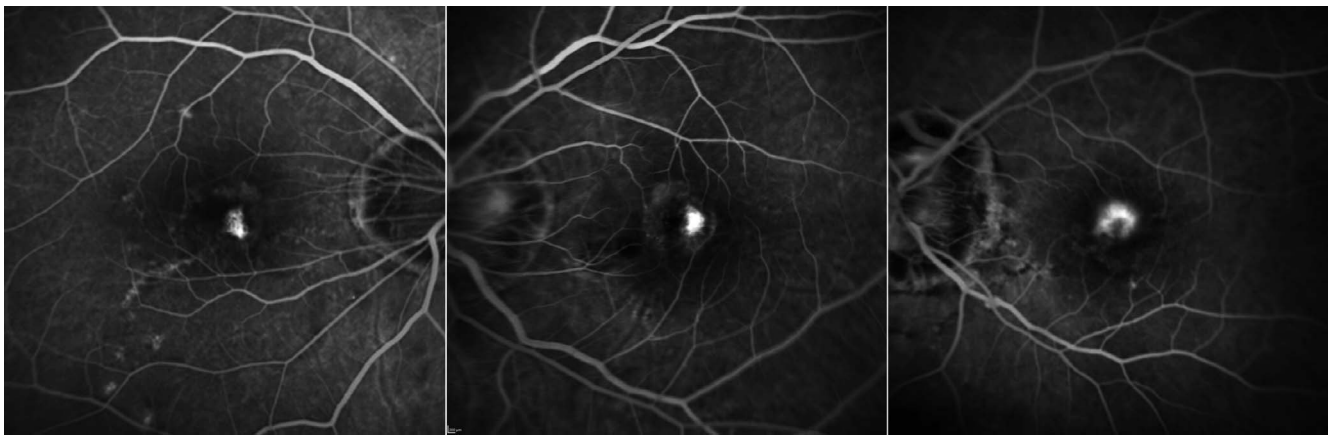

FIGURE 1. Leakage patterns of CNV secondary to pathologic myopia. *Left*: CNV no leakage. *Center*: CNV with minimal leakage. *Right*: CNV with profuse leakage.

The agreement between the two retinal specialists in determining the absence/presence and type of leakage reached a κ value of 0.96 with just one case of discordance on a single subject, finally identified as a case of minimal leakage CNV after the third operator's report.

The no leakage CNV pattern, considered inactive CNV, was identified in three eyes (5%) and was characterized by absence of any exudative manifestation on SD-OCT. Patients with inactive CNV were simply followed without initial treatment (Table 1). Strict monthly monitoring was applied to reveal any sign of CNV activity or visual impairment.

Of 18 eyes (35%) with minimal and 30 (59%) with profuse leakage CNV, intraretinal cysts were noted in 33% and 46%, subretinal fluid in 11% and 20%, SHE in 27% and 70%, and ELM interruption in 88% and 96%, respectively (Fig. 2).

Even though the comparison between minimal versus profuse leakage CNV subtypes revealed no difference regarding baseline and final BCVA, CNV area and subfoveal choroidal thickness, eyes characterized by minimal leakage CNV had a lower percentage of subretinal hyperreflective material (27% vs. 70%, $P = 0.0039$) and required fewer intravitreal ranibizumab injections compared to eyes with profuse leakage CNV (2 vs. 3.4 respectively; $P = 0.003$), and showed a baseline smaller CMT (252 vs. 327 μm, respectively; $P = 0.004$). Moreover, a single intravitreal ranibizumab injection was sufficient to achieve CNV stabilization in 44% of eyes with minimal and 3% with profuse leakage CNV ($P = 0.001$).

The agreement related to each morphologic OCT feature considered in our study was as follows: intraretinal cysts, $\kappa = 0.87$; subretinal fluid, $\kappa = 0.92$; SHE, $\kappa = 1.00$; ELM interruption, $\kappa = 1.00$.

The patients were further categorized according to the baseline presence/absence of SHE in the active CNVs (Table 2). Overall, 26 patients presenting with SHE showed a similar baseline BCVA compared to 22 without exudation, whereas they displayed a greater final BCVA improvement. In addition, CMT was greater at the baseline examination in this subgroup of eyes and the reduction also was more marked, with a similar final CMT. No difference was detected in the subfoveal choroidal thickness at the baseline and final examinations. The CNV area decreased in both subgroups, although it reached a statistically significant reduction only in patients with SHE.

Analysis of the distribution of OCT alterations revealed that patients with SHE always exhibited an ELM interruption, whereas such findings could not be identified in three of the cases (13.7%) without SHE. In these patients, the CNV activity could be identified only on FA, there not being any other signs of activity on SD-OCT.

Lastly, eyes with SHE received a greater number of injections than eyes without SHE (3.2 vs. 2.3, $P = 0.04$).

Inactive CNV was clinically and anatomically stable over the 12-month follow-up. It is interesting that, beyond the scope of this study, two of three inactive CNVs revealed subsequent activation (characterized by FA leakage, and subretinal fluid with interruption of ELM visibility on SD-OCT) after 24 and 30 months, respectively, and required treatment.

Univariate regression analysis revealed that the type of leakage ($P < 0.0001$), presence/absence of SHE ($P = 0.009$), and baseline CNV area ($P < 0.0001$) were significantly associated with the number of intravitreal ranibizumab injections (IVRI) (Table 3). Multiple stepwise linear regression analysis identified the type of leakage ($P = 0.0008$) and baseline CNV area ($P = 0.0198$) as the explanatory variables for the final number of IVRI. Overall, a higher proportion of CNV recurrences during follow-up were significantly associated with a baseline pattern of profuse CNV leakage and a baseline greater area of CNV.

## DISCUSSION

The advent of anti-VEGF treatment has greatly improved the management of mCNV, but the need to perform frequent retreatments has enhanced the importance of a reliable monitoring procedure. FA generally is considered the gold standard in detecting mCNV activity based on the identification of dye leakage. Nevertheless, although OCT is very practical and quick, enabling CNV and related retinal morphologic alterations to be identified, the correlation between FA and OCT reveals discrepancies between the two imaging techniques.[4–13]

Our data showed that three main patterns can be distinguished based on FA leakage: inactive, minimal, and profuse leakage CNVs. Inactive CNV showed no exudative manifestation on SD-OCT, with stable visual acuity over the planned 1-year follow-up. Nevertheless, the condition of inactive CNV looks to be just a temporary stage between onset of the CNV, which was not perceived by the patients, and the subsequent CNV growth, which was documented in two of three patients during subsequent follow-up.

The specific analyses of the characteristics of minimal and profuse leakage CNVs require a thorough discussion. The FA characterization used in our investigation, merely based on dye leakage, has a direct clinical impact, because eyes affected by

**Table 1.** FA and OCT Characteristics of Patients With Subfoveal CNV Secondary to Pathologic Myopia

| | Profuse Leakage CNV (30 Eyes) | Minimal Leakage CNV (18 Eyes) | Inactive CNV (3 Eyes) |
|---|---|---|---|
| Intraretinal cysts | 46.6% | 33% | 0% |
| Subretinal fluid | 20% | 11% | 0% |
| ELM interruption | 96% | 88% | 0% |
| SHE | 70% | 27% | 0% |
| Baseline subfoveal choroidal thickness (μm) | 65.6 | 58 | 63 |
| Baseline CNV area ($mm^2$) | 0.70 | 0.74 | 0.45 |
| Baseline CMT (μm) | 327 | 252 | 229 |
| Overall number of IVRIs | 3.4 | 2 ($P = 0.004$ compared to profuse subtype) | 0 |
| Baseline BCVA (logMAR) | 0.50 | 0.53 ($P = 0.60$ compared to profuse subtype) | 0.33 |
| Final BVA | 0.36 | 0.38 ($P = 0.79$ compared to profuse subtype) | 0.33 |

A statistically significant difference was registered just comparing minimal and profuse leakage CNVs for SHE ($P = 0.001$), CMT ($P = 0.001$) and the number of IVRIs ($P = 0.004$).

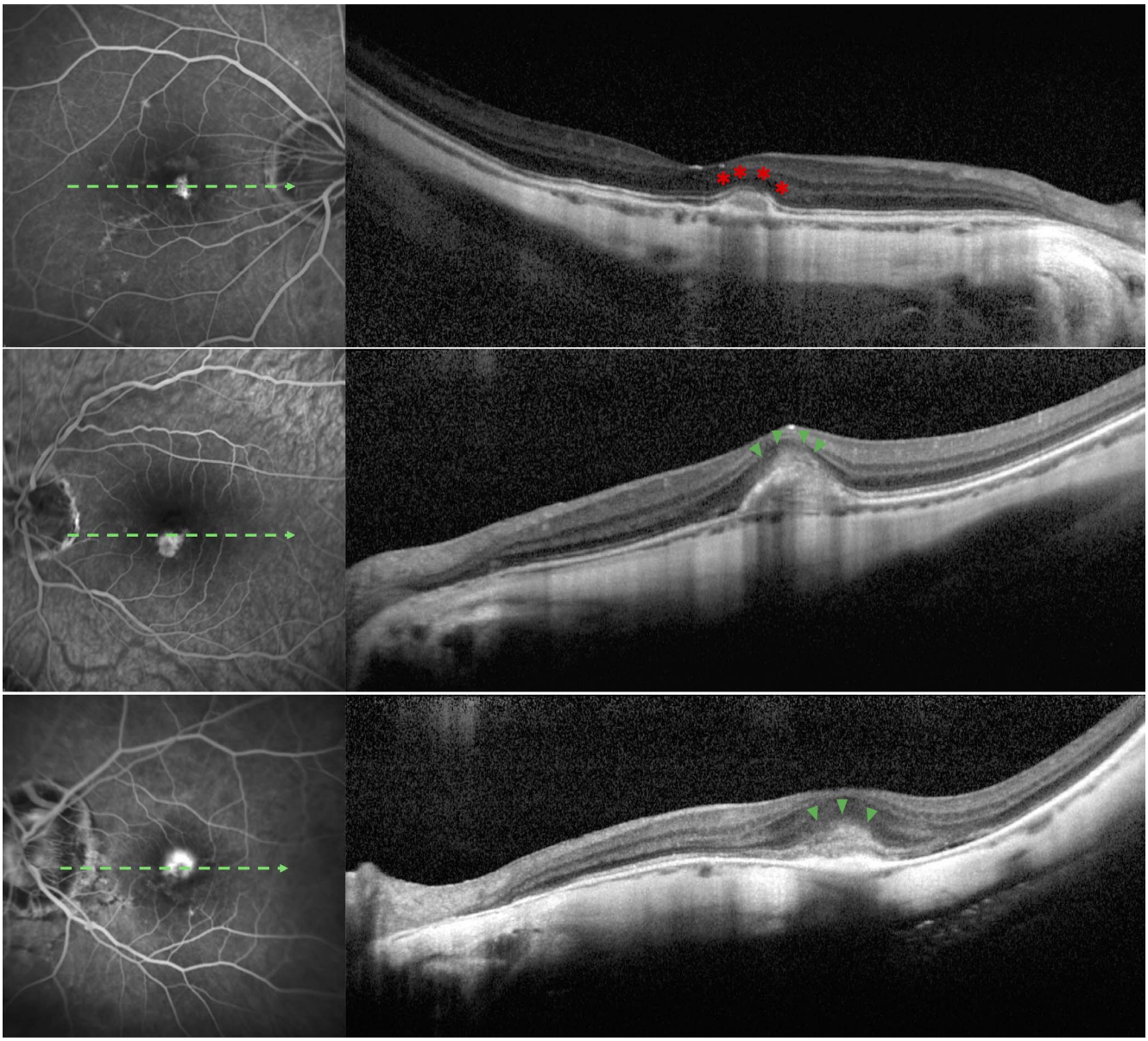

**Figure 2.** OCT correlates in the different fluorescein angiography leakage patterns of choroidal CNV secondary to pathologic myopia. *Top*: OCT structural scan passing through a CNV with no leakage; no SHE is detectable (*red stars*). *Middle*: SHE can be observed on top of a neovascular membrane showing minimal leakage (*green arrowheads*). *Bottom*: similarly, signs of SHE are evident in the occurrence of CNV with profuse leakage (*green arrowheads*).

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**Table 2.** Clinical Characteristics of Patients Affected by Subfoveal mCNV With and Without SHE

| | 26 Eyes With SHE | 22 Eyes Without SHE | *P* Value |
|---|---|---|---|
| Baseline BCVA | 0.54 ± 0.22 | 0.48 ± 0.23 | 0.33 |
| Final BCVA | 0.37 ± 0.32 ($P = 0.004$)* | 0.36 ± 0.34 ($P = 0.07$)* | 0.92 |
| Baseline CMT | 332 ± 86 | 259 ± 80 | 0.003 |
| Final CMT | 249 ± 87 ($P = 0.001$)* | 219 ± 103 ($P = 0.16$)* | 0.27 |
| Baseline choroidal thickness | 59 ± 28 | 67 ± 42 | 0.43 |
| Final choroidal thickness | 56 ± 35 ($P = 0.39$)* | 64 ± 41 ($P = 0.26$)* | 0.49 |
| Baseline CNV area | 0.66 ± 0.57 | 0.77 ± 0.63 | 0.52 |
| Final CNV area | 0.48 ± 0.51 (0.009)* | 0.58 ± 0.63 (0.15)* | 0.53 |
| Number of IVRI | 3.26 ± 1.7 | 2.36 ± 1.21 | 0.04 |

* *P* value calculated in the comparison between baseline and final values.

naïve minimal leakage CNV require a lower number of injections (2 vs. 3.4) than those with profuse leakage CNV. Moreover, 44% of eyes with minimal leakage CNV required a single injection to achieve CNV stabilization over the 1-year follow-up, compared to 3% of eyes with profuse leakage CNV. Looking at the SD-OCT features, the only variables that could differentiate minimal from profuse leakage CNV were baseline SHE and CMT.

The other SD-OCT features related to the exudative manifestations do not help recognize the CNV subtype. Thus, in the light of our data, assessment of FA dye leakage at baseline can provide an immediate and precise characterization of mCNV with practical clinical relevance.

Our data were further processed to evaluate the effects of the presence of the subretinal hyperreflective material on the course of ranibizumab treatment. Overall, the eyes showing SHE achieved a statistically significant visual improvement and obtained a meaningful CMT and CNV area reduction. However, they required more ranibizumab treatments than eyes not exhibiting this feature.

Regression analysis further confirmed these results. A baseline pattern of profuse leakage, baseline greater area of the CNV, and presence of SHE were associated with a higher rate of CNV recurrences during follow-up. However, on multivariate regression analysis, the type of leakage and CNV area were significantly and independently associated with recurrent CNV activity, bestowing a greater value on these variables as predictive factors for CNV activity.

Our data partially differed from the results of a recent study by Bruyère et al.,[10] which investigated the characteristics of SHE in a cohort of 31 patients with mCNV receiving anti-VEGF therapy over a 6-month follow-up.[10] In this retrospective study, there was no meaningful improvement in visual acuity and the reasons for this were thought to be related to the presence of SHE as an early sign of CNV activation. According to this line of thought, the SHE formed before loss of visual acuity and, therefore, the anti-VEGF therapy was able to block the CNV and avoid visual loss. The lack of improvement in visual acuity observed in this retrospective study may simply be related to the study's population. which was composed mainly of patients who had undergone previous therapy (80%) and probably displayed more advanced retinal damage, which was able to limit the potential visual acuity recovery. The exact role of SHE as a prognostic factor for final visual acuity or as a retreatment criterion is not yet well established.

In our study, SHE was compared to CNV activity on FA only at baseline and FA was not performed on a monthly basis; in Bruyère's study,[10] FA was performed only at the examiner's discretion. The design of these studies made it impossible to tell on FA whether gradual resolution of SHE actually was associated with leakage reduction. Studies with a strict monthly monitoring and a direct comparison between FA and SD-OCT would enable a more precise interpretation of SHE to be made, as well as providing a clearer picture of the clinical behavior of the mCNV during anti-VEGF therapy.

There is clear evidence that the treatment of mCNV requires new SD-OCT indicators of CNV activity. In the RADIANCE study, 20% of subjects presented with active dye leakage on FA at the 12-month examination, whereas subretinal fluid was observed in just 4.3% of cases and intraretinal fluid in 8.6%.[15] We currently adopted retreatment criteria based on the presence of intraretinal/subretinal fluid and the interruption of ELM visibility, which was shown in our previous investigation to be a more reliable SD-OCT parameter for evaluating CNV activity than intraretinal/subretinal fluid collection.[9] SHE currently is under investigation as a retreatment criterion; however, it should be noted that it is present in 50% to 60% of cases. Our approach is further supported by the high level of agreement attained by retinologists well-trained in the interpretation of CNV activity, especially when ELM visibility and SHE are considered.

We acknowledge that our study has several limitations, including, first of all, the small number of patients and the brief follow-up. Secondly, the CNV characterization on FA was based

**Table 3.** Predictive Factors in mCNV Activity Receiving IVRIs Over 12-Month Follow-Up Study: Linear Regression Analysis of Morphological Parameters

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| Variables | Regression Coefficient (SE) | *P* | Regression Coefficient (SE) | *P* |
| Leakage (profuse, minimal, or none) | 1.46 (0.32) | <0.0001 | 1.34 (0.37) | 0.0008 |
| SHE | 1.18 (0.44) | 0.009 | – | – |
| Baseline CNV area | 0.80 (0.39) | <0.0001 | 0.81 (0.33) | 0.0198 |
| Baseline CMT | 0.003 (0.002) | 0.17 | – | – |
| Baseline choroidal thickness | 0.003 (0.006) | 0.57 | – | – |

On univariate analysis, a statistically significant correlation was measured between the type of leakage, presence of SHE, baseline CNV area with activity of mCNV during the 12-month follow-up study. On multivariate stepwise linear regression analysis, the type of leakage and baseline CNV area were identified as the most important biomarkers for mCNV activity.

on a qualitative judgment, rather than a quantitative assessment, even though the interobserver agreement was high. Theoretically, the amount of leakage on FA may reflect different levels of vessel maturation and fibrous scarring, but the limited duration of the CNV based on the referred symptoms would indicate similar anatomic conditions. In addition, it can be hard to detect SD-OCT features with total confidence; the CNV must be carefully scanned over its entire extent, entailing the presence of skilled OCT operators and highly cooperative patients. Moreover, our FA and SD-OCT assessment was performed purposely at the baseline examination to ascertain which prognostic features were important for the final functional outcomes.

In conclusion, our study identified three main subtypes of mCNV based on dye leakage on FA. Profuse leakage CNV is characterized by greater CMT and a higher rate of SHE. Minimal leakage CNV requires fewer intravitreal injections of ranibizumab, with the clinical picture being stabilized with a single treatment in almost half of the cases. Further investigations involving studies with larger samples and longer-term follow-ups are warranted to confirm our observations.

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