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Natural History of Treatment-Naïve Quiescent Choroidal Neovascularization in Age-Related Macular Degeneration Using OCT Angiography

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Purpose: To describe the evolution of treatment-naïve quiescent choroidal neovascularizations (CNVs) in age-related macular degeneration (AMD) by means of OCT angiography (OCTA).

Design: Prospective, observational, consecutive case series.

Participants: Fifteen eyes (7 right eyes and 8 left eyes) of 14 patients (8 women and 6 men) fulfilled the criteria of quiescent CNV in AMD among an overall pool of 950 neovascular AMD patients.

Methods: Consecutive patients with treatment-naïve quiescent CNV seeking treatment at 2 tertiary referral centers were followed up longitudinally for 1 year after diagnosis. The study included 3 visits at different time points. Each visit included measurement of best-corrected visual acuity, dilated fundus biomicroscopy, structural OCT, and OCTA. At baseline, fluorescein angiography and indocyanine green angiography also were performed to confirm diagnosis. Qualitative and quantitative analysis were assessed during a 12-month follow-up period.

Main Outcome Measures: Qualitative and quantitative assessment of OCTA images and evaluation of the rate of clinical activation.

Results: Fifteen eyes of 14 patients were included in the analysis. Fourteen of 15 CNVs remained quiescent, and the rate of clinical activation was 6.6%. Qualitative analysis disclosed that the CNV core was visible in 2 of 14 eyes at baseline and in 3 of 14 eyes at 6 and 12 months; the CNV margin was well defined in 10 of 14 eyes and the CNV location was foveal involving in 8 of 14 eyes at all time points; CNV growth was displayed in 3 of 14 eyes at 6 months and in 10 of 14 eyes at 12 months compared with baseline images. Quantitative analysis revealed that despite an increase in CNV area ($P = 0.039$), CNV vessel density did not change ($P = 0.731$) in quiescent CNVs during follow-up.

Conclusions: We demonstrated biological activity of quiescent CNV by showing lesion growth over 12 months. Biological activity was not paralleled by clinical activity in most cases because of absence of exudation development over time, possibly because of unchanged CNV vessel density despite growth. *Ophthalmology Retina 2018;■:1–9 © 2018 by the American Academy of Ophthalmology*

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Treatment-naïve quiescent choroidal neovascularization (CNV) is a term first introduced by Querques et al[1] to describe an additional pattern of neovascular age-related macular degeneration (AMD). Quiescent CNV is defined as the absence of intraretinal or subretinal exudation on repeated structural spectral-domain (SD)-OCT examinations over at least 6 months[1] for treatment-naïve CNVs detected on fluorescein angiography (FA) and indocyanine green angiography (ICGA; the current gold standard to diagnose quiescent CNVs).[1] It is noteworthy that 2 studies[2,3] in the 1970s showed that CNV could exist in eyes with nonexudative AMD in which histopathologic analyses of postmortem eyes were performed. Moreover, in the 1990s, Schneider et al[4] and Hanutsaha et al[5] performed ICGA to detect this subclinical lesion in situ in patients with nonexudative AMD. In accordance with the classification of Gass,[6] this type of CNV remains beneath the retinal pigment epithelium, but unlike typical type 1 CNV, it is not associated with clinical signs of activity (i.e., subretinal or intraretinal exudation).[7–9]

The usefulness of OCT angiography (OCTA) in CNV detection in different ocular conditions has been described extensively in literature, and recently our group reported good sensitivity and specificity of quiescent CNV detection by OCTA in the setting of AMD.[10] However, previous studies mostly have had a cross-sectional design and have been conducted with traditional imaging techniques.[1,10] Therefore, CNV modifications during follow-up are still

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largely unknown, in particular on OCTA scans. The aim of our study was to describe, during a 12-month follow-up period, the evolution of quiescent CNVs by means of OCTA through a qualitative and a quantitative analysis. Moreover, we assessed the rate of activation of treatment-naïve quiescent CNVs into exudative stages after 1 year of follow-up.

Methods

In this prospective, observational study, consecutive patients with treatment-naïve quiescent CNV among the overall pool of patients with neovascular AMD (exudative and nonexudative lesions) seeking treatment at 2 tertiary referral centers (the Medical Retina and Imaging Unit, Department of Ophthalmology, University Vita-Salute San Raffaele, Milan, Italy, and the Department of Ophthalmology, University Paris Est, Creteil, France) between June 2015 and April 2017 were followed up longitudinally for 1 year after diagnosis. The study was conducted in agreement with the tenets of the Declaration of Helsinki for research involving human subjects and was approved by the local institutional review board at both sites; included patients signed a written informed consent to participate in observational studies.

Treatment-naïve quiescent CNVs were defined as late-phase ill-defined hyperfluorescent lesions without late-phase leakage or pooling of dye on FA; on ICGA, they appear as a hypercyanescent neovascular network in the early-mid phases, and in the late phase, we can delineate the fibrovascular plaque. Moreover, CNVs were not associated with intraretinal or subretinal exudation, or both, on repeated structural SD-OCT for at least 6 months.

Inclusion criteria were age older than 50 years, diagnosis of treatment-naïve quiescent CNV in AMD, adequate pupillary dilation, and fixation to permit high-quality OCTA imaging. Exclusion criteria included history of any intraocular surgery except for uneventful cataract extraction less than 6 months before the beginning of this study, contraindication to mydriasis, quality of OCTA images with a low signal strength (signal strength index thresholds are reported below for each device), eye disorders other than neovascular AMD (including dry AMD, polypoidal choroidal vasculopathy, central serous chorioretinopathy, angioid streaks, retinal vasculopathies, vitreoretinal diseases, and previous retinal detachment), and previous ocular treatments (including anti−vascular endothelial growth factor [VEGF] intravitreal injections, photodynamic therapy, laser photocoagulation, or vitrectomy in the study eye).

The present study included 3 visits at different time points (baseline and 6 and 12 months after diagnosis). Each visit included measurement of best-corrected visual acuity (BCVA), dilated fundus biomicroscopy, structural SD-OCT (Spectralis + HRA; Heidelberg Engineering, Heidelberg, Germany), and OCTA. At baseline, FA and ICGA also were performed to confirm diagnosis. Automated central macular thickness (CMT) and retinal thickness in the affected sector measurements were generated by Spectralis SD-OCT using a 19-horizontal line protocol (6 × 6-mm area), each consisting of 1024 A-scans per line; each line was corrected manually for any errors.

OCT Angiography Image Acquisition and Analysis

In all patients, a scanning area of 3 × 3 mm was adopted, centered on the fovea or on the CNV when the lesion was not included completely in the 3 × 3-mm foveal image. OCT angiography imaging was obtained with the AngioPlex Cirrus HD-OCT model 5000 (Carl Zeiss Meditec, Inc, Dublin, CA) or with the AngioVue RTVue XR Avanti (Optovue, Fremont, CA). All follow-up images were obtained with the same device used during the first examination.

The AngioPlex Cirrus HD-OCT model 5000 uses optical microangiography and contains an A-scan rate of 68 000 scans per second, using a superluminescent diode centered at 840 nm; the resultant 3 × 3 angio cube contains 245 B-scan slices repeated 4 times at each B-scan position, and each B-scan is made of 245 A-scans.[11−13] All acquisitions were performed using FastTrac retinal tracking technology (Carl Zeiss Meditec, Inc., Dublin, CA) to reduce motion artifacts. Minimum signal strength threshold of 7 of 10 was required for OCTA image inclusion.

The AngioVue RTVue XR Avanti relies on a split-spectrum amplitude-decorrelation angiography algorithm.[14] This instrument has an A-scan rate of 70 000 scans per second, using a light source centered at 840 nm and a bandwidth of 50 nm. Each OCTA volume contains 304 A-scans in each B-scan, repeated twice along both the horizontal and the vertical direction. The split-spectrum amplitude-decorrelation angiography was used to extract the OCTA information. Minimum signal strength of 50 was required for OCTA image inclusion. All acquisitions were performed by 2 expert ophthalmologists (R.S. and V.C.).

To evaluate CNV features, projection artifacts were removed to identify better the CNV, and the automatic choriocapillary segmentation provided by the OCTA software was adjusted manually by 2 expert retina specialists (A.C. and A.M.) for correct visualization of the capillary plexus, outer retinal layers, and choriocapillaris to identify better the CNV plane and to optimize the appearance of the CNV at baseline and during follow-up. Disagreement regarding interpretation of the different features was resolved by open adjudication.

Qualitative Analysis

We performed a qualitative analysis of different OCTA images on the basis of OCTA criteria previously described in literature.[10,15,16] Two independent expert readers (A.C. and A.M.) qualitatively assessed OCTA images at the 3 chosen time points for each patient, evaluating (1) CNV core, (2) CNV margin, (3) CNV location (as defined previously),[10,15,16] and (4) CNV growth. The CNV core has been defined as a vessel of greater caliber or a so-called trunk vessel from which other smaller vessels branch off[17] that could be visible or not visible. The CNV margin on OCTA was classified as well defined or poorly defined on the basis of its aspect and its borders. The CNV location was classified as foveal involving if the lesion involved the foveal center or as foveal sparing if CNV lesions spared the foveal center. Finally, CNV growth was evaluated subjectively by analyzing OCTA images at 6 and 12 months compared with baseline OCTA images. Each disagreement regarding the interpretation of the different qualitative features of OCTA images was resolved by open adjudication.

Quantitative Analysis

All 3 × 3 OCTA images were exported into the National Institutes of Health ImageJ software version 1.50 (National Institutes of Health, Bethesda, MD). Quiescent CNVs were outlined manually using the polygon selection tool in the selected slab, and their dimensions expressed in square millimeters were calculated. The quiescent CNV area was measured by 2 independent readers (A.C. and A.M.), and the mean measurement was used for the analysis. Vessel density was quantified using image thresholding and binarization, similarly to previous studies.[18−20] Specifically, the Otsu threshold was used to binarize each image. Vessel density