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Detection of Non-exudative Choroidal Neovascularization and Progression to Exudative Choroidal Neovascularization Using Optical Coherence Tomography Angiography

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Abstract

Objective: To detect non-exudative choroidal neovascularization (CNV) in age-related macular degeneration with optical coherence tomography angiography (OCTA) and determine risk of developing exudative CNV compared to eyes without non-exudative CNV.

Design: Prospective longitudinal observational study

Participants: Consecutive patients with drusen and pigmentary changes in the study eye and exudative neovascular AMD in the fellow eye.

Methods: Study participants underwent spectral domain OCTA (AngioVue, Optovue, Inc), clinical exam, and structural OCT at baseline and six-month intervals for two years. OCTA images were exported for custom processing to remove projection artifact and calculate CNV vessel area.

Main Outcome: Rate of developing exudation in eyes with and without non-exudative CNV as detected by OCTA on regular follow-up.

Results: Sixty-three prospective study participants were followed every 6 months and 48 completed the 2-year study. Mean age was 78 years and 60.3% were female. On the baseline visit, 5 eyes (7.9%) were found to have non-exudative CNV by OCTA and 3 of them developed exudation. Over the 2 years of follow-up, 5 more eyes developed non-exudative CNV on a follow-

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Study concept and design: Bailey and Jia

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Bailey, Thaware, Jia, Hwang, Huang

Administrative, technical, or material support: All authors.

Study supervision: Jia, Bailey.

CONFLICT OF INTEREST

Oregon Health & Science University (OHSU) and Drs. Huang and Jia have a significant financial interest in Optovue, a company that may have a commercial interest in the results of this research and technology. These potential conflicts of interest have been reviewed and managed by OHSU.

up visit and all of them developed exudation. Overall, 8 of the 10 eyes with non-exudative CNV developed exudation with a mean time of 8 months and a mean CNV area growth rate of 20%/month (exponential model, p=0.014). Initiation of anti-angiogenic treatment halted their growth. In comparison, exudation occurred in only 6 of the 53 eyes in which no non-exudative CNV were detected. Cox proportional hazard analysis showed that having a non-exudative CNV detected was associated with 18.1-fold increase in the rate of subsequently developing exudation (P<0.0001).

Conclusions: Non-exudative CNVs are frequently detected by OCTA in the fellow eyes of exudative CNV. These lesions carry a high risk of developing exudation within the first year after detection and could benefit from close monitoring. The high risk of progression may justify prophylactic treatment; further studies are needed.

Precis

Optical coherence tomography angiography detected non-exudative CNV in asymptomatic eyes. Non-exudative CNV carries high risk for exudation during the first year after detection. Close follow-up is recommended; however, a prophylactic treatment study may be warranted.

Introduction

Age-related macular degeneration (AMD) is a leading cause of vision loss and blindness.[1] Choroidal neovascularization (CNV), the hallmark feature of neovascular AMD, refers to pathologic angiogenesis from the choroid which can result in exudation, hemorrhage, and fibrosis formation damaging the outer retina resulting in vision loss.[2] Current treatment of neovascular AMD with anti-vascular endothelial growth factor (VEGF) is effective at preventing vision loss, however only 30–40% of patients have vision improvement.[3–5] Earlier detection of CNV and timely anti-VEGF treatment prior to vision loss should result in better visual outcomes.

Historically, the gold standard for CNV diagnosis is fluorescein angiography (FA).[6] CNV endothelium is incompetent allowing fluorescein molecules to exit the vasculature resulting in characteristic hyperfluorescence patterns allowing CNV diagnosis. Therefore, by definition, CNV detected with FA is exudative. It would be better to have a test that can identify CNV prior to the development of exudation. A prior study using indocyanine green angiography (ICGA) in a cohort of 432 study eyes with drusen and CNV in the fellow eye; 11% were found to have an abnormal ICGA. Eyes abnormal ICGA were almost three times as likely to develop exudative neovascular AMD after a mean follow-up of 21.7 months. Because ICGA is not widely used clinically and it is invasive, this is not likely to be utilized as a screening technique. Structural optical coherence tomography (OCT) is non-invasive and is useful for detecting and monitoring exudation associated with CNV and there are several characteristic features on structural OCT in addition to fluid that suggest the presence of CNV such as pigment epithelial detachment (PED) or subretinal hyper-reflective material. However, structural OCT is not able to clearly distinguish blood vessels from hemorrhage or variable reflective material within pigment epithelial detachments.[6,7] In 2013, Querques et al. described treatment naïve quescient CNV based on multi-model imaging including FA, ICGA, and OCT. These subclinical lesions harbored CNV that grew slowly over time and did not develop exudation over a two year period.[8]

OCT angiography (OCTA) is a functional extension of OCT, which uses intrinsic contrast generated by the motion of blood cells to visualize retinal and choroidal blood vessels. OCTA does not rely on dye leaking patterns for CNV detection. Instead, the 3- dimensional nature of OCTA allows CNV to be detected as pathologic blood flow in the outer retinal/RPE slab, between the outer boundary of the outer plexiform layer (OPL) and Bruch's Membrane (BM).[9] Because OCTA does not rely on exudation to detect CNV, it is possible to detect CNV prior the development of exudation and vision loss.[10–18] In addition to detection CNV, OCTA-derived CNV quantitative metrics can be used to monitor non-exudative CNV growth over time.[15,17]

In this study, we selected eyes at high risk for developing CNV based on risk factors identified in the Age-Related Eye Disease Study (AREDS).[19] Fellow eyes of exudative neovascular AMD were followed with semi-annual OCTA to determine the rate of non-exudative CNV detection and the risk for developing exudation.

Methods

This prospective study was approved by the institutional review board of Oregon Health and Sciences University (OHSU) and included patients who were recruited from the retina clinics at the Casey Eye Institute, OHSU (Portland, OR) from September 22nd, 2014 to February 8th, 2016. The inclusion criteria for study eyes required drusen and pigmentary changes without hemorrhage or exudation on clinical exam and no intraretinal fluid (IRF) or subretinal fluid (SRF) on structural OCT. Fellow eyes were required to have a history of exudative neovascular AMD. Exclusion criteria for the study eyes were vision worse than 20/200 and media opacity that would interfere with OCTA image quality. Study visits occurred every six months (+/− 1 month) for a minimum of two years. Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity, dilated fundus examination, structural spectral-domain-OCT (Spectralis, Heidelberg Engineering, Germany) and OCTA scans were obtained at each visit. Once enrolled in the study, if neovascular AMD developed, diagnosis and need for FA was determined by the treating physician (STB, TSH, AKL, PL, CJF). All cases of neovascular AMD were reviewed in a retrospective manner to confirm appropriate diagnosis by author STB.

The Avanti/AngioVue OCT/OCTA system (Optovue, Inc., Fremont, CA) was used for OCTA scanning. Both 3×3-mm^2 and 6×6-mm^2 scans of the macula were obtained at each visit. Each volumetric scan consisted of 304×304 transverse locations. Flow signal was computed with commercial version of the split-spectrum amplitude-decorrelation algorithm (SSADA).[20] Two orthogonal raster scans - one vertical-priority and one horizontal-priority raster scans - were registered and merged to form a single volume to reduce motion artifacts.[21]

Two certified graders (AH and OT) reviewed images on the AngioVue OCTA system including both *en face* and cross-sectional OCTA images. If CNV was suspected, scans were exported for custom processing. To suppress projection artifact, the projection resolved (PR) OCTA algorithm was used. [22,23] An automated algorithm,[24] was applied to segment the outer retinal slab as between the outer boundary of OPL to BM. A grader inspected the

segmentation boundary and applied manual correction if necessary. *En face* OCTA images of the outer retinal slab were generated by maximum projection. CNV was detected as flow within this slab. If CNV was detected, cross-sectional PR-OCTA was reviewed to classify flow as type 1, flow detected between BM and retinal pigment epithelium (RPE); type 2, flow in outer retina above RPE; and type 3, flow in outer retina that was contiguous with flow signal from the deep retinal capillary plexus. [25] Senior graders (STB and YJ) adjudicated instances of uncertainty or grader disagreement. All cross-sectional structural OCT images were reviewed to determine the presence or absence of IRF and SRF and classify the CNV as either exudative or non-exudative. CNV flow signal was distinguished from the background speckle noise by a saliency-based CNV detection algorithm and CNV vessel area was determined by the number of pixels containing flow.[26] After detection of non-exudative CNV, treating physicians were notified and OCTA was attempted to be captured at follow-up visits intervals at their detection. If signs of exudation such as IRF or SRF, the treating physician determined the need for treatment and the need for FA.

The follow-up data were plotted as Kaplan-Meier survival curves. If non-exudative CNV was detected, the baseline was set at the time of detection. Otherwise the baseline was the initial enrollment date. For the survival analyses, data were censored if the participant completed the study or were lost to follow-up.

The growth of CNV vessel area were measured using both linear and exponential models. Simple linear regression was applied to the vessel area in the linear model. In the exponential model, the vessel areas were converted to a logarithmic scale prior to linear regression. The log-scale slope was then converted to percent change per month.

All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

Of 65 study participants, two were excluded due to poor image quality. For the remaining 63 study participants, mean age was 78 years old and 60.3% were female. Mean EDTRS visual acuity was 0.14 LogMAR units. Fifteen study participants dropped out during the follow-up period due to either poor health, death, or preference to be seen at a satellite clinic where OCTA was not available. Forty-eight study participants completed 24 months of follow-up.

At the enrollment visit, non-exudative CNV was detected by OCTA in 5 of 65 eyes (7.9%). Three of these eyes developed exudation an average of 10 months (range: 6–12) after detection. During subsequent follow-up, 5 more eyes had non-exudative CNV detected. All of these eyes developed exudation a mean 6 months (range: 1–12) after detection. Overall, OCTA detected non-exudative CNV in 10 eyes and eight of these (80%) developed exudation. Seven of these eight eyes developed exudation in the area of the non-exudative CNV that was being followed. One case had an exudative CNV that arose from a different location and was not associated with the non-exudative CNV that was being followed. The average time for all non-exudative CNV to convert exudation was seven months and 23 days after first detection with OCTA.

All cases of non-exudative CNV were asymptomatic at the time of diagnosis. The mean distance from the center of the foveal avascular zone to the non-exudative CNV cases was 1.04 mm with a range of 0.37 – 1.81 mm. Non-exudative CNV were detected throughout the macular including: inferior in 3 eyes, inferior nasal in 1 eye, superior in 1 eye, temporal in 2 eyes, superior temporal in 2 eyes, and nasal in 1 eye. There was no evidence of a specific distance from the fovea or sector increased risk of exudation. The fellow eye was under anti-VEGF treatment at the time of detection of non-exudative CNV for all cases except case #9, in this case a treatment naïve exudative CNV was detected on the baseline visit. The detection of non-exudative CNV was not associated with any reduction in visual acuity (Table 1), with the exception of Case #3 in which visual acuity loss was attributable to geographic atrophy. Interestingly, in this case, an irregular RPE elevation was suspicious for type 1 CNV between areas of geographic atrophy, however no flow was detected with OCTA. Six months later, a non-exudative CNV was detected within this RPE elevation. Exudation developed 11 months after first detection and the IRF resolved with anti-VEGF treatment (Figure 1). Of the eight eyes that developed exudation, visual acuity loss occurred in 3 eyes because of foveal involvement. The vision returned to baseline in two eyes after treatment. Five eyes developed exudation without foveal involvement and treatment was provided prior to vision loss.

Two eyes with non-exudative CNV never developed exudation (Table 1). In one case, follow-up was limited to five months because the patient developed a stroke (Case #10). In the other case (Case #9), a subfoveal non-exudative CNV remained inactive for 42 months of clinical follow-up and the visual acuity remained stable. The study participant had 15 months of OCTA follow-up scans prior to transferring care to a satellite clinic that lacked OCTA. Over 15 months, this non-exudative CNV slowly enlarged, however exudation never developed (Figure 2). The growth rate in this case was 2% per month, which was the slowest among the non-exudative CNV cases.

In 6 cases of non-exudative CNV (Cases #3–6) vessel areas were measured at both the time of detection and exudation (Table 1). The non-exudative CNV vessel area increased from 0.14 ± 0.16 mm^2 (mean ± standard deviation) to 0.63 $mm^2 \pm 0.68$. The mean exponential growth rate of 20% per month was significantly above zero (p=0.014). The mean linear growth rate was 0.04 mm^2/month (p=0.09).

In two cases, CNV growth rates were measured both before and after exudation (Figure 3). In Case #3, a type 1 non-exudative CNV that had a linear growth rate of 0.017 mm^2/month and an exponential growth rate of 4%/month. After the onset of exudation and initiation of PRN anti-VEGF treatment, the CNV shrunk at a linear rate of −0.014 mm^2/month and exponential rate of −3% per month. In Case #7, a type 3 precursor lesion was detected as flow in the outer retina contiguous with the deep retinal capillary plexus. The linear growth rate was 0.01 mm^2/month and the exponential growth rate was 43% per month. After initiating anti-VEGF treatment, the lesion shrunk at a linear rate of −0.004 mm^2/month and an exponential rate of - 5% per month.

Of the 14 eyes that developed exudation, OCTA detected precursor non-exudative CNV in eight eyes (57%). In the six eyes where OCTA did not detect precursor lesions, the average

time between the prior negative OCTA scans and presentation of exudation was 4.2 months (range 2–7 months). It is unknown if an intermediary precursor non-exudative CNV was present in these eyes prior to their development of exudation.

Kaplan-Meier survival analysis (Figure 4) showed that eyes with OCTA-detected non-exudative CNV developed exudation at a faster rate (P< 0.0001, log rank test) than study eyes without non-exudative CNV. The Cox proportional hazard ratio was 18.1.

Discussion

It has been well documented that fellow eyes of eyes with exudative CNV carry high risk for developing exudative CNV and eyes with drusen and pigmentary changes the rate approaches 50% over a five-year period.[19] Because OCTA is non-invasive and can be rapidly acquired without disrupting a busy clinical practice, it has potential to become a useful screening tool. Several studies have demonstrated OCTA can detect asymptomatic CNV prior to exudation, however this is the first study we are aware of that uses OCTA at regular fixed intervals to detect non-exudative CNV and monitor their growth.

Pooled rates of fellow eyes developing neovascular AMD for the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA) and the Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular degeneration (ANCHOR) study was 32.1% at two years.[27] The two-year rate in the Comparison to Age-related Macular Degeneration Treatment Trial (CATT) was 18.6%.[28] Our rate of 29% of fellow eyes developing neovascular AMD was similar to these larger multi-site clinical trials. OCTA detected a precursor non-exudative lesion in Just over half of the eyes that developed exudation over two years.

Two previous studies have reported prevalence rates of non-exudative CNV detected with OCTA. A study by de Oliveira Dias's et al. detected subclinical macular neovascularization (their term for non-exudative CNV) with OCTA in 14.4% of 160 fellow eyes of exudative AMD.[14] Another study, by Yanagi, et al. detected non-exudative CNV in 19% of eyes. This cohort consisted of 60% with polypoidal choroidopathy and 40% had "typical" AMD. Our prevalence rate was calculated from the number of non-exudative CNV detection with OCTA on the first study visit and was 7.9%. This rate is lower than the other two studies, however given the relatively small sample sizes and different patient characteristics, some variability is not surprising.

Several smaller case reports using OCTA have suggested non-exudative CNV may be relatively benign.[12,15,16,29] Other recent and larger studies have found non-exudative CNV carries increased risk of developing exudation. Yanagi et al. reported that 22.2% (4/18) of eyes with non-exudative neovascularization developed exudation after 6 months and the odds ratio for developing exudation was 10.3 (P=0.01) [17]. In an additional study, de Oliveira Dias, et al. reported the development of exudation in 21.1% of eyes with subclinical macular neovascularization (their term for non-exudative CNV) over 12 months of follow-up.[14] In our study, the presence of non-exudative CNV increased the risk of developing exudation

18-fold (Cox proportional hazard ratio P<0.0001). There are several explanations why our study had a higher rate (80%) of developing exudation. First, our follow-up period was longer, thus allowing longer time for exudation to develop. Second, our study design was different and all eyes underwent regularly scheduled OCTA every 6 months. Five eyes with non-exudative CNV were detected at the first study visit and 5 eyes developed new non-exudative CNV during a follow-up study visit with a prior normal baseline OCTA. All five eyes with non-exudative CNV detected during a follow-up visit developed exudation. Non-exudative CNV lesions that were discovered at the first OCTA imaging may have pre-existed for a long time without developing exudation and therefore had a selection bias for being less active. Collectively, these studies suggest non-exudative CNV carries significant risk for exudation. However, the absolute incidence varies from study to study.

Several authors have used different terms to describe treatment naïve choroidal neovascularization in AMD that lack exudation. The term non-exudative CNV detected with OCTA likely is the same entity or very similar as “subclinical macular neovascularization.” Studies following these eyes required the fellow eye to have exudative AMD. The term treatment naïve quiescent CNV carried slightly different inclusion criteria than our study and others. First, eyes with these lesions required 6 months of follow-up without development of exudation prior to enrollment in their longitudinal studies. Second, the fellow eye was not required to have exudative CNV. The two differences may explain the reported lower rate of exudation (6.6%) after 1 year of follow-up. [30]

It is unclear if treatment of non-exudative CNV with anti-VEGF injections is necessary. Because non-exudative CNV may serve to recapitulate the choriocapillaris and protect against geographic atrophy, some have suggested treating non-exudative CNV may hasten geographic atrophy and lead to negative long-term visual effects. [10,14,31–33] However, given the high rate of exudation in our series, early treatment may prevent vision loss associated with SRF, IRF or hemorrhage. Three patients lost vision due to exudation in our study and fortunately, two of them had their vision return to baseline after treatment with anti-VEGF injections. Because most patients do not gain vision with anti-VEGF treatment, it is reasonable to hypothesize that prophylactic treatment preventing exudation could save vision. Therefore, there is need for a randomized controlled trial to evaluate both the short and long-term effects of treating non-exudative CNV versus frequent observation.

One difficulty with designing a prophylactic treatment trial is determining appropriate clinical endpoints that could guide treatment for non-exudative CNV. Current treatment of exudative CNV is based on presence or absence of fluid with structural OCT. Because non-exudative CNV lacks exudation, an alternative metric is needed. OCTA derived vessel density is a non-invasive metric that may help guide treatment. We observed growth of non-exudative CNV as well as a trend that slower growth was inversely associated with developing exudation. Halting the rapid growth of CNV could be a plausible treatment endpoint, as we have demonstrated that anti-VEGF injection could reverse the growth of these lesions in our study (Fig 3). The range of growth rates reported in this paper could serve as a preliminary reference for what constitute slow versus rapid growth.

The limitations of this study include the relatively small sample size and a moderate dropout rate. We did not use ICGA to confirm the non-exudative CNV detected by OCTA, as such validation had been provided by previous studies.[10,11,16] Finally, we had to export the OCTA data for processing by custom software to remove projection artifacts and provide automated quantification of CNV area. Because projection artifacts can result in false positive identification of CNV, it is important this artifact is removed to prevent false positive CNV detection.[34] Our results may not be applicable to routine clinical practice using currently available commercial technology because we utilized custom software and certified graders. However, the commercial OCTA platforms are rapidly advancing and some systems have adapted projection resolution and semi-automated CNV area measurement software.

In summary, routine screening with OCTA can detect non-exudative CNV that are asymptomatic and are undetectable with clinical examination or structural OCT. Non-exudative CNV is a high-risk precursor for conversion to exudative CNV and frequent follow-up is suggested. Non-exudative CNV of known recent origin (previous negative OCTA) or higher growth rate may suggest even higher risk for exudation. A clinical trial to assess the potential benefit of prophylactic anti-VEGF treatment is warranted and CNV vessel area growth could be a metric for titrating treatment.

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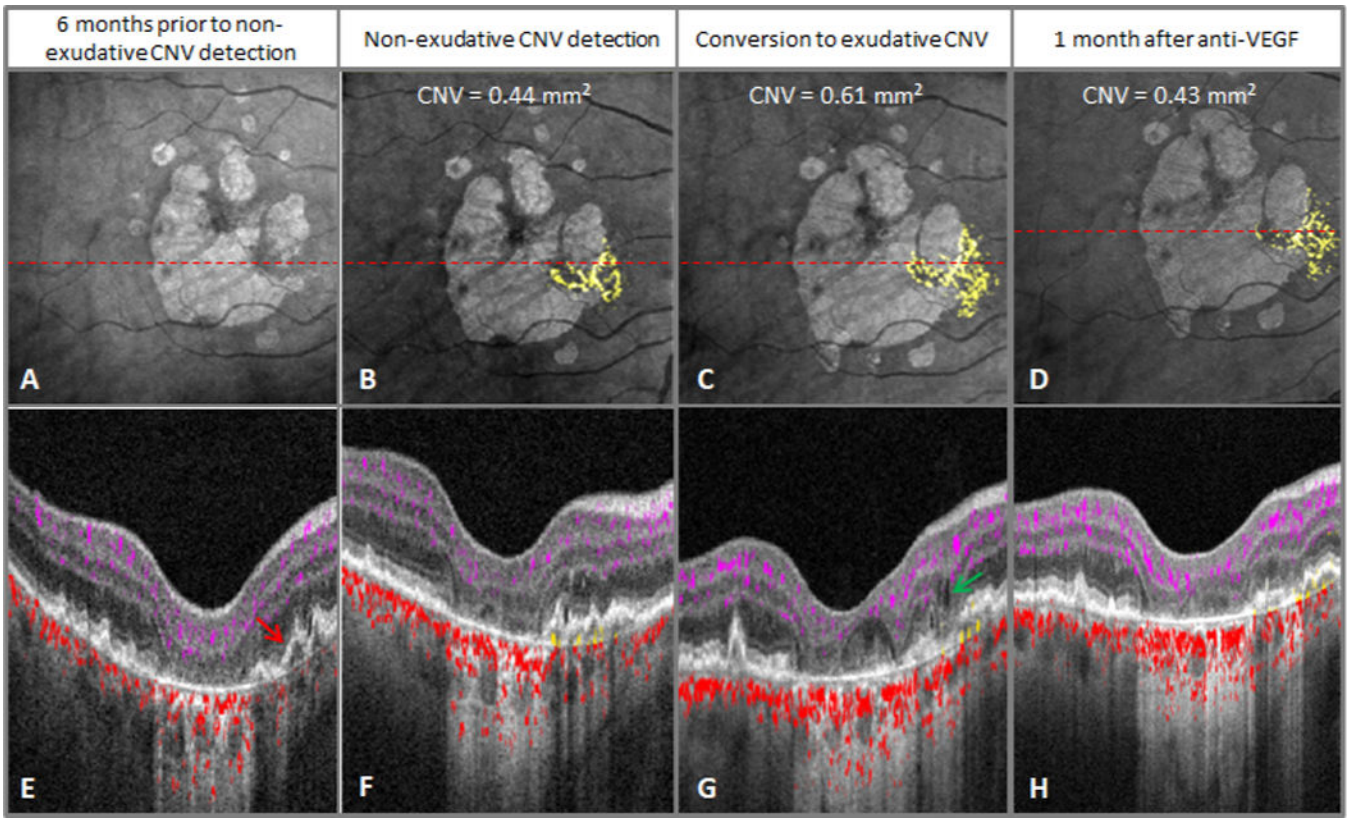

Figure 1.

Development of non-exudative CNV between areas of geographic atrophy. 6X6 mm *en face* outer retinal OCTA displayed over *en face* structural OCT (A-D) with red dashed line corresponding to cross-sectional OCTA (E-H). The CNV vessel area (mm^2) presented on respective *en face* images (B-D). Six months prior to non-exudative CNV detection, *en face* structural OCT reveals geographic atrophy without flow detected with overlying outer retinal *en face* OCTA (A) and no flow present in irregularly elevated RPE with cross-sectional OCTA (E – red arrow). Non-exudative CNV first detected (B,F - CNV flow highlighted with yellow) in between areas of geographic atrophy. Over 11 months, increased CNV vessel area with growth along the edges of geographic atrophy (C). Conversion to exudation with intra-retinal fluid (IRF) detected (G – green arrow). Reduced CNV flow (D) and resolution of prior IRF (H) one month after anti-VEGF treatment.

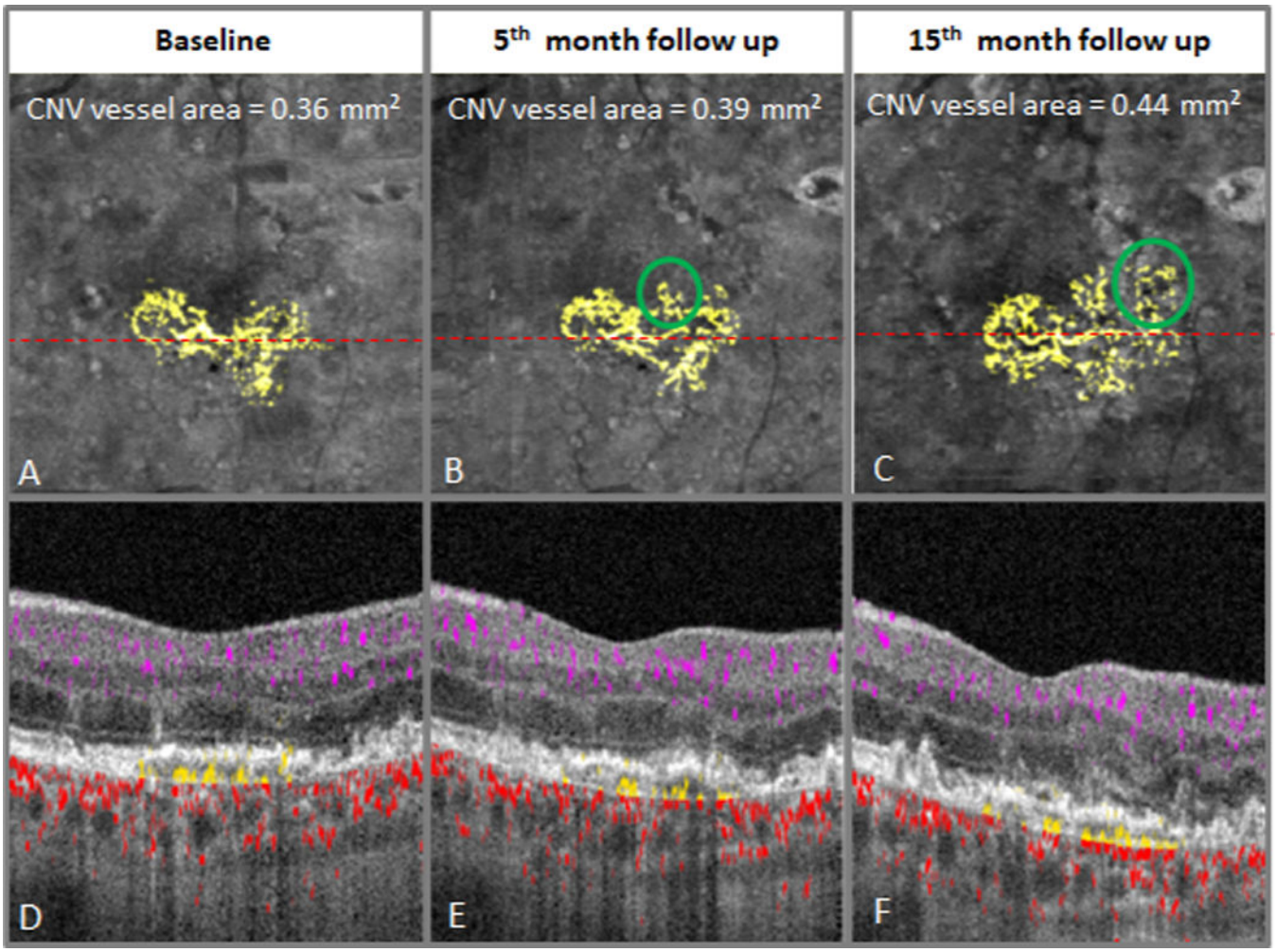

Figure 2.

Slow enlargement of non-exudative choroidal neovascularization (CNV) over 15 months. 3X3 mm *en face* outer retinal OCTA displayed over *en face* structural OCT (A-C) with CNV flow highlighted with yellow. Baseline (A) *en face* OCTA with subfoveal CNV. Emerging vascular branches (green circles) at 5 (B) and 15 (C) month follow-up visit. Cross-sectional OCTA (D-F) demonstrated flow between Bruch's membrane and retinal pigment epithelium (yellow) without development of exudation.

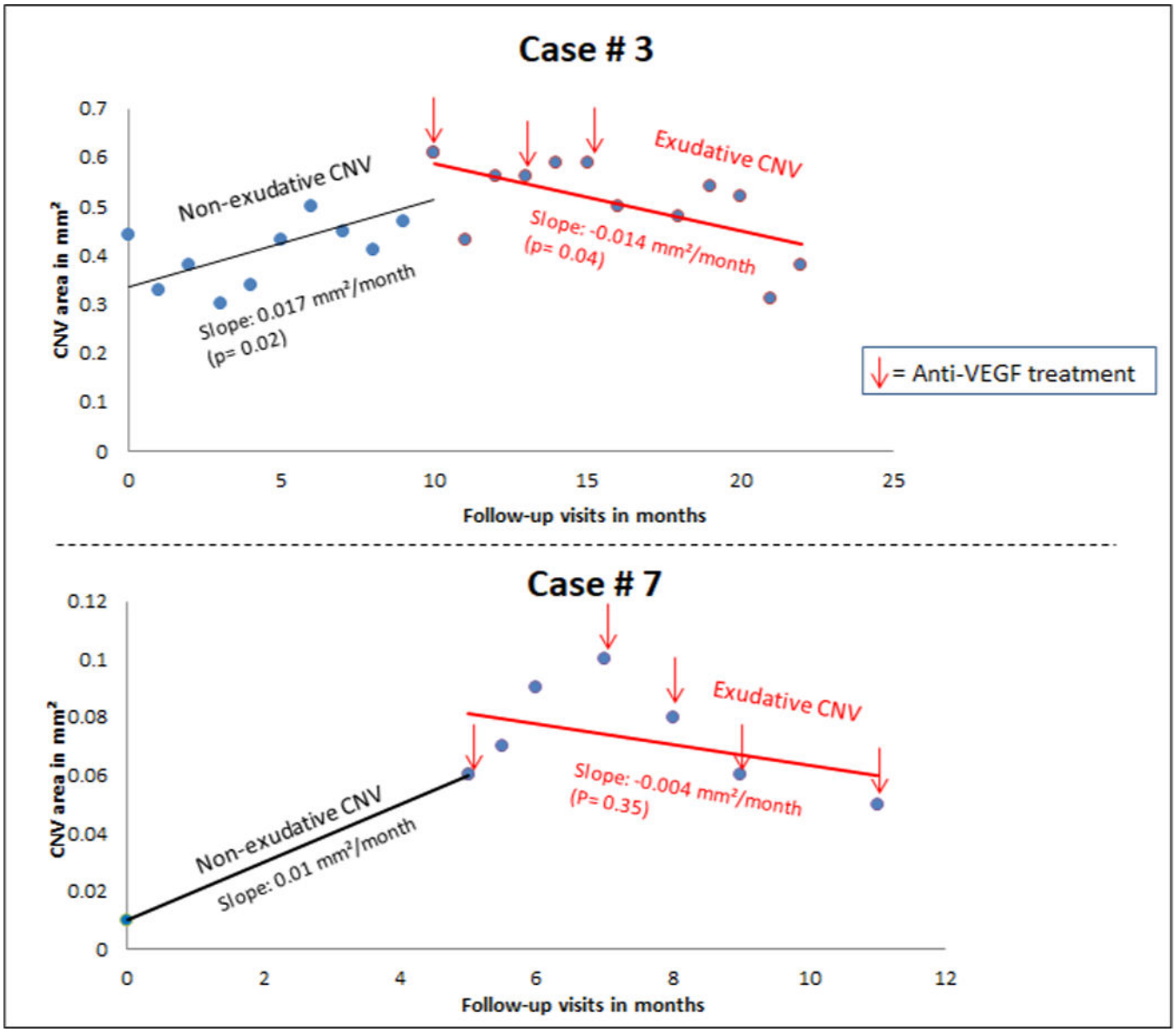

Figure 3:

Choroidal neovascularization (CNV) vessel area (mm^2) plotted over time (months) for Case #3 and Case #7. Non-exudative CNV slope (black line) calculated from first detection until exudation. Exudative CNV slope (red line) calculated from first signs of exudation to last follow-up while under pro-re-nata anti-vascular endothelial growth factor (VEGF) treatment (red arrows). Statistically significant ($P<0.05$) linear regression growth rate/month.

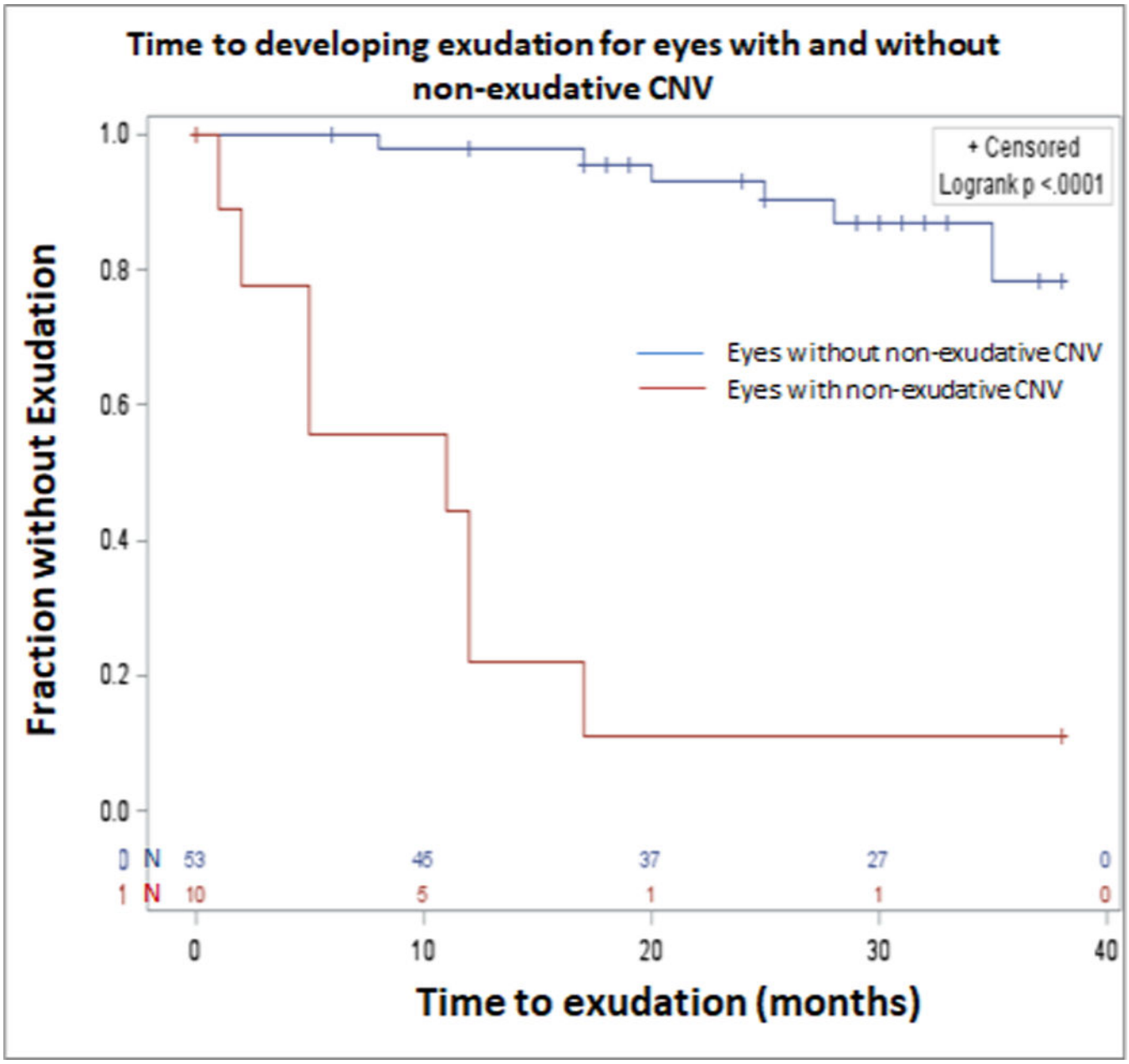

Figure 4:

Kaplan-Meier plots showing time to exudation for eyes with (red) and without (blue) OCTA-detected non-exudative CNV. For eyes with non-exudative CNV, baseline visit is defined when non-exudative CNV was first detected. N = number of subjects at risk.

Table 1:

Characteristics of Non-exudative Choroidal Neovascularization

Subject	Age (years)	CNV type	Baseline ETDRS VA	ETDRS VA at detection	EDTRS VA at exudation	Time to exudation (months)	Vessel area at detection (mm^2)	Vessel area at conversion (mm^2)	Linear growth rate (mm^2/ month)	Exponential growth rate (%/month)
1	82	1	20/40	20/32	20/32	2	0.05	N/A	-	-
2	81	1	20/32	20/32	20/25	1	0.01	N/A	-	-
3	77	1	20/25	20/50	20/63	11	0.44	0.61	0.02	4%
4	82	1	20/32	20/25	20/25	12	0.18	1.9	0.14	22%
5	66	1	20/40	20/50	20/50	4	0.09	0.21	0.03	20%
6	89	1	20/25	20/25	20/40	12	0.07	0.24	0.014	11%
7	79	3	20/20	20/20	20/50	5	0.01	0.06	0.01	43%
8	70	1	20/20	20/20	20/40	14	0.03	0.75	0.04	20%
9	67	1	20/32	20/32	N/A	N/A	0.36	N/A	0.01	2%
10	88	1	20/25	20/25	N/A	N/A	0.28	N/A	-	-

• ETDRS VA: Early Treatment Diabetic Retinopathy Study Visual Acuity

• Conversion indicates the initial detection of exudation in a previously nonexudative choroidal neovascularization (CNV)

• N/A – not applicable, no conversion to exudation during the study period.