Changes in Choroidal Thickness After Intravitreal Injection of Anti-Vascular Endothelial Growth Factor in Pachychoroid Neovasculopathy

Noel Padrón-Pérez,1 Luis Arias,1 Marcos Rubio,1 Daniel Lorenzo,1 Pere García-Bru,1 Jaume Catalá-Mora,1,2 and José M. Caminal1

Department of Ophthalmology. Bellvitge University Hospital, Barcelona, Spain
Department of Ophthalmology. Sant Joan de Déu Hospital, Barcelona, Spain

Purpose. We evaluate changes in choroidal thickness after intravitreal injection (IVI) therapy for pachychoroid neovasculopathy (PNV).

Methods. An observational, retrospective, consecutive case series was studied of 18 patients (18 eyes) who underwent anti-vascular endothelial growth factor (VEGF) therapy for PNV. The 18 fellow eyes in these patients were used as controls. All eyes were evaluated with swept-source optical coherence tomography (SS-OCT) and optical coherence tomography angiography (OCTA).

Results. Mean patient age was 68.3 ± 7.0 years. Mean follow-up was 16.4 ± 2.0 months. No differences in the best-corrected visual acuity (BCVA) of the affected eyes were observed between baseline and 12-month follow-up (median Early Treatment of Diabetic Retinopathy Study [ETDRS] score, 77.5 vs. 76 letters, P = 0.074; median logMAR, 0.22 vs. 0.22, P = 0.455). However, subfoveal choroidal thickness (SFCT) decreased significantly from a mean of 317.7 ± 39.9 μm at baseline to 266.9 ± 56.3 μm at 12 months (P ≤ 0.001). Median change in SFCT at 12 months was 44.0 μm (range, 17–153 μm). SFCT decreased by 16% from baseline to month 12. The change in SFCT at 12 months was highly correlated with the number of IVI (rs = 0.762, P ≤ 0.001). No significant changes in SFCT were observed in the fellow eyes over the 12-month study period (median, 267.5 vs. 267.0 μm; P = 0.930).

Conclusions. Choroidal thickness decreased significantly from baseline to month 12 in eyes with PNV treated with anti-VEGF injections. This reduction might be attributable to a reduction in choroidal vascular permeability and, thus, with a decrease in PNV activity. Prospective studies are needed to confirm these findings.

Keywords: pachychoroid neovasculopathy, pachychoroid clinical spectrum, choroidal thickness, anti-VEGF

Pachychoroid neovasculopathy (PNV) is considered a late complication of pachychoroid pigment epitheliopathy (PPE) and chronic central serous chorioretinopathy (CSC).1 Pachychoroid refers to an increase in choroidal thickness or dilation of the outer choroidal vessels (pachyvessels) with attenuation of choriocapillaris.1 PNV can be distinguished from neovascular age-related macular degeneration (AMD) by a relative absence of drusen, younger age at onset of neovascularization, and a thick choroid with pachyvessels. Elderly patients may display clinical characteristics of PNV and neovascular AMD, although a growing number of patients present in their 50s and 60s with well-defined pachychoroid characteristics without the presence of drusen.2

Recent advances in retinal imaging based on swept-source optical coherence tomography (SS-OCT) have enabled better structural and functional analysis of the choroid; thus, providing new insights into PNV. Optical coherence tomography angiography (OCTA), a new technique derived from en face OCT, also improves the noninvasive visualization of retinal and choroidal structure.3

Although several studies have shown changes in the subfoveal choroidal thickness (SFCT) after administration of intravitreal anti-vascular endothelial growth factor (VEGF) in patients with neovascular AMD,4–7 other studies have not found any changes.8–10 To our knowledge, no previous studies have investigated these changes in patients with PNV.

In this context, we evaluated changes in choroidal thickness in patients with PNV treated with anti-VEGF.

Methods

This was an observational, retrospective, consecutive case series study of patients diagnosed with PNV and treated with anti-VEGF intravitreal injections (IVI) at our institution between January 2014 and September 2016. The study was conducted in accordance with the tenets of the Declaration of Helsinki. Written informed consent was considered not necessary for the study, as it was a retrospective analysis of our usual everyday work. Patient data were anonymized for the purposes of this analysis. Patient confidentiality was protected according
national legislation. This study has been approved for publication by the Clinical Research Ethics Committee of Bellvitge University Hospital.

We studied 18 patients (18 eyes) diagnosed with unilateral PNV. The untreated fellow eyes (18) were used as controls. Inclusion criteria were diagnosis of PNV treated with anti-VEGF IVI and ≥12 months of follow-up. PNV diagnosis was based on the presence of type 1 neovascularization in patients without any features of AMD or other degenerative changes. All cases showed localized areas of choroidal thickening directly below the neovascular tissue in the affected eye and/or pachyvessels with attenuation of choriocapillaris with RPE abnormalities.

All patients underwent bilateral ophthalmologic examination, including measurement of best-corrected visual acuity (BCVA) assessed according to the Early Treatment Diabetic Retinopathy Study (ETDRS) criteria and converted to logMAR values, refractive error (spherical equivalent), anterior segment examination, dilated funduscopy, examination, fundus autofluorescence (FAF), SS-OCT, OCTA, and fluorescein angiography (FA). In uncertain cases, indocyanine green angiography (ICGA) also was performed to confirm the diagnosis.

The involved eyes were treated with ranibizumab 0.5 mg (Lucentis; Novartis, Basel, Switzerland) and/or aflibercept 2.0 mg (Eylea; Leverkusen, Germany) IVI with three consecutive monthly injections, after which additional treatment was administered using a pro re nata (PRN) regimen. Additional IVI were administered if persistent or recurrent subretinal or intraretinal fluid was visible on OCT and/or a new macular hemorrhage was detected. Fellow eyes were used as controls; importantly, note that none had received treatment at least 2 years before its inclusion in the study. This point is crucial because there were no differences between the groups at baseline or during follow-up except for the use of anti-VEGF injections.

At each consultation, which were scheduled monthly for ≥12 months, we performed BCVA testing, slit-lamp examination, and OCT imaging of the affected and fellow eyes. Choroidal thickness, defined as the distance from the outer portion of the hyperreflective line at RPE to the inner surface of the choroidal-scleral junction, was obtained for both eyes at baseline and at 1, 3, 6, 9, and 12 months.

SS-OCT equipment first became available at our department in the year 2013. The first SS-OCT unit was a prototype (Atlantis; Topcon Corporation, Tokyo, Japan), which was later replaced (April 2015) with the final commercial version of the SS-OCT and OCTA (Triton; Topcon Corporation). All patients were examined with this SS-OCT (Triton) and the final results were based on the findings obtained from this device that included the measurements acquired with the previous Atlantis model.

For the SS-OCT analysis, we used a three-dimensional (3D) scan pattern and a radial scan pattern consisting of 12 linear B-scans with a length of 12 mm centered on the fovea. The SS-OCT had a 1050 nm wavelength and a speed of 100,000 A-scans per second, with 20 μm lateral and 2.6 μm in-depth resolutions. For the OCTA, we performed 4.5 × 4.5 and 6 × 6 mm scans in all eyes with PNV (with eye tracking in the latest version) to improve image quality with fewer artifacts.

Choroidal thickness was calculated automatically and presented as a topographic map with nine subfields as defined by the ETDRS-style grid. The nine automatically calculated ETDRS subfields included central subfield thickness (defined as subfield choroidal thickness for choroid) in the inner ring, nasal parafoveal, superior parafocal, temporal parafocal, inferior parafocal, nasal perifoveal, superior perifoveal, temporal perifoveal, and inferior perifoveal, which were surrounded by rings measuring 1, 3, and 6 mm in diameter. Choroidal thickness is defined as the thickness from Bruch’s membrane to the inner scleral border. The automated scans were reviewed and any inaccuracies were corrected manually. To assess the results of the scan, the first author (N.P.P.) asked three of the researchers (L.A., M.R., D.L.; group 1) to evaluate the treated eyes from nine patients and the untreated fellow eyes from a different set of patients. The other three researchers (P.G.B., J.C.M., J.M.C.; group 2) were tasked with evaluating the remaining nine treated and nine untreated eyes. To ensure objectivity, all six of these clinicians were blinded initially to the purpose of the study, nor did they receive any information about the patients’ past ophthalmic history or diagnosis of the eye.

Both groups, working as individuals and as a group, used SS-OCT to measure the choroid and noted the presence or absence of intraretinal or subretinal fluid. Each group was assigned different dates for 18 eyes to take the measurements that corresponded at baseline, and months 1, 3, 6, 9, and 12. Groups 1 and 2 evaluated 216 images (108 per group). Group 1 manually corrected seven of these images while group 2 corrected nine images. To make the corrections, the researchers reviewed all vertical and horizontal scans and, by consensus agreement, corrected the inaccurate limits of the choriocapillaris and/or choroid. Once the margins had been redefined, a new grid was obtained with the correct measures.

All measurements were performed at the same time of day, between 8:30 and 11:30 AM, as confirmed by the computerized health records database. All SS-OCT data, including the time and date performed, are registered automatically in the system. In the present series, the treated and untreated eyes were evaluated at the same time (i.e., no more than 1.5 hours between all measures performed).

Patient clinical and demographic characteristics and follow-up data were recorded in a database file in the IBM-SPSS Statistics Program, v. 22 (IBM, Inc., Armonk, NY, USA). A descriptive analysis was performed and measures of central tendency (mean and median) and dispersion (standard deviation, range) were determined depending on the distribution of the variable (Shapiro-Wilk test). For quantitative variables, nonparametric tests (such as Wilcoxon) were used to evaluate changes in BCVA and to compare SFCT values measured at baseline and after anti-VEGF treatment. SFCT was assessed in the affected and fellow eyes.

Correlations between age, spherical equivalent, BCVA, number of IVI, and choroidal thickness change difference (defined as the difference between the mean baseline measure [V1] and mean final [V12] choroidal thickness) were assessed by the Rho Spearman’s rank correlation test. The percent change (Pch) in choroidal thickness (SFCT, parafoveal, and perifoveal) also was obtained (calculated as follows: Pch = V12 − V1/V1 * 100). A P value <0.05 was considered to be statistically significant.

**RESULTS**

A total of 36 eyes were included in the study (18 diagnosed with PNV and treated with anti-VEGF IVI and 18 untreated fellow eyes). The sample consisted of seven females (38.9%) and 11 males (61.1%). Mean age was 68.3 ± 7.0 years (range, 54–79 years). Table 1 shows the demographic and clinical characteristics of the sample.

Before IVI treatment, eight of the 18 eyes with PNV had a history of CSC (44.4%); two of these eight eyes had received IVI (bevacizumab) and one had been treated with photodynamic therapy ( PDT), and both had been treated two or more years before study inclusion. Most of the fellow eyes (16/18 eyes; 88.9%) had a history of one of the following entities included in the pachychoroidal clinical spectrum: CSC (five eyes,
27.8%), pachychoroid pigment epitheliopathy (four eyes, 22.2%), and polypoidal choroidal vasculopathy (seven eyes, 38.9%).

Eight (44.4%) of the fellow eyes had received prior treatment with either anti-VEGF IVI (seven eyes) or PDT (one eye). None of the fellow eyes received treatment during the follow-up period, nor had any received treatment in the 2 years before study inclusion. Mean refractive error (spherical equivalent) was −0.22 ± 1.31 diopters (D) in the affected eye and −0.19 ± 1.31 D in the fellow eye (P = 0.705; Table 1).

All 18 affected eyes presented with type 1 neovascularization (NV), diagnosed in all cases by FA and OCTA (once it became available). Median number of IVI was 7.5 (range, 4–12 injections). Median number of ranibizumab (0.5 mg) and aflibercept (2.0 mg) injections was 4.0 (range, 0–8 and 0–12, respectively). Eight eyes (44.4%) were treated alternately (switching from one drug to the other) with ranibizumab and aflibercept, while six (33.3%) and two (11.1%) eyes received aflibercept or ranibizumab alone, respectively (Table 1).

Mean follow-up was 16.4 ± 2.0 months (range, 13.1–20.2 months). Baseline BCVA (median letters) was 65 (range, 45–80). At 3, 6, 9, and 12 months, respectively, the median number of letters were 67 (40–82), 66 (40–81), 70 (40–80), and 72 (40–80). BCVA (logMAR) was 0.4 (range, 0.8–0.1) at baseline, 0.35 (range, 0.9–0.1) at months 3 and 6, and 0.3 (range, 0.9–0.1) at 9 and 12 months (Table 1). Compared to baseline, the BCVA (ETDRS) did not improve significantly at 3, 6, 9, or 12 months (P = 0.185, 0.796, 0.232, and 0.89, respectively). Similarly, no significant differences were observed in logMAR BCVA between baseline and months 3, 6, 9, and 12 (P = 0.171, 0.654, 0.522, and 0.380, respectively). Gains in letters were as follows: two eyes (11.1%) gained between one and five letters, five eyes (27.8%) gained between six and 10 letters, and six eyes (33.3%) gained more than 10 letters. In total, the BCVA improved in 13 of the treated eyes (72.2%) and did not improve in the remaining five eyes (27.8%). Of the five eyes that did not improve, three (16.7%) lost between six and 10 letters and two (11.1%) lost more than 20 letters. In the fellow eyes, no significant changes were observed between baseline BCVA and the 12-month follow-up (ETDRS: median, 77.5 letters [range, 48–84] vs. 76 letters [range, 46–84], P = 0.074; logMAR: median, 0.22 [range, 0.0–0.8] vs. 0.22 [range, 0.0–0.8], P = 0.455, respectively).

Of the 18 PNV eyes, 11 (61.1%) had an SFT ≥ 300 μm at baseline. Mean SFT decreased significantly from 517.7 ± 39.9 μm at baseline to 307.5 ± 40.5 μm at 1 month (P ≤ 0.001), 302.0 ± 42.4 μm at 3 months (P ≤ 0.001), 292.6 ± 47.9 μm at 6 months, 279.8 ± 54.3 μm at 9 months (P ≤ 0.001), and 266.9 ± 56.3 μm at 12 months (P ≤ 0.001). At 12 months, seven eyes (39.8%) had a SFT ≥ 300 μm. The change difference in SFT at 12 months was a median of 44.0 μm (range, 17–135 μm). At month 12, SFT had decreased by 16% versus baseline. The choroidal thickness in the parafoveal and perifoveal areas also showed a significant reduction compared to baseline measurements (Table 2).

The SFT change difference at 12 months was not correlated with BCVA (rs = 0.383, P = 0.117) or the spherical equivalent (rs = 0.121, P = 0.632) in the affected eyes, nor was the BCVA correlated with the number of IVI (rs = 0.2, P = 0.426); by contrast, the change in SFT was highly correlated with the number of IVI (rs = 0.762, P ≤ 0.001). The decrease in choroidal thickness in the parafoveal nasal, parafoveal temporal, and perifoveal nasal quadrants also correlated with the number of IVI (rs = 0.555 [P = 0.022], rs = 0.564 [P = 0.015], rs = 0.542 [P = 0.020], respectively).

Of the 18 fellow eyes, six (33.3%) had a SFT ≥ 300 μm at baseline versus seven (38.9%) at 12 months. Median SFT in the control eyes did not change significantly during the study period. Median SFT values were 207.5 μm (range, 169–318 μm) at baseline, 269.0 μm at 1 month (P = 0.326), 264.0 μm (range, 181–326 μm) at 3 months (P = 0.285), 269.5 μm (range, 173–335 μm) at 6 months, 267.0 μm (range, 172–320 μm) at 9 months (P = 0.327), and 267.0 μm (range, 172–320 μm) at 12 months (P = 0.930). Choroidal thickness in the parafoveal and

<table>
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<th>Patient Number</th>
<th>Age, y*</th>
<th>Sex</th>
<th>SE*</th>
<th>Number IVI</th>
<th>Follow-up Time, Mo*</th>
<th>Previous History, Affected Eye</th>
<th>Previous Treatment, Affected Eye</th>
<th>logMAR, Baseline†</th>
<th>logMAR, 12 Mo†</th>
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<td>CSC</td>
<td>-</td>
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MCT (SD or range) 68.3 ± or 7.5 (4–12) 16.4 ± 2.0 0.4 (0.8–0.1) 0.5 (0.9–0.1)

BCZ, bevacizumab; CSC, central serous chorioretinopathy; F, female; M, male; MCT, measures of central tendency; SE, spherical equivalent.
* Mean and SD were obtained for “Age,” “SE,” and “follow-up time.”
† Median and range were obtained for “Number IVI” and “logMAR” at baseline and at 12 month follow-up.

### Table 1. Demographic Characteristics and BCVA at Baseline and at 12-Month Follow-Up in Patients With PNV
perifoveal areas also remained unchanged versus baseline measurements (Table 2).

Significant differences between the treatment and control eyes were observed at baseline and at 1, 3, and 6 months ($P = 0.001$, $P = 0.002$, $P = 0.002$, and $P = 0.012$, respectively). By contrast, there were no significant differences at 9 and 12 months ($P = 0.316$ and $P = 0.695$, respectively; Fig.).

**DISCUSSION**

Reductions in choroidal thickness after anti-VEGF IVI therapy have been described previously in patients with neovascular AMD, but to our knowledge this is the first study to assess eyes with PNV involvement alone. Importantly, several studies have not found any changes in SFCT after anti-VEGF therapy. The main aim of our study was to evaluate changes in choroidal thickness in patients with PNV treated with anti-VEGF intravitreal injections. Our main finding was that choroidal thickness in the affected eyes decreased significantly after 12 months of anti-VEGF treatment. In addition, the number of injections was highly correlated with the decrease in choroidal thickness, with more injections leading to a greater decrease in thickness.

PNV is one of the conditions within the spectrum of diseases that include PPE, CSC, and polypoidal choroidal vasculopathy (PCV). Several studies have suggested that PCV may be a manifestation of longstanding type 1 neovascularization. Fung et al. in a retrospective series of 22 patients with longstanding CSC, observed polypoidal neovascular structures within the type 1 neovascular lesions and Pang et al. suggested that PNV could be considered a “forme fruste” of PCV that eventually could progress into PCV. Given this context, together with the fact that, to our knowledge, no previous publications have assessed changes in SFCT in patients with PNV alone, it seems reasonable to discuss our results in the context of similar studies that have analyzed changes in SFCT after anti-VEGF therapy in patients with...
conditions on the same disease spectrum, particularly PCV due to its similarity with PNV.

We found a significant posttreatment (12 months) reduction in SFCT and in choroidal thickness in the parafoveal and perifoveal areas in all 18 treated eyes, with a significant (16%) decrease in SFCT from baseline to month 12. We also found significant decreases in choroidal thickness in the nasal, temporal, inferior, and superior macular quadrants (parafoveal and perifoveal). By contrast, in the control group, we observed no changes from baseline in SFCT, parafoveal, or perifoveal thickness.

Koizumi et al.\(^4\) evaluated the short-term outcomes of IVI (aflibercept) for PCV in 91 eyes, finding that the mean SFCT decreased significantly from 270 µm at baseline to 232 µm at 3 months. Hikichi et al.\(^5\) prospectively assessed 89 consecutive eyes to determine the relation between changes in SFCT and outcomes after 12 months of ranibizumab IVI for PCV, and reported a significant reduction in mean SFCT (from 271 to 212 µm; \(P = 0.001\)). In addition, 12 months after the first IVI, the amplitude of change in the SFCT in eyes in which the polypoidal lesions had resolved was 89 ± 94 µm. Ting et al.\(^6\) also described changes in choroidal thickness at 12 months, reporting a reduction in SFCT in typical AMD (213.7 to 190.3 µm, \(P < 0.001\)) and PCV (240.8 to 231.4 µm, \(P < 0.01\)), representing a decrease of 11.2% and 11.6%, respectively, from baseline.

In our study, BCVA analysis was included as a secondary endpoint. We found no statistically significant changes in the affected eyes over the 12-month follow-up, although 11 of the 18 eyes (61.1%) gained more than five letters. In addition, we observed an improvement in the median BCVA in the treated eyes, which increased from 65 (baseline) to 72 (12-month follow-up visit) letters. However, note that two eyes lost more than 20 letters due to atrophy of the external retinal layers. Given that only 18 eyes were evaluated in our series, the impact of a large variation (e.g., the loss of >20 letters) in this small sample may have influenced the statistical significance of the nonparametric tests. To verify this hypothesis, we performed a Wilcoxon test that excluded cases #8 and #16 (both of which had lost more than 20 letters). That analysis revealed significant differences between BCVA at baseline and at the 12-month follow-up in treated eyes (\(P = 0.004\)). We also performed the same analysis excluding only case #8 (loss of 30 letters) and the result also was significant (\(P = 0.023\)). Similar results were obtained for logMAR BCVA, with significant differences between BCVA at baseline and 12-month follow-up when cases #8 and #16 were excluded (\(P = 0.006\)) and when only case #8 was excluded (\(P = 0.034\)).

Another important finding in this study is the significant correlation between the number of anti-VEGF injections and changes in choroidal thickness. The decrease in SFCT and choroidal thickness in some areas (parafoveal nasal, parafoveal temporal, and perifoveal nasal) was highly correlated with the total number of injections. However, BCVA was not correlated with the number of injections, nor with the change in SFCT at 12 months.

Although anti-VEGF IVI therapy appears to promote choroidal thinning, Ting et al.\(^6\) found no correlation between changes in SFCT and BCVA and the number of injections (by Pearson’s correlation test) over a 12-month period. Ting et al.\(^6\) found no association between age, refractive error, type of exudative AMD, number or type of anti-VEGF injections, and significant choroidal thinning. However, the results of that study should be interpreted cautiously given that few injections were administered between months 6 and 12 and most patients (77%) received bevacizumab. By contrast, in our study, each eye received at least four injections of ranibizumab or aflibercept, which might explain the differences in our outcomes versus those of Ting et al. However, Yamazaki et al.\(^3\) also failed to find any correlation between the change ratio from baseline to 12 months and the number of IVIs administered over the 12-month period (\(rs = 0.15, P = 0.42\)).

The mechanism of action underlying the decrease in choroidal thickness after anti-VEGF treatment may be due to a reduction in vascular permeability in PNV eyes. Given the similarities between PNV and PCV, we expected that PNV would display a similar response to anti-VEGF injection therapy, and our findings confirmed this. Ranibizumab has been shown to reduce the abnormal hyperpermeability of the choroidal vessels in PCV lesions,\(^5\) suggesting that ranibizumab (or aflibercept) could reduce the diameter of dilated choroidal vessels. Another possible mechanism of action that could explain the reduction in choroidal thickness during anti-VEGF treatment is decreased leakage from the PNV lesions. In a retrospective study involving 144 eyes (86 with PCV; 59.7%), Koizumi et al.\(^10\) evaluated SFCT after intravitreal aflibercept at 12 months. After a loading phase of 3-monthly 2.0-mg aflibercept, the patients were treated bimonthly (with additional rescue injections in cases with worsening), with a 13.3% decrease in SFCT from baseline (versus 16% in our study). In addition, mean SFCT in treated eyes decreased from 268.1 µm at baseline to 233.0 µm at 3 months and 232.4 µm at 12 months, a decrease of 35.7 mm over 12 months.

Choroidal thickness may vary with refractive status, age, and time of a day.\(^7\) Ting et al.\(^6\) defined significant choroidal thinning as a decrease of ≥16 µm, which is 10 times the annual
choroidal reduction rate (1.56 μm/year) reported previously.21 SFCT decreases by 15 μm for every 1 D increase in myopia.19 As noted above, the median reduction in SFCT in our sample was 44 μm over the 12-month study, a result that far exceeds expected age-related changes. The mean spherical equivalent was <1 D in affected eyes and, thus, the impact of myopia on choroidal thickness was likely to be minimal. In terms of diurnal variation in SFCT, given that the OCT was performed in all eyes between 8:30 and 11:30 AM, any effect is likely to be minimal. Although it is difficult to assure that the median decrease in SFCT (44 μm) observed in the eyes treated with anti-VEGF is clinically relevant (using SS-OCT), our data showed that the eyes treated with anti-VEGF presented a significant reduction in SFCT and other choroidal thickness areas compared to the untreated fellow eyes.

**Strengths and Limitations**

The main limitations of this study are its retrospective design and small sample size, which make it difficult to draw definitive conclusions. We did not evaluate separately the effect of each anti-VEGF because nearly half of the patients were treated with both drugs. An important strength of the study is the use of SS-OCT to evaluate PNV. SS-OCT uses a longer wavelength than conventional SD-OCT. Given that the main objective of our study was to evaluate the choroid, the advantage of this technology (SS-OCT) is that it can achieve deeper penetration and, thus, provide better imaging of choroidal structures.

**CONCLUSIONS**

Our study revealed a significant reduction in choroidal thickness after 12 months of anti-VEGF intravitreal injections in eyes with PNV. Since PNV is part of the pachychoroid clinical spectrum, the decreased choroidal thickness in our patients might be attributable to a reduction in choroidal vascular permeability. The total number of intravitreal injections was highly correlated with the decrease in choroidal thickness.

To our knowledge, this is the first study to assess changes in choroidal thickness in patients with PNV treated with anti-VEGF therapy. Further randomized controlled trials are needed to confirm the association between anti-VEGF treatment and changes in choroidal thickness in this patient population.

**Acknowledgments**

The authors thank Bradley Londres for editing and improving the manuscript.

Disclosure: N. Padrón-Pérez, None; L. Arias, Allergan (C), Bayer (C), Novartis (C); M. Rubio, None; D. Lorenzo, None; P. García-Brú, None; J. Catalá-Mora, None; J.M. Caminal, None

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