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Clinical Features and Optical Coherence Tomography Angiography in Neovascular Age-Related Macular Degeneration and Pachychoroid Neovasculopathy

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Abstract

Purpose: To investigate differences in baseline characteristics, outcomes, and metrics of swept-source optical coherence tomography (SS-OCT) angiography between drusen-associated neovascular age-related macular degeneration (nAMD) vs pachychoroid neovasculopathy. **Methods:** This prospective cohort study enrolled 1 eye per patient with treatment-naïve nAMD or pachychoroid neovasculopathy who underwent 3 monthly bevacizumab injections followed by a treat-and-extend regimen for 12 months or longer. Eligible patients were classified into 2 groups: those with drusen-associated nAMD and those with pachychoroid neovasculopathy. Drusen-associated nAMD refers to macular neovascularization (MNV) or polypoidal lesions surrounded by subretinal drusenoid deposits or soft drusen 63 μm or larger in diameter. The outcomes were collected at baseline, 6 months, and 12 months. **Results:** Patients with drusen-bordering MNV (51 cases) were older (mean 69.6 years vs 64.2 years) and had a smaller ratio of low-density to high-density lipoprotein cholesterol (mean 1.85 vs 2.14), longer daily sleep hours (mean 7.03 hours vs 6.07 hours), a smaller proportion of patients with a history of central serous chorioretinopathy (CSCR) (0% vs 12.5%), and smaller baseline central choroidal volume compared with those with pachychoroid neovasculopathy (57 cases). At 12 months, eyes with drusen exhibited a lower choroidal vascularity index, larger foveal thickness (mean 327 μm vs 273 μm), and more antivascular endothelial growth factor injections per year (mean 7.0 vs 5.2) compared with eyes with pachychoroid neovasculopathy. Regarding secondary outcomes, a closed-circuit vascular pattern was associated with persistent retinal fluid at study completion. **Conclusions:** Patients with pachychoroid neovasculopathy appear to carry some systemic risk factors for CSCR, whereas patients with drusen-related nAMD had inferior responses to bevacizumab monotherapy and greater choriocapillaris hypoperfusion (characterized by thinner choroidal volume and lower choroidal vascularity index values).

Keywords
avastin, drusen, MNV, OCTA, pachychoroid, PLEX Elite

Introduction

The clinical appearance of age-related macular degeneration (AMD) can vary among patients, but those with advanced-stage AMD may share some characteristics that typically belong to neovascular AMD (nAMD), including choriocapillaris alterations, retinal pigment epithelium (RPE) atrophy, and macular neovascularization (MNV).[1,2]

In early-stage AMD, the development of either soft drusen secondary to basal linear deposits or subretinal drusenoid deposits has been marked as a transition from the normal degenerative process to a pathological change.[3] The geographic distribution of choroidal insufficiency or genetic factors may contribute to the dissimilar phenotypes of these 2 varieties of common drusen. Following a long history of macular drusen, the choriocapillaris likely becomes depleted, giving rise to neovascular choroidal vessels. Although both features can be expressed within the same AMD spectrum, the progression of drusen has been associated with dysregulated lipid metabolism,[4] whereas neovascular complications were found to be driven by several other contributors, including outer retinal hypoxia.[5]

In recent years, pachychoroid-driven nAMD or pachychoroid neovasculopathy were distinguished from typical drusen-associated nAMD due to their differences in pathogenicity.

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Nonetheless, AMD classifications and the definitions of each element in the pachychoroid spectrum have remained ill-defined because of the nuances in overlapping features, such as polypoidal lesions or the optical coherence tomography (OCT)–graded classification of MNV, which could alter treatment outcomes.[6,7] Apart from genetic factors, little is known about the complexity of the pathophysiology and modifiable risk factors between these 2 entities.[8] Therefore, we aimed to determine differences in comprehensive characteristics at baseline examination, treatment outcomes, and findings of swept-source OCT (SS-OCT) angiography between drusen-related nAMD and pachychoroid neovasculopathy. We also investigated OCT angiography (OCTA) morphologies during the post–antivascular endothelial growth factor (anti-VEGF) loading visits that correlated with suboptimal responses to anti-VEGF therapy over a 12-month period.

Methods

Participants

This prospective cohort study included 1 eye per patient aged 50 years or older with treatment-naïve nAMD who had a best-corrected visual acuity (BCVA) between 20/40 and 20/320 and subsequently received bevacizumab for a minimum of 12 months. All participants who met inclusion criteria were consecutively enrolled from September 2021 to April 2023. To circumvent problems originating from codependent variables in each patient, the worse-seeing eye was selected in cases of bilateral nAMD.

nAMD refers to eyes with MNV, pachychoroid neovasculopathy, or polypoidal lesions. Drusen-associated nAMD refers to eyes with neovascular complications surrounded by subretinal drusenoid deposits or intermediate to large soft drusen according to the Age-Related Eye Disease Study (size ≥63 μm in diameter). Discrete pachydrusen was precluded from this group because of different pathogeneses.[9] The diagnosis of subretinal drusenoid deposits was confirmed with nearly infrared and fundus autofluorescence, in addition to standard fundus photography and OCT. Eyes with a mixture of soft drusen and subretinal drusenoid deposits were coded as having subretinal drusenoid deposits due to the association with reduced choroidal vascular index and increased risk of advanced AMD.[10,11]

Patients with cuticular drusen or refractile drusen were excluded due to the small number of cases. We also excluded type 3 MNV or retinal angiomatous proliferation due to the specific nature of refractory diseases. Additional exclusion criteria encompassed patients with the following conditions: obscuring imaging views, submacular fibrosis, pathological myopia, MNV secondary to non-AMD conditions. Patients with a history of intraocular surgery, macular laser, ocular trauma, or uveitis also were excluded if these incidents occurred within 12 months before the study initiation.

Pachychoroidopathy is characterized by the presence of either subfoveal choroidal thickness greater than 270 μm with enlarged choroidal vascular lumens in the Haller layers (pachyvessels),[6] or one of the pachychoroid-related findings comprising pachychoroid pigment epitheliopathy, pachydrusen, choroidal excavation, central serous chorioretinopathy (CSCR), or choroidal vascular hyperpermeability seen on indocyanine green angiography (ICGA).

Treatment

Eligible patients were treated with 3 monthly loading injections of 1.25 mg/0.05 cc bevacizumab, followed by monthly injections, until subretinal fluid (SRF) or intraretinal fluid (IRF) disappeared. Patients then received a treat-and-extend regimen with an extension of the follow-up interval in 2-week increments. Shallow serous pigment epithelial detachment (PED) with a maximum height of less than 200 μm unaccompanied by SRF, IRF, a double layer sign,[12] or polypoidal lesions seen on ICGA was tolerated if the size remained unchanged throughout the treatment. In the absence of polypoidal lesions, we substituted bevacizumab with 2 mg/0.05 cc aflibercept when there was an increase in SRF or IRF after 6 consecutive bevacizumab injections (including 3 initial loading doses). All patients who underwent a switch of anti-VEGF agents were excluded from the analysis of the 12-month outcomes.

Outcome Measurements

The primary outcome was the comparison of baseline ocular and systemic biomarkers between drusen-related nAMD and pachychoroid neovasculopathy. Secondary outcomes were differences in the treatment results, SS-OCTA metrics (PLEX Elite 9000, Carl Zeiss Meditec), and the OCTA patterns of MNV between the 2 groups. Collected data included demographic data, current medications, medical history, risk factors associated with systemic vascular diseases or pachychoroidopathy, drusen subtypes, and the presence of pachychoroid disorders in the fellow eyes. Sleep duration was determined by averaging the number of hours slept over 3 nights (1 night per week) between the first and second follow-ups. Despite polysomnography being the gold standard for sleep measurements, this study opted for digital wrist actigraphy for its more naturalistic approach, enabling at-home monitoring.[13] Concerning the systemic laboratory, while the association is established only for high-density lipoprotein cholesterol and drusen, not low-density lipoprotein cholesterol, the ratio of low-density lipoprotein cholesterol to high-density lipoprotein cholesterol was included as 1 of the baseline risk factors because this parameter is becoming increasingly recognized for its connection to cardiovascular and other systemic vascular diseases.[14,15] Standard ocular and structural OCT (Spectralis, Heidelberg Engineering) parameters related to AMD were collected at baseline, 6 months, and 12 months.

Simultaneous fluorescein angiography and ICGA were performed at baseline examination. OCTA images were obtained at the third month after the anti-VEGF loading visits to prevent

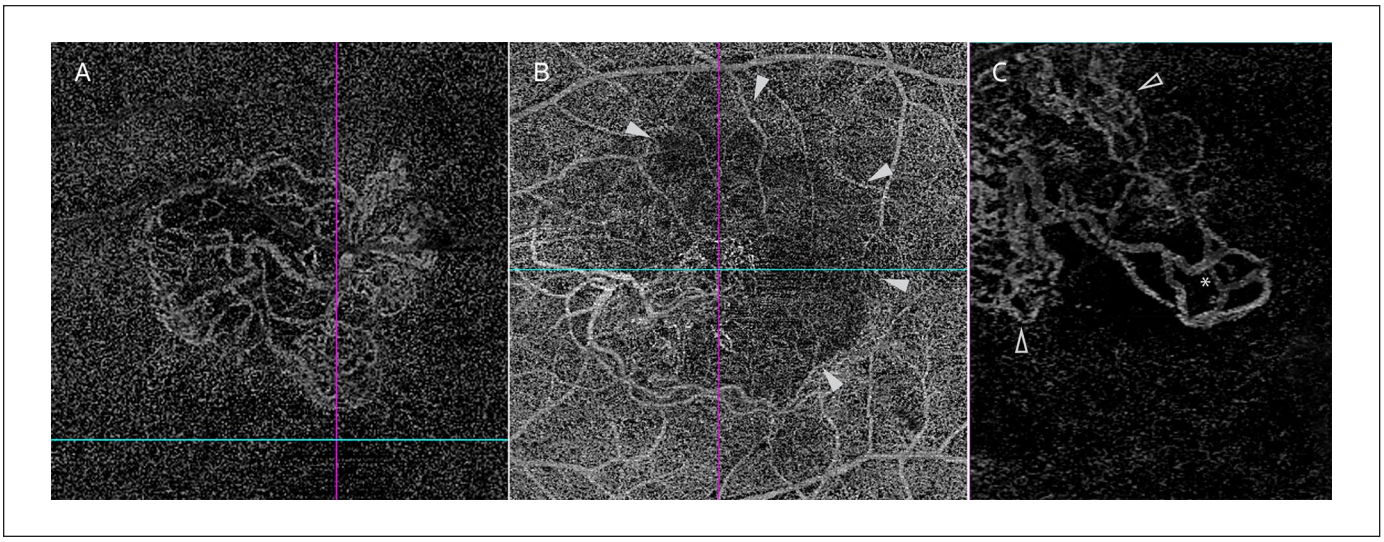

Figure 1. Swept-source optical coherence tomography angiography images depicting 3 types of macular neovascularization (MNV) patterns. (A) Well-demarcated tangled MNV with >50% of identifiable borders. (B) A choriocapillaris halo (solid arrowheads) encircling >50% of the MNV outline. (C) A closed-circuit vascular pattern (asterisk) connected to the neovascular complex (hollow arrowheads).

obscured view or segmentation errors due to the retina swelling that can occur during initial presentation. Selected images drawn from the 6×6 mm^2 scans were uploaded to the online software provided by the ZEISS Advanced Research and Innovation Network, which automatically analyzed the submitted images and reported the metrics, including a 3 mm^2 choroidal volume, 3 mm^2 PED volume, and central 5 mm^2 choroidal vascular index. Using the 6 × 6 and 3 × 3 mm^2 scans, the clearest images (offering the most complete outline of the entire MNV complex) taken from the choriocapillaris level, or those slightly anterior, were chosen to classify the MNV structures as follows: (1) well, circumscribed, sea fan–shaped vessels with more than 50% of identifiable MNV borders; (2) the presence of choriocapillaris dropout or halo encircling more than 50% of the total MNV outline; and (3) MNV feeder vessels in a loop pattern situated within 500 μm of the fovea and adjacent to the capillary fringe or filamentous vessels (Figure 1).[16]

Notably, the previously described entity termed the "branching neovascular network" may appear partly similar to the loop vascular pattern in this study; however, its morphology is highly variable and depends on the type of imaging device.[2,17] Each patient was allowed to have 0 to 3 patterns. To ensure the accuracy of the results, only OCTA images with an adequate resolution of more than 50% of the total MNV area were included and were graded separately by A.K. and Y.C. When any discrepancies in the results arose, we consulted another retina specialist who was not involved in the study.

Statistical Analysis

Subfoveal choroidal thickness is 1 of the main results that is measurable and has been thoroughly investigated. Hence, we based the sample size calculation on a previous study observing a mean ± SD subfoveal choroidal thickness in the pachychoroid neovasculopathy of 300 ± 79 μm. Based on our retrospective data, we expected that baseline subfoveal choroidal thickness in eyes with drusen-associated nAMD would decrease by 20% compared with those with pachychoroid neovasculopathy.[18,19] Using Stata, a sample size of at least 32 eyes per group was calculated to have 80% power to detect the proposed difference at a 2-sided 0.05 level using a 2-sample *t* test. All mean values are ± SD.

To determine the differences in 12-month Early Treatment Diabetic Retinopathy Study (ETDRS) letter gain between the 2 groups, we performed a multivariate linear regression analysis controlling for age, baseline logMAR BCVA, and total number of anti-VEGF injections. Regarding the analysis of central subfield thickness (CST) and PED volume, the multivariate linear regression was adjusted for age, baseline MNV areas, total number of injections, and their baseline values (PED height or central foveal thickness, respectively). The persistency of retinal fluid after 1 year was classified as SRF or IRF. A mixture of both types was labeled as IRF, as this suggests a more advanced stage of the disease and poorer visual outcomes.[20–22] Regarding changes in subfoveal choroidal thickness, we performed a multivariate linear regression analysis adjusting for mean arterial pressure and age. The mixed effect model was not used in this analysis due to a lack of sufficient time points, particularly the exclusion of the baseline, which resulted in an inadequate ability to detect the progression rates of outcomes.

For the secondary outcome, we applied a multiple logistic regression to identify OCTA patterns at the 3-month follow-up that were associated with a persistency in SRF or IRF at 12 months. Patients who had incomplete or suboptimal responses to anti-VEGF therapy were defined as those whose 12-month change in BCVA did not exceed 5.2 ETDRS letters—the cut-off

Table 1. Demographic and Baseline Characteristics.

Variable	Drusen-Bordering Macular Neovascularization (n=51)	Pachychoroid Neovasculopathy (n=57)	*P* Value
Demographics and medical history			
Mean age (y) ± SD	69.6 ± 9.7	64.2 ± 8.9	.004
Female, n (%)	21 (36.8)	30 (58.8)	.41
Mean BMI (kg/m^2) ± SD	25.89 ± 3.91	24.67 ± 4.33	.13
Hypertension, n (%)	27 (47.37)	33 (64.71)	.93
Mean arterial pressure ± SD	97.2 ± 11.9	98.7 ± 10.7	.48
Dyslipidemia, n (%)	25 (43.8)	32 (62.7)	.74
Obstructive sleep apnea			.13
Total patients	n = 46	n = 53	
n (%)	2 (4.35)	7 (13.2)	
Mean sleep duration (h/d) ± SD	7.03 ± 1.55	6.07 ± 1.31	.053
History of prolonged steroid use[a]			.24
Total patients	n = 47	n = 55	
n (%)	11 (23.4)	18 (32.7)	
Smoking >15 pack-years			.33
Total patients	n = 46	n = 53	
n (%)	21 (46.65)	20 (37.74)	
Antiplatelet use			.66
Total patients	n = 47	n = 55	
n (%)	9 (19.15)	13 (23.64)	
History of central serous chorioretinopathy			.046
Total patients	n = 46	n = 48	
n (%)	0 (0)	6 (12.5)	
Mean systemic laboratory values ± SD			
Complete blood count			
Platelet count (×1000)	235 ± 78	245 ± 60	.52
Mean platelet volume	9.45 ± 0.86	9.62 ± 0.86	.41
Lipid profile (mg/dL)			
Total cholesterol	179.8 ± 44.3	179.2 ± 41.5	.95
Triglyceride	118.5 ± 58.4	144.9 ± 73.2	.11
Low-density lipoprotein cholesterol	96.4 ± 29.5	106.6 ± 36.8	.08
High-density lipoprotein cholesterol	58.34 ± 17.6	54.0 ± 16.0	.13
Low-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio	1.85 ± 0.78	2.14 ± 0.98	.05

Abbreviation: BMI, body mass index.
[a]Prolonged use of systemic, nasal, or topical steroids ≥12 months.

value that was determined from the receiver operating characteristic curve and consistent with the definitions established in previous studies.[23,24]

Results

Demographic and Systemic Characteristics

After excluding patients who matched the exclusion criteria, 108 of the initial 133 eligible patients remained. Eighteen patients, excluded from the study due to the regimen switching (7 eyes and 11 eyes in the drusen-associated MNV and pachychoroid neovasculopathy groups, respectively), received aflibercept injections with a variable interval ranging from 5 to 8 weeks throughout the 12-month period. Compared with the patients with pachychoroid neovasculopathy (57 eyes), those with drusen-bordering MNV (51 eyes) were statistically older (69.6 ± 9.7 years vs 64.2 ± 8.9 years), had a smaller low-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (1.85 ± 0.78 vs 2.14 ± 0.98), longer daily sleep hours (7.03 ± 1.55 hours vs 6.07 ± 1.3 hours), and a smaller proportion of cases with CSCR history (0% vs 12.5%) (Table 1, Figure 2, Supplemental Figure S2).

Among the patients with drusen, eyes with subretinal drusenoid deposits demonstrated a trend toward greater mean high-density lipoprotein cholesterol (63.3 mg/dL vs 54.6 mg/dL) and lower triglyceride levels (97.0 mg/dL vs 120.5 mg/dL), compared with those with soft drusen. Nonetheless, after controlling for age, sex, and use of statins, these differences were not sustained. The mean subfoveal choroidal thickness of eyes with subretinal drusenoid deposits was significantly thinner

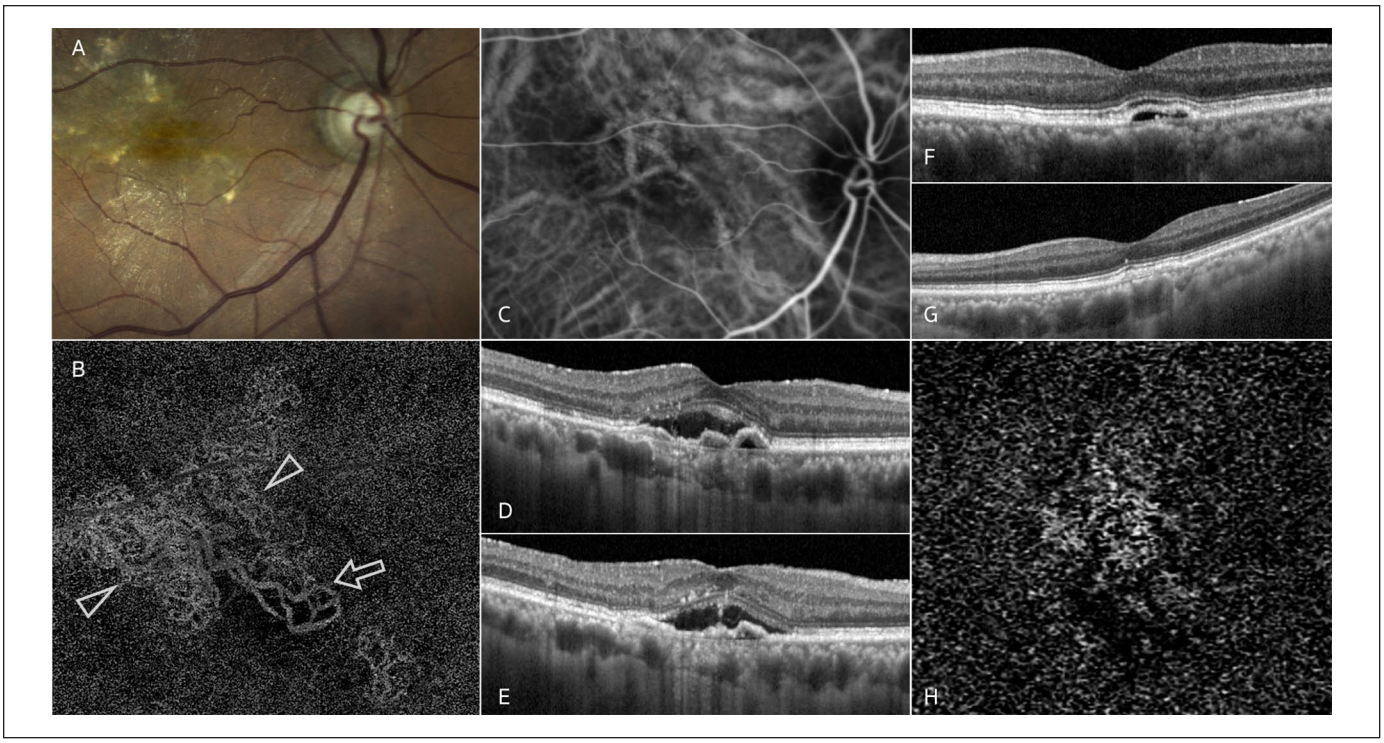

Figure 2. Multimodal images of 2 patients, a younger and older sibling, both diagnosed with normotensive glaucoma, pachychoroid neovasculopathy, and pachychoroidopathy in the fellow eyes without neovascular age-related macular degeneration (nAMD). (A) A 64-year-old man with a history of heavy smoking (66 pack-years) presented with subretinal fluid complicating nAMD. Average sleep duration was 5 hours 30 min, and his low-density lipoprotein cholesterol (132 mg/dL) to high-density lipoprotein cholesterol (34 mg/dL) ratio was 3.88. (B) A 6 × 6 mm^2 scan of the optical coherence tomography angiography (OCTA) image revealed a closed-circuit vascular pattern (arrow) connected to the neovascular complex (arrowhead). (C) These findings were not detected by conventional indocyanine green angiography. (D) Subretinal fluid (SRF) at baseline examination (E) resolved after 3 initial loading injections of bevacizumab. (E) However, the fluid recurred every time the follow-up interval was extended from 4 to 6 weeks, resulting in persistent SRF at 12 months. (F) A 75-year-old man without a history of smoking presented with progressive enlargement of double-humped pigment epithelial detachment. (G) It completely resolved after 3 injections of bevacizumab. His average sleep duration was 7 hours 30 min (recorded by wrist actigraphy), and his low-density lipoprotein cholesterol (105 mg/dL) to high-density lipoprotein cholesterol (42 mg/dL) ratio was 2.5. (H) A 3 × 3 mm^2 scan of the OCTA image showed poorly defined, fine capillary strands underneath the fovea.

than in those with soft drusen (150 μm vs 206 μm; adjusted difference, 71.0 μm; $P < .001$).

Ocular Features

There was a trend toward greater proportions of pachychoroidopathy (47.3% vs 33%) in the fellow non-nAMD eyes of patients with pachychoroid neovasculopathy (Table 2, Figure 2, Supplemental Figures S2 and S3). Likewise, patients with drusen had a smaller mean central 3 mm^2 choroidal volume at baseline examination. These dissimilarities were observed in both nAMD eyes and the fellow eyes (1.65 mm^3 vs 2.0 mm^3 and 1.46 mm^3 vs 1.95 mm^3, respectively). Further analysis revealed that the baseline 5 mm^2 choroidal vascular index values were comparable between the 2 groups; however, as the treatment period progressed, these results for both arms gradually diverged, whereby the drusen group showed lower 12-month choroidal vascular index values after we implemented a linear regression analysis adjusted for age, MNV area, and mean arterial pressure (Table 3).

Treatment Outcomes

After adjusting for age, baseline MNV areas, and numbers of bevacizumab injections, we found that patients with drusen had thicker 1 mm^2 CST than that seen in the pachychoroid neovasculopathy group at 6 and 12 months (327 ± 154 μm vs 273 ± 83 μm) and showed a trend toward persistent retinal fluid (51.3% vs 28.2%; $P = .08$) at 12 months. Specifically, the presence of IRF tended to be more prevalent in the drusen cohort after 12 months (7/37 eyes [18.9%] vs 3/39 eyes [7.7%]; $P = .07$) (Table 2).

After controlling for age, baseline BCVA, and numbers of bevacizumab injections, we observed that eyes with pachychoroid neovasculopathy showed greater visual improvement in the first 6 months; however, this difference was not sustained at the 12-month follow-up. The visual outcomes and CST remained similar even with the inclusion of polypoidal lesions as a controlled variable. Notably, the improvement in BCVA at 12 months was comparable between the 2 groups, despite the patients with pachychoroid neovasculopathy receiving fewer

Table 2. Comparisons of Clinical Outcomes and Standard Ocular Parameters.

Ocular Parameters	Drusen-Associated Macular Neovascularization (n = 51)	Pachychoroid Neovasculopathy (n = 57)	P Value	Adjusted Difference (95 % CI)
Reticular pseudodrusen, n (%)	14 (27.4)	N/A	N/A	
Large submacular hemorrhage during presentation, %[a]	4.5 (3/66 eyes)	17.9 (12/67 eyes)	.02	
OCT-based type 1 MNV, n (%)	35 (68.6)	39 (68.4)	.96	
Polypoidal lesions on ICGA, n (%)			.12	
Total patients	n = 37	n = 43		
n (%)	8 (21.6)	21 (48.8)		
Pachychoroid diseases in the fellow eye, n (%)[b]	17 (33.3)	27 (47.3)	.08	
Geographic atrophy (%)				
Baseline	8 (15.6)	7 (12.2)	.61	
12 months	11 (21.5)	8 (14.0)	.12	
Mean best-corrected visual acuity (logMAR) ± SD				
Baseline	0.77 ± 0.58	0.69 ± 0.58	.49	
6-month[c]	0.66 ± 0.43	0.45 ± 0.48	.01	0.18 (0.14-0.32)
12-month[c]	0.64 ± 0.49 (37 eyes)	0.51 ± 0.61 (39 eyes)	.11	0.07 (−0.15 to 0.28)
12-month changes[d]	−0.18 ± 0.21	−0.30 ± 0.61	.24	
Mean 1 mm^2 central subfield thickness (nAMD eyes) ± SD				
Baseline	402 ± 173	411 ± 202	.80	
6 months[e]	322 ± 122	279 ± 92	.01	48 (11-85)
12 months[e]	327 ± 154 (37 eyes)	273 ± 83 (39 eyes)	.05	53 (12-105)
12-month changes[d]	−161 ± 244	−225 ± 240	.21	
Presence of SRF or IRF[d]				
6 months (%)			.10	
Total patients	n = 43	n = 49		
n (%)	24 (55.8)	19 (38.8)		
12 months (%)			.08	
Total patients	n = 37	n = 39		
n (%)	19 (51.3)	11 (28.2)		
Persistent SRF at 12 months[d]			.32	
Total patients	n = 37	n = 39		
n (%)	12 (32.4)	8 (20.5)		
Persistent IRF with or without SRF at 12 months[d]			.07	
Total patients	n = 37	n = 39		
n (%)	7 (18.9)	3 (7.7)		
Mean subfoveal choroidal thickness (μm) ± SD				
Baseline[f]				
nAMD eye	227 ± 101	295 ± 114	.03	−44 (−85 to −4)
Fellow eye	229 ± 88	280 ± 122	.18	
12 months[f]				
nAMD eye	220 ± 93	286 ± 111	.19	
Fellow eye	225 ± 91	312 ± 134	.07	−50 (−106 to 5)
12-month changes[f]				
Total eyes, n	37	39		
nAMD eye	−65 ± 111	−101 ± 133	.20	
Fellow eye	−64 ± 101	−64 ± 122	.95	
Subretinal fibrosis involving fovea at 12 months			.71	
Total patients	n = 37	n = 39		
n (%)	4 (10.8)	5 (12.8)		
Mean total injections of anti-VEGF ± SD	7.02 ± 2.83	5.19 ± 2.72	.002	2.06 (0.86-3.27)

Abbreviations: anti-VEGF, antivascular endothelial growth factor; ICGA, indocyanine green angiography; IRF, intraretinal fluid; MNV, macular neovascularization; nAMD, neovascular age-related macular degeneration; OCT, optical coherence tomography; SRF, subretinal fluid.

[a]Incidence was calculated using the initial 133 enrolled patients. A large submacular hemorrhage refers to a hemorrhagic pigment epithelial detachment or subretinal blood presenting with a maximal height of >1000 μm. Some of these eyes were excluded from the subsequent analysis because they underwent pneumatic displacement combined with switched anti-VEGF agents.

[b]Pachychoroid pigment epitheliopathy, retinal pigment epithelium alteration, central serous chorioretinopathy, or focal choroidal excavation.

[c]Analysis controlled for age, baseline best-corrected visual acuity, and total number of injections.

[d]Analysis controlled for age and total number of injections.

[e]Analysis of 1 mm^2 central subfield thickness (CST) was controlled for age, baseline CST values, and total number of injections.

[f]Analysis of mean choroidal thickness at baseline examination and its 12-month changes were controlled for age and mean arterial pressure, whereas the analysis at the 12-month follow-up was controlled for age, mean arterial pressure, and baseline values.

Table 3. Comparisons of OCTA Measurements.

OCTA Metrics	Drusen-associated Macular Neovascularization (n = 51)	Pachychoroid Neovasculopathy (n = 57)	*P* Value	Adjusted Difference (95% CI)
Baseline MNV areas (mm^2)	3.072	2.638	.14	
Mean pigment epithelial detachment volume (mm^3) ± SD	0.26 ± 0.31	0.18 ± 0.29	.20	
Mean central 3 mm^2 choroidal volume (mm^3) ± SD				
Baseline[a]				
nAMD eye	1.65 ± 0.76	2.0 ± 0.84	.03	0.09 (0.03-0.22)
Fellow eye	1.46 ± 0.71	1.95 ± 0.84	.002	0.30 (0.004-0.60)
12 months[a]				
nAMD eye	1.57 ± 0.69	1.92 ± 0.87	.10	
Fellow eye	1.69 ± 0.83	2.05 ± 0.83	.11	
12-month change[a]				
nAMD eye	−0.82 ± 0.94	-0.99 ± 1.13	.40	
Fellow eye	−0.44 ± 0.95	-0.94 ± 1.30	.02	0.36 (0.09-0.81)
Mean central 5 mm^2 choroidal vascularity index ± SD				
Baseline[b]				
nAMD eye	0.58 ± 0.02	0.58 ± 0.03	.65	−0.003 (−0.014 to 0.008)
Fellow eye	0.58 ± 0.05	0.59 ± 0.05	.31	
6 months [b]				
nAMD eye	0.55 ± 0.02	0.58 ± 0.03	.28	−0.03 (−0.06 to 0.02)
Fellow eye	0.58 ± 0.05	0.59 ± 0.02	.59	
12 months [b]				
nAMD eye	0.53 ± 0.02	0.57 ± 0.03	.053	−0.03 (−0.08 to −0.004)
Patterns of neovascular complex based on OCTA findings				
Well circumscribed with >50% demarcation of sea fan–shaped vessels			.12	
Total patients	n = 29	n = 31		
n (%)	8 (27.6)	15 (48.4)		
Looped vessels adjacent to the MNV			.57	
Total patients	n = 29	n = 31		
n (%)	18 (62.0)	17 (54.8)		
Choriocapillaris halo (%)			0.29	
Total patients	n = 28	n = 31		
n (%)	20 (71.4)	18 (58.1)		

Abbreviations: MNV, macular neovascularization; nAMD, neovascular age-related macular degeneration; OCTA, optical coherence tomography angiography.
[a]Analysis of mean choroidal thickness at the baseline visit and its 12-month changes were controlled for age and mean arterial pressure; the analysis at 12-month follow-up was controlled for age, mean arterial pressure, and baseline values.
[b]Analysis of 5 mm^2 choroidal vascular index was adjusted for age, choroidal neovascularization areas, and mean arterial pressure.

anti-VEGF injections (5.2 ± 2.7 vs 7.0 ± 2.8 injections per year) (Table 2).

OCTA Characteristics

There were no significant discrepancies in OCTA patterns between the 2 groups; thus, we combined all OCTA images to determine the patterns potentially associated with the 12-month outcomes. Among the MNV patterns at the postloading visits, after controlling for age, baseline CST, and MNV areas, we noted an association between the closed-circuit vascular pattern connected to the neovascular complex and the persistence of SRF or IRF at the 12-month evaluation (adjusted odds ratio, 2.22), regardless of drusen subtype (Supplemental Table S1, Figure 2). There was no OCTA pattern associated with a 12-month visual improvement of 5.2 ETDRS letters or less (Supplemental Table S2).

After including patients who underwent a switch of anti-VEGF agents into the analysis, patients with pachychoroid neovasculopathy (68 eyes) exhibited more sleep apnea (10/64 eyes [15.6%] vs 2/53 eyes [3.7%]; $P = .04$) and greater number of well-circumscribed MNV areas (20/42 [47.6%] vs 9/36 [25%; $P = .02$), compared with the drusen group (58 eyes). The pachychoroid neovasculopathy cohort also showed a trend toward smaller baseline MNV areas (2.58 mm^2 vs 3.18 mm^2; $P = .08$) and a higher incidence of subretinal fibrosis at 12 months (10/50 [20% vs 4/44 eyes [9.1%]; $P = .06$).

Conclusions

In this study, patients with drusen-associated nAMD exhibited some clinical features and results of treatment that were different than those with pachychoroid neovasculopathy. Patients with pachychoroid neovasculopathy were younger than those with typical drusen, which concurs with the results of a previous study and could suggest that, apart from degenerative processes, there may be additional factors that affect the development of MNV.[7,25] Specifically, some risk factors of CSCR presented in a significant number of individuals with pachychoroid neovasculopathy.[8] These included ocular features such as increased choroidal volume or the presence of pachychoroidopathy in the fellow eyes as well as some systemic risk factors, such as chronic sleep deprivation and history of CSCR, as seen in our cohort (Table 2). These findings partly correspond with previous research that indicated a positive correlation between choroidal thickness and individuals with primary insomnia.[26] It is noted that actigraphy might overestimate sleep duration and has not been validated for monitoring sleep stages.[13]

Only 1 study has compared medical history between patients with these 2 entities, and the investigators reported a greater prevalence of smoking in the pachychoroid neovasculopathy group.[20] However, we did not observe such occurrences in our patient cohort with a smoking history of more than 15 pack-years. In clinical practice, although no treatment has been confirmed to decelerate the progression of pachychoroid diseases, modification of identifiable risk factors of pachychoroidopathy in patients with pachychoroid neovasculopathy could be a reasonable approach.

In contrast, drusen-related nAMD has been associated with risk factors that affect systemic microcirculation, which may deteriorate choroidal vascular supply, leading to a global depletion of choroidal vasculature.[27–29] The process of outer retinal hypoxia could be further intensified by progressive confluence of drusen that blocks nutrients and oxygen to the outer retina.[30,31] In our study, more extensive choroidal hypoperfusion was evidenced by the thinner choroidal volume and lower choroidal vascular index values in the drusen-related patient group. Notably, while there is an association between the risk factors that are present in each variant of nAMD, the benefits of modifying these factors on future treatment success is yet to be established.

Dysregulated lipid metabolism that affects capillary hypoperfusion partly contributes to the pathophysiology of drusen formation. In general, the RPE cells attain their high-energy demand by active lipid consumption through several pathways, including uptake of plasma lipoproteins via class B scavenger receptors, low-density lipoprotein receptors, and very-low-density lipoprotein receptors.[32,33] The difference between the composition of plasma very-low-density lipoprotein and that of drusen indicates that, rather than being placed directly from circulating blood cholesterol, the deposits are formed by endogenous synthesis caused by the degraded macrophage-like (phagocytosis) activity of the RPE, with insufficient clearance of incompletely digested photoreceptors' outer segments.[34] Furthermore, high-density lipoprotein cholesterol competitively binds to the scavenger receptor class B type 1 receptors that normally function as the internalization of photoreceptor outer segments into the RPE digestion process and reduce phagocytosis activity.[32] Therefore, the cholesterol profile has effects on drusen progression that are opposite those observed with cardiovascular risk, in which patients with elevated high-density lipoprotein cholesterol, low triglyceride, low low-density lipoprotein cholesterol, or low very-low-density lipoprotein cholesterol levels showed a tendency toward increased risk of advanced AMD.[35] This may explain our study's findings in which patients with drusen had a lower low-density lipoprotein cholesterol: high-density lipoprotein cholesterol ratio, whereby reduced low-density lipoprotein cholesterol levels should reduce the low-density lipoprotein receptor activities of the degraded RPE cells, causing an unstable supply of energy from plasma apolipoproteins.[36] Such dysfunction of the RPE may lead to a decrease in phagocytosis and shuttling of the digested photoreceptor matrix into the choroid.[33]

With respect to the framework of the nAMD classification, the significant differences in the baseline values of subfoveal choroidal thickness and choroidal volume support prior research, which proposes that nAMD could be primarily categorized as pachychoroid driven and drusen driven. While the pachychoroid spectrum was commonly identified as bilateral, it is possible that genetic or undetermined vascular factors could

also play a role in variations of laterality (Supplemental Figure S3)[37] because approximately half of our patients with pachychoroid neovasculopathy did not express pachychoroid disorders in their fellow eyes (Table 2). Furthermore, 2 overlapping features comprising the presence of polypoidal lesions and the 3 types of the OCT-based MNV classification should be clearly defined in each individual because they express different responses to the treatment.[38]

Although the difference is not significant, the prevalence of polypoidal lesions is greater in the pachychoroid neovasculopathy group (21/57) than in the drusen group (8/51). The increased cases of polypoidal lesions in the pachychoroid neovasculopathy group possibly indicate a higher occurrence of large submacular hemorrhage in this group prior to the exclusion of individuals who received pneumatic displacement combined with switched anti-VEGF agents (Table 2). However, none of the patients in the study cohort underwent photodynamic therapy.

After 1 year of bevacizumab treatment, the individuals with pachychoroid neovasculopathy had a lower chance of having retinal fluid and a comparable small risk of subretinal fibrosis in comparison with those with drusen. In particular, eyes exhibiting pachychoroid neovasculopathy demonstrated a lower frequency of IRF (7.7% vs 18.9%; $P = .07$), a condition linked to disease chronicity resulting from the breakdown of the external limiting membrane or more extensive MNV involvement.[39] Similarly, earlier studies have indicated that those with pachychoroid neovasculopathy had a greater proportion of dry macula, fewer total injections, and longer treatment intervals during the maintenance phase of anti-VEGF therapy.[40] These results could be partly attributed to a global depletion of choroidal vasculature, complicating nAMD treatment in the drusen-associated eyes as represented by a greater reduction in the 5 mm^2 choroidal vascular index (Table 3). This association holds true even in atrophic AMD, and a previous study reported that the presence of drusen surrounding geographic atrophy was a strong predictor of reduced central choroidal thickness over a 12-month follow-up period.[41] In comparison, prolonged exposure to high-pressure pachyvessels likely creates focal, discrete areas of choriocapillaris closure that subsequently governs a co-localization of pathology, including pachychoroid neovasculopathy.[9,42,43]

Altogether, this may reflect the distinct character of pachychoroid neovasculopathy, in which choroidal hypoperfusion appears less generalized than that of drusen-related nAMD. We propose that this focal, rather than widespread, involvement of choriocapillaris ischemia may explain its relatively improved RPE function and superior anatomic outcomes (reduced 12-month CST) after anti-VEGF treatment despite fewer anti-VEGF injections compared with patients with drusen (Table 2). A similar correlation had been documented showing that lesions with more choroidal vascularity generally demonstrated better VA and vice versa.[5,44] Although MNV in both groups was likely driven by a similar pathogenesis comprising choriocapillaris ischemia and outer retinal hypoxia, a higher incidence of large submacular hemorrhage observed in the pachychoroid neovasculopathy group without polypoidal lesions may result from patients who had an enlargement of macular choroidal lumens primarily caused by choroidal venous overload. This can in turn act as a blood reserve, leading to a plentiful source of bleeding (Table 2, Supplemental Figures S1 and S2).[45] This concept is supported by the higher incidence of thick subretinal fibrosis in the pachychoroid neovasculopathy group (20% vs 9.1%) at the 12-month follow-up, when including individuals who showed no improvement after receiving monthly bevacizumab injections. These patients likely have more aggressive MNV with increased vascular maturity, shown by the higher frequency of the clearly outlined pattern (47.6% vs 25%), regardless of the presence of polypoidal lesions.

Close-circuited vessels are presumed to have an intrinsic circulation that constantly supplies the adjacent tangled neovascular branches. Histologically, this mature configuration with larger vascular diameters may contain more pericytes and greater blood flow in the trunk vessels, which may trigger intermittent reactivation of the fine capillary vessels near the lesion's border.[46] Typically, the peripheral network reemerges with the return of retinal fluid on OCT B-scans at approximately 4 to 6 weeks postinjection or when the effects of anti-VEGF cease. Hence, compared with the other patterns predominantly encompassing filamentous neovascularization, the limited effectiveness or partial resistance to anti-VEGF treatment in MNV displaying a loop vascular arrangement may contribute to persistent retinal fluid after 12 months (Supplemental Table S1).[46–48]

SS-OCTA images from a recent investigation disclosed this loop arrangement adjacent to the areas of recurrent polypoidal lesions.[49] At the 3-month follow-up, we observed that in some patients, this vascular pattern was located near the polypoidal lesion initially seen on ICGA; however, these comparisons may not be valid because the 2 tests were conducted at different times.

Previous investigators have suggested that a dark halo surrounding MNV may be an indicator of a vascular steal phenomenon or preexisting ischemia of the choriocapillaris.[50] Although both instances may reflect a sign of neovascularization activity,[51,52] and well-circumscribed neovascular branches have been associated with type 2 MNV,[53] our analysis indicated no link between visual outcomes and fluid persistency across both morphologies.

Although qualitative features such as MNV type and the presence of polypoidal lesions have been adjusted in most independent analyses, the imprecise categorization of AMD could be a major impediment to the success of the study. For example, eyes that feature both drusen and pachychoroid characteristics would be placed in the drusen category, despite the unknown influences of pachychoroid on such patients (Supplemental Figure S3). In addition, the OCTA program did not enable us to quantify magnitudes of the anteroposterior extents of MNV. Specifically, type 2 MNV has the potential to affect the persistency of retinal fluid after anti-VEGF therapy due to development of IRF following a breakdown of the external limiting

membrane barrier.[20] Moreover, after the initial 3 bevacizumab injections, there could be alterations in MNV patterns, which therefore should not be compared with those observed in other studies investigating baseline presentation.

Further limitations involve the absence of genetic testing, the homogeneity of the patients' ethnic background (Thai), and the merging of eyes with subretinal drusenoid deposits and eyes with soft drusen into a single group. Considering the controversial characterization of pachychoroid disorders that cover a broad spectrum of conditions, some individuals may have an engorged choroidal plexus that is not indicative of a disease process. Thus, the presence of either pachyvessels or choroidal thickening alone may not necessarily contribute to AMD progression.[7,8] To lower the chances of such coincidences, particularly in the drusen-free cohort, the diagnosis criteria were designed to include both ICGA findings (performed in 73.5% of all patients) and the presence of choroidal pathologies associated with pachychoroidopathy in the fellow eyes. Lastly, the use of bevacizumab monotherapy to enhance the patient homogeneity might not reflect real-world situations as some patients may require changing their regimen or combining it with photodynamic therapy. From a clinical perspective, it could be worthwhile to prospectively investigate the effects of modifying identifiable risk factors in patients with pachychoroid neovasculopathy.

We found dissimilar risk factors related to these 2 varieties of nAMD, some of which were modifiable. Patients with pachychoroid neovasculopathy appear to feature factors associated with pachychoroid diseases, including CSCR, while drusen-associated nAMD was associated with dysregulated lipid homeostasis and greater choriocapillaris hypoperfusion (characterized by a thinner baseline choroidal volume and lower 12-month choroidal vascular index values). Patients with drusen demonstrate an inferior response to bevacizumab monotherapy compared with those with pachychoroid neovasculopathy.

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Ethical Approval

This study was approved by the Institutional Review Board of the Faculty of Medicine Vajira Hospital (COA NO. 181/2564), was conducted in accordance with the principles outlined in the Declaration of Helsinki, and followed good clinical practice (International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use).

Statement of Informed Consent

All participants who met inclusion criteria provided informed consent for publication of this study.

Declaration of Conflicting Interests

No potential conflicts of interests are relevant to the contents of this study, and no conflicting relationship exists for any authors. Because the funding was obtained after the approval of the institution review board, the sponsor or funding organization had no role in the design or conduct of this research.

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Data Availability Statement

The datasets generated during the current study are not publicly available to ensure the protection of the patient's personal information. They are available from the corresponding author on request.

Supplemental Material

Supplemental material is available online with this article.

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