European Journal of Ophthalmology / Vol. 17 no. 1, 2007 / pp. 75-83

The nature and frequency of neovascular age-related macular degeneration

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PURPOSE. *This study was designed to evaluate the frequency and nature of neovascularization in age-related macular degeneration (ARMD) utilizing the combination of digital imaging techniques, fluorescein angiography (FA), indocyanine green (ICG) angiography, and optical coherence tomography (OCT).*
METHODS. *A complete clinical examination was performed on 100 eyes of 93 consecutive newly diagnosed patients with neovascular ARMD. Digital fluorescein angiography, ICG angiography, and OCT were also used in evaluating those patients. Comparison of the imaging techniques to determine their value in studying the nature of the lesions.*
RESULTS. *On the basis of existing fluorescein standards, 15 eyes were diagnosed with classic choroidal neovascularization (CNV), 15 with minimally classic CNV, and 70 with occult CNV. ICG angiography was superior for detecting the active vascular component in polypoidal CNV (16 eyes) and retinal angiomatous proliferation (14 eyes). OCT was more sensitive than FA for determining the presence of cystoid macular edema evident in the vast majority of eyes with retinal angiomatous proliferation (RAP).*
CONCLUSIONS. *These results suggest that FA, ICG angiography, and OCT, when used in combination, will assist clinicians in best determining the precise nature of the neovascular process in ARMD. (Eur J Ophthalmol 2007; 17: 75-83)*

KEY WORDS. *Age-related macular degeneration, Choroidal neovascularization, Fluorescein angiography, Indocyanine green angiography, Optical coherence tomography*

Accepted: July 31, 2006

INTRODUCTION

In recent years the spectrum of neovascular age-related macular degeneration (ARMD) has expanded. The associated neovascularization has been defined exclusively on the basis of fluorescein angiography (FA) findings. Classic and occult choroidal neovascularization (CNV) and combinations of these subsets have constituted categories used in clinical trials. However, indocyanine green (ICG) angiography has served to image distinct neovascular subsets of neovascular ARMD, specifically polypoidal CNV and retinal angiomatous proliferation (RAP) (1). This ICG system also provides enhanced imaging of the choroid to discriminate the vascular from the avascular components of detachments of the retinal pigment epithelium in occult neovascularization (2-5).

The authors have no financial interest in any aspect of this paper.
Presented at the annual meeting of the ARVO; Fort Lauderdale, FL; May 3, 2005

1120-6721/075-09$15.00/0

The nature of the overall neovascular complex in ARMD has also been studied with optical coherence tomography (OCT) (6, 7). This photohistologic imaging technique has been particularly useful in detecting secondary retinal abnormalities, particularly cystoid macular edema (CME) (8). The combination of these three diagnostic adjuncts (FA, ICG, and OCT) is currently used in clinical and investigational settings to determine the size, composition, and secondary retinal effects of neovascular ARMD. However, there is still no analysis of a series of newly diagnosed patients studied with all three existing diagnostic adjuncts. The exact frequency and nature of the new vessels in newly diagnosed patients with neovascular ARMD might be of value for designing future studies to determine the potential efficacy of a given treatment modality. This is a report of a prospective consecutive series of patients who were newly diagnosed with neovascular ARMD and studied with FA, ICG, and OCT to determine the precise size and nature of the underlying neovascularized complex. In addition, the study was also designed to evaluate the utility of these individual diagnostic adjuncts in determining clinical and angiographic features that might be useful in investigating various forms of therapies.

PATIENTS AND METHODS

A consecutive series of 100 eyes of 93 newly diagnosed patients with neovascular ARMD were recruited prospectively from December 2003 to August 2004 from the private practice of Vitreous-Retina-Macula Consultants of New York. The practice sites were both primary and secondary retinal referral centers, including a primary center in Manhattan, satellite offices in Brooklyn, and a clinic population at the associated institution (Manhattan Eye, Ear and Throat Hospital). The majority of the 93 patients were white (83 patients). However, there were also 6 Hispanics, 2 Asians, and 2 African Americans. Each patient was at least 55 years of age. The classification of neovascular ARMD in our study was made using definitions from the Macular Photocoagulation Study (MPS) group (9). All patients with other forms of neovascularized maculopathy, including pathologic myopia, infectious or inflammatory chorioretinal diseases, angioid streaks, trauma, hereditary disorders, and tumors, were excluded. A clinical examination utilizing slit lamp biomicroscopy, indirect ophthalmoscopy, and fluorescein angiography was performed on every patient. ICG angiography and OCT were performed on 93 and 91 eyes, respectively. Some patients presented with recent imaging from the referring ophthalmologist and thus did not need to have studies repeated. The digital FA and the ICG angiogram were performed with the Topcon IMAGEnet H1024 digital imaging system (Topcon, Inc., Paramus, NJ). Using IMAGEnet 2000 software (Topcon), lesion characteristics were assessed and the total lesion size area and greatest linear dimension (GLD) were measured. OCT was performed using the Stratus tomographer (Zeiss, Dublin, CA). Each angiogram and OCT was reviewed by at least two authors. If there were any uncertainties a referee author (L.A.Y.) also reviewed the images. Data on the patients were collected based on the three different imaging modalities (FA, ICG, and OCT) as well as from color photography. Fluorescein angiography was used to determine the size, composition, and location of lesion. ICG angiography was used to determine the size and where appropriate, the composition of the lesion. OCT was used to determine presence of subretinal fluid, pigment epithelium detachment (PED), and cystoid macular edema (CME). Color photography was used to determine presence and location of blood. The study was approved by the institutional review board of the Manhattan Eye, Ear and Throat Hospital.

Definitions

The following standards and definitions were used to describe the related clinical and angiographic abnormalities in patients with neovascularization and visual symptoms evaluated in the study.

Classic choroidal neovascularization (classic CNV)

Classic CNV is a well-defined area of choroidal hyperfluorescence in the early phase of the fluorescein angiogram that during mid and late phases has progressive leakage of fluorescein that extends beyond the boundaries of the original hyperfluorescent area. If classic CNV was present, the area of classic CNV was assessed relative to the area of the entire lesion at baseline. A lesion had a predominantly classic composition or was termed predominantly classic CNV when the area of classic CNV was at least 50% of the area of the entire lesion. A lesion had a minimally classic composition or was termed minimally classic CNV when the area of classic CNV was less than 50%

but more than 0% of the area of the entire lesion. A lesion is defined as including all CNV along with contiguous areas of thick blood, elevated blocked fluorescence from turbid fluid or RPE hyperplasia, and serous pigment epithelial detachment.

Occult choroidal neovascularization (occult CNV)

Occult CNV is classified according to two characteristic patterns. Identification of either pattern within an area of the retina is sufficient to confirm the presence of occult CNV.

The first pattern, termed fibrovascular PED, is an area of irregular elevation of the RPE. Unless the overlying RPE is depigmented, a discrete or intensely bright area of early fluorescence is not usually present within this elevated tissue. Rather, an area of stippled or granular hyperfluorescence, which is not as bright as classic CNV, emerges usually within 1 to 2 minutes of fluorescein injection, although it may be discerned in the early-phase frames as well. By the late-phase frames, these areas often intensify in fluorescence to a certain degree and demonstrate persistent staining or leakage beyond the boundaries of fluorescence, elevation, or both as identified in earlier-phase frames.

The second pattern, termed late leakage of undetermined source, is noted in late-phase frames as speckled hyperfluorescence or punctate fluorescence with minimal leakage at the level of the RPE that often is associated with fluorescein pooling into the subsensory space.

Polypoidal choroidal neovascularization (polypoidal CNV)

Polypoidal CNV is a form of occult CNV characterized by the presence of branching inner choroidal vessels with terminal aneurysm-like dilations. These polypoidal lesions may be of variable size and are often associated with serosanguineous detachments of the neurosensory retina and RPE (10-17). The vascular abnormality stains with ICG angiography.

Retinal angiomatous proliferation (RAP)

RAP is a form of neovascularization that originates in the inner retina layers (stage I or intraretinal neovascularization), progresses into the subretinal space (stage II or subretinal neovascularization), and may eventually become associated with new vessel growth from the choroid (stage III or choroidal neovascularization), forming a retinal–choroidal anastomosis (RCA) (18). Clinically there are preretinal and retinal hemorrhages, cystoid spaces in the retina, and very often an associated pigment epithelial detachment (PED). ICG angiography reveals hyperfluorescence of the retinal and choroidal vascular component and hypofluorescence of associated exudative detachments including PEDs.

Extrafoveal CNV

Extrafoveal CNV is posterior border of the lesion greater than 200 micrometers from the center of the foveal avascular zone (FAZ).

Juxtafoveal CNV

Juxtafoveal CNV is posterior border of the lesion 1 to 199 micrometers from the center of the FAZ.

Subfoveal CNV

Subfoveal CNV is directly beneath the geometric center of the FAZ.

RESULTS

A total of 100 eyes of 93 patients with neovascular ARMD were recruited for the study. There were 32 men and 68 women. The mean age was 79 years (SD 7.3), with a range from 61 to 95 years. All patients had serosanguineous complications of the neovascularization in the fundus. However, there were no patients who had a large submacular hemorrhage that precluded the use of FA. The lesions were measured and then studied with FA to classify the neovascularization by existing standards (9, 19). They were then reviewed with ICG angiography and OCT imaging to determine whether any differences in size, location, and composition of the neovascularization existed.

Fluorescein angiography

Based upon the FA interpretation, 13% of the eyes were diagnosed as purely classic CNV, 2% as predominantly classic CNV, 15% as minimally classic CNV, and 70% as occult CNV (Tab. I). The two predominantly classic eyes were included in the classic CNV category for further analysis. The size and composition of the lesions are summarized in Table II.

Classic CNV (includes both classic and predominately classic CNV)

In the eyes with classic CNV, the average lesion size area was 6.30 mm^2 (range 0.5 to 27.5 mm^2). The average greatest linear dimension (GLD) was 2.81 mm (range 1.0 to 6.4 mm). Nine of 15 eyes had subfoveal lesions, 5 eyes had extrafoveal lesions, and 1 eye had a juxtafoveal lesion. Four of the 15 eyes had lipid exudation. In 11 of the 15 eyes there was subretinal blood. The average area of blood present was 2.2 mm^2 and this represented 34.9% of the overall lesion size. In the 2 eyes with predominantly classic CNV there was a vascularized PED with an average area of 2.57 mm^2 (40.8% of the entire lesion). Fibrosis was present in only one eye. The average presenting visual acuity was 20/100 (range 20/25 to 3/200).

Minimally classic CNV

In the eyes with minimally classic CNV, the average lesion size was 9.66 mm^2 (range 0.5 to 18.7 mm^2). The average GLD was 3.95 mm (range 1.1 to 6.1 mm). Twelve of the 15 eyes had subfoveal lesions, 1 eye had extrafoveal lesions, and 2 eyes had juxtafoveal. Five of the 15 eyes had lipid exudation. In 8 of 15 eyes there was blood present (5 eyes with subretinal blood, 2 with intraretinal, and 1 with both). The average area of blood present was 1.15 mm^2 and this represented 12% of the overall lesion size. Eight of 15 eyes had a vascularized PED with an average area of 5.51 mm^2 (57% of the entire lesion). No eyes presented with fibrosis. The average presenting visual acuity was 20/80 (range 20/20 to 20/800).

Occult CNV

In the eyes with occult CNV, the average lesion size was 9.60 mm^2 (range 0.2 to 44.9 mm^2). The average GLD was 3.82 mm (range 0.5 to 8.5 mm). Fifty-four of the 70 eyes had subfoveal lesions, 11 eyes had extrafoveal lesions, and 5 had juxtafoveal lesions. Twenty of the 70 eyes had lipid exudation. In 50 of 70 eyes there was blood present (25 eyes with subretinal, 18 with intraretinal, and 7 with both). The average area of blood present was 3.3 mm^2 and this represented 34.4% of the overall lesion size. Twenty-four of the 70 eyes had a vascularized PED with an average area of 3.21 mm^2 (33.4% of the entire lesion). Fibrosis was present in 4 of the 70 eyes. The average presenting visual acuity was 20/80 (range 20/20 to 3/200).

TABLE I - LESION TYPE BASED ON FLUORESCEIN ANGIOGRAPHY

Type	Classic CNV	Predominantly classic CNV	Minimally classic CNV	Occult CNV
No. eyes	13	2	15	70

CNV = Choroidal neovascularization

TABLE II - FLUORESCEIN ANGIOGRAPHY (FA) AND INDOCYANINE GREEN (ICG) FINDINGS

Type CNV (no. eyes)	Average area mm^2 (FA)	Average area mm^2 (ICG)	Average GLD mm (FA)	Average GLD mm (ICG)	Further subtype classification of neovascularization (FA and ICG)
Classic (15)	6.30	6.33	2.81	3.25	No RAP or Polypoidal
Minimally classic (15)	9.66	6.65	3.95	3.16	4 RAP, 1 Polypoidal
Occult (70)	9.60	6.26	3.82	3.27	12 RAP, 13 Polypoidal

CNV = Choroidal neovascularization; GLD = Greatest linear diameter; RAP = Retinal angiomatous proliferation

ICG angiography

Classic CNV. The ICG angiography was helpful only in confirming the size of the neovascularization initially determined with FA. In the two patients with predominantly classic CNV the ICG images reduced the lesion size by subtracting the serous component of the vascularized PED.

Minimally classic CNV. In this group, size and composition of the neovascularization were better delineated with ICG angiography. In fact, the ICG angiography allowed better determination of the neovascular component of the lesions and eliminated the staining of serous detachment seen with FA. Thus, the size of the lesion was smaller when measured by ICG as compared to FA, with reduction of the lesion size by subtraction of the serous component of a vascularized PED. The average lesion size area was 6.65 mm^2 (range 0.1 to 17.3 mm^2). The average GLD was 3.16 mm (range 0.4 to 5.3 mm). There were no differences regarding the localization of the neovascularization; however, ICG angiography proved very useful in revealing the nature of the lesion. That is, one of the 15 eyes was further classified as polypoidal CNV and 4 eyes as RAP.

Occult CNV. There were also differences with ICG angiography in this group with regard to size, localization, and composition. ICG angiography showed a smaller lesion, again by elimination of the serous component of a vascularized PED. The average lesion size area was 6.26 mm2 (range 0.07 to 32.0 mm^2). The average GLD was 3.27 mm (range 0.3 to 7.0 mm). In this group ICG angiography showed meaningful differences in further classifying the neovascularization. Thirteen of the 70 eyes were classified as polypoidal CNV and 12 as RAP.

Optical coherence tomography (OCT)

The OCT was helpful in determining the presence of cystoid changes in the retina as well as detachment of the pigment epithelium. The OCT revealed cystoid changes in 5 of the 15 eyes with classic CNV, 7 of the 15 eyes with minimally classic CNV, and 25 of the 70 eyes with occult CNV. Subretinal reflectivity was evident at sites of blood, exudates, and fibrovascular tissue in all eyes. The cystoid exudation could be documented in only four eyes with FA where one had classic CNV and one minimally classic CNV and two occult CNV.

TABLE III - OPTICAL COHERENCE TOMOGRAPHY FINDINGS

Type CNV (no. eyes)	CME	PED
RAP (16)	15	12
Polypoidal (14)	1	12

CNV = Choroidal neovascularization; CME = Cystoid macular edema; PED = Pigment epithelium detachment; RAP = Retinal angiomatous proliferation

In polypoidal CNV cystoid changes were detected in only one eye with the OCT, while a PED was evident in 12 eyes. In RAP patients the OCT demonstrated cystoid changes in 15 of 16 eyes, as well as detachment of the pigment epithelium in 12 of 16 eyes (Tab. III).

DISCUSSION

In recent years the spectrum of neovascular ARMD has expanded. Digital ICG angiography has enhanced our imaging of occult CNV, and has served to identify neovascular subsets, specifically polypoidal CNV and RAP (1-5). The large plasma-bound ICG molecule, its larger bioconjugate, its relative impermeability to the choriocapillaris, and its near infrared penetration of the RPE and serosanguineous complications have improved imaging of choroidal vessels, both normal and abnormal. In addition, OCT imaging has been useful in detecting secondary retinal abnormalities, particularly subtle macular detachment and cystoid changes in the retina (6-8, 20). To our knowledge, there has not been a previously published series which has used these diagnostic adjuncts in conjunction with standard FA to classify a consecutive series of newly diagnosed neovascular ARMD patients prospectively. In the past, the lesion in neovascular ARMD was based exclusively on FA findings, specifically stereo film images. Today, however, there is an increasing trend towards centers relying on digital imaging. The lesion of neovascularization based on FA is known to be restricted by the presence of blood and exudates which may obscure choroidal extension. Furthermore, presence of CME in the retina is often difficult to document with FA alone. Previous landmark studies involving PDT and antiangiogenic drugs did not use OCT to determine the status of the retina and its potential effect on the visual outcomes. Our study which utilized three modalities in combination provides data on the exact nature and frequency of the neovascular complex in ARMD and the status of the retina overlying the lesions. It also offers guidelines to physicians regarding the utility of these techniques, when they are needed, and what additional clinical information they provide in managing patients. For example, OCT imaging provides more sensitive identification of cystoid edema, which is often not recognized by clinical examination or FA alone. In addition, polypoidal CNV and RAP require ICG angiography for precise documentation of the active neovascularization in both variants.

The overall results of our study were analyzed with regard to these specific factors. Perhaps the most important contribution of these data relates to the frequency of the composition of the new vessels. Classic CNV presented in 13% of the patients. When a small number, 2%, of patients with predominantly classic CNV is added to this group, it is clear that any treatment modality which is effective in this portion of the neovascularized spectrum is likely to benefit only a small percentage of newly diagnosed patients, estimated in our study to be 15%.

In these patients, ICG angiography proved to be of limited benefit beyond the imaging with FA. This observation is expected since the small and highly permeable capillary proliferation associated with classic CNV is of a dimension which is not suitable for the large ICG molecule and its larger bioconjugate. An exception was a classic CNV membrane which was bordered by a fringe of subretinal blood or exudate. Blood blocked the neovascularization with FA while the ICG study imaged through the blood to detect the full extent of the neovascularization. Exudates contiguous with the classic CNV would reduce the size of the lesion when studied with ICG angiography. This finding was expected since the ICG molecule does not stain the subretinal pigment epithelial space associated with serous detachment. In this regard, the so called vascular lesions were reduced in size by the ICG findings.

The OCT was superior to the FA and ICG studies in detecting changes within the retina. While the FA was able to detect the presence of CME in only 4 eyes of our patients, the OCT examination demonstrated the presence of CME in 37 eyes of our series of patients. It was essential to make this determination with accuracy. The presence of CME is still of uncertain clinical relevance, but it could be important in the natural course, the visual prognosis, and response to treatment. Response to therapy, for example the visual outcome with PDT, may be related to the presence of CME as suggested by previous investigators (21). In theory, a photosensitizing dye such as verteporfin could leak into the cystic cavities leading to subsequent phototoxic damage to the macula when the excitatory laser is applied to the central macula. Persistent CME is known to be associated with irreversible damage to the retina and a poor visual recovery potential from cystic macular degeneration or foveal atrophy (22). Unfortunately, OCT was not available for use in the trial used to study the effects of PDT with verteporfin (19, 25). One other consideration with OCT imaging of CME in neovascular ARMD is the potential response to administration of an antivasogenic drug as an independent form of monotherapy or in combination with PDT. The available forms of drugs for neovascular ARMD treatment have a distinct antipermeability effect as well as a theoretical antivasogenic benefit. Only OCT can give an accurate assessment of the intraretinal status in these patients based on the results of our study.

FA in this study prevails as the gold standard for determining the presence of neovascular disease, but not necessarily its size or nature. For classic CNV, in general fluorescein imaging is all that is needed; however, better definition of the vascular nature of the lesion can be provided with the use of ICG imaging, specifically in the presence of significant blood and detachment of the pigment epithelium. A vascularized PED may have a mixed or purely serous component to the elevated tissue layer and subretinal blood may or may not indicate neovascularization.

With minimally classic CNV and occult CNV, representing a larger portion of the spectrum of neovascular ARMD, at 85% based on our study, the ICG angiography was of greater benefit. First, there was a difference in size of the lesion noted on the ICG angiograms in some patients. The average area measured on FA was 9.66 mm^2 and 9.60 mm^2 for minimally classic CNV and occult CNV, respectively. However, the average lesion area in these patients was smaller when measured with ICG angiography, 6.65 mm^2 and 6.26 mm^2 for minimally classic CNV and occult CNV, respectively. The difference between these two imaging modalities was due to leakage of fluorescein into anatomic spaces such as serous PEDs. The serous PED fluorescence was included in the overall size with fluorescein, but not with ICG angiography. Theoretically, a smaller lesion size could require a smaller area of treatment with PDT and thus may translate to reduced fluency of laser energy and theoretically reduce either cell damage and/or the upregulation of endothelial growth factors.

In the spectrum of neovascular ARMD, the role of ICG angiography is the most important in polypoidal CNV and RAP. The ICG angiogram revealed a difference in neovascular composition in some patients in these categories. A number of eyes had polypoidal CNV, one in the minimally classic CNV group and 13 in the occult CNV subset. Another composition determination with ICG angiography was in RAP eyes where 4 of the minimally classic CNV and 12 of the occult CNV group were diagnosed with this form of neovascular ARMD.

The frequencies of polypoidal CNV and RAP were higher in our study than in previous reports (1, 15, 18). This may be partially related to a referral bias since approximately 75% of the patients in this study were recruited from our Manhattan office which is a referral center. In a previous study (18) we found polypoidal to be present in 9% of newly diagnosed patients and other reports have found RAP in 12 to 15% of newly diagnosed patients (23). Polypoidal CNV is seen predominantly in African American, Hispanic, and Asian patients but also in Caucasians (18). Our population in New York City and Brooklyn was mixed racially, but predominantly Caucasian, although demographic data are difficult to control with accuracy in this category. Nevertheless, an accurate diagnosis of these neovascularized subsets is best achieved with ICG angiography. The importance of making accurate diagnoses with respect to subsets of neovascular ARMD again lies in likely differences regarding natural course, visual prognosis, and response to therapy.

The former is likely to be associated with large hemorrhages, and both are virtually always present in association with serous PED. In these forms of neovascular ARMD, the pigment epithelium detachment does not constitute the vascular nature of the lesion; rather the new blood vessels represent a distinctly smaller percentage of the overall detachment. In future studies which involve the use of limited PDT designed to reduce collateral damage and treat only the vascular component of the lesion, ICG would be essential in determining the baseline and outcome of the treatment response. Such a therapeutic approach may require a new definition of the neovascular lesion, which is currently based exclusively on fluorescein imaging, specifically a stereo film based determination. In the current digital era, combined fluorescein and ICG diagnosis of the lesion is preferred based on our study. Another important aspect of the nature of the vascular lesion determined by our study involves the role of OCT. This diagnostic modality most accurately determines the presence and nature of the cystoid change within the retina. The clinical and angiographic examinations alone may not be reliable for making that determination. If cystoid change within the retina proves to be an important factor in the visual outcome to treatment with PDT or an anti-permeability pharmacologic agent or both, then it is essential to use OCT imaging to establish a baseline and a treatment outcome, given the findings in our study. Although the polypoidal CNV eyes seldom had associated CME (7%), cystic changes in the retina were present as expected at a very high frequency in eyes with RAP (94%). This is characteristic of this subset which has angiomatous proliferation in the retina and associated leakage early in the course of its typical vasogenic sequence (18). The difference in OCT detection of CME again reinforces the concept that a specific form of neovascularization will have variable clinical manifestations. Finally, the knowledge of the expanded neovascular spectrum in ARMD is crucial in designing future studies involving each form of the disease and the relative value of a chosen therapeutic modality.

To our knowledge, this is the first analysis of a prospective series of patients with neovascular ARMD using the combination of FA, ICG, and OCT. Although FA has traditionally been accepted as the standard imaging modality, to define the so-called neovascular lesion, the additional use of OCT to study the retina and ICG in selected cases to define composition may be useful in designing studies in the future and in identifying eyes that may respond to certain forms of treatment (24). Furthermore, composition and size have become increasingly important in visual prognosis and preferred form of treatment. Specifically, large occult lesions have been less likely to respond favorably to PDT (25). In our study, extent of the neovascularization was often overestimated when FA alone was used to measure the lesion. OCT was helpful in identifying characteristic intraretinal features that aid in patient evaluation and management; and ICG was of most value in eyes with minimally classic or occult CNV and particularly in eyes with PED.

In short, FA, ICG, and OCT when used in combination will provide the clinician with a better opportunity to clarify the true size and nature of the neovascular process.

ACKNOWLEDGEMENTS

The authors thank the retinal physicians of Vitreous-Retina-Macula consultants of New York (Y. Fisher, K. Bailey Freund, J.M. Klancnik, R. Klein, J.A. Sorenson, and R.F. Spaide) for their assistance in recruiting patients for this study.
This work was supported by The Macula Foundation Inc., New York, NY.

The authors have no financial interest in any aspect of this paper.

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