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Tomographic Biomarkers Predicting Progression to Fibrosis in Treated Neovascular Age-Related Macular Degeneration: A Multimodal Imaging Study

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Purpose: To describe the photoreceptor–retinal pigment epithelium (RPE) interface changes and to analyze the relationships between these features and hyperreflective material (HRM) with scarring and atrophy at the macula of patients with neovascular age-related macular degeneration (nAMD).

Design: Retrospective single-center observational study.

Participants: A total of 150 eyes from 144 patients with naive nAMD were included.

Methods: All patients had OCT (HRA-OCT Spectralis, Heidelberg Engineering, Heidelberg, Germany) at baseline and at 1, 3, 6, and 12 months. Macular scar and macular atrophy (MA) were determined on multimodal imaging, including color fundus (CF) and near-infrared imaging at baseline and month 12 (M12).

Main Outcome Measures: Change in HRM type (undefined and well-defined) and location, development of fibrotic or nonfibrotic macular scar, MA, and best-corrected visual acuity (BCVA) at M12.

Results: At baseline, eyes with fibrin on CF had thicker and wider HRM on OCT that correlated strongly with presence of undefined HRM. The proportion of eyes with undefined HRM fell dramatically by month 1 but well-defined HRM increased. At M12 defined HRM was strongly associated with macular scar (chi-square, 82.1; $P < 0.001$). Ordinal regression showed that both the thickness and the width of HRM were significant risk factors for development of fibrotic scar ($P < 0.001$ and $P = 0.02$) but not nonfibrotic scars ($P = 0.67$ and $P = 0.65$). Fibrotic macular scar ($P = 0.001$) but not nonfibrotic scar ($P = 0.129$) negatively affected visual acuity at M12. Ordinal regression showed that the risk factors for progression to MA were reticular pseudodrusen and thinner HRM ($P = 0.017$ and $P = 0.028$, respectively). MA negatively affected BCVA at M12 ($P < 0.001$).

Conclusion: Our study supports the role of HRM as an important biomarker for the evolution of macular scar and atrophy in patients with nAMD undergoing treatment with anti-VEGF therapies. Undefined HRM can resolve with treatment, whereas well-defined HRM likely contains vascular complexes and fibrotic elements. *Ophthalmology Retina 2017;■:1–11 © 2017 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

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Choroidal neovascularization (CNV) at the macula of patients with age-related macular degeneration (AMD) can lead to severe vision loss in more than 40% of patients by 3 years if left untreated.[1] Scarring and atrophy at the macula negatively affect the natural history of untreated neovascular AMD (nAMD).[2]

Although the widespread use of intravitreal anti–vascular endothelial growth factor (anti-VEGF) treatment has substantially improved the long-term prognosis of nAMD,[3] retinal scarring and atrophy have been identified as predictors of vision loss even in patients with nAMD who have been treated with anti-VEGF therapies.[3–5]

Subretinal hyperreflective material is an optical coherence tomography (OCT) finding in nAMD that has been found to correlate with fluorescein angiography (FA) leakage in eyes with active CNVs,[6] especially with subretinal (SR) CNVs.[7] In the Comparison of Age-related macular degeneration Treatments Trials (CATT) study, the presence of SR hyperreflective material on OCT was found to correlate with retinal scar development after treatment.[8] Because we recently showed that this material can be located in compartments other than SR, we preferred to use the term *hyperreflective material* (HRM).[9] We observed that when HRM is undefined and subretinally

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located, it strongly correlates with the presence of fibrin exudation seen on color photography before initiation of treatment.[9] We also observed that the characteristics of the change in HRM over time during anti-VEGF treatment became more defined and located mostly in the subretinal pigment epithelium (sub-RPE) compartment, suggesting evolution into scar tissue.[9] With upcoming treatment modalities targeting fibroblast proliferation and with potential to limit scarring,[10] there has been increasing interest for the early detection of biomarkers of fibrosis on tomography.[11] Notably, associations between newly recognized OCT features and retinal scar evolution have been described.[12]

A systematic analysis including novel OCT biomarkers and macular scar and atrophy has not been performed and may clarify the pathophysiology of these events over time in eyes treated with anti-VEGF.

The goals of our study were (1) to describe in detail the morphologic alterations over time at the photoreceptor−RPE interface in the different neovascular AMD subtypes; (2) to study the development of HRM type, presence, location, and macular scar and atrophy evolution; and (3) to explore relationships with visual acuity (VA) over time in eyes treated with anti-VEGF.

Methods

Design

This was a retrospective analysis using data from electronic medical care records and associated imaging repositories of patients seen in a single tertiary referral eye care center. The institutional review board of Belfast Trust determined that approval was not required for this study because it contains findings from an aggregated analysis of functional and imaging data and no patient identifiers are included.

Population and Study Protocol

We identified 1671 new patients in the electronic medical care records who were patients at the retina clinics at the Belfast Health and Social Care Trust between January 2012 and April 2014. Our hypothesis was that HRM composition and location would differ by nAMD subtype. To ensure sufficient representation of these categories, we prespecified a sample of 150 eyes because previous experience[9] suggested that we would expect around 35 to 40 eyes of type 1 and type 2 nAMD, a similar proportion of mixed (types 1 and 2), some 25 retinal angiomatous proliferation and 15 cases of polypoidal choroidal vasculopathy (PCV). After exclusion of other diagnoses, we selected 144 consecutive patients, 6 of whom had bilateral presentation and all of whom had confirmed neovascular AMD, yielding a total of 150 eyes eligible for inclusion. For eligibility, we specified the following: (1) commencement of treatment with an anti-VEGF; (2) follow-up of at least 12 months; (3) CF imaging performed at baseline and month 12 (M12); (4) OCT imaging performed at baseline and at months 1, 3, 6, and 12; and (5) FA and indocyanine green angiography performed at baseline for purposes of nAMD classification. CF imaging was performed on the Visucam Pro NM (Carl Zeiss Meditec AG, Jena, Germany) or as multicolor (MC) scanning laser imaging on the Heidelberg system (Heidelberg Retinal Angiograph, Heidelberg Engineering, Heidelberg, Germany). Optical coherance tomography, near-infrared (NIR), fundus autofluorescence, FA, and indocyanine green angiography were performed in all patients on the Heidelberg system. The OCT scan protocol included 37-line raster scans (20 × 15 degrees) consisting of 512 A-scans for every line. The "follow-up" mode of the eyetracking-assisted system (AutoRescan, Heidelberg Spectralis) was used during the follow-up visits.

There were no visual acuity (VA) eligibility criteria.

The study patients had treatment with either ranibizumab or aflibercept and received a loading dose of 3 injections given monthly. On completion of the loading phase, patients receiving ranibizumab were retreated using as-needed criteria[13]: evidence of new retinal hemorrhage, or recurrence or persistence of intraretinal (IR) or SR fluid on OCT. Those receiving aflibercept were on a fixed regimen of bimonthly injections for 1 year.[14]

Grading

We graded for presence of fibrin, blood, and lipid using CF and/or MC without reference to any other imaging modality. Subsequent to this grading, all other gradings were performed using a multimodal approach. At baseline, fundus autofluorescence was graded to rule out the presence of hyper-autofluorescent signal suggestive of vitelliform material, which represented a criterion of exclusion.

Fluorescein angiography and indocyanine green angiography images were graded to determine the type of nAMD using the definitions provided by a multimodal imaging classification,[15] after which the eyes were classified as occult (type I); classic (type II); retinal angiomatous proliferation (type III); mixed (with classic and occult component); and polypoidal choroidal vasculopathy (PCV).

We next delineated areas of macular scarring and atrophy using all available imaging modalities. Macular scar and atrophy were graded using the following definitions. MA was defined as a single or multiple areas of hypopigmentation with well-defined borders and visible large choroidal vessels on CF that corresponded to window defects on angiography and/or to the loss of cellular layers (outer retina, RPE, and choriocapillaris) on the accompanying tomograms.

Macular scar identification was based on both color and fluorescein characteristics. On CF or MC, scar was said to be present if there were well-delineated areas of yellow-white tissue with corresponding initial hypofluorescence, with late hyperfluorescence and staining on fluorescein angiograms. Lesions were further categorized as showing fibrotic and nonfibrotic scars using definitions identical to those of the CATT study.[16]

At M12, retinal angiography was not available on the vast majority of eyes; therefore we graded for the presence of scar and MA on CF, MC, and/or near-infrared imaging.

A graded categorical approach was used to determine the extent of fibrotic and nonfibrotic scarring: no scar; barely visible, for a scar involving approximately 25% of the lesion; mild, for a scar involving approximately 50% of the lesion; moderate, for a scar involving approximately 75% of the lesion; and severe, when the entire lesion consisted of a scar. A similar scoring system was applied to grade for MA (no atrophy, barely visible, mild, moderate, and severe when the entire lesion area was atrophic).

Optical coherance tomography images were generally available at all visits, but we chose to grade only those from baseline and from months 1, 3, 6, and M12 visits. We used the recently developed consensus for definitions on OCT nomenclature.[17] The RPE was defined as the hyperreflective band between the choriocapillaris and the interdigitation zone (this band is not normally separable from the Bruch membrane in the scans from the current generation of spectral-domain OCT and therefore is defined as the RPE−Bruch complex). The ellipsoid zone (EZ) was defined as the second hyperreflective band internal to the RPE. The external limiting membrane (ELM) was defined as a discrete