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Published in:
Ophthalmology Retina

Document Version:
Publisher's PDF, also known as Version of record

Queen's University Belfast - Research Portal:
Link to publication record in Queen's University Belfast Research Portal

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Download date:28. Jan. 2024
Hyperreflective Material Boundary Remodeling in Neovascular Age-Related Macular Degeneration

A Post Hoc Analysis of the AVENUE Trial

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**Objective:** To describe the spatial and temporal characteristics of hyperreflective material (HRM) on spectral-domain OCT (SD-OCT) in neovascular age-related macular degeneration (nAMD) during antiangiogenic treatment and explore associations with best-corrected visual acuity (BCVA) and macular atrophy (MA).

**Design:** Retrospective regrading of SD-OCT-images from the multicenter, randomized controlled AVENUE trial (NCT02484690, conducted from August 2015 to September 2017).

**Participants:** Treatment-naive nAMD patients enrolled from 50 sites in the US.

**Methods:** Retrospective regrading and secondary analysis.

**Main Outcome Measures:** Spectral-domain OCT images from 207 study eyes that fit criteria for the present analysis were graded for HRM features, its evolution, and associated hypertransmission into choroid (HTC), a proxy for MA. The appearance of a well-defined hyperreflective inner boundary that separated persistent HRM from the neurosensory retina continuous with the adjacent retinal pigment epithelium layer was defined as hyperreflective material boundary remodeling (HRM-BR). Patterns of HRM composition/evolution were defined as follows: (1) no subretinal HRM at baseline, (2) fully resolved, (3) persistent with complete HRM-BR, or (4) partial/absent HRM-BR. Associations of HRM patterns with BCVA and HTC were analyzed. Predictive factors for complete HRM-BR were explored.

**Results:** Of 207 included eyes, subretinal HRM was present in 159 (76.8%) at baseline and persisted until month 9 in 118 (57.0%) eyes. Of these 118 eyes, 44.9% developed complete HRM-BR and had similar BCVA outcomes by month 9 compared with no/fully resolved subretinal HRM. Partial/absent HRM-BR had a strong negative association with BCVA outcome (−6.1 ETDRS letters; \( P = 0.016 \)) and a higher frequency of intralesional HTC (69.2%) compared with eyes with complete HRM-BR (20.8%) at month 9. Older age (odds ratio [OR], 0.96; \( P = 0.054 \)) and presence of intralesional HTC (OR, 0.06; \( P = 0.010 \)) at baseline were associated with lower odds of complete HRM-BR at month 9.

**Conclusions:** In nAMD eyes under antiangiogenic treatment, complete HRM-BR occurred frequently and was associated with better BCVA than when HRM-BR was only partial/absent.

**Financial Disclosure(s):** Proprietary or commercial disclosure may be found in the Footnotes and Disclosures at the end of this article. Ophthalmology Retina 2023;7:990-998 © 2023 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/).

Supplemental material available at www.ophthalmologyretina.org.
However, the compartmental location of hyperreflective material (HRM), whether restricted to the subretinal or subretinal pigment epithelial (RPE) spaces, is hard to determine because the RPE layer can become incorporated into the lesion and can show similar reflectivity to HRM. Therefore, in the current study, we employ the term “HRM” because it reflects all compartmental locations, and we use “SHRM” only when referring to findings reported in other publications.

A detailed characterization of HRM on OCT should include textural characteristics, location, inner and outer boundaries, and associated macular atrophy (MA). The change in the inner limits of the HRM with antiangiogenic therapy from undefined to well-defined has been characterized. However, none of these other characteristics of HRM have been systematically evaluated. Also, because these prior studies were small and undertaken in routine care settings, there has been limited evaluation of associations with function. Here, we used a data set from a controlled, clinical trial to characterize the location and evolution of HRM and explore the associations with function. Here, we used a data set from the AVENUE trial (available at ClinicalTrials.gov: NCT02484690), a 9-month, prospective, multicenter, phase II randomized clinical trial. Briefly, 273 patients with treatment-naïve nAMD in the study eye were randomized to 1 of 5 dose regimens for treatment with faricimab and/or ranibizumab administered intravitreally at different intervals. The AVENUE trial design and outcomes have been published in detail. The trial adhered to the tenets of the Declaration of Helsinki and was compliant with the Health Insurance Portability and Accountability Act. The protocol was approved by institutional review boards or ethics committees or as applicable. Participants provided written, informed consent for their data to be used in future medical research and analyses.

Grading of Images

The AVENUE trial image repository consisted of SD-OCT scans (19-line or 49-line B-scans covering a 20 × 20-degree area of the macula centered on the fovea) captured at every visit using the Spectralis SD-OCT (Heidelberg Engineering). In the present analysis, study eyes were required to have had 49-line cube scans at baseline and at month 1 or 3, resulting in the inclusion of 207 eyes. Two ophthalmologists (S.Y., I.B.) graded the SD-OCT images from 5 time points (baseline; day 7; months 1, 3, and 9) according to a grading protocol developed specifically for this study (Supplemental Methods, available at www.ophthalmologyretina.org).

Hyperreflective material was defined as the presence of a medium-to-highly reflective mass external to the neurosensory retina as seen on SD-OCT. When HRM was present, its location in relation to the RPE was graded as “sub-RPE only,” “subretinal and sub-RPE,” or “subretinal only.” The morphology of the inner limit of any subretinal HRM (Fig 1, solid arrows) was classified as “well-defined,” “partially defined,” or “undefined,” depending

Figure 1. Hyperreflective material (HRM) evolution on spectral-domain OCT (SD-OCT) in 3 study eyes over time. (A1–A4) At baseline, there is subretinal HRM, the inner limit of which is partially defined (A1, solid arrow) and the outer limit of which is bounded by a hyperreflective band continuous with the retinal pigment epithelium (RPE), i.e., visible outer boundary (A1, hollow arrow). Under antiangiogenic treatment, a well-defined hyperreflective band continuous with the adjacent RPE layer develops (complete HRM boundary remodeling [HRM-BR]; A3–A4, solid arrows). By month 9, the outer boundary is no longer visible (A4, hollow arrow). B1–B4, Baseline SD-OCT shows an undefined inner limit of the subretinal HRM (B1, solid arrow). Under antiangiogenic treatment, gradual resolution of the HRM is observed, with complete HRM-BR by month 1 (B3, solid arrow). The outer boundary remains visible throughout all visits (B1–B4, hollow arrows). C1–C4, At baseline, the inner limit of HRM is partially defined (C1, solid arrow). There is a RPE tear, which has resulted in an undetectable outer boundary (C1, hollow arrow). Under antiangiogenic treatment, the inner limit becomes well defined, without exhibiting a hyperreflective band (absent HRM-BR; C2–C4, solid arrows). The outer boundary remains undetectable (C2–C4, hollow arrows).
the proportion (≥75%, 26%–74%, or ≤25%) that was clearly distinguishable from the neurosensory retina. In addition, we introduced a novel dynamic subclassification of the inner boundary of persistent subretinal HRM: hyperreflective material boundary remodeling (HRM-BR), defined as the appearance of a new, well-defined, hyperreflective band at the inner aspect of the subretinal HRM that was continuous with the RPE layer adjacent to the lesion. For this feature, longitudinal OCT images are required. All B-scans of the cube were scrutinized, and, if the inner boundary was constituted by the well-defined, hyperreflective band in ≥90% of the scans covering the HRM, HRM-BR was deemed “complete”; otherwise, it was deemed “partial/absent.” Regarding the outer limit of any subretinal HRM, we looked for a hyperreflective band continuous with the RPE, which was then defined as the “outer boundary” of the subretinal portion (Fig 1, hollow arrows) and graded as “visible,” “partially visible,” or “undetectable,” depending on the proportion that was traceable (≥75%, 26%–74%, or ≤25%).

The foveal B-scan was identified, and the maximum height and width of subretinal HRM were measured on it. The foveal scan was also graded for HRM-associated MA features: hypertransmission into choroid (HTC) of ≥250 μm in diameter, disruption of the external limiting membrane (ELMD), and disruption of the ellipsoid zone (EZD), as defined in the Classification of Atrophy Meetings (CAM) criteria.6 The location of HTC was characterized as “intralesional” (overlapping with the HRM) or “marginal” (contiguous). In eyes with no HRM at baseline, we recorded the presence of HTC, ELMD, and EZD in the foveal retina.

AVENUE fundus fluorescein angiography (FA) images had been graded for the presence of fibrosis previously; these data were used in the present analysis to classify study eyes as exhibiting fibrosis based on this established modality. Fluorescein angiography images had also been graded for MNV type (occult; classic and occult; classic); these data were used for adjustment of the statistical models.

**Statistical Analysis**

Intergrader agreement was analyzed in a random subset of 35 SD-OCT volume scans and reported as Cohen κ values with agreement rates. Continuous data were summarized by medians and interquartile ranges, and categorical data were summarized by counts and percentages. Box plots show BCVA at baseline and month 9 by HRM evolution patterns (see Results section). Multiple linear regression was used to examine associations of baseline BCVA and BCVA outcomes at month 9 with HRM patterns after adjusting for age, baseline BCVA, baseline MNV type, and treatment arm. Two independent regression models examined the cross-sectional association between BCVA and foveal HRM height or width after adjusting for age, baseline MNV type, and treatment arm at several time points. Multiple linear regression was used to test the cross-sectional association of BCVA with MA features (HTC, ELMD, and EZD) at month 9, adjusted for age, baseline BCVA, baseline MNV type, and treatment arm. Bar graphs show the frequency of SD-OCT features of MA by HRM pattern. A chi-square test was used to analyze the association between HRM outer-boundary status and HRM-BR. Two logistic regression models were used to calculate the odds of complete HRM-BR, with predictors from baseline and month 1. We cross-tabulated the presence of fibrosis based on the FA gradings and HRM features on SD-OCT to look at agreement between these modalities and performed a Fisher exact test. Statistical significance was set to 5% (2-sided tests). No correction was applied for multiple testing because this was hypothesis-generating work. Analyses were performed using the R statistical software (version 4.0.3).

**Results**

Intergrader agreement was high between the 2 masked graders (Table S1, available at www.ophthalmologyretina.org).

**HRM Evolution Patterns and Associations with BCVA**

Morphologic features during the follow-up are summarized in Table S2 (available at www.ophthalmologyretina.org). Any HRM was present in 193 (93.2%) eyes at baseline. Among these, the distribution was as follows: subretinal only (16.6%), subretinal and sub-RPE (65.8%), and sub-RPE only (17.6%).
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Table 4. Linear Regression model Showing Associations between Adjusted BCVA at Baseline or at Month 9 and HRM Evolution Patterns

<table>
<thead>
<tr>
<th>HRM Evolution Patterns</th>
<th>Baseline BCVA</th>
<th>Month 9 BCVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: No subretinal HRM</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>2: Resolved subretinal HRM during follow-up</td>
<td>−5.44 (2.32)</td>
<td>3.06 (2.65)</td>
</tr>
<tr>
<td>3: Persistent subretinal HRM with complete HRM-BR</td>
<td>−10.78 (2.51)</td>
<td>3.60 (2.95)</td>
</tr>
<tr>
<td>4: Persistent subretinal HRM with partial/absent HRM-BR</td>
<td>−14.53 (2.18)</td>
<td>−7.41 (2.72)</td>
</tr>
</tbody>
</table>

*The model was adjusted for age, baseline BCVA, baseline MNV type, and treatment arm. Of these, only significant variables are reported in this table. Boldface indicates P < 0.05.

At baseline, the inner limit of HRM was unde ned in 68.6%, well defined in < 10%, and partially defined in the rest. Complete resolution of subretinal HRM was seen in 18.9% of eyes by month 1, increasing to 25.8% by month 9. In the eyes with persistent subretinal HRM, the inner limits became well defined in 34.2% by day 7, 76.0% by month 1, and approximately 90% by month 3, remaining at this level at month 9. A completely remodeled inner boundary was seen in 53 (44.9%) of all eyes with persistent subretinal HRM by month 9. Based on the presence and location of HRM at baseline and its subsequent resolution or remodeling of its boundary, we grouped study eyes as follows: pattern 1 (no HRM at baseline or with sub-RPE HRM only; n = 48), pattern 2 (baseline subretinal HRM fully resolved during follow-up; n = 41), pattern 3 (persistent subretinal HRM with complete HRM-BR; n = 53), and pattern 4 (persistent subretinal HRM with partial or absent HRM-BR; n = 65).

Table 6. Linear Regression Model Showing Cross-Sectional Associations between Adjusted BCVA and HRM-Associated MA Features at Month 9

<table>
<thead>
<tr>
<th>Explanatory Variable*</th>
<th>Regression Coefficient (SE)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline BCVA, ETDRS letters</td>
<td>0.66 (0.08)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HTC</td>
<td>−4.59 (3.61)</td>
<td>0.205</td>
</tr>
<tr>
<td>Intraretinal</td>
<td>−6.26 (2.24)</td>
<td>0.006</td>
</tr>
<tr>
<td>Intralesional</td>
<td>−4.61 (3.46)</td>
<td>0.184</td>
</tr>
<tr>
<td>ELMD</td>
<td>−0.60 (3.25)</td>
<td>0.854</td>
</tr>
</tbody>
</table>

BCVA = best-corrected visual acuity; ELMD = external limiting membrane disruption; EZD = ellipsoid zone disruption; HRM = hyperreflective material; HTC = hypertransmission into choroid; MA = macular atrophy; MNV = macular neovascularization; NA = not applicable; SE = standard error.

*The reference level for HTC and intraretinal photoreceptor layer disruption is "none"; the reference value for baseline BCVA is "0.05.

When investigating the associations of BCVA with the HRM patterns, Figure 2 reveals a decreasing gradient in BCVA across the 4 categories, with improvements by month 9 across all patterns except pattern 4 (Fig 2; summary of statistics in Table S3, available at www.ophthalmologyretina.org). The regression model (Table 4), with pattern 1 as the reference category, shows that adjusted baseline BCVA was significantly lower in eyes with baseline subretinal HRM (pattern 2: −5.4 ETDRS letters; pattern 3: −10.8 ETDRS letters; pattern 4: −14.5 ETDRS letters; P < 0.05). Group assignment is retrospective as information on morphologic change at month 9 is required for group membership. By month 9, the adjusted BCVA of patterns 2 and 3 was similar to pattern 1. Only pattern 4 continued to have poorer BCVA outcomes (−7.4 ETDRS letters; P = 0.007).

Association of HRM Dimensions and HRM-Associated MA with BCVA

We investigated the cross-sectional association of subretinal HRM dimensions and HRM-associated MA with BCVA. Foveal HRM width was significantly associated with lower BCVA at all visits (association coefficients ranged from −0.31 ETDRS letters per 100 μm [P = 0.002] at baseline to −0.63 ETDRS letters per 100 μm [P = 0.002] at month 9). There was no significant association between foveal HRM height and BCVA at any time points (Table S5, available at www.ophthalmologyretina.org).

We observed HRM-associated HTC in 19.2% of all eyes at baseline, increasing to 47.8% at month 9. External limiting membrane disruption and EZD were present in 74.6% and 85.5% of eyes, respectively, at baseline and in 53.8% and 62.0% of eyes, respectively, at month 9 (Table S2, available at www.ophthalmologyretina.org). After adjusting for baseline BCVA, intraretinal HTC was associated with a deficit of 6.3 (P = 0.006) ETDRS letters at month 9. The presence of ELMD and EZD did not show a significant association with adjusted BCVA at month 9 (Table 6).

Association of HRM Evolution Patterns with MA

The percentages of intraretinal HTC, ELMD, and EZD at baseline and at month 9 were different across the 4 HRM patterns (Fig 3).
Hypertransmission into choroid frequency at month 9 was lowest in pattern 3 (20.8%) and highest in pattern 4 (69.2%). At month 9, ELMD and EZD were observed at frequencies of 22.6% and 39.6%, respectively, in pattern 3, and at frequencies of 87.7% and 90.8% in pattern 4.

Predictive Factors for HRM-BR Outcomes at Month 9

An undetectable outer boundary was uncommon at baseline (7.5%), but its frequency increased to 20.9% at month 1 and 57.6% at month 9 (Table S2, available at www.ophthalmologyretina.org).

At month 9, a higher proportion of the eyes with complete HRM-BR had an undetectable outer boundary ($P = 0.12$), compared with those without (Table S7, available at www.ophthalmologyretina.org).

The multivariate logistic regression analysis (Table 8) showed that intraretinal HTC was significantly associated with lower odds of complete HRM-BR at month 9 (odds ratio [OR], 0.06 [$P = 0.010$] at baseline; OR, 0.18 [$P < 0.001$] at month 1). Older age may be associated with decreased odds of complete HRM-BR (OR, 0.96 [$P = 0.054$] at baseline; OR, 0.96 [$P = 0.068$] at month 1) and an undetectable outer boundary with increased odds of complete HRM-BR (OR, 1.64 [$P = 0.568$] at baseline; OR, 2.33 [$P = 0.218$] at month 1), although the difference did not reach statistical significance in this study. Hyperreflective material dimensions were not significantly associated with the development of HRM-BR.

Table 8. Multivariate Logistic Model Showing Estimated Associations of HRM Morphologic Features at Baseline or Month 1 and Complete HRM Boundary Remodeling at Month 9

| Explanatory Variable* | At Baseline | | | At Month 1 | | |
|-----------------------|-------------|-------------|-------------|-------------|-------------|
|                       | OR (SE)     | P Value     | OR (SE)     | P Value     |
| Age, yrs              | 0.97 (0.02) | 0.140       | 0.97 (0.02) | 0.153       |
| HTC                   |             |             |             |             |
| Marginal              | 0.92 (0.71) | 0.918       | 0.31 (0.21) | 0.088       |
| Intralesional         | 0.06 (0.07) | 0.011       | 0.23 (0.12) | 0.004       |
| Outer boundary        |             |             |             |             |
| Partially visible     | 0.84 (0.37) | 0.697       | 1.34 (0.78) | 0.612       |
| Undetectable          | 1.62 (1.44) | 0.589       | 3.01 (2.14) | 0.120       |
| HRM dimension at fovea|             |             |             |             |
| HRM height, μm        | 1.00 (0.002) | 0.777       | 1.00 (0.002) | 0.839       |
| HRM width, μm         | 1.00 (0.003) | 0.312       | 1.00 (0.003) | 0.548       |

HRM = hyperreflective material; HTC = hypertransmission into choroid; OR = odds ratio; SE = standard error.

*The reference levels are “none” for HTC and “visible” for outer boundary; the reference value for age, HRM height, and HRM width is “0.” Boldface indicates $P < 0.05$. 

Figure 3. Frequencies of intraretinal hypertransmission into choroid, disruption of the external limiting membrane, and disruption of the ellipsoid zone, grouped by hyperreflective material (HRM) evolution pattern at baseline (white bars) and month 9 (gray bars). BCVA = best-corrected visual acuity.
Table 9. Agreement between Fibrosis Detected on FA and HRM on SD-OCT

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n = 205)</th>
<th>Month 3 (n = 152)</th>
<th>Month 9 (n = 136)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No HRM</td>
<td>Any subretinal HRM</td>
<td>Sub-RPE HRM only</td>
</tr>
<tr>
<td>Fibrosis on FA</td>
<td>No</td>
<td>14</td>
<td>157</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

FA = fluorescein angiography; HRM = hyperreflective material; RPE = retinal pigment epithelium; SD-OCT = spectral-domain OCT.

Agreement between HRM on SD-OCT and Fibrosis on FA

Fibrosis was graded as absent in all study eyes on FA at baseline and was found in 31 eyes at month 3, increasing to 61 eyes by month 9. The agreement between fibrosis on FA and HRM on SD-OCT is shown in Table 9 for baseline, month 3, and month 9. When fibrosis was present on FA, HRM was always detected on SD-OCT. When no HRM was seen on SD-OCT, fibrosis was never graded as present on FA. When the HRM was subretinal, the probability of detecting fibrosis on FA was extremely high compared with when the HRM was sub-RPE only at month 9 (Fisher exact test $P < 10^{-6}$).

Discussion

By systematically characterizing the HRM changes during antiangiogenic treatment on SD-OCT in a data set from a controlled clinical trial, we made several key observations. First, we characterized the timing and proportions of subretinal HRM transitioning from undefined to well defined. Second, we defined patterns of subretinal HRM evolution based on either complete resolution or alterations to its inner boundary when persistent. Third, we demonstrated that the HRM patterns have distinct relationships with BCVA. Fourth, we showed associations with MA development.

Hyperreflective material on OCT has been described as well defined or undefined based on its delineation and reflectivity.$^6,5$ It is known that, when persistent, undefined HRM changes to well defined with anti-VEGF therapy.$^7$ Subretinal hyperreflective material has been identified as a risk factor for unfavorable visual outcomes in nAMD in many studies.$^5,8–11$ However, to date, none has systematically characterized the compartmental localization and early temporal changes.

In our study, > 90% of eyes had HRM at treatment initiation; of these, < 20% had HRM located exclusively in the sub-RPE HRM compartment. Complete resolution of subretinal HRM occurred in one fifth of eyes by month 1 and only minimally increased up to month 9, similar to the findings of Pokroy et al.$^{11}$ However, others have reported higher resolution rates (e.g., 44.4% by 1 year in CATT)$^9$ despite a similar prevalence of subretinal HRM at baseline.$^9,12$ We contend that, in the presence of a remodeled inner boundary, residual HRM may have been classified as “resolved” in other studies, because this feature may have been construed as lying external to the RPE and, therefore, not subretinal. In our study, unlike in others,$^3,13$ when graded at baseline as subretinal, we deemed any persistent HRM (either remodeled or not) to be subretinal.

Subretinal HRM became well defined in one third of eyes within 1 week and in three quarters by month 1, reaching 90% by month 3, similar to another report.$^3$ We also provided a comprehensive characterization of the changes at the both inner and outer limits of persistent subretinal HRM during treatment and the development of a characteristic hyperreflective band continuous with the RPE adjacent to the lesion, which we termed HRM-BR. On further classification as complete or partial/absent, around one half of study eyes had complete HRM-BR, with this process visible as early as 1 month.

Morphologic changes that are analogous to HRM-BR were reported by Dolz-Marco et al,$^{14}$ who introduced the concept of “envelopment of the MNV by the RPE.” They described an “infrequent” regression of type 2 into type 1 MNV lesions after anti-VEGF therapy, which was associated with better BCVA.$^{14}$ Although Casalino et al$^{13}$ reported “enveloped HRM” at a prevalence of 26.7%, neither study provided a full characterization of the temporal changes by compartmental location.

We showed negative cross-sectional associations between foveal HRM width and BCVA at all visits, in accord with a prior report.$^9$ However, foveal HRM height was not associated with BCVA at any time point. The horizontal extent of the lesion is likely more relevant to BCVA, because a larger area of RPE and photoreceptors is affected.$^{13}$ A novel finding was the association between better BCVA and complete HRM-BR. Interestingly, even at the treatment-naïve stage, there was a gradient of decreasing BCVA by the 4 HRM evolution patterns, indicating the presence of predictive baseline characteristics in both HRM and RPE that have an impact on subsequent functional outcome.

We assessed HRM-associated MA features (i.e., HTC, ELMD, and EZD), as described by the CAM group.$^3$ We observed that intralesional HTC was present in 13.0% of eyes at baseline and incident in 28.3% at month 9. An association between HTC and HRM has not been investigated previously. In the IVAN trial, frequencies of 9.6% MA at baseline and 24.4% incident MA at month 24 were reported inside the footprint of the neovascular lesion during anti-VEGF treatment,$^{15}$ and, although the definitions for MA and observation periods differ, our results were similar. The frequencies of MA reported in HARBOR using CAM criteria are also comparable to ours.
The present analysis provides additional information on HRM dynamics and outer retinal preservation, which are critical to BCVA. We observed lower ELMD and EZD rates in eyes that were free of subretinal HRM at treatment initiation or showed full resolution. When subretinal HRM persisted, ELM/EZ was better preserved if eyes underwent complete HRM-BR, which is in accord with the lower rates of intralesional HTC contributing to the better BCVA in these eyes. Kumar et al 17 found that SHRM resolution was associated with intact EZ, whereas persistent SHRM correlated with disrupted EZ; in the CATT trial, EZD, but not ELMD, was related to the presence of underlying SHRM. 9 Of note, MA development is likely multifactorial and may partly evolve independently from neovascular lesions.14

Our logistic regression model revealed predictive factors associated with complete HRM-BR. The odds of complete HRM-BR, although not statistically significant in this study, may increase when the outer boundary is undetectable, a finding that was infrequently observed at baseline (7.5%) or month 1 after treatment initiation (20.9%) but rose to 57.6% at month 9. The presence of a well-defined dense inner boundary may result in poor penetration of the signal and lead to an undetectable outer boundary. In addition, increased HRM thickness, intraretinal fluid, and blood may alter the visibility of the outer boundary. However, we do not discount the possibility that RPE cells at the outer boundary migrate to form an inner boundary. In vivo and postmortem studies support the view that RPE cells can migrate and envelop nAMD vessel complexes.13,14,19–22 The regression model also found intralesional HTC and older age at baseline to be associated with lower odds of complete HRM-BR. Our findings indicate that an adequate RPE monolayer is needed for complete HRM-BR, serving as a proxy for a functioning RPE layer and preserving photoreceptor function. This is in accord with the better BCVA outcome and lower frequencies of intralesional HTC, ELMD, and EZD in eyes with complete HRM-BR compared with those without. Histopathologic correlation studies are needed to validate our hypothesis that a remodeled inner boundary is constituted from RPE cells.

Our results demonstrate that visual outcomes are not only impacted by persistent HRM but are also strongly influenced by its location in relation to the RPE and its inner boundary changes. There is support in the literature that persistent, well-defined HRM is a proxy for fibrosis.5,11 However, a consensus definition of fibrosis on OCT has not yet been reached,23 and, to the best of our knowledge, no study has examined agreement between fibrosis detected on FA and HRM detected on OCT. We observed that in the absence of any HRM on OCT, fibrosis was never graded as present on FA. Conversely, when fibrosis was graded present on FA, HRM was always present on OCT. Notably, the location of HRM played an important role in the detectability of fibrosis on FA. When HRM was sub-RPE only, the probability of detection on FA was extremely low, in contrast with the high probability of detection when the HRM was subretinal.

The strengths of our study are its large size and use of data from a clinical trial with standardized BCVA measurements, frequent follow-up visits, and high-quality images. However, this is a post hoc retrospective analysis and further studies are needed to confirm our findings. Our study has several other limitations, such as lack of information from other imaging modalities. Blood, better seen on color fundus photography than OCT, may behave differently than other forms of HRM, which might bias our results.5 Other factors that have an impact on visual outcome were not considered in the present analysis, such as angiographic characteristics of MNV size, residual IRF, and abnormal retinal thickness.24 Further study is needed to validate the results of our work, when taking into consideration these factors.

In summary, we defined 4 HRM patterns that influenced BCVA outcomes. Our work suggests that the appearance of complete HRM-BR in persistent subretinal HRM is associated with better BCVA outcomes and lower odds of MA. In contrast, persistent HRM without complete HRM-BR can be a critical OCT biomarker and potential end point in future nAMD trials due to its association with worse functional and anatomic outcomes. The analysis of predictive factors for HRM-BR identified novel associations with HRM outer boundary detectability, age, and MA, providing a framework to further study OCT biomarkers in the outer retina/RPE/Bruch’s membrane complex in nAMD eyes under antiangiogenic treatment.

Data Sharing Statement

For eligible studies, qualified researchers may request access to individual patient level clinical data through a data request platform. At the time of writing this manuscript, request platform is Vivli: https://vivli.org/ourmember/roche/. For up to date details on Roche’s Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here: https://go.roche.com/data_sharing. Anonymized records for individual patients across more than one data source external to Roche cannot, and should not, be linked due to a potential increase in risk of patient re-identification.

Acknowledgments

Assistance in formatting and submission of this manuscript was provided by Envision Pharma Group, with no writing support.
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11. Pokroy R, Mimouni M, Barayev E, et al. Prognostic value of limiting membrane disruption; ELM = external limiting membrane disruption; EZ = ellipsoid zone; EZD = ellipsoid zone disruption; FA = fluorescein angiography; HRM = hyperreflective material; HRM-ER = hyperreflective material boundary remodeling; HTC = hypertransmission into choroid; MA = macular atrophy; MNV = macular neovascularization; nAMD = neovascular age-related macular degeneration; OR = odds ratio; RPE = retinal pigment epithelial; SD-OCT = spectral-domain OCT; SE = standard error; SHRM = subretinal hyperreflective material.

Keywords: Hyperreflective material, Fibrosis, Neovascular age-related macular degeneration, Antiangiogenic treatment, Spectral-domain OCT.

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References
Recurrence of Intraretinal Infiltration of Vitreoretinal Lymphoma

OCT angiography of a 53-year-old man with vitreoretinal lymphoma showed hyperreflective punctate lymphoma infiltration lesions distributed around retinal vessels on the en face image, which resemble flower buds on branches and are called perivascular flower-bud-like lesions for short. In cross-sectional OCT, perivascular flower-bud-like lesions appeared as full-thickness intraretinal lesions (A). After intravitreal methotrexate chemotherapy, partial remission was achieved (B). Due to progression to central nervous system disease, methotrexate-based systemic chemotherapy was initiated and ocular treatment was suspended. After 4 cycles of systemic chemotherapy, an early recurrence of perivascular flower-bud-like lesions was observed at a subsequent ophthalmic visit (C). (Magnified version of Figure A-C is available online at www.ophthalmologyretina.org).

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