AMERICAN ACADEMY™ OF OPHTHALMOLOGY

Predictive Value of Retinal Morphology for Visual Acuity Outcomes of Different Ranibizumab Treatment Regimens for Neovascular AMD

Sebastian M. Waldstein, MD,[1] Jonathan Wright, MSc,[2] James Warburton, MBBS,[3] Philippe Margaron, PhD,[3] Christian Simader, MD, MSc,[1] Ursula Schmidt-Erfurth, MD[1]

Purpose: To establish the predictive value of defined retinal morphologic parameters on visual outcomes and re-treatment needs in patients with neovascular age-related macular degeneration (nAMD) receiving ranibizumab treatment.

Design: Post hoc analysis of a prospective, 12-month, multicenter, phase IIIb trial.

Participants: Three hundred fifty-three treatment-naïve patients with nAMD.

Methods: Available data from 319 treatment-naïve patients receiving ranibizumab 0.3 mg monthly (frequent regimen; n = 102) or ranibizumab 0.3 or 0.5 mg quarterly (pooled 0.3/0.5 mg = infrequent regimen; n = 217) were analyzed to assess the correlations between baseline retinal morphologic parameters and best-corrected visual acuity (BCVA) change (structure−function correlations). The BCVA was measured at monthly visits. Optical coherence tomography scans were acquired monthly for quantitative measures of the central retinal thickness and qualitative assessment of retinal morphologic features. Assessed morphologic parameters included intraretinal cystoid fluid (IRC), subretinal fluid (SRF), pigment epithelial detachment, and vitreomacular interface configuration classification comprising vitreomacular adhesion and posterior vitreous detachment (PVD). An analysis of covariance was conducted to evaluate the impact of retinal morphologic features on BCVA change at month 12.

Main Outcome Measures: Change in BCVA from baseline to month 12 compared between frequent and infrequent treatment arms.

Results: Relevant predictive factors for BCVA change at month 12 were baseline SRF ($P = 0.05$), PVD ($P = 0.03$), IRC ($P = 0.05$), treatment frequency ($P < 0.01$), and BCVA ($P < 0.01$). The presence of both SRF and PVD at baseline was associated with similar BCVA gains regardless of treatment frequency (mean difference in BCVA gains at month 12 of +2.6 letters in favor of infrequent treatment). Subretinal fluid was present in 71% of patients, and PVD was present in 64% of patients.

Conclusions: In patients with both SRF and PVD at baseline, similar BCVA outcomes were observed regardless of treatment frequency. These patients may require less frequent treatments compared with patients without SRF, without PVD, or without either who may require more frequent injections for maintenance of vision. This finding may have implications in clinical practice by helping to tailor an individualized re-treatment interval in nAMD patients. *Ophthalmology 2016;123:60-69 © 2016 by the American Academy of Ophthalmology.*

Supplemental material is available at www.aaojournal.org.

With a global prevalence estimated at 8.7%,[1] age-related macular degeneration (AMD), including both neovascular and nonneovascular forms, is a leading cause of worldwide blindness in the elderly. Several multicenter clinical trials have established the efficacy and safety of anti−vascular endothelial growth factor (VEGF) agents, including ranibizumab (Lucentis; Novartis AG, Basel, Switzerland, and Genentech, South San Francisco, CA), in the management of neovascular AMD (nAMD).[2–4] However, these trials also have revealed individual heterogeneity in the magnitude and durability of the stabilization or restoration of visual acuity (VA) in response to anti-VEGF therapy. Although some evidence has suggested that monthly treatment is more effective than less frequent dosing

http://dx.doi.org/10.1016/j.ophtha.2015.09.013
ISSN 0161-6420/15

regimens,[5–7] other studies have shown good VA outcomes with personalized regimens such as pro re nata (PRN)[8,9] or treat-and-extend regimens.[10,11] Given the financial and logistical burden of frequent administration, added to concerns over the risk of overdosing and the small but still real intravitreal procedural risk, the reduction of treatment frequency to the minimum required to control the disease is an important goal in the management of nAMD.

In this respect, the identification of retinal morphologic parameters (or imaging biomarkers) that could guide less frequent treatment reliably would be of great assistance; however, this still represents an unmet medical need. Although retinal characteristics such as central retinal thickness (CRT) and the presence of intraretinal cystoid fluid (IRC) have been associated with VA outcomes, the exact mechanisms responsible for individual response patterns remain unclear.[12]

Optical coherence tomography (OCT) has been used widely, in addition to quantitative metrics, for qualitative assessment of different retinal compartments (intraretinal, subretinal, and subpigment epithelial).[13] A detailed qualitative analysis of these compartments in patients with nAMD may reveal functionally relevant microstructural changes not captured by measurements of total CRT. These include retinal pigment epithelium changes, IRC, pigment epithelial detachment (PED), subretinal fluid (SRF), as well as pathologic features of the vitreomacular interface (VMI) such as vitreomacular adhesion or posterior vitreous detachment (PVD). Some of these retinal morphologic parameters already have been identified as predictors of treatment responses; however, the value of morphologic parameters as predictors of VA responses as a function of different treatment regimens has yet to be determined.[14–17]

The Efficacy and Safety of Ranibizumab in Patients with Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration (EXCITE) study,[18] designed to compare the efficacy of 2 fixed treatment regimens (frequent vs. infrequent) of intravitreal ranibizumab in patients with nAMD, was deemed appropriate for post hoc analysis investigating structure–function correlations in relation to treatment frequency. Although results of the EXCITE study suggested the superiority of the frequent treatment regimen, this analysis was designed to identify patients who may not derive added benefit from frequent versus less frequent injections based on their baseline retinal characteristics. The objective thus was to establish the predictive value of defined retinal morphologic parameters on visual outcomes and re-treatment needs in patients with nAMD receiving ranibizumab treatment.

Methods

Study Design

This post hoc analysis was conducted on data obtained from the EXCITE study (clinicaltrials.gov identifier, NCT00275821). Details on study design, inclusion and exclusion criteria, and patient assessment have been published.[18] The EXCITE study was conducted in a total of 59 study centers in 16 European countries, Australia, Brazil, Israel, and Turkey in compliance with the tenets of the Declaration of Helsinki and the International Conference on Harmonization of Good Clinical Practice guidelines. Approval was obtained from the independent ethics committee or institutional review board at each participating center. All patients provided written informed consent before enrollment into the trial.

The trial was designed to assess the efficacy and safety of monthly versus quarterly dosing of intravitreal ranibizumab in patients with nAMD. Key inclusion criteria were older than 50 years of age, active primary or recurrent subfoveal choroidal neovascularization secondary to AMD (all lesion types), and a best-corrected visual acuity (BCVA) score from 24 to 73 letters (Early Treatment Diabetic Retinopathy Study charts; initial testing distance, 4 m). Key exclusion criteria included a wide range of pretreatments and concomitant disease entities compromising VA.

A total of 353 patients were assigned randomly to monthly injections of ranibizumab 0.3 mg (total of 12 injections per year) or quarterly injections of ranibizumab 0.3 or 0.5 mg after a loading phase of 3 consecutive monthly injections (total of 6 injections per year) in a 1:1:1 ratio, with a balanced distribution for lesion type, size, BCVA, age, and gender. Patients in the quarterly arm received monthly sham injections after the loading phase for masking purposes. Because no difference in any outcome parameter was observed between the ranibizumab 0.3-mg and 0.5-mg doses, all patients receiving quarterly injections were pooled in a single arm for this analysis.[18] Henceforth, the 0.3-mg monthly regimen is referred to as *frequent* and the 0.3- or 0.5-mg quarterly regimen is referred to as *infrequent*.

Study Assessments

The main outcome measures were change in BCVA and CRT from baseline to month 12 and the incidence of adverse events. Best-corrected VA was measured at each monthly visit using Early Treatment Diabetic Retinopathy Study charts. A complete and standardized eye examination was carried out monthly after pupil dilation and before active or sham injection. Time-domain OCT (Carl Zeiss Meditec, Dublin, CA) scans were acquired by certified operators at each monthly visit using the fast macular thickness map scan mode (six 6-mm radial sections with a resolution of 128 A-scans per section) for quantitative measures of the CRT, and a 6-mm crosshair scan mode (two 6-mm sections perpendicular to each other with a resolution of 512 A-scans per section) for qualitative assessment of retinal morphologic features.

An independent masked central reading center, the Vienna Reading Center, reviewed raw, masked OCT images sent digitally from all participating sites for each monthly assessment of CRT and retinal morphologic features, whereas a separate independent masked central reading center (Digital Angiography Reading Center) classified the lesion types and assessed lesion area and leakage activity based on fluorescein angiography at months 6 and 12.

All OCT scans were graded for the presence of IRC, SRF, and PED using validated computer-assisted grading software by graders specifically trained according to the individual protocol of the Vienna Reading Center. Intraretinal cystoid fluid was described as round, minimally reflective spaces within the neurosensory retina, and SRF was described as a nonreflective space between the neurosensory retina and the retinal pigment epithelium. Pigment epithelial detachment was defined as a focal elevation of the reflective retinal pigment epithelium band over an optically clear or moderately reflective space, either higher than 200 μm or wider than 400 μm.[19]

In addition, classification of the vitreomacular interface configuration, including vitreomacular adhesion and PVD, was determined based on the positioning of the posterior vitreous boundary, as previously described and validated.[15] This boundary layer was described as a thin, continuous, reflective layer at or above the level of the internal limiting membrane of the retina.

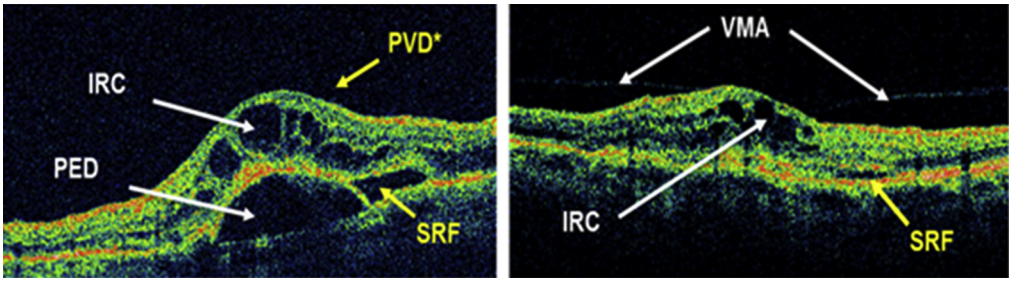


Figure 1. Optical coherence tomography images of eyes with neovascular age-related macular degeneration showing the presence of various retinal morphologic features. *Posterior vitreous boundary is not visible. IRC = intraretinal cystoid fluid; PED = pigment epithelial detachment; PVD = posterior vitreous detachment; SRF = subretinal fluid; VMA = vitreomacular adhesion.

The scan set was graded as vitreomacular adhesion if a preretinal vitreous boundary in direct contact with the central macular surface could be identified. If the posterior vitreous boundary could not be identified on any section of the scan set, it was assumed that the boundary was located beyond the scanning range, and the scan set was graded as PVD.

Grading supervisors reviewed all scans that were unclear to the graders as well as a random 10% of scans for quality control of the grading process. Examples of the grading categories and related morphologic OCT findings are provided in Figure 1.

Statistical Analysis

An analysis of covariance was used to assess the impact of OCT-based retinal morphologic features, adjusting for the presence of IRC, SRF, PED, and classification of VMI configuration (PVD vs. other) on change in BCVA from baseline to month 12. In addition to these retinal morphologic parameters, other potential predictor variables included treatment frequency, ranibizumab dose (0.3 vs. 0.5 mg), and the baseline values of BCVA and CRT. Based on the results of the full model analysis, another analysis of covariance was conducted using a simplified model analysis adjusting for parameters found to be the most relevant in the full model (using a backward-stepwise approach where $P < 0.1$ was used for variable retention).

The variables identified as predictive of VA gain then were analyzed further to estimate how they interact with treatment frequency. The purpose was to identify any variables associated with visual responses that were different between frequent and infrequent treatments compared with those of the overall population. The overall P values for the interaction terms were noted, and for those found to be statistically significant, the differences in responses between frequent and infrequent treatments were assessed. Because this analysis was exploratory, any numerical differences identified were not analyzed statistically.

The analyses were carried out for the intent-to-treat population (i.e., all randomized patients) with available retinal morphologic data. The last observation carried forward method was used to impute missing BCVA values. All analyses were performed with SAS software version 9.4 (SAS Inc, Cary, NC).

Results

Patients

Of the 353 patients randomized in the EXCITE study, 319 patients for whom data on retinal morphologic features were available were included in this post hoc analysis. A total of 217 patients received infrequent injections and 102 patients received frequent injections. Baseline characteristics of the 353 patients enrolled in the EXCITE trial were comparable across the 3 treatment groups in the intent-to-treat population.[18] Among the patients included in this post hoc analysis, the mean age and baseline ocular characteristics, including BCVA, CRT, lesion size, as well as the distribution of morphologic variables, were well matched in the frequent and infrequent treatment arms (Table 1).

Analysis of Covariance

In the full model analysis, 3 morphologic factors were identified as significant predictors of BCVA gains at month 12, namely SRF ($P = 0.05$), PVD ($P = 0.03$), and IRC ($P = 0.05$; Table 2). Other factors found to be significantly predictive of BCVA gains were treatment frequency ($P = 0.04$) and baseline BCVA ($P < 0.01$). Interaction terms between treatment frequency and SRF or PVD status also were tested separately and were found to be significant ($P < 0.001$ for SRF; $P = 0.007$ for PVD). To facilitate the interpretation of the estimates for the main effects, these interaction terms were not included in the model for Table 3. An interaction test between treatment frequency and IRC status showed no evidence for an interaction.

The simplified model analysis was subsequently conducted adjusting for treatment frequency, as well as baseline BCVA, PVD, and SRF status. Both PED and CRT were not analyzed further because they were not found to be significantly predictive of BCVA gain in the full model analysis after backward-stepwise covariate selection. In this simplified model analysis, factors that were found to predict BCVA change significantly at month 12 were presence of PVD at baseline ($P = 0.03$), presence of IRC at baseline ($P = 0.03$), baseline BCVA ($P < 0.01$), and treatment frequency ($P < 0.01$; Table 3). Subretinal fluid status was no longer strictly predictive of BCVA change at the 0.05 level ($P = 0.10$).

Comparison of Visual Outcomes with Different Treatment Frequencies

The impacts of these morphologic factors on BCVA gains then were analyzed. Differences in BCVA gains between the frequent and infrequent treatment arms were assessed as a function of the presence or absence of SRF, PVD, and IRC. Overall results from the EXCITE study demonstrated that BCVA mean changes from baseline to month 12 were +8.0 and +3.4 letters with frequent and infrequent treatment, respectively, representing a mean difference in BCVA gains of +4.6 letters in favor of the frequent regimen.[15] This post hoc analysis showed that patients without SRF at baseline also had higher BCVA gains with frequent dosing

Table 1. Baseline Ocular Characteristics of All Patients with Subretinal Fluid and Vitreomacular Interface Data at Baseline (Intent-to-Treat Population)

Baseline Characteristics	Treatment Group: *Frequent* (*n* = 92)	Treatment Group: *Infrequent* (*n* = 185)	Total (n = 277)
BCVA (letters)			
No.	91	185	276
Mean (SD)	56.2 (12.7)	55.9 (12.8)	56.0 (12.7)
Median (range)	59 (24–74)	58 (17–78)	58 (17–78)
Q1–Q3	46.0–67.0	47.0–67.0	46.5–67.0
CRT (μm)			
No.	92	183	275
Mean (SD)	324 (97.6)	326 (95.8)	325 (96.2)
Median (range)	314 (160–588)	317 (145–767)	316 (145–767)
Q1–Q3	249–394	265–367	259–379
SRF, no. (%)			
No	23 (25.0)	58(31.4)	81 (29.2)
Yes	69 (75.0)	127 (68.6)	196 (70.8)
PVD, no. (%)			
No	34 (37.0)	66 (35.7)	100 (36.1)
Yes	58 (63.0)	119 (64.3)	177 (63.9)
IRC, no. (%)			
No	42 (45.7)	89 (48.1)	131 (47.3)
Yes	48 (52.2)	95 (51.4)	143 (51.6)
PED, no. (%)			
No	15 (16.3)	41 (22.2)	56 (20.2)
Yes	77 (83.7)	142 (76.8)	219 (79.1)
Lesion size (mm^2)			
No.	92	185	277
Mean (SD)	6.8 (6.0)	8.0 (6.4)	7.6 (6.2)
Median (range)	6 (0–23)	7 (0–32)	7 (0–32)
Q1–Q3	1.0–10.0	3.0–12.1	2.8–11.4
Age (yrs)			
No.	92	185	277
Mean (SD)	75.1 (8.5)	75.5 (6.8)	75.4 (7.4)
Median (range)	76 (52–93)	76 (52–92)	76 (52–93)

BCVA = best-corrected visual acuity; CRT = central retinal thickness; IRC = intraretinal cystoid fluid; PED = pigment epithelial detachment; PVD = posterior vitreous detachment; Q1 = first quartile; Q3 = third quartile; SRF = subretinal fluid; SD = standard deviation.

Table 2. Variables in Full Analysis of Covariance Model for Mean Change in Best-Corrected Visual Acuity*

Variable	Estimate	Standard Error	95% Confidence Interval	*P* Value
Baseline BCVA	−0.2	0.07	−0.4 to −0.1	<0.01
Treatment, frequent (vs. infrequent)	4.1	1.92	0.3–7.9	0.04
Baseline CRT	0.0	0.01	−0.0 to 0.0	0.85
Baseline SRF absent (vs. present)	−3.5	1.81	−7.1 to 0.0	0.05
Baseline PVD absent (vs. present)	−3.5	1.62	−6.7 to −0.4	0.03
Baseline IRC absent (vs. present)	3.5	1.76	−0.0 to 6.9	0.05
Baseline PED absent (vs. present)	2.5	2.01	−1.5 to 6.4	0.22
Ranibizumab dose, 0.3 mg (vs. 0.5 mg)	0.8	1.92	−3.0 to 4.6	0.67

BCVA = best-corrected visual acuity; CRT = central retinal thickness; IRC = intraretinal cystoid fluid; PED = pigment epithelial detachment; PVD = posterior vitreous detachment; SRF = subretinal fluid.
*Adjusting for baseline BCVA (letters), treatment, baseline CRT (micrometers), baseline SRF, PVD status, baseline IRC, baseline PED, and ranibizumab dose.

compared with infrequent dosing (Fig 2). However, when SRF was present at baseline, visual gains of patients receiving infrequent treatment were comparable with those of patients receiving frequent treatment. The differences in mean BCVA letter gain at month 12 between frequent and infrequent treatment arms were +12.3 for patients without SRF and +0.9 for patients with SRF at baseline (Fig 2). In addition, patients in the infrequent treatment arm had higher BCVA gains when SRF was present at baseline compared with patients without SRF (Fig 2).

Similarly, patients in the infrequent treatment arm had higher BCVA gains when PVD was present at baseline compared with patients without PVD (Fig 3). As a result, although patients without PVD at baseline demonstrated higher BCVA gains with frequent treatment, patients with PVD had similar visual outcomes regardless of treatment frequency (Fig 3). For patients without PVD at baseline, the difference in mean BCVA letter gain at month 12 between the frequent and infrequent treatment arms was +9.1, compared with +0.9 for patients with PVD at baseline (Fig 3).

This result was characterized further by analyzing the combination between SRF and PVD parameters. Patients with both SRF and PVD present at baseline had similar visual outcomes regardless of treatment frequency, with a mean BCVA letter gain difference of −2.6 letters between frequent and infrequent treatment arms at month 12 (Fig 4). However, patients with SRF who did not have PVD present at baseline did not respond as well with infrequent treatment compared with frequent treatment (mean BCVA letter gain difference of +7.0; between frequent and infrequent treatment arms Fig 4).

Conversely, patients without SRF at baseline benefited more from frequent treatments regardless of PVD status (Fig 5). In this group of patients without SRF, the difference in mean BCVA letter gain at month 12 between frequent and infrequent treatment arms was +10.6 letters when PVD was absent at baseline and +15.3 letters when PVD was present (Fig 5). The outcomes are summarized in Figure 6, which displays the mean changes in BCVA at month 12 in response to the 2 ranibizumab regimens based on PVD and SRF status at baseline.

As expected by the lack of interaction between IRC status and treatment regimen, IRC did not have any significant impact on differences in visual outcomes as a function of treatment frequency. Patients performed better with frequent treatment than with infrequent treatment by the same margin regardless of whether IRC was present at baseline (mean BCVA gain difference of +4.6 and +4.3 letters for IRC being present and IRC being absent, respectively; Fig 7, available at www.aaojournal.org).

The distribution of IRC and PED as well as mean BCVA, CRT, and lesion size at baseline as a function of SRF and PVD status at

Table 3. Estimates of Variables in Simplified Analysis of Covariance Model for Mean Change in Best-Corrected Visual Acuity*

Variable	Estimate	Standard Error	95% Confidence Interval	P Value
Baseline BCVA	−0.2	0.07	−0.3 to −0.1	<0.01
Treatment, frequent (vs. infrequent)	4.4	1.65	1.2–7.7	<0.01
Baseline SRF absent (vs. present)	−2.8	1.71	−6.2 to −0.6	0.10
Baseline PVD absent (vs. present)	−3.5	1.60	−6.6 to −0.3	0.03
Baseline IRC absent (vs. present)	3.6	1.67	0.3–6.9	0.03

BCVA = best-corrected visual acuity; IRC = intraretinal cystoid fluid; PVD = posterior vitreous detachment; SRF = subretinal fluid.
*Adjusting for baseline BCVA (letters), treatment, baseline SRF, PVD status, and baseline IRC.

baseline is given in Table 4. Although mean BCVA, CRT, and lesion size at baseline were relatively well balanced between the different SRF and PVD statuses, the proportion of patients with IRC or PED varied depending on their SRF status at baseline. In patients with SRF, the proportion of IRC was found to be lower and that of PED was found to be higher compared with patients without SRF, regardless of their PVD status.

Discussion

This post hoc analysis of the EXCITE study investigated the influence of several retinal morphologic parameters, such as SRF, VMI (including PVD), PED, and IRC, on visual outcomes of ranibizumab therapy for nAMD as a function of different treatment regimens (i.e., treatment frequency). The analysis identified the presence of SRF, PVD, and IRC as key predictive factors of BCVA change at month 12, along with baseline BCVA and treatment regimen. An analysis of covariance based on this result also suggested that IRC and PVD are the predominant predictive morphologic factors compared with SRF. Furthermore, and most important, patients with both SRF and PVD at baseline responded as well to infrequent treatment with no further benefits obtained from more frequent injections (mean BCVA letter gain difference at month 12 of 2.6 letters in favor of infrequent treatment). This is in contrast with the results of the entire patient group in the EXCITE study, which suggested superiority of the frequent treatment regimen over the infrequent regimen.[18] As shown in Figure 6, the substantial differences in visual outcomes observed between the 2 regimens in patients without SRF or PVD at baseline drive the result observed in the overall study population.

These findings are in line with published results that identified PVD as an imaging biomarker of patients with nAMD for whom infrequent treatment may be sufficient to maintain optimal outcomes.[15,16] In a previous subanalysis of data from the EXCITE study, VMI was identified as a potential predictor of VA outcomes and re-treatment needs with ranibizumab.[15] Similarly, a recent post hoc analysis of another randomized multicenter trial also found that VMI status affects functional outcomes and retreatment requirements, confirming that patients with PVD achieve optimal results with fewer injections.[16]

By analyzing the impact of other morphologic parameters from the relevant retinal compartments, this analysis further specifies the group of patients who may benefit from infrequent treatment by adding baseline SRF as a key predictor of retreatment requirements. These results suggest that the subgroup of patients with both SRF and PVD present at baseline may be the most likely to have their disease optimally controlled with a reduced injection frequency.

Most patients (70.8%) had SRF at baseline, a percentage in line with previous studies.[12] In addition, PVD constitutes the most frequent condition of the VMI in the typical AMD age group. In this study population, it was reported in 63.9% of patients, a percentage also in line with previous studies.[20] If confirmed, the finding of this analysis therefore

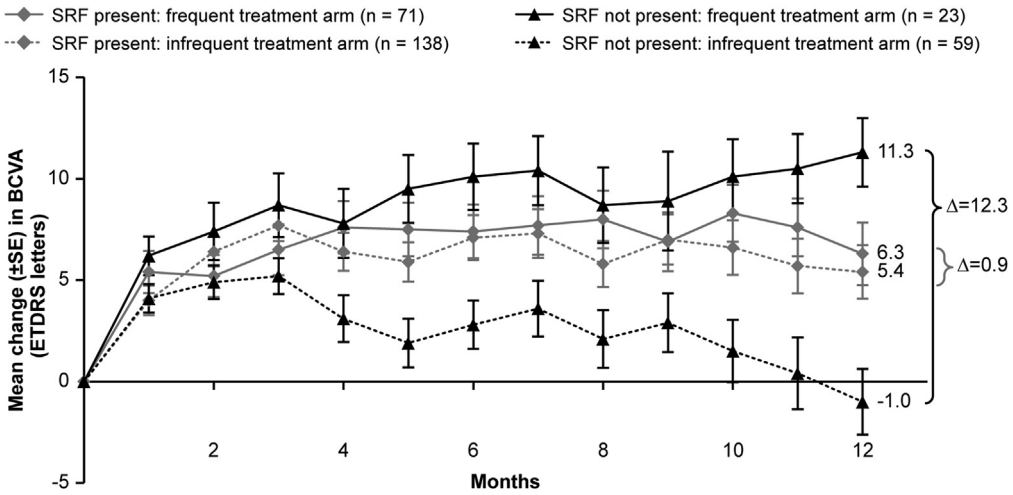


Figure 2. The mean change in best-corrected visual acuity (BCVA) from baseline to month 12 in patients with or without subretinal fluid (SRF) at baseline (intent-to-treat population [last observation carried forward]). ETDRS = Early Treatment Diabetic Retinopathy Study; SE = standard error.

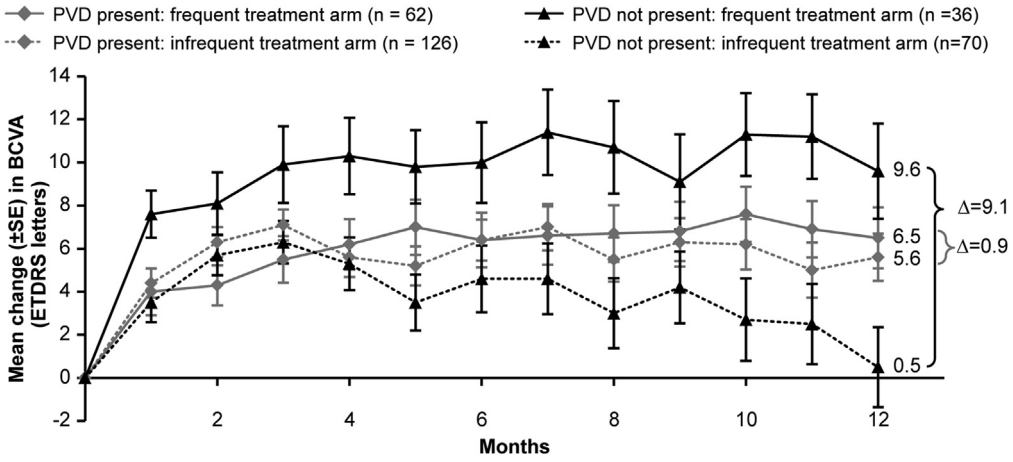


Figure 3. The mean change in best-corrected visual acuity (BCVA) from baseline to month 12 in patients with or without posterior vitreous detachment (PVD) at baseline (intent-to-treat population [last observation carried forward]). ETDRS = Early Treatment Diabetic Retinopathy Study; SE = standard error.

may have significant implications on individualized treatment of nAMD with anti-VEGF therapy. Imaging biomarkers such as those investigated here have the potential to enable physicians to reduce treatment frequency while maintaining optimal visual outcomes in a significant proportion of patients.

Although reviews of a few trials concluded that monthly ranibizumab treatment had superior efficacy over less frequent injections,[5,7] other multicenter randomized controlled trials, including Comparison of Age-Related Macular Degeneration Treatments Trials (CATT),[8] Phase III, Double-Masked, Multicenter, Randomized, Active Treatment-Controlled Study of the Efficacy and Safety of 0.5-mg and 2.0-mg Ranibizumab Administered Monthly or on an As-Needed Basis (PRN) in Patients with Subfoveal Neovascular Age-Related Macular Degeneration (HARBOR),[9] and Inhibition of Vascular Endothelial Growth Factor in Age-Related Choroidal Neovascularization (IVAN),[21] found PRN treatment to be similarly effective to monthly injections in improving visual outcomes after 1 year. One possible explanation for these conflicting findings is that re-treatment criteria were more exhaustive and factored in OCT-derived parameters in the HARBOR, CATT, and IVAN studies compared with earlier PRN trials. It also should be noted that in Ranibizumab in Subjects with Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration (PIER) and EXCITE, infrequent regimens were underdosed for most patients, with no possibility to adjust the treatment in the case of poor response, as in PRN. The finding of the present analysis now suggests that disparity in baseline morphologic characteristics, including PVD and SRF, also may account partly for the inconsistency of these trial results. Thus, this finding also may have potential implications for the design of future trials, which may benefit from stratified randomization according to the presence of these 2 biomarkers.

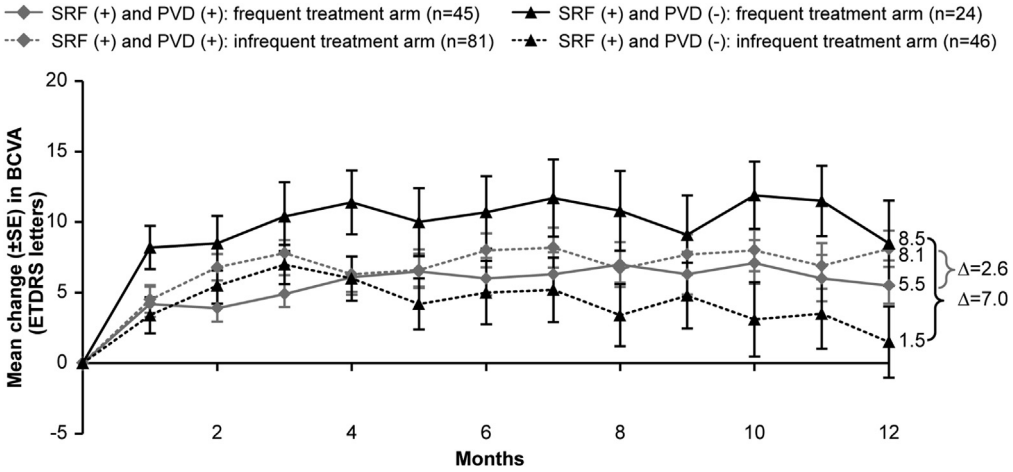


Figure 4. The mean change in best-corrected visual acuity (BCVA) from baseline to month 12 in patients with subretinal fluid (SRF) and with or without posterior vitreous detachment (PVD) at baseline (intent-to-treat population [last observation carried forward]). ETDRS = Early Treatment Diabetic Retinopathy Study; SE = standard error.

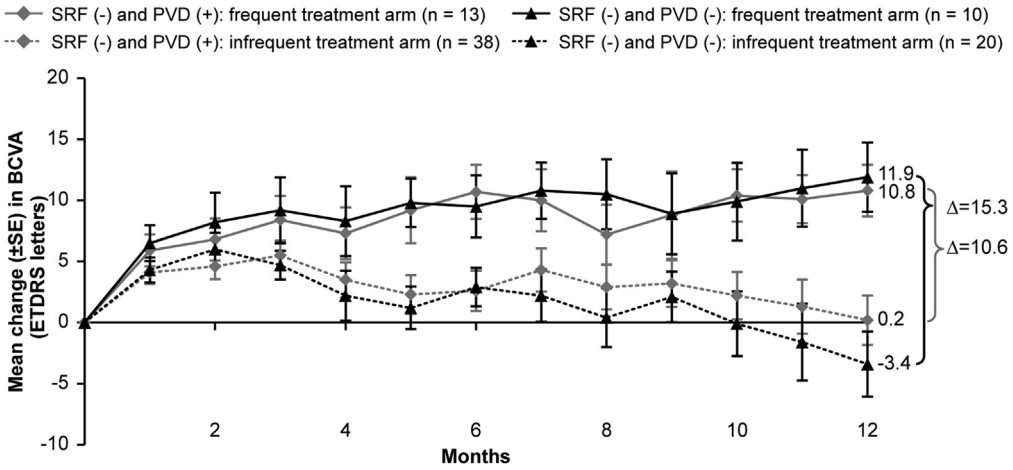
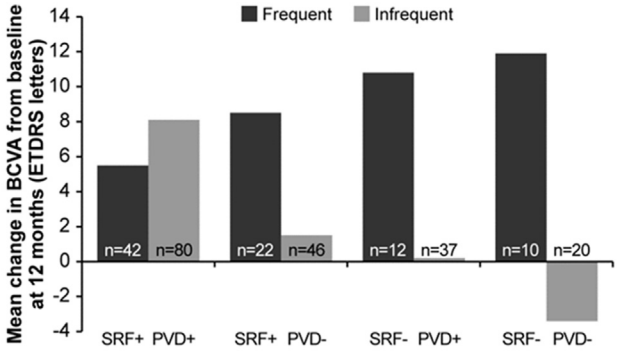


Figure 5. The mean change in best-corrected visual acuity from baseline to month 12 in patients without subretinal fluid (SRF) and with or without posterior vitreous detachment (PVD) at baseline (intent-to-treat population [last observation carried forward]). ETDRS = Early Treatment Diabetic Retinopathy Study; SE = standard error.

Other OCT-derived imaging biomarkers have been identified in AMD, including CRT and IRC. However, it is now recognized that CRT, particularly after the loading phase, has poor sensitivity for detecting change in VA compared with other markers.[12,22] Intraretinal cystoid fluid is exceptionally functionally relevant because its presence at baseline has been correlated with lower VA and reduced VA gains in general.[12,23,24] The functional relevance of IRC has been confirmed in this analysis, in which IRC status also was found to be predictive of BCVA gain (estimate for mean BCVA change of +3.6 when IRC is absent vs. present). However, it is important to differentiate between imaging biomarkers for overall VA outcomes independent of drug or regimen (such as IRC) and imaging biomarkers for VA outcomes as a function of treatment regimens (SRF and PVD). These results suggest that IRC at baseline does not change the relative effect of frequent and infrequent treatments; therefore, IRC status may not be relevant in predicting visual gain as a function of particular treatment regimens. Further analyses evaluating dynamic change in characteristics are ongoing, but currently no imaging biomarkers have been established as reliable predictors of treatment response. By focusing on anatomic characteristics at baseline, this post hoc analysis suggests that combined alterations of SRF and PVD have the potential to fill this gap as predictors of the need for re-treatment, thereby guiding regimen choice in individual patients with nAMD.



	Baseline BCVA (SD)			
	SRF+PVD+	SRF+PVD-	SRF-PVD+	SRF-PVD-
Frequent	56.7 (12.3)	56.5 (12.7)	52.4 (15.5)	58.5 (11.2)
Infrequent	56.9 (12.2)	56.3 (10.7)	53.3 (15.0)	56.1 (15.2)

Figure 6. The mean change in best-corrected visual acuity (BCVA) at month 12 in patients as a function of posterior vitreous detachment (PVD) and subretinal fluid (SRF) status (intent-to-treat population [last observation carried forward]). ETDRS = Early Treatment Diabetic Retinopathy Study; SD = standard deviation.

The question remains as to why patients with SRF and PVD may not require intensive treatment. With regard to PVD, it was hypothesized previously that pharmacokinetic mechanisms may account for the differential response of the various VMI subtypes.[15] The presence of PVD, which results in a larger fluid compartment between the vitreous and retina, may facilitate the transport of ranibizumab into the retina. Moreover, aqueous cytokine levels (including VEGF) were shown to be lower in eyes with PVD in a recent study.[25] This would explain why frequent treatment is not required for optimal BCVA gains in eyes with PVD (Figs 3 and 6).

An unequal repartition of certain disease morphologic components may suggest some pathomechanistic hypotheses on the particular role of SRF as a predictive factor of BCVA change. Other morphologic alterations in patients without SRF, such as IRC or PED, may be indicators for a more aggressive lesion subtype that may require more intensive treatment. Conversely, patients with SRF at baseline may have a more benign disease subtype, resulting in smaller absolute VA gains and a lower difference in VA outcomes between frequent and infrequent treatments.

In addition, patients with SRF at baseline seemed to have a lower rate of IRC compared with patients without SRF at baseline (45.9% vs. 65.4%, respectively). As mentioned previously, IRC has been shown multiple times to be the major driver for BCVA loss and, if present at baseline, indicates preexisting and irreversible retinal damage.[12,23,24] Intraretinal cystoid fluid also has been shown to recur most rapidly

Table 4. Summary Statistics by Subretinal Fluid and Posterior Vitreous Detachment (Vitreomacular Interface Category) Status at Baseline and Treatment (Intent-to-Treat Population)

	Subretinal Fluid Present and Posterior Vitreous Detachment Present	Subretinal Fluid Present and Posterior Vitreous Detachment Absent	Subretinal Fluid Absent and Posterior Vitreous Detachment Present	Subretinal Fluid Absent and Posterior Vitreous Detachment Absent
No.	126	70	51	30
BCVA (letters), mean (SD)				
Frequent	56.7 (12.3)	56.5 (12.7)	52.4 (15.5)	58.5 (11.2)
Infrequent	56.9 (12.2)	56.3 (10.7)	53.3 (15.0)	56.1 (15.2)
Total	56.8 (12.2)	56.4 (11.3)	53.1 (15.0)	56.9 (13.9)
CRT (μm), mean (SD)				
Frequent	335 (92.8)	304 (117)	342 (89.7)	293 (74.7)
Infrequent	331 (98.8)	328 (88.9)	307 (89.0)	336 (113)
Total	333 (96.3)	320 (99.1)	316 (89.6)	322 (102)
IRC, no. (%)				
Frequent	21 (46.7)	10 (41.7)	11 (84.6)	6 (60.0)
Infrequent	40 (49.4)	19 (41.3)	24 (63.2)	12 (60.0)
Total	61 (48.4)	29 (41.4)	35 (68.6)	18 (60.0)
PED, no. (%)				
Frequent	41 (91.1)	21 (87.5)	9 (69.2)	6 (60.0)
Infrequent	63 (77.8)	42 (91.3)	26 (68.4)	11 (55.0)
Total	104 (82.5)	63 (90.0)	35 (68.6)	17 (56.7)
Lesion size (mm^2), mean (SD)				
Frequent	6.6 (5.9)	7.7 (6.4)	7.1 (5.9)	5.3 (6.2)
Infrequent	9.1 (7.1)	7.4 (6.5)	7.9 (5.1)	5.2 (3.4)
Total	8.2 (6.8)	7.5 (6.4)	7.7 (5.3)	5.2 (4.4)

BCVA = best-corrected visual acuity; CRT = central retinal thickness; IRC = intraretinal cystoid fluid; PED = pigment epithelial detachment; SD = standard deviation.

between treatments.[12] Thus, in eyes with a predisposition for IRC recurrence (for which the absence of SRF could be a surrogate marker), infrequent treatment may lead to a pronounced increase in IRC together with irreversible visual loss, and therefore such patients may benefit from more aggressive treatment. The difference in IRC distribution in patients with different SRF status, however, is insufficient to explain the results of this study, because patients without IRC also have been shown to benefit more from frequent treatment and by the same margin as patients with IRC. Interestingly, SRF at baseline has been associated with a lower incidence of macular atrophy in HARBOR and CATT,[26] or better VA outcomes,[23,24] which also is in line with the current finding (Sadda S, Tuomi L, Ding B, Hopkins JJ. Development of Atrophy in Neovascular AMD Treated with Anti-VEGF Therapy: Results of the HARBOR Study. Paper presented at: AAO Annual Meeting, Retina subspecialty day, October 17, 2014; Chicago).

In any case, the latest evidence suggests that the presence of SRF is not associated with a decline of visual function. Results from a recent study show that SRF refractory to monthly treatment with ranibizumab still resulted in good visual improvement and maintenance over 3 years.[27] In addition, recently published analyses of the CATT study did not find any association between the presence of SRF and subsequent sporadic and sustained VA loss (which can occur in some patients despite anti-VEGF therapy), also supporting evidence that SRF presence is not associated with VA decline.[28,29] In line with the findings of the present analysis, altogether these results suggest that patients with SRF may benefit from a less intensive treatment paradigm. The fact that PVD and SRF had to be present at the same time for the eye to respond optimally to infrequent treatment suggests a combined effect of these 2 disease components; however, the mechanism by which this may occur remains unclear.

Study Limitations

Retinal morphologic characteristics have attracted increased interest in recent years because of the availability of more sophisticated imaging techniques such as spectral-domain or swept-source OCT. Time-domain OCT, the imaging technique used in this study, was the gold standard technology at the time the EXCITE trial was conducted. However, since then, the resolution and speed of retinal scans have improved with the introduction of these newer systems. Although a comparative study suggested that the ability of detecting vitreoretinal surface disorders is comparable between time-domain and spectral-domain OCT, it also demonstrated that a significant proportion of SRF (16.3%) can be missed with time-domain OCT.[30] However, this risk is mitigated by multiple consecutive examinations to refine categorization of patients, as performed in this study. In any case, lower resolution is unlikely to impact the results of this analysis because the same resolution applies in both the frequent and infrequent treatment arms. Finally, the use of Stratus OCT allowed only a dichotomous characterization of retinal morphologic changes in this study. With the availability of advanced computational analysis techniques, future studies performing full 3-dimensional quantification of fluid lesions will provide

additional pathophysiologic insight and may allow further individualization of treatment response profiles.[31]

It also should be kept in mind that this study is a post hoc analysis; therefore, the assessment of morphologic characteristics of the retina and their impact on treatment visual outcomes was not part of the original protocol of the EXCITE trial. Although this constitutes a limitation, it should be noted that the Vienna Reading Center readers were masked to the data when the OCT scans were evaluated, which confers to the analysis some of the advantages of a prospective study. Because of the limited sample size of subgroups stratified for PVD and SRF, other functional outcome measures, such as the proportions of patients gaining or losing 3 lines of vision, were not investigated. Generally, the fact remains that it is challenging to base treatment decisions on post hoc analyses, and other studies should be conducted prospectively to confirm our findings.

In conclusion, this post hoc analysis used morphologic assessment to identify patients who may benefit from less frequent treatment in nAMD. In the population studied, SRF and PVD emerged as the key baseline prognostic factors for stable VA outcomes in infrequent treatment. If confirmed by prospective studies, this finding may facilitate a reduction of treatment intervals without jeopardizing functional outcomes in a substantial number of patients with nAMD.

Acknowledgments. The authors thank Marie-Catherine Mousseau, Global Business Services, Novartis Ireland Limited, Dublin, Ireland, for medical writing services toward the development of this article, funded by Novartis Pharma AG, Basel, Switzerland.

References

1. Wong WL, Su X, Li X, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. Lancet Glob Health 2014;2:e106–16.
2. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355:1419–31.
3. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med 2006;355:1432–44.
4. Brown DM, Michels M, Kaiser PK, et al. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: two-year results of the ANCHOR study. Ophthalmology 2009;116:57–65.e5.
5. Mitchell P, Korobelnik JF, Lanzetta P, et al. Ranibizumab (Lucentis) in neovascular age-related macular degeneration: evidence from clinical trials. Br J Ophthalmol 2010;94:2–13.
6. Abraham P, Yue H, Wilson L. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER study year 2. Am J Ophthalmol 2010;150:315–324.e1.
7. Hariprasad SM, Morse LS, Shapiro H, et al. Fixed monthly versus less frequent ranibizumab dosing and predictors of visual response in exudative age-related macular degeneration. J Ophthalmol 2012;2012:690641.
8. Martin DF, Maguire MG, Fine SL, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. Ophthalmology 2012;119:1388–98.
9. Busbee BG, Ho AC, Brown DM, et al. Twelve-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. Ophthalmology 2013;120:1046–56.
10. Berg K, Pedersen TR, Sandvik L, Bragadottir R. Comparison of ranibizumab and bevacizumab for neovascular age-related macular degeneration according to LUCAS treat-and-extend protocol. Ophthalmology 2015;122:146–52.
11. Abedi F, Wickremasinghe S, Islam AF, et al. Anti-VEGF treatment in neovascular age-related macular degeneration: a treat-and-extend protocol over 2 years. Retina 2014;34:1531–8.
12. Simader C, Ritter M, Bolz M, et al. Morphologic parameters relevant for visual outcome during anti-angiogenic therapy of neovascular age-related macular degeneration. Ophthalmology 2014;121:1237–45.
13. Sakata LM, Deleon-Ortega J, Sakata V, Girkin CA. Optical coherence tomography of the retina and optic nerve: a review. Clin Exp Ophthalmol 2009;37:90–9.
14. Lee SJ, Koh HJ. Effects of vitreomacular adhesion on anti-vascular endothelial growth factor treatment for exudative age-related macular degeneration. Ophthalmology 2011;118:101–10.
15. Mayr-Sponer U, Waldstein SM, Kundi M, et al. Influence of the vitreomacular interface on outcomes of ranibizumab therapy in neovascular age-related macular degeneration. Ophthalmology 2013;120:2620–9.
16. Waldstein SM, Ritter M, Simader C, et al. Impact of vitreomacular adhesion on ranibizumab mono- and combination therapy for neovascular age-related macular degeneration. Am J Ophthalmol 2014;158:328–336.e1.
17. Cuilla TA, Ying GS, Maguire MG, et al. Influence of the vitreomacular interface on treatment outcomes in the Comparison of Age-Related Macular Degeneration Treatments Trials. Ophthalmology 2015;122:1203–11.
18. Schmidt-Erfurth U, Eldem B, Guymer R, et al. Efficacy and safety of monthly versus quarterly ranibizumab treatment in neovascular age-related macular degeneration: the EXCITE study. Ophthalmology 2011;118:831–9.
19. Ritter M, Elledge J, Simader C, et al. Evaluation of optical coherence tomography findings in age-related macular degeneration: a reproducibility study of two independent reading centres. Br J Ophthalmol 2011;95:381–5.
20. Itakura H, Kishi S. Evolution of vitreomacular detachment in healthy subjects. JAMA Ophthalmol 2013;131:1348–52.
21. Chakravarthy U, Harding SP, Rogers CA, et al. Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial. Lancet 2013;382:1258–67.
22. Kiss CG, Geitzenauer W, Simader C, et al. Evaluation of ranibizumab-induced changes in high-resolution optical coherence tomographic retinal morphology and their impact on visual function. Invest Ophthalmol Vis Sci 2009;50:2376–83.
23. Jaffe GJ, Martin DF, Toth CA, et al. Macular morphology and visual acuity in the comparison of age-related macular degeneration treatments trials. Ophthalmology 2013;120:1860–70.
24. Schmidt-Erfurth U, Waldstein SM, Deak GG, et al. Pigment epithelial detachment followed by retinal cystoid degeneration leads to vision loss in treatment of neovascular age-related macular degeneration. Ophthalmology 2015;122:822–32.
25. Takahashi H, Nomura Y, Tan X, et al. Effects of posterior vitreous detachment on aqueous humour levels of VEGF and inflammatory cytokines. Br J Ophthalmol 2015;99:1065–9.

26. Grunwald JE, Daniel E, Huang J, et al. Risk of geographic atrophy in the comparison of age-related macular degeneration treatments trials. Ophthalmology 2014;121:150–61.
27. Jang L, Gianniou C, Ambresin A, Mantel I. Refractory subretinal fluid in patients with neovascular age-related macular degeneration treated with intravitreal ranibizumab: visual acuity outcome. Graefes Arch Clin Exp Ophthalmol 2015;253:1211–6.
28. Kim BJ, Ying GS, Huang J, et al. Sporadic visual acuity loss in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT). Am J Ophthalmol 2014;158:128–135.e10.
29. Ying GS, Kim BJ, Maguire MG, et al. Sustained visual acuity loss in the comparison of age-related macular degeneration treatments trials. JAMA Ophthalmol 2014;132:915–21.
30. Mojana F, Cheng L, Bartsch D-UG, et al. The role of abnormal vitreomacular adhesion in age-related macular degeneration: spectral optical coherence tomography and surgical results. Am J Ophthalmol 2008;146:218–227.e1.
31. Roberts P, Mittermueller TJ, Montuoro A, et al. A quantitative approach to identify morphological features relevant for visual function in ranibizumab therapy of neovascular AMD. Invest Ophthalmol Vis Sci 2014;55:6623–30.

Footnotes and Financial Disclosures

Originally received: June 12, 2015.
Final revision: September 10, 2015.
Accepted: September 13, 2015.
Available online: October 18, 2015. Manuscript no. 2015-964.

[1] Christian Doppler Laboratory for Ophthalmic Image Analysis, Department of Ophthalmology, Vienna Reading Center, Vienna, Austria.

[2] Numerus Ltd, Wokingham, United Kingdom.

[3] Novartis Pharma AG, Basel, Switzerland.

Presented as a poster at: the 14th European School for Advanced Studies in Ophthalmology (ESASO) Retina Academy, November 2014, Istanbul, Turkey; European Society of Retina Specialists (EURETINA) Congress, September 2014, London, United Kingdom; American Academy of Ophthalmology Annual Meeting, October 2014, Chicago, Illinois.

Financial Disclosure(s):
The author(s) have made the following disclosure(s): S.M.W.: Consultant - Novartis Pharma AG, Basel, Switzerland

J.W.: Consultant - Novartis Pharma AG, Basel, Switzerland

J.W.: Employee - Novartis Pharma AG, Basel, Switzerland

P.M.: Employee - Novartis Pharma AG, Basel, Switzerland

U.S.-E.: Consultant - Alcon Laboratories, Inc. (Fort Worth, TX); Bayer Healthcare AG (Berlin, Germany); Boehringer Ingelheim GmbH (Ingelheim, Germany); Novartis Pharma AG, (Basel, Switzerland).

The EXCITE study was funded by Novartis Pharma AG, Basel, Switzerland. This post hoc analysis was supported by a grant from Novartis Pharma AG, Basel, Switzerland; and the Austrian Federal Ministry of Science, Research and Economy and the National Foundation for Research, Technology (Vienna, Austria).

Author Contributions:

Conception and design: Waldstein, Warburton, Margaron, Schmidt-Erfurth

Analysis and interpretation: Waldstein, Wright, Warburton, Margaron, Simader, Schmidt-Erfurth

Data collection: Waldstein, Simader, Schmidt-Erfurth

Obtained funding: Waldstein, Schmidt-Erfurth

Overall responsibility: Waldstein, Wright, Warburton, Margaron, Simader, Schmidt-Erfurth

Abbreviations and Acronyms:
AMD = age-related macular degeneration; **BCVA** = best-corrected visual acuity; **CATT** = Comparison of Age-Related Macular Degeneration Treatments Trials; **CRT** = central retinal thickness; **EXCITE** = Efficacy and Safety of Ranibizumab in Patients with Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration; **IRC** = intraretinal cystoid fluid; **nAMD** = neovascular age-related macular degeneration; **OCT** = optical coherence tomography; **PED** = pigment epithelial detachment; **PRN** = pro re nata; **PVD** = posterior vitreous detachment; **SRF** = subretinal fluid; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor; **VMI** = vitreomacular interface.

Correspondence:
Ursula Schmidt-Erfurth, MD, Christian Doppler Laboratory for Ophthalmic Image Analysis, Vienna Reading Center, Department of Ophthalmology, Medical University of Vienna, Spitalgasse 23, 1090 Vienna, Austria. E-mail: ursula.schmidt-erfurth@meduniwien.ac.at.