Quantitative Subanalysis of Optical Coherence Tomography after Treatment with Ranibizumab for Neovascular Age-Related Macular Degeneration

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Purpose. To investigate the effects of ranibizumab on retinal morphology in patients with neovascular age-related macular degeneration (AMD) using optical coherence tomography (OCT) quantitative subanalysis.

Methods. Data from 95 patients receiving intravitreal ranibizumab for neovascular AMD were collected. StratusOCT images were analyzed using custom software that allows precise positioning of prespecified boundaries on every B-scan. Changes in thickness/volume of the retina, subretinal fluid (SRF), subretinal tissue (SRT), and pigment epithelial detachments (PEDs) at week 1 and at months 1, 3, 6, and 9 after treatment were calculated.

Results. Total retinal volume reached its nadir at month 1, with an average reduction of 0.43 mm^3 ($P < 0.001$). By month 9, this initial change had been reduced to a mean reduction of 0.32 mm^3 ($P = 0.0011$). Total SRF volume reached its lowest level by month 1, with an average reduction of 0.24 mm^3 ($P < 0.001$). This reduction lessened subsequently, to 0.18 mm^3, by month 9. There was an average 0.3-mm^3 decrease in total PED volume by month 1 ($P < 0.001$), and this later declined further, to 0.45 mm^3, by month 9 ($P = 0.0014$). Total SRT volume was reduced by an average of 0.07 mm^3 at month 1 ($P = 0.0159$) and subsequently remained constant.

Conclusions. Although neurosensory retinal edema and SRF showed an early reduction to nadir after the initiation of ranibizumab therapy, the effect on the retina was attenuated over time, suggesting possible tachyphylaxis. PED volume showed a slower but progressive reduction. Manual quantitative OCT subanalysis may allow a more precise understanding of anatomic outcomes and their correlation with visual acuity. (*Invest Ophthalmol Vis Sci.* 2008;49:3115–3120) DOI:10.1167/iovs.08-1689

Age-related macular degeneration (AMD) is the leading cause of blindness in the developed world among people older than 50 years.[1] The most common form of AMD resulting in severe visual loss is characterized by the development of choroidal neovascularization (CNV).[2] Current treatment options for this neovascular form of AMD include thermal laser photocoagulation, photodynamic therapy with verteporfin, pegaptanib (Macugen; OSI-Eyetech, Inc., Melville, NY), ranibizumab (Lucentis; Genentech, Inc., South San Francisco, CA), and the off-label use of agents such as intravitreal bevacizumab (Avastin; Genentech).[3–7] The efficacy of these treatments is primarily determined by assessing visual acuity outcomes; however, fluorescein angiography (FA) and optical coherence tomography (OCT) measurements are often used as secondary outcome parameters.[8]

StratusOCT (Carl Zeiss Meditec, Dublin, CA) software provides automated detection of the inner and outer retinal boundaries and, as a result, is commonly used in clinical trials to provide quantitative information regarding central retinal thickness.[8,9] StratusOCT is also widely used for qualitative assessment to establish the presence of retinal cysts, subretinal fluid (SRF), pigment epithelial detachments (PEDs), and other morphologic characteristics.[9] However, many of these additional features, visible on OCT, cannot be quantified by existing StratusOCT software algorithms. Furthermore, the limited quantitative information that is available is frequently flawed because of inaccurate detection of the inner and outer boundaries of the retina.[10–12]

To improve the accuracy of retinal thickness measurements and to obtain quantitative information regarding other morphologic characteristics, we developed a software tool, OCTOR, that allows the user to draw the boundaries of all structures of interest manually.[13] Grading rules and conventions for delineating OCT morphologic features in neovascular AMD, as well as the reproducibility of this approach, have been previously reported.[14]

Ranibizumab, a recombinant monoclonal antibody fragment designed to neutralize all known active forms of vascular endothelial growth factor (VEGF)-A, is the first treatment for neovascular AMD that not only prevented visual acuity loss but also improved visual acuity in large numbers of patients in phase 3 clinical trials.[6,15] To date, clinical trials of ranibizumab have reported StratusOCT-derived measures of central retinal thickness as their only quantitative OCT data.[8,9] We used OCTOR-generated OCT subanalysis to provide quantitative information regarding the longitudinal effects of intravitreal ranibizumab on the morphology of the retina in patients with neovascular AMD.

Materials and Methods

Data Collection

Ranibizumab was approved by the US Food and Drug Administration (FDA) on June 30, 2006, for use in CNV secondary to AMD. For this retrospective study, data from all patients receiving initial intravitreal injections of ranibizumab between July 2006 and September 2007 at the Doheny Eye Institute were collected and reviewed. Approval for

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data collection and analysis was obtained from the institutional review board of the University of Southern California. The research adhered to the tenets set forth in the Declaration of Helsinki.

For inclusion in the study, eyes were required to have subfoveal CNV secondary to AMD and to have undergone StratusOCT imaging no more than 3 weeks before the first injection and during at least one follow-up visit. If patients received ranibizumab treatment in both eyes, only the first eye injected was included. Patients were excluded if they received intravitreal ranibizumab injections at other institutions before initial treatment at the Doheny Eye Institute or if they participated in a clinical trial. Our analysis was not limited to patients who met a minimum follow-up period. Any patient switched to an alternative treatment for neovascular AMD in the study eye was excluded from further analysis from that point forward. Because this was not a prospective study, the dosing or retreatment strategy for all patients and visits was not standardized. Patients were treated at the discretion of the physician applying an OCT-guided ranibizumab-retreatment protocol similar to that described in the PrONTO study.[9]

StratusOCT images were collected at 1 week and at 1, 3, 6, and 9 months after initial injection of intravitreal ranibizumab. Images were obtained using the Radial Lines protocol of six high-resolution B-scans on a single StratusOCT machine. The Fast Macular Scan protocol was used only when photographers were unable to obtain adequate high-resolution images, most commonly in patients with unstable fixation or poor cooperation. Data for each patient were exported to a disk using the export feature available in the StratusOCT version 4.0 analysis software.

The number and type of any previous treatments for CNV secondary to AMD in the study eye were recorded. The interval between the last treatment and the initial ranibizumab injection was also noted. After the initial treatment, additional injections of ranibizumab were given at the discretion of the treating physician based on response to therapy. The number and timing of these retreatments were recorded for each patient. Other data collected were age, sex, best-corrected Snellen visual acuity, and angiographic CNV lesion classification at the time of initial intravitreal ranibizumab injection.

Computer-Assisted Grading Software

The software program used for OCT analysis, OCTOR, was written by Doheny Image Reading Center software engineers to facilitate viewing and manual grading. OCTOR is publicly accessible at http://www.driamd.org and has been described and validated in previous reports.[13,14] This software, which effectively operates as a painting program and calculator, imports data exported from the StratusOCT machine and allows the grader to use a computer mouse to draw various boundaries in the retinal cross-sectional images (Fig. 1).

After the grader draws the required layers in each of the six B-scans, the software calculates the distance in pixels between the manually drawn boundary lines for each of the various defined spaces. Using the dimensions of the B-scan image, the calculated pixels are converted to micrometers to yield a thickness measurement at each location. The thickness at all unsampled locations between the radial lines is then interpolated based on a polar approximation to yield a thickness map analogous to the StratusOCT output data. After interpolation, thickness values are converted to volumes (in cubic millimeters) by multiplying the average thickness measurement by the sampled area. The interpolation algorithm, intergrader reliability, and intragrader reproducibility have previously been validated.[13,14]

Analogous to the StratusOCT software, OCTOR provides a report showing the calculated thickness/volume values for the nine Early Treatment Diabetic Retinopathy Study macular subfields. Means and standard deviations of the foveal center point thickness are also calculated. In contrast to the StratusOCT output, OCTOR provides separate maps for the various macular spaces (e.g., retina, subretinal fluid, subretinal tissue, pigment epithelial detachment).

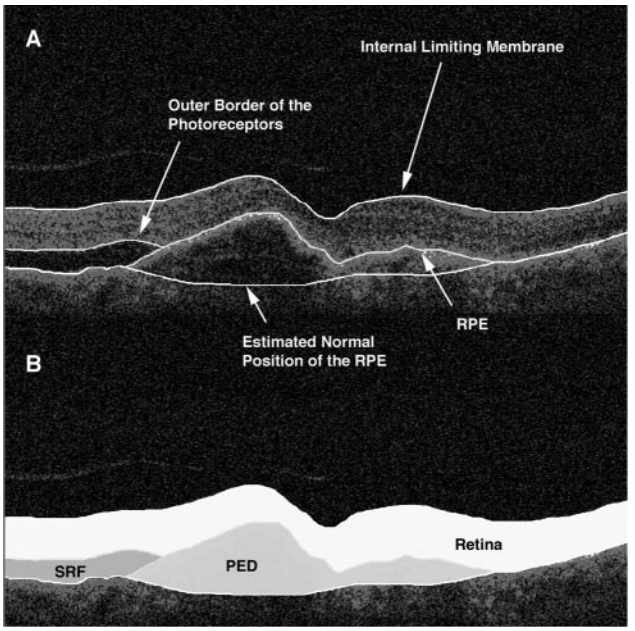

FIGURE 1. OCT B-scan of an eye demonstrating SRF accumulation and PED. Clinically relevant boundaries (internal limiting membrane, outer photoreceptor border, RPE, and estimated normal position of the retinal pigment epithelial layer [**A**]) are graded using OCTOR, which then computes the volumes of the spaces (retina, SRF, and PED) defined by these boundaries (**B**).

Grading Procedure

OCT scans were analyzed by certified OCT graders at the Doheny Image Reading Center who were masked to any related clinical information at the time of grading. All OCT scans included in this study met reading center criteria for sufficient image quality, including the absence of significant artifactual variations in signal intensity or generalized reductions in signal strength. Boundaries drawn in each of the six OCT B-scans included the internal limiting membrane, outer border of the photoreceptors, borders of subretinal fluid and subretinal tissue (if present), inner surface of the RPE, and estimated normal position of the retinal pigment epithelial layer (in instances of retinal pigment epithelial elevation). All boundaries were drawn in accordance with the standard OCT grading protocol of the Doheny Image Reading Center.[14]

After grading was completed, OCTOR was used to calculate output parameters for the various spaces (retina, subretinal fluid, subretinal tissue, and pigment epithelial detachment). In addition, the combined parameters, inner retinal surface height from the RPE, and inner retinal surface height from the choroid, were also calculated.

Statistical Analysis

The mean ± SD of the foveal center point (FCP) thickness and the total volume (subfields 1–9) were calculated for each space in each case. Volume was measured in cubic millimeters, and thickness was measured in micrometers.

Change from baseline in thickness and volume measurements was calculated at each available follow-up visit. To analyze these changes, a paired *t*-test or Wilcoxon signed rank test was performed, depending on whether the data were normally distributed. For each paired statistical test, casewise deletion of missing data was performed if one variable had a missing value. $P < 0.05$ was considered statistically significant. Statistical analysis was performed using commercially available software (Intercooled Stata for Windows, version 9; StataCorp LP, College Station, TX).

TABLE 1. Treatment Data

	Month 3	Month 6	Month 9
	Mean ± SD (median [range])		
No. injections before study follow-up	1.8 ± 0.6 (2 [1–3])	3.1 ± 1.2 (3 [1–6])	4.4 ± 1.8 (4 [1–10])
Days between last reinjection and study follow-up	46.9 ± 20.1 (37 [8–105])	64.9 ± 42.8 (42 [23–168])	84.3 ± 53.3 (77 [21–245])

RESULTS

Patient Enrollment and Follow-up

One hundred forty patients received their initial intravitreal injections of ranibizumab in the Doheny Eye Institute between July 2006 and September 2007. Ninety-five patients receiving their initial intravitreal injections of ranibizumab met the inclusion criteria for the study. Forty-five patients were excluded from the study for the following reasons: 12 patients had received intravitreal injections of ranibizumab at other institutions before their initial treatment in the Doheny Eye Institute; 5 patients had received intravitreal injections of ranibizumab as part of a clinical trial before their initial treatment in the Doheny Eye Institute; 15 patients were excluded for lack, or unavailability, of StratusOCT imaging within the 3-week period before their initial injection; 6 patients were excluded for lack of StratusOCT imaging at any follow-up visit; 6 patients were excluded for receiving intravitreal injections of ranibizumab for conditions other than AMD; 1 patient's fellow eye was excluded.

Ten patients received treatment with intravitreal bevacizumab at some point after their initial treatment with intravitreal ranibizumab; consequently, their subsequent StratusOCT images were excluded from our analysis.

StratusOCT images were available for analysis at follow-up time points as follows: 95 patients at baseline, 15 patients at week 1, 80 patients at month 1, 84 patients at month 3, 58 patients at month 6, 37 patients at month 9.

Baseline Characteristics

Of the 95 patients included in our analysis, 59 (62%) were women and 36 (38%) were men. The mean age of patients was 81 years (SD, 7), and the median age was also 81 years (range, 55–96 years). Forty-three (46%) patients underwent previous treatment for CNV in the study eye, 25 (26%) received previous intravitreal injections of bevacizumab, 15 (16%) underwent previous photodynamic therapy with verteporfin, 4 (4%) underwent previous thermal laser photocoagulation, and 9 (9%) received previous intravitreal pegaptanib. Patients who had previously received intravitreal bevacizumab had a mean of 2.3 injections (range, 1–5 injections), with the last injection occurring a mean of 81 days (range, 19–264 days) before the first ranibizumab injection. Mean visual acuity was 20/129 at baseline, 20/103 at week 1, 20/112 at month 1, 20/115 at month 3, 20/115 at month 6, and 20/126 at month 9. At baseline, the neovascular lesions were categorized by fluorescein angiography as predominantly classic (17 eyes, 18%), minimally classic (15 eyes, 16%), and occult with no classic (57 eyes, 60%). Angiographic classification at baseline was unavailable for 6 eyes (6%).

Treatment with Ranibizumab

Mean and median numbers of injections of intravitreal ranibizumab for the study period were 3.3 (SD, 2.0) and 3.0 (range, 1–10 injections), respectively. The number of injections between baseline and each study visit and the time between the most recent reinjection and each study visit were recorded and are summarized in Table 1.

Morphologic Outcome Using OCTOR Analysis

Change in OCT parameters as calculated by OCTOR after manual grading are summarized in Table 2.

Effect on the Neurosensory Retina. The retinal space showed an average 44.83-μm decrease from baseline in FCP thickness by month 1 ($P < 0.001$; Fig. 2). This initial decrease lessened during the remainder of the study, with an average reduction (compared with baseline) of 30.55 μm at month 6 ($P = 0.0178$), and 16.95 μm at month 9 ($P = 0.2642$). Total retinal volume reached its nadir at month 1, with an average reduction of 0.43 mm^3 ($P < 0.001$). By month 9, this initial change had been reduced to a mean reduction of 0.32 mm^3 ($P = 0.0011$).

TABLE 2. Change in OCT Parameters for the Various Spaces and Subfields, from Baseline, Provided by OCTOR and by Stratus OCT Automated Analysis

Mean Change from Baseline		Week 1	Month 1	Month 3	Month 6	Month 9
OCTOR retina	FCP thickness (μm)	−55.8 ± 87.89*	−44.83 ± 91.54†	−30.52 ± 94.5†	−30.55 ± 78.11*	−16.95 ± 133.25
	Total volume (mm^3)	−0.37 ± 0.53†	−0.43 ± 0.78†	−0.33 ± 0.88†	−0.28 ± 0.63†	−0.32 ± 1.07†
Subretinal fluid	Total volume (mm^3)	−0.11 ± 0.15†	−0.24 ± 0.50†	−0.24 ± 0.47†	−0.19 ± 0.47†	−0.18 ± 0.48†
Subretinal tissue	Total volume (mm^3)	−0.03 ± 0.15	−0.07 ± 0.3*	−0.05 ± 0.38	−0.06 ± 0.34	−0.06 ± 0.5
Pigment epithelial detachment	Total volume (mm^3)	−0.23 ± 0.6	−0.3 ± 0.87†	−0.18 ± 1.03†	−0.35 ± 0.93†	−0.45 ± 1.12†
Height from RPE	FCP thickness (μm)	−69.27 ± 92.15†	−87.74 ± 95.53†	−67.61 ± 118.08†	−58.28 ± 84.92†	−52.76 ± 142.61†
	Total volume (mm^3)	−0.51 ± 0.64†	−0.88 ± 1.34†	−0.63 ± 1.19†	−0.54 ± 1.03†	−0.54 ± 1.44†
Height from choroid	FCP thickness (μm)	−130.07 ± 143.69†	−90.56 ± 136.76†	−69.52 ± 175.65†	−75.78 ± 130.30†	−68.79 ± 205.51†
	Total volume (mm^3)	−0.74 ± 0.86†	−1.03 ± 1.57†	−0.8 ± 1.87†	−0.86 ± 1.54†	−1.01 ± 2.10†
StratusOCT retina	FCP thickness (μm)	−82.47 ± 82.58†	−73.09 ± 93.43†	−59.82 ± 102.32†	−55.38 ± 85.27†	−44.68 ± 131.55*
	Total volume (mm^3)	−0.60 ± 0.59†	−0.63 ± 1.26†	−0.55 ± 1.43†	−0.47 ± 0.94†	−0.56 ± 1.43†

Mean change from baseline was calculated by subtracting the value at baseline from the value at follow-up for each patient and then taking the mean value across all patients.

* $P < 0.05$; † $P < 0.01$.

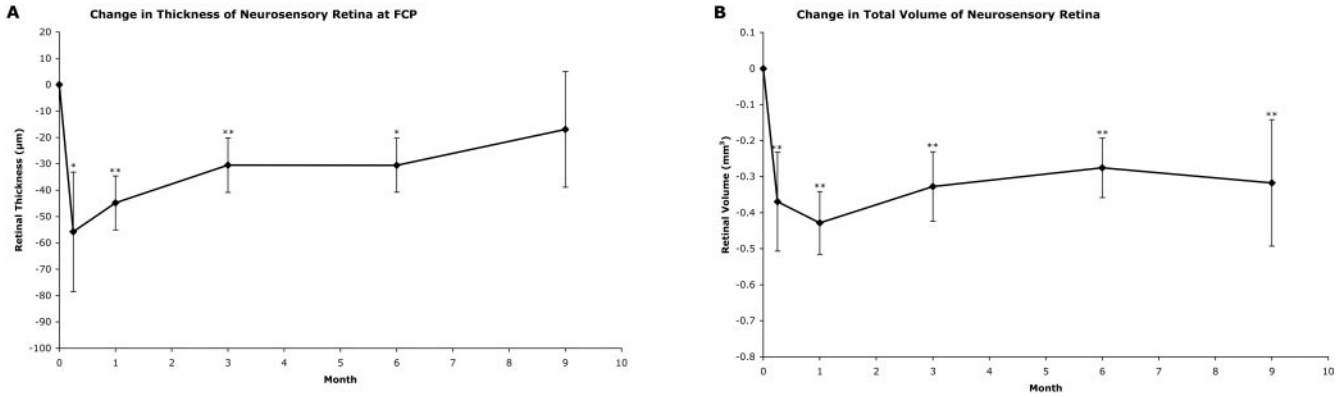

FIGURE 2. Neurosensory retina outcomes as provided by OCTOR. (**A**) Mean change from baseline in thickness of the neurosensory retina at the FCP. (**B**) Mean change from baseline in total volume of the neurosensory retina. Vertical lines, 1 SEM. $^{*}P < 0.05$; $^{**}P < 0.01$.

Effect on Subretinal Fluid. The total volume of subretinal fluid reached its lowest level by month 1, with an average reduction from baseline of 0.24 mm^3 ($P < 0.001$; Fig. 3). This reduction was maintained at month 3 but lessened subsequently, with an average reduction of 0.18 mm^3 by month 9.

Effect on Subretinal Tissue. Total volume of subretinal tissue was reduced by an average of 0.07 mm^3 by month 1 ($P = 0.0159$). This reduction appeared to be maintained through the remainder of the study period, though subsequent changes compared with baseline were not statistically significant (Fig. 3).

Effect on Pigment Epithelial Detachment. There was an average 0.3-mm^3 decrease in total PED volume by month 1 ($P < 0.001$) and a further decrease during the study, to an average of 0.45 mm^3 by month 9 ($P = 0.0014$; Fig. 4).

Effect on Inner Retinal Surface Height from the RPE. The inner retinal surface height from the RPE showed an average 87.74-μm decrease from baseline in FCP thickness by month 1 ($P < 0.001$; Fig. 5). This initial decrease lessened during the remainder of the study, with an average reduction 52.76 μm at month 9 ($P = 0.0073$). Again, the total macular volume reached its lowest level at month 1, with an average reduction of 0.88 mm^3 ($P < 0.001$). By month 9, this initial change had been reduced to a mean level of 0.54 ($P < 0.001$).

Effect on Inner Retinal Surface Height from the Choroid (spanning the distance from the inner limiting membrane to the base of any PED). The inner retinal surface height from the choroid at the FCP reached its lowest level by week 1, with an average reduction from baseline of 130.07 μm ($P < 0.001$). This initial decrease lessened during the remainder of the study, with an average reduction of 68.79 μm at month 9 ($P = 0.0055$). In contrast, total volume reached its lowest level at month 1, with an average reduction of 1.03 mm^3 ($P < 0.001$). A change of similar magnitude was detected at the study conclusion, with an average reduction of 1.01 mm^3 ($P < 0.001$).

Morphologic Outcome Using StratusOCT Analysis

The automated StratusOCT software also provides thickness and volume values. Although these values are said to represent the retina, they are often erroneous in CNV patients[12] and typically include the neurosensory retina and the subretinal space. The StratusOCT-derived FCP showed an average 73.09-μm decrease from baseline by month 1 ($P < 0.001$). This initial decrease lessened during the remainder of the study, with an average reduction 44.68 μm by month 9 ($P = 0.0124$). The StratusOCT-derived total retinal volume had an average reduction of 0.63 mm^3 ($P < 0.001$) at month 1. By month 9, this initial change had been reduced to an average level of 0.56 mm^3 ($P < 0.001$).

DISCUSSION

In this retrospective, longitudinal study, we performed manual OCT subanalysis with the OCTOR software to evaluate the effects of intravitreal ranibizumab on the morphologic characteristics of the retina in eyes with neovascular AMD. These characteristics were examined over a 9-month period and in-

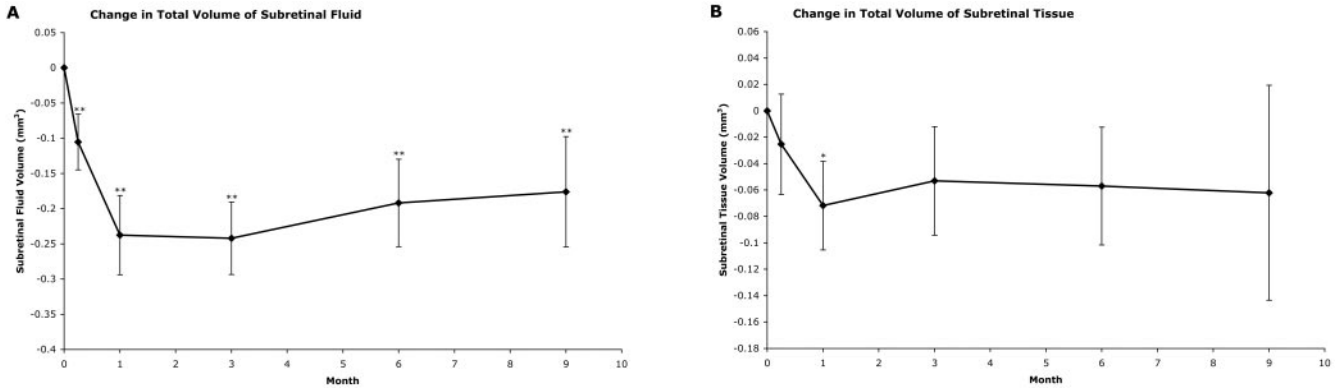

FIGURE 3. Subretinal outcomes as provided by OCTOR. (**A**) Mean change from baseline in total volume of SRF. (**B**) Mean change from baseline in total volume of SRT. Vertical lines, 1 SEM. $^{*}P < 0.05$; $^{**}P < 0.01$.

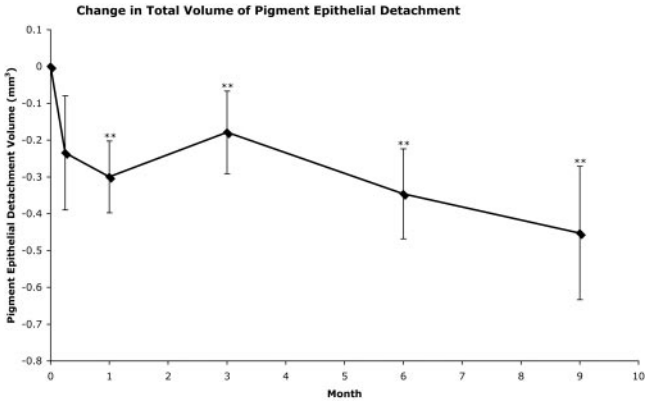

FIGURE 4. Mean change from baseline in total volume of retinal pigment epithelial detachment as provided by OCTOR. Vertical lines, 1 SEM $^{*}P < 0.05$; $^{**}P < 0.01$.

cluded the neurosensory retina, subretinal fluid, subretinal tissue, and pigment epithelial detachments.

OCTOR analysis of the neurosensory retina demonstrated a large reduction in total retinal volume as early as 1 week after initial treatment with intravitreal ranibizumab (Fig. 2). After this initial significant reduction, the total retinal volume reached a nadir at month 1 and then appeared to increase at subsequent follow-up. The large initial reduction in total retinal volume appeared to be secondary to a significant reduction in intraretinal edema, which we suspect was mediated by the antipermeability effects of ranibizumab. Subsequent increases in the total volume of the retinal space appeared to be secondary to the recurrence of intraretinal cysts or the development of diffuse retinal edema. One possible explanation for this apparent subsequent increase in total retinal volume may be a tachyphylaxis phenomenon by which repeated injections yield decreasing anatomic benefits. Another possible explanation is cystoid degeneration of the retina overlying an older or more chronic CNV lesion. This phenomenon may also be an artifact of the dosing or retreatment strategy used by the physicians in this study. It is possible that a sustained reduction in retinal thickness would be observed if therapy was administered monthly (rather than based on OCT findings) in accordance with the primary FDA label. OCTOR analysis of the subretinal space demonstrated similar effects. The subretinal space may be occupied by fluid (hyporeflective) or other material (hyperreflective). Our study demonstrated a significant decrease in subretinal fluid by month 1 of follow-up. In fact, the significant decrease in SRF seemed to occur as early as 1 week after initial treatment. The change in SRF at month 1 was maintained through month 3 but appeared to diminish in the ensuing months.

We assigned the generic label subretinal tissue to any hyperreflective material in the subretinal space. SRT decreased significantly at month 1, and this reduction was maintained, though not at statistically significant levels, for the remainder of the study. Interpretation of this finding is complicated because hyperreflective material in the subretinal space may include fibrovascular tissue, hemorrhage, lipid, or thick fibrin. Hemorrhage, lipid, and thick fibrin are clinically apparent markers of CNV leakage, more commonly seen in acute phases of neovascular AMD.[4] Studies of longer duration may provide more reliable information regarding the evolution of fibrovascular scar tissue over time. Further study will also clarify the relationship between scar formation and loss of neural tissue from the retina, as well as its association with visual function.

Total volume of the PEDs appeared to decrease slowly in the initial months of the study; however, unlike other morphologic parameters, this decrease was sustained and progressive throughout the study period. Previous studies evaluating qualitative OCT changes after anti–VEGF therapy for neovascular AMD have observed that PEDs appear to regress more slowly than subretinal or intraretinal fluid.[7,9] Our study provides quantitative evidence to support these previous observations. Ranibizumab is an antibody fragment designed, in part, to facilitate penetration of the retina. Penetration throughout the retina may initially be reduced in the context of retinal thickening, SRF, and SRT. Subsequent reductions in these parameters, after treatment, may facilitate penetration through the outer layers of the retina and RPE and thus may explain the lagging regression of the PED space. PED subtypes include serous, hemorrhagic, fibrovascular, and drusenoid, with each subtype having its own natural history and prognosis for final visual outcome.[16] In this study, manual OCT subanalysis did not distinguish between these subtypes, in part because of the limited characterization of the subretinal pigment epithelial space afforded by StratusOCT.

Our central retinal thickness findings differ from those of other longitudinal studies of intravitreal ranibizumab using automated StratusOCT measurements.[8,9] In these studies, initial significant decreases in retinal thickness were maintained, or progressed, during the remainder of the 12-month study periods. Furthermore, these studies demonstrated a substantially greater magnitude of central retinal thickness change compared with our findings. These discrepancies may occur, in part, because StratusOCT software typically combines the subretinal space with the neurosensory retina in thickness calculations. Therefore, true changes in the thickness of the

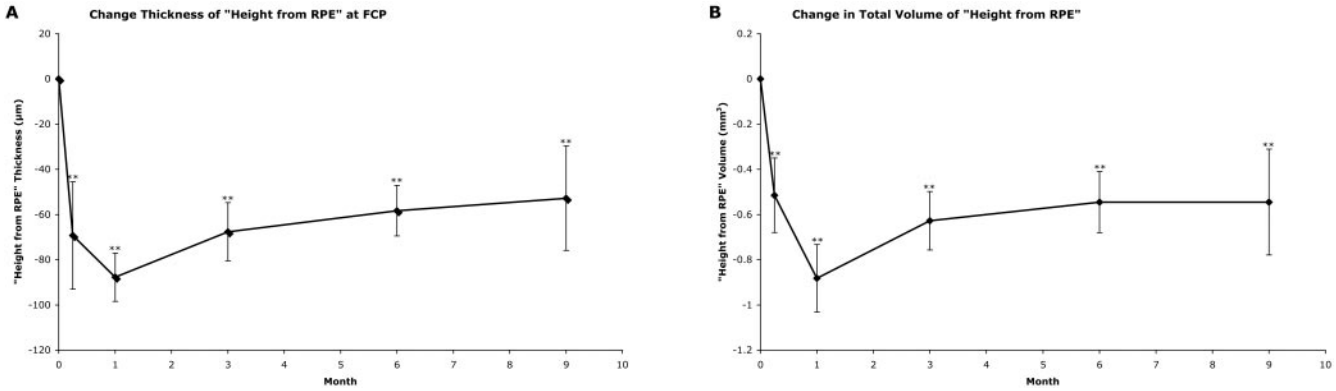

FIGURE 5. Height from retinal pigment epithelium outcomes as provided by OCTOR. (**A**) Mean change from baseline in height from RPE at FCP. (**B**) Mean change from baseline in total volume of height from RPE. Vertical lines, 1 SEM. $^{*}P < 0.05$; $^{**}P < 0.01$.

retina (e.g., increasing intraretinal cysts or diffuse retinal edema) may be masked by changes in the thickness of the subretinal space. In addition, the segmentation of these boundaries by the StratusOCT is frequently erroneous in patients with AMD.[12] With manual OCT subanalysis, the subretinal space is quantified separately from retinal thickness; therefore, a more accurate measure of retinal thickness is obtained. The OCTOR software also allows calculation of height from the RPE, a measure of retinal thickness that includes any subretinal material and is analogous to the retinal thickness measurements provided by StratusOCT. When we examined height from the RPE, our findings were closer in magnitude to those of the earlier studies but still significantly different. The measurement in earlier studies might also have been affected by inaccuracies in the Stratus OCT segmentation. Direct comparison is difficult, however, because our study did not exclude patients with permanent structural damage to the foveal center, patients with foveal thickness measurements below a minimum level, or patients who had previously received other forms of treatment for neovascular AMD in the study eye.

These clinical trials typically use StratusOCT-generated FCS or FCP retinal thickness values as the OCT secondary outcome measure. Even with accurate boundary detection, these parameters may be erroneous because of the failure of scans to pass through the anatomic center of the fovea or because of the presence of eccentrically positioned neovascular lesions. Therefore, we believe that consideration of the total volume of each morphologic space is preferable to the calculation of thickness at a single point or subfield, and this consideration is facilitated by manual grading with OCTOR software.

Our study has a number of limitations. It is a retrospective, longitudinal study; as a result, OCT data are not available at every visit for every patient, and follow-up is not uniform. Furthermore, intravitreal ranibizumab treatment by multiple physicians was assessed with no prespecified, standardized retreatment criteria. Another limitation is the relatively small sample size, particularly given the heterogeneous morphologic features of neovascular AMD lesions. Nonetheless, this study does suggest that quantitative OCT subanalysis may be of value in monitoring the differential morphologic effects of intravitreal ranibizumab treatment for neovascular AMD over time. Preliminary observations suggest an apparent tachyphylaxis in the effect of an anti–VEGF agent on the thickness/volume of the retina, but this requires further study in a prospective trial with standardized retreatment guidelines. Future studies may allow us to determine how the differential morphologic effects correlate with visual acuity results and to determine which subgroups of patients are likely to have specific morphologic outcomes. Because of time limitations, manual grading with OCTOR is unlikely to be performed in clinical practice, though the ongoing development of accurate, automated OCT segmentation algorithms may increase the relevance of these findings. In the interim, manual quantitative OCT subanalysis may be of value in clinical trials, allowing a more precise understanding of anatomic outcomes.

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