

EFFECT OF RANIBIZUMAB RETREATMENT FREQUENCY ON NEUROSENSORY RETINAL VOLUME IN NEOVASCULAR AMD

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Purpose: To determine the characteristics of patients with neovascular age-related macular degeneration who show initial anatomic improvements on optical coherence tomography in response to treatment with ranibizumab, but who subsequently regress toward their anatomic baseline.

Methods: Data from 50 consecutive patients, receiving ranibizumab therapy for neovascular age-related macular degeneration, were collected. Raw StratusOCT images were analyzed using custom software ("OCTOR"). Changes in volume of neurosensory retina at months 1, 3, and 6 were calculated. Baseline demographic and morphologic characteristics were compared.

Results: Forty-two patients (84%) showed a reduction in total retinal volume 1 month after initial treatment with ranibizumab. Of the patients that initially showed a reduction, 16 (38%) maintained this reduction through month 6, whereas 26 patients (62%) demonstrated a subsequent increase in retinal volume. Patients who maintained a reduction in edema received 3.75 ± 1.18 injections of ranibizumab versus 2.96 ± 1.34 injections for patients who did not ($P = 0.049$). Regression of initial anatomic improvements was associated with worsening of visual acuity ($r = 0.599$, $P = 0.002$).

Conclusion: Patients receiving fewer injections of ranibizumab appeared less likely to maintain anatomic improvements achieved following commencement of ranibizumab therapy; regression of these improvements was associated with deterioration in visual acuity.

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Ranibizumab (Lucentis; Genentech, Inc., San Francisco, CA), an antibody fragment that blocks all isoforms of vascular endothelial growth factor-A, is the first treatment for neovascular age-related macular degeneration (AMD) that has been shown to lead to significant improvements in visual acuity in Phase III clinical trials.^{1,2} In the MARINA and ANCHOR trials,

patients received monthly injections of ranibizumab over a 2-year period—a retreatment regimen that has both practical and economic implications, particularly with the availability of inexpensive alternatives, such as bevacizumab (Avastin; Genentech).^{3,4} As a result, much effort has focused on the development of alternative treatment regimens, which would reduce the number of injections required, while maintaining the efficacy demonstrated in the MARINA and ANCHOR studies.^{5,6}

Optical coherence tomography (OCT) formed the basis for retreatment in the recently published PRONTO study,⁵ and OCT-guided retreatment protocols have become widely adopted in clinical practice. Caution is required, however, when utilizing quantitative information from OCT in a clinical setting, as significant errors are known to occur in data obtained from the widely used StratusOCT analysis software.⁷

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Drs. Walsh and Sadda are coinventors of Doheny intellectual property related to optical coherence tomography that has been licensed by Topcon Medical Systems. However, it is not related to the article's subject matter.

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To address this issue, we have previously developed publicly available custom image-measurement software, entitled “OCTOR.”^{8,9} This software facilitates accurate and reproducible manual segmentation of OCT images and allows quantitative analysis of any area of interest in these images, e.g., retina, subretinal fluid, subretinal tissue, or pigment epithelium detachment (PED).

Quantitative OCT data derived from accurate segmentation of the neurosensory retina may facilitate retreatment decisions, although its precise role remains unresolved.^{5,10} Using OCTOR, we have previously reported results from a cohort of patients treated with ranibizumab according to an OCT-guided retreatment regimen.¹¹ In this previous study, the effect of ranibizumab on the neurosensory retina appeared to be attenuated over time—a finding we speculated was secondary to treatment tachyphylaxis. In the present study, we aim to determine if there are differences in the characteristics of patients with neovascular AMD who show anatomic regression after initial response to therapy, versus those who maintain anatomic improvement, as determined by OCT.

Materials and Methods

Data Collection

For this retrospective study, we collected and reviewed data from all patients receiving their initial intravitreal injections of ranibizumab at the Doheny Eye Institute between July 2006 and September 2007. Approval for 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 choroidal neovascularization (CNV) secondary to AMD; StratusOCT imaging performed before their initial treatment with ranibizumab; and a total of 6 months of subsequent follow-up, with StratusOCT imaging at each visit. Any patient switched to an alternative treatment for neovascular AMD, during this follow-up period, was excluded from the study.

StratusOCT images were collected at baseline and at Months 1, 3, and 6 after initial treatment with ranibizumab. Images were obtained with a single StratusOCT machine using the Radial Lines protocol of six high-resolution B-scans. The Fast Macular Thickness 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 case were exported to 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. After their initial intravitreal injection, patients were treated at the discretion of the physician based on assessment of disease activity as determined by OCT and/or fluorescein angiography, and utilizing many of the criteria specified in the PrONTO study.⁵ In the PrONTO study, ranibizumab retreatment was performed if one of the following changes was observed: a loss of five letters in conjunction with fluid in the macula as detected by OCT, an increase in OCT central retinal thickness of at least 100 μm , new-onset classic CNV, new macular hemorrhage, or persistent macular fluid detected by OCT at least 1 month after the previous injection of ranibizumab. The number and timing of retreatments were recorded for each patient. Other data collected included patient age and gender, as well as best-corrected Snellen visual acuity at the time of initial ranibizumab injection. Fluorescein angiographic images taken for each patient at the time of initial treatment were also collected.

Baseline Patient Characteristics

Fifty consecutive patients, receiving their initial intravitreal injections of ranibizumab at the Doheny Eye Institute, and meeting the inclusion criteria were included in this study. Two patients were excluded from consideration as they were switched to an alternative treatment (intravitreal bevacizumab) during the course of follow-up. Of the 50 patients included, 30 (60%) were women, whereas 20 (40%) were men. The mean age of patients was 80 years (SD = 7), whereas the median age was 81 years (range, 63–92 years). Mean visual acuity at time of initial treatment with ranibizumab was 20/123. Twenty-eight (56%) patients had undergone prior treatment for CNV in their study eye, consisting of photodynamic therapy with verteporfin, thermal laser photocoagulation, pegaptanib, or bevacizumab.

Computer-Assisted Grading Software

The software used for OCT analysis (entitled “OCTOR”) was written by Doheny Image Reading Center software engineers to facilitate viewing and manual grading. OCTOR is publicly accessible at <http://www.diesel.la> (accessed June 23rd, 2008) and has been described and validated in previous reports.^{8,9,11–13} 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.

After the grader draws the required layers in each of the 6 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 into 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 into volumes (mm^3) by multiplying the average thickness measurement by the sampled area. The interpolation algorithm, intergrader reliability, and intragrader reproducibility have previously been validated.^{8,9}

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. The 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 of interest.

Grading Procedure

Optical coherence tomography scans were analyzed by certified OCT graders at the Doheny Image Reading Center (PAK, SL, KTC). 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 retinal pigment epithelium and estimated normal position of the retinal pigment epithelium layer (in cases of retinal pigment epithelium elevation). All boundaries were drawn in accordance with the standard OCT grading protocol of the Doheny Image Reading Center.⁸ After completion of the grading, OCTOR was used to calculate output parameters for the various spaces: retina, subretinal fluid, subretinal tissue, and PED.

Angiographic CNV lesion type at baseline was determined by certified FA graders at the Doheny Image Reading Center (PAK, KTC) using the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy Study grading protocol.¹⁴ Disagreement regarding angiographic classification of CNV lesion type was resolved by open adjudication and consensus between graders, in accordance with standard reading center practices.

Data Analysis and Statistical Methods

The change from baseline in total retinal volume was determined for each patient at Month 1. Patients showing an initial reduction in total retinal volume by Month 1 were used to formulate two groups for the purposes of comparison. Patients who maintained, or had further reduction, in total retinal volume, between Month 1 and the final examination at Month 6 were included in the first group; patients demonstrating an increase in retinal volume from Month 1 to Month 6 were included in the second group (Figure 1).

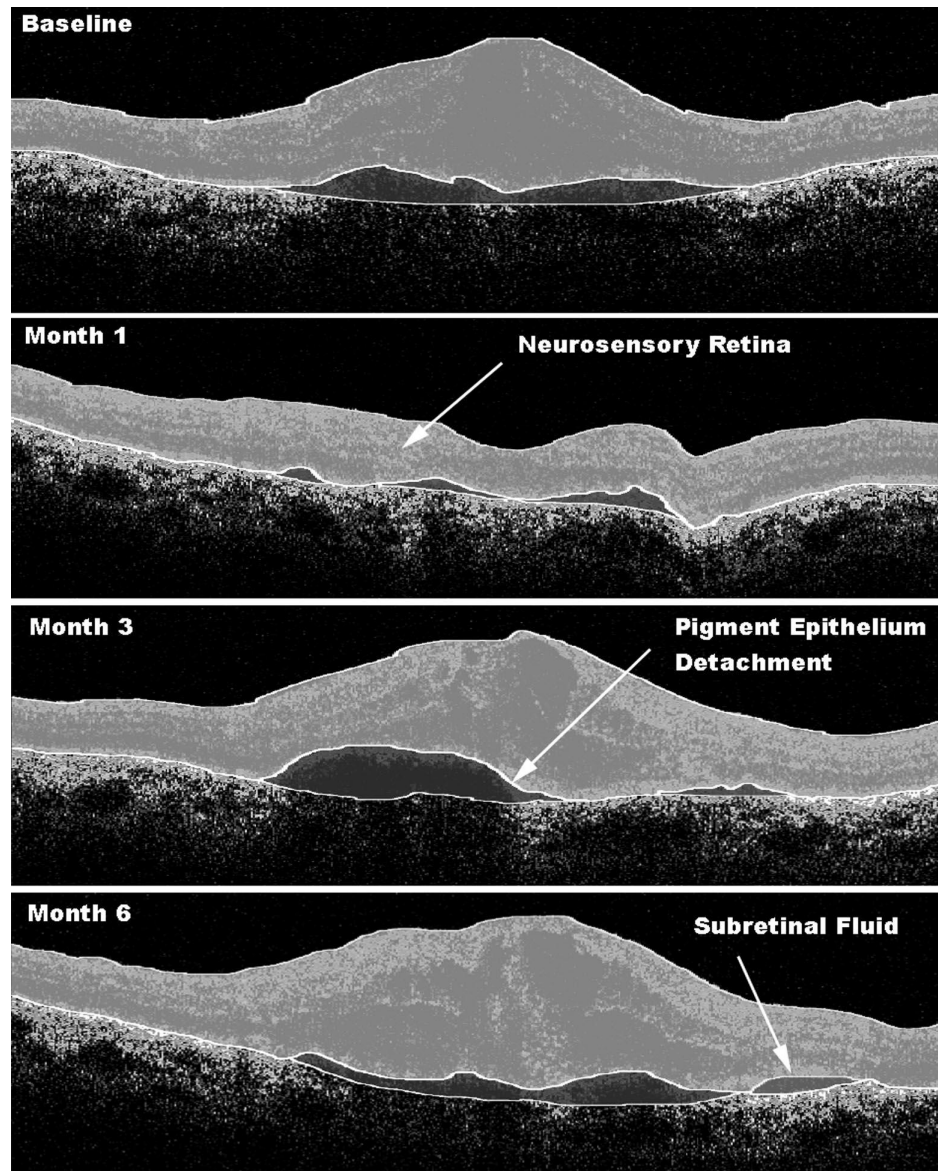
Groups were compared for each of the following variables: age, gender, previous treatment for neovascular AMD, angiographic CNV lesion classification at baseline, visual acuity at baseline, and number of injections of ranibizumab received. OCTOR software was also used to compare the volumes of neurosensory retina, subretinal fluid, PED, and subretinal tissue, between the two groups at baseline and at each follow-up. For each comparison between groups, a *t*-test (2-tail distribution) was used in the case of normally distributed interval variables, whereas a chi-square test or Fisher's Exact Test was used in the case of categorical variables. For each group the mean change from baseline, in total volume of the neurosensory retina, was also calculated at each follow-up visit, and analyzed using a paired *t*-test. *P* values <0.05 were considered statistically significant. Statistical analysis was performed using commercially available software (Intercooled Stata for Windows, Version 9, Statacorp LP).

Results

Baseline Morphologic Characteristics

At baseline, the neovascular lesions were categorized by fluorescein angiography as predominantly classic (10 eyes, 20%), as minimally classic (8 eyes, 16%) and as occult with no classic (32 eyes, 64%). The total area of visible classic CNV and occult CNV was considered the area of CNV leakage. The CNV lesion was defined as the area of CNV leakage plus any contiguous areas of thick hemorrhage, blocked fluorescence, staining scars or serous PED which could be obscuring the boundaries of the CNV. The mean total CNV lesion area was 5.7 ± 5.1 Disk Areas, whereas the mean total area of CNV leakage was 3.8 ± 3.2 Disk Areas. The mean greatest linear dimension (GLD) of CNV lesions was 3.9 ± 1.7 mm, whereas the mean GLD of CNV leakage was 3.5 ± 1.6 mm. The total volume of the neurosensory retina, measured using OCTOR, was $7.35 \pm 0.65 \text{ mm}^3$ for the entire cohort at baseline. The total volume of

Fig. 1. Optical coherence tomography B-scans (each at 90°) from a subject demonstrating initial anatomic improvements, with subsequent regression and associated decline in visual acuity. Baseline, Patient is newly diagnosed with neovascular age-related macular degeneration. Visual acuity is 20/40 and the patient is treated with intravitreal ranibizumab. Month 1, Treatment with ranibizumab leads to a significant reduction in total retinal volume. Visual acuity is 20/30, and patient is observed. Month 3, Regression of anatomic changes is clearly evident. Visual acuity is 20/80 and the patient is treated with a second intravitreal injection of ranibizumab. Month 6, Total retinal volume remains elevated. Visual acuity is 20/100, and patient receives third injection of ranibizumab.



subretinal fluid at baseline was $0.34 \pm 0.58 \text{ mm}^3$, whereas that of subretinal tissue was $0.29 \pm 0.49 \text{ mm}^3$. The total volume of PED was $1.04 \pm 1.79 \text{ mm}^3$ for the entire cohort at baseline. The total volumes of subretinal fluid, PED, and subretinal tissue, at baseline and at each follow-up, are summarized in Table 1.

Morphologic Outcomes—Baseline to Month 1

Forty-two patients (84%) showed a reduction in total retinal volume 1 month after their initial treatment with ranibizumab—“Initial Responders.” Eight patients (16%) showed an increase in total retinal

volume at Month 1, despite treatment with intravitreal ranibizumab—“Initial Non-Responders” (Figure 2). Patients who demonstrated an initial anatomic response had a greater total retinal volume at baseline than those who failed to respond ($7.45 \pm 0.61 \text{ mm}^3$ versus $6.84 \pm 0.68 \text{ mm}^3$, $P = 0.035$).

No statistically significant difference was found between “Initial Responders” and “Initial Non-Responders” in terms of age ($P = 0.781$), baseline visual acuity ($P = 0.115$), previous treatment for neovascular AMD ($P = 0.277$), total CNV lesion area ($P = 0.914$), total CNV leakage area ($P = 0.541$), GLD of

Table 1. Additional Morphologic Outcomes Derived From “OCTOR” Analysis (Mean $\pm$ Standard Deviation)

	Total (n = 50)	Sustained Responders (n = 16)	Regressors (n = 26)	P*
Subretinal fluid				
Baseline—total vol. (mm ³)	0.36 $\pm$ 0.60	0.39 $\pm$ 0.71	0.34 $\pm$ 0.53	0.506
Month 1—total vol. (mm ³)	0.09 $\pm$ 0.26	0.10 $\pm$ 0.21	0.09 $\pm$ 0.29	0.202
Month 3—total vol. (mm ³)	0.11 $\pm$ 0.24	0.16 $\pm$ 0.32	0.08 $\pm$ 0.15	0.956
Month 6—total vol. (mm ³)	0.09 $\pm$ 0.21	0.06 $\pm$ 0.16	0.12 $\pm$ 0.24	0.171
Pigment epithelium detachment				
Baseline—total vol. (mm ³)	1.01 $\pm$ 1.76	0.52 $\pm$ 0.42	1.31 $\pm$ 2.17	0.490
Month 1—total vol. (mm ³)	0.73 $\pm$ 1.51	0.61 $\pm$ 1.26	0.80 $\pm$ 1.67	0.804
Month 3—total vol. (mm ³)	0.66 $\pm$ 1.02	0.93 $\pm$ 1.40	0.48 $\pm$ 0.67	0.546
Month 6—total vol. (mm ³)	0.52 $\pm$ 0.79	0.52 $\pm$ 0.88	0.52 $\pm$ 0.75	0.659
Subretinal tissue				
Baseline—total vol. (mm ³)	0.30 $\pm$ 0.52	0.43 $\pm$ 0.78	0.23 $\pm$ 0.25	0.141
Month 1—total vol. (mm ³)	0.23 $\pm$ 0.34	0.21 $\pm$ 0.39	0.24 $\pm$ 0.31	0.310
Month 3—total vol. (mm ³)	0.24 $\pm$ 0.40	0.26 $\pm$ 0.45	0.22 $\pm$ 0.37	0.671
Month 6—total vol. (mm ³)	0.25 $\pm$ 0.33	0.21 $\pm$ 0.29	0.27 $\pm$ 0.35	0.611

*Ranksum test.

lesion ($P = 0.524$), GLD of leakage ($P = 0.541$), or angiographic classification of CNV at baseline ($P = 0.312$). Additional analysis with OCTOR software found no statistically significant difference between the groups in terms of baseline subretinal fluid volume ($P = 0.665$), subretinal tissue volume ($P = 0.207$), or PED volume ($P = 0.761$).

Morphologic Outcomes—Month 1 to Month 6

Of the patients who initially responded, 16 (38%) maintained or had further reduction through to the final examination at Month 6—“Sustained Responders” (Figure 3). Of the 42 patients who initially showed a reduction in total retinal volume by Month 1,

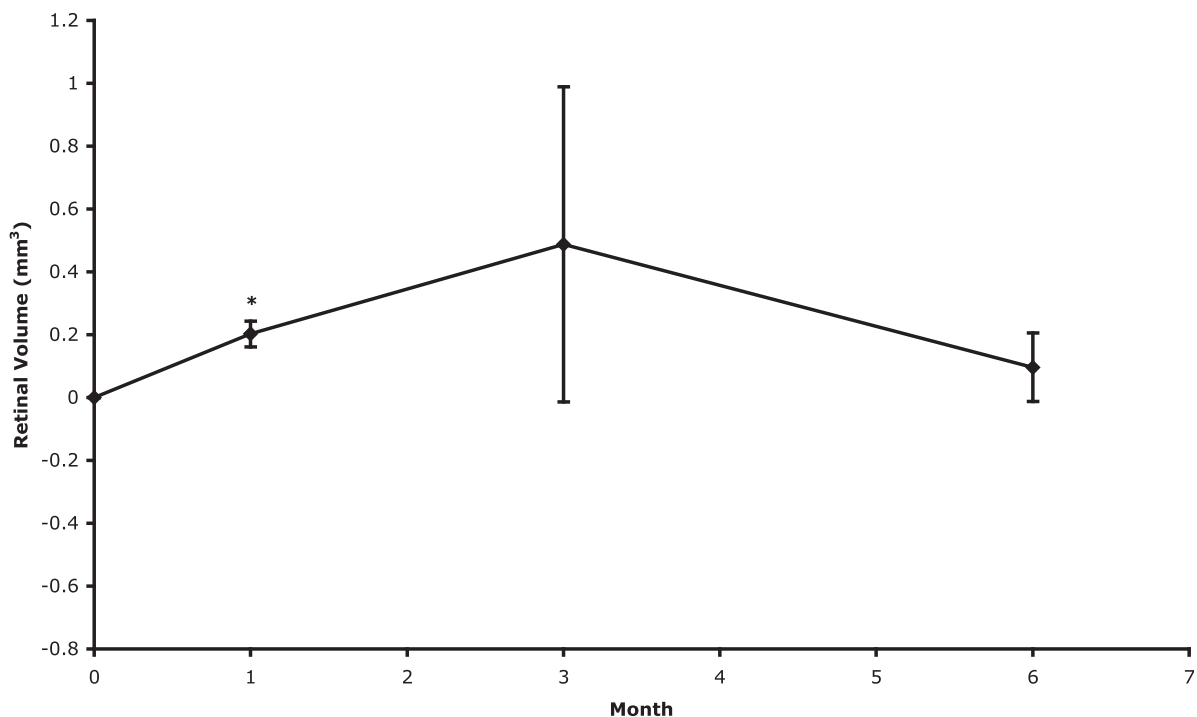


Fig. 2. Mean change from baseline in total volume of neurosensory retina—patients who failed to respond anatomically to initial treatment with intravitreal ranibizumab (“Initial Non-Responders”). Vertical lines, 1 standard error of the mean. * $P < 0.05$.

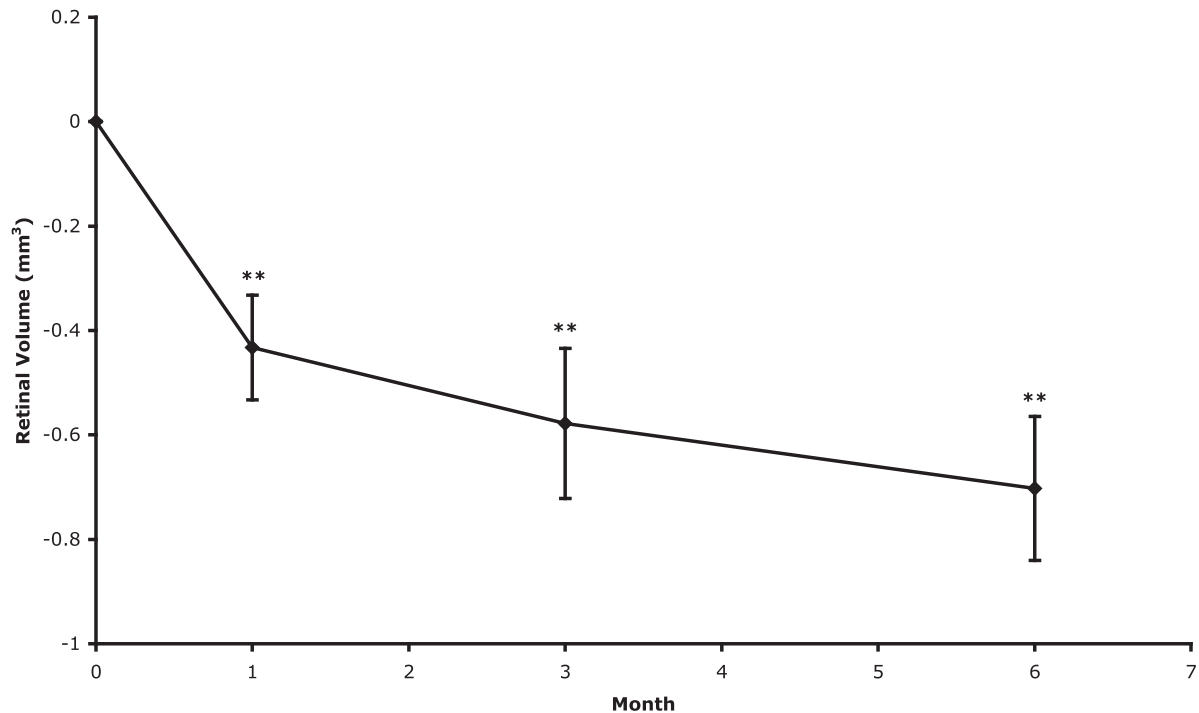


Fig. 3. Mean change from baseline in total volume of neurosensory retina—patients who responded initially, and who continued to respond by month 6 (“Sustained Responders”). Vertical lines, 1 standard error of the mean. ** $P < 0.01$.

26 patients (62%) had regressed toward baseline retinal volume measurements between Month 1 and Month 6—“Regressors” (Figure 4). The patients who maintained the Month 1 reduction received 3.75 ± 1.18 injections of ranibizumab versus 2.96 ± 1.34 injections for the patients who did not ($P = 0.049$).

No statistically significant difference was found between the groups in terms of age ($P = 0.196$), baseline visual acuity ($P = 0.321$), previous treatment for neovascular AMD ($P = 0.907$), baseline neurosensory retinal volume ($P = 0.579$), total CNV lesion area ($P = 0.303$), total CNV leakage area ($P = 0.493$), GLD of lesion ($P = 0.847$), GLD of leakage ($P = 0.471$), or angiographic classification of CNV at baseline ($P = 0.180$). Additional analysis with OCTOR software found no statistically significant difference between the groups in terms of subretinal fluid volume, subretinal tissue volume, or PED volume, at baseline, or at any of the follow-up visits (Table 1).

Visual Outcomes

The mean changes from baseline in visual acuity for each of the subgroups are illustrated in Figure 5. The change in visual acuity between baseline and Month 1 was not correlated with the change in total retinal volume over the same time period for any of the

subgroups: “Initial Responders” ($P = 0.609$), “Initial Non-Responders” ($P = 0.201$), or entire cohort ($P = 0.638$). In addition, the change in visual acuity between baseline and Month 6 was not correlated with the change in total retinal volume between baseline and Month 6 ($P = 0.221$). However, between Month 1 and Month 6, a statistically significant correlation was detected between the change in visual acuity and the change in total retinal volume ($r = 0.359$, $P = 0.014$). This correlation was also seen for “Initial Responders” ($r = 0.400$, $P = 0.011$), “Initial Non-Responders” ($r = 0.7617$, $P = 0.078$), and for “Regressors” ($r = 0.599$, $P = 0.002$). For the same time period, no correlation was detected between the change in visual acuity and the change in total retinal volume for the “Sustained Responders” ($r = 0.235$, $P = 0.399$).

Discussion

In this study, we analyzed changes in neurosensory retinal volume occurring in response to treatment with ranibizumab for neovascular AMD to determine the characteristics of patients who initially respond to treatment, but who subsequently regress toward their anatomic baseline.

OCTOR analysis of the neurosensory retina revealed that cases showing initial anatomic improve-

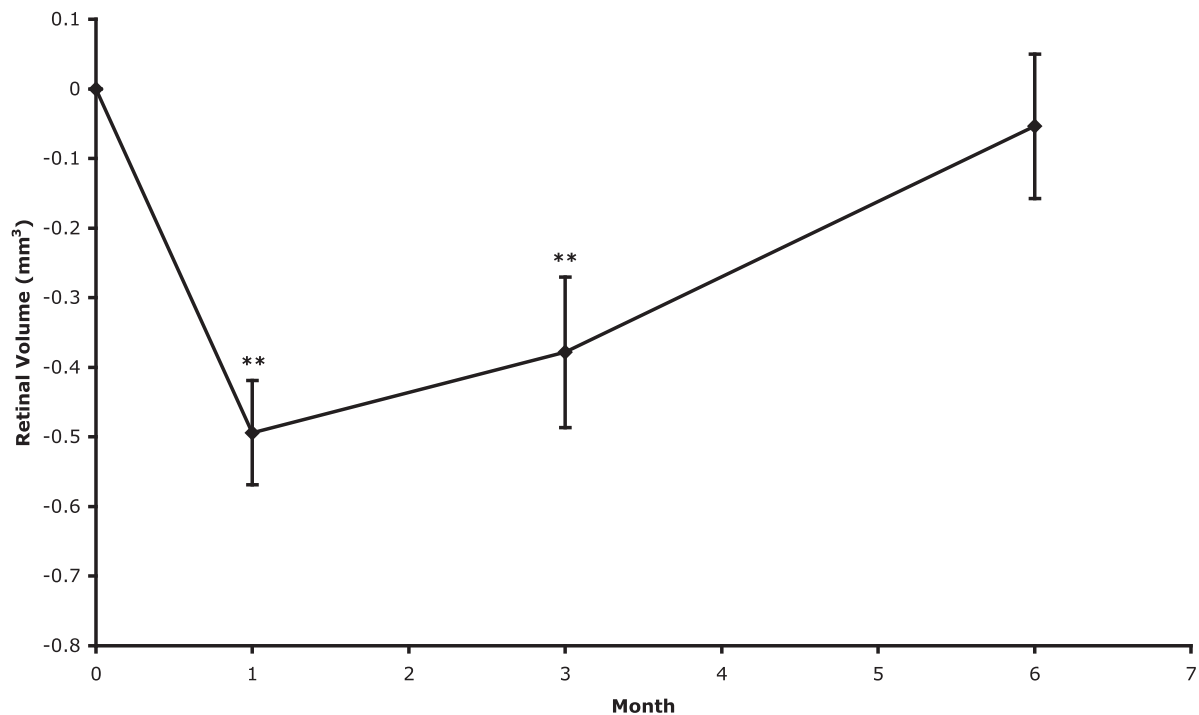


Fig. 4. Mean change from baseline in total volume of neurosensory retina—patients who responded initially, but who subsequently regressed toward their anatomic baseline by month 6 (“Regressors”). Vertical lines, 1 standard error of the mean. ** $P < 0.01$.

ment, but subsequent regression, received fewer injections of intravitreal ranibizumab than cases demonstrating a sustained anatomic response. Although our study did not use a fixed retreatment schedule, our findings appear consistent with anatomic results from the recent phase IIIb PIER Study, the aim of which was to assess the efficacy of a less frequent ranibizumab-dosing regimen (monthly for 3 months and then quarterly).⁶ In the PIER Study, the transition to less frequent therapy was associated with increased central retinal thickness on OCT, as well as increased CNV leakage on fluorescein angiography.^{6,15} Although quarterly ranibizumab therapy in the PIER Study maintained baseline VA, it was associated with a 4.5-letter decline in the maximal VA benefit achieved during the initial “induction” period of therapy. It is possible that the return of retinal edema contributed, at least in part, to the decline in the maximal VA benefit achieved. Our study provides additional evidence that some patients with neovascular AMD may require more frequent ranibizumab injections to control CNV leakage and OCT features of exudation.

The alternative dosage regimen used in the PIER Study was selected on the basis of evidence from Phase I/II studies indicating that the pharmacodynamic activity of ranibizumab administered monthly

for three doses might persist for a subsequent 90 days.^{16,17} Despite this evidence, it appears from our study, and the PIER trial results, that any persistence in the activity of ranibizumab may not be sufficient to maintain initial anatomic benefits over an extended period. Alternatively, a rebound effect may explain the anatomic changes observed. Experience with other pathophysiological systems has shown that rebound hyperfunction commonly develops on withdrawal of a drug.¹⁸ Clinical evidence of rebound macular edema has previously been described in a small case series of patients receiving another antivascular endothelial growth factor therapy (bevacizumab), in the context of retinal vein occlusion.¹⁹ If a rebound phenomenon occurs, the underlying mechanism may involve transient up-regulation of vascular endothelial growth factor production within the eye secondary to administration of ranibizumab, and a more frequent treatment regimen (as in the MARINA and ANCHOR trials) may be required to overcome this factor.

Quantitative OCT subanalysis using OCTOR revealed that cases showing initial anatomic improvement, but subsequent regression, did not differ from cases demonstrating a sustained anatomic response in terms of baseline subretinal fluid volume, baseline subretinal tissue volume, or baseline PED volume. Furthermore, there was no statistically significant dif-

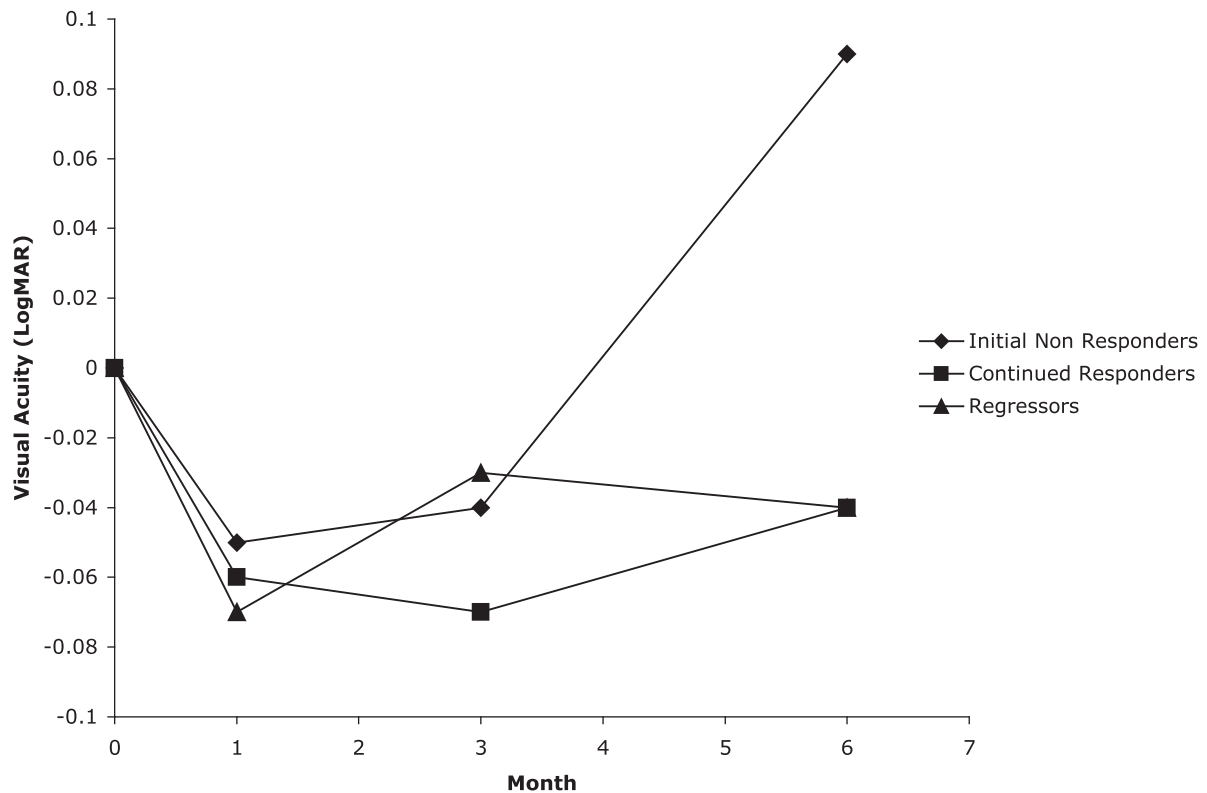


Fig. 5. Mean change from baseline in visual acuity (Snellen visual acuities converted to LogMAR units for the purposes of statistical analysis).

ference between the groups in terms of age, previous treatment for neovascular AMD, CNV lesion area, CNV leakage area, CNV classification, or baseline visual acuity—findings consistent with subgroup analyses from the MARINA, ANCHOR, and PIER trials.^{6,20,21} From these trials, it appears that CNV lesion classification and size have limited prognostic value for ranibizumab therapy and, consequently, fluorescein angiography may play a less prominent role in ranibizumab therapy than it has for photodynamic therapy with verteporfin.

OCTOR analysis also demonstrated that the initial treatment with ranibizumab led to reductions in total retinal volume in the majority of eyes, but that this decrease was not correlated with an improvement in visual acuity, either at Month 1 or at Month 6. However, the change in visual acuity between Month 1 and Month 6 was found to correlate with the change in total retinal volume over this time period, and this correlation was particularly evident in the “Regressors” subgroup. In other words, increases in total retinal volume, after initial decreases, were strongly associated with deterioration in visual acuity. Many studies have failed to find a consistent correlation between changes in central retinal thickness on OCT,

and visual acuity, in patients with neovascular AMD.^{4,15,22} As a result, our findings may be of considerable interest if they can be replicated in larger prospective studies utilizing Early Treatment Diabetic Retinopathy Study visual acuities obtained with protocol refractions.

Our study has a number of limitations. The breakdown of patients into subgroups for comparison, although hypothesis-driven, was an arbitrary construct. In addition, the patient cohort examined was small and collected retrospectively; therefore, all conclusions must be considered preliminary. Although patients in our study were treated utilizing many of the criteria specified in the PrONTO study, the purpose of our study was not specifically to address the merits of OCT-guided retreatment. The PrONTO study has provided evidence that an OCT-guided variable dosing regimen could result in visual acuity outcomes similar to the Phase III clinical studies, but require fewer injections.⁵ Despite these excellent results, the issue of ranibizumab retreatment remains controversial, and a number of alternative retreatment regimens have been suggested, e.g., “inject and extend.”¹⁰ Large phase III clinical trials (EXCITE trial, SUSTAIN trial), evaluating retreatment regimens based on disease activity,

are currently underway, and may provide more definitive guidance regarding ranibizumab dosing.^{23,24}

In summary, patients receiving fewer injections of ranibizumab appeared less likely to maintain anatomic improvements achieved following commencement of ranibizumab therapy. Furthermore, regression of initial anatomic improvement was strongly associated with worsening of visual acuity. These phenomena, if confirmed in other studies, may have implications for the future design of ranibizumab retreatment regimens in neovascular AMD.

Key words: age-related macular degeneration, optical coherence tomography, ranibizumab.

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