Macular Atrophy Progression and 7-Year Vision Outcomes in Subjects From the ANCHOR, MARINA, and HORIZON Studies: the SEVEN-UP Study*

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• PURPOSE: **To assess the incidence and progression of macular atrophy and other key anatomic outcomes over 7 to 8 years in an early cohort of ranibizumab-treated exudative age-related macular degeneration patients.**

• DESIGN: **Follow-up analysis of long-term outcomes in a multicenter treatment cohort.**

• METHODS: **Fourteen study sites enrolled 65 previous subjects from the ranibizumab treatment arms of the ANCHOR, MARINA, and HORIZON trials. In a single update visit, clinical assessment and retinal imaging studies were performed, with comparison with each subject's prior results from the previous trials. Early Treatment Diabetic Retinopathy Study visual acuity was the primary outcome. Secondary outcomes, including area of macular atrophy and selected anatomic factors, were analyzed for associations with long-term vision outcomes.**

• RESULTS: **At a mean 7.3 years after ANCHOR or MARINA enrollment, mean visual acuity was 54 letters, study eyes having received a mean 1.6 injections per year since the HORIZON study. Macular atrophy was present in 98% of study eyes, the mean area increasing from 0.83 ± 0.96 mm^2 at the ANCHOR or MARINA year 2 exit to 2.22 ± 1.6 mm^2 at the SEVEN-UP visit, a growth rate of 0.28 mm^2/year. Progression of macular atrophy was associated significantly with visual decline over this 5-year period ($P < .001$), and final macular atrophy lesion size was related significantly to final vision ($P < .001$). Other key anatomic outcomes (macular thickening, thinning, or fluid and submacular fibrosis) did not have significant effects on vision outcomes.**

• CONCLUSIONS: **Seven years after initiation of intensive ranibizumab therapy for exudative age-related macular degeneration, macular atrophy progression and severity were the primary anatomic determinants of visual outcomes.** **(Am J Ophthalmol 2015;159(5):915–924.**

EXUDATIVE AGE-RELATED MACULAR DEGENERATION (AMD) is a chronic disease that can require protracted treatment with ocular anti–vascular endothelial growth factor (VEGF) therapies. Since intravitreal ranibizumab (Lucentis; Genentech, Inc, South San Francisco, California, USA) was clinically approved in 2006, many patients have now been receiving this treatment for 7 years or more. Although the significant visual benefits of ranibizumab, off-label intravitreal bevacizumab (Avastin; Genetentech, Inc) and intravitreal aflibercept (Eylea; Regeneron Pharmaceuticals, Tarrytown, New York, USA) have been demonstrated for AMD patients in major phase 3 randomized controlled multicenter trials,[1–7] available results are limited largely to 1- or 2-year studies. Longer-term evidence to describe vision outcomes and to guide the ongoing management of exudative AMD patients remains incomplete.[8] In addition, macular anatomic outcomes over an extended therapeutic course and their relationship to long-term vision outcomes have not been elucidated.

The Seven-Year Observational Update of Macular Degeneration Patients Post-MARINA/ANCHOR and HORIZON Trials (SEVEN-UP) study (ClinicalTrials.gov identifier, NCT01256827)[9] previously reported visual outcomes in a cohort of AMD patients who were among the first to receive ranibizumab: those who had been study participants 7 to 8 years previously in the phase 3 Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR)[2,10] trial (ClinicalTrials.gov identifier, NCT00061594) and Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA)[1] trial (ClinicalTrials.gov identifier, NCT00056836) and who had continued in the treatment

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arms of the Open-Label Extension Trial of Ranibizumab for Choroidal Neovascularization Secondary to Age-Related Macular Degeneration (HORIZON) extension study[11] (ClinicalTrials.gov identifier, NCT00379795). In these subjects, who offer the longest available treatment history, the SEVEN-UP study found divergent vision outcomes. After 2 years of intensive monthly ranibizumab treatments followed by what is now considered low treatment frequency in the HORIZON study and off-study thereafter with ranibizumab and intravitreal bevacizumab (Avastin), 37% of eyes had 20/70 or better Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA), whereas 37% of eyes had 20/200 or worse ETDRS BCVA.

As previously reported,[9] a high proportion of eyes at this late stage displayed continued choroidal neovascular leakage and macular edema, submacular fibrosis, and macular atrophy (loss of retinal pigment epithelium [RPE], outer retina, and choriocapillaris). In the current analyses, additional access to the original ANCHOR and MARINA imaging databases made it possible to track the progression of macular atrophy in individual subjects over an approximate 5-year period to assess the effect on vision change in this group of treated AMD patients. Also, in multivariate regression analyses, key anatomic outcomes could be evaluated to distinguish their relative impact on vision outcomes. The hypothesis is that long-term visual outcomes in treated AMD patients are affected by the development of specific types and severity of macular pathologic features. Identifying such anatomic markers could assist clinicians in understanding the highly variable long-term vision outcomes observed among AMD patients and could guide treatment strategies over extended durations.

METHODS

• **STUDY DESIGN:** The SEVEN-UP study was a follow-up analysis of long-term outcomes in a multicenter treatment cohort of AMD patients who were originally in the ANCHOR, MARINA, and HORIZON trials. Health Insurance Portability and Accountability Act and Declaration of Helsinki guidelines were followed, and approval granted by Institutional Review Boards for each participating center. All subjects gave informed consent to participate. Study visits were conducted from November 2010 through November 2011.

• **OUTCOME MEASURES:** The predetermined primary outcome measure was the percentage of study eyes with ETDRS BCVA of 20/70 or better. Predetermined secondary outcome measures included the presence of cystoid macular edema, subretinal fluid, or both, as well central subfield thickness (CST) and the presence and location of submacular fibrosis. Macular atrophy was another predetermined secondary outcome measure in terms of percentage of eyes affected, area, and progression from baseline in ANCHOR or MARINA.

• **STUDY COHORT:** The SEVEN-UP study represented 14 clinical trial sites in the United States from the original ANCHOR, MARINA, and HORIZON studies. All subjects who had participated previously at 1 of these 14 sites in the ranibizumab-treatment arms of ANCHOR or MARINA (including both the 0.3-mg and 0.5-mg dosing assignments) who also completed 24 months in the treatment arms (0.5 mg ranibizumab as needed) of the HORIZON extension study were eligible and were recruited by invitation.[9] Through ANCHOR or MARINA and HORIZON, 357 patients completed their assignment in the ranibizumab treatment arms; 155 of these were eligible from the 14 participating SEVEN-UP study clinical sites. By outreach from the original sites of their participation, 65 subjects were enrolled for a single update visit. For this group, the mean duration since entry into ANCHOR or MARINA was 7.3 years, and the mean duration since completing month 24 of HORIZON was 3.4 years.

• **SEVEN-UP STUDY PROTOCOL:** The single visit study evaluation included BCVA measurements with ETDRS vision test by a certified examiner using standard protocols. A complete ophthalmologic examination was performed, and clinical report forms recorded assessments by investigators. Patient records also were reviewed retrospectively when available for key events in the previous 6 months, as well as for treatment history over the interim since exit from the HORIZON study. A panel of retinal imaging studies included spectral-domain optical coherence tomography (SD OCT), fundus photography, fluorescein angiography (FA), and fundus autofluorescence (FAF) imaging. No interventions or treatments were included as part of the SEVEN-UP protocol.

• **IMAGING ANALYSIS:** All image data collected at SEVEN-UP visit were analyzed at the Doheny Imaging Reading Center by independent, masked, certified graders according to a predetermined standardized and validated grading protocol. Imaging studies from prior study participation were obtained for SEVEN-UP subjects from the ANCHOR and MARINA databases, provided by the Wisconsin Reading Center.

• **MACULAR ATROPHY ASSESSMENT:** For an analysis of macular atrophy progression over time, study eyes were assessed by red-free photographs and early and late FA frames at the month 24 ANCHOR or MARINA exit visit, and by red-free images, early and late FA frames, and FAF images at the SEVEN-UP visit. FAF imaging was available only for year 7 and was used for analyses restricted to year 7 outcomes. Where analyses required comparison with earlier time points, measurements were based on red-free

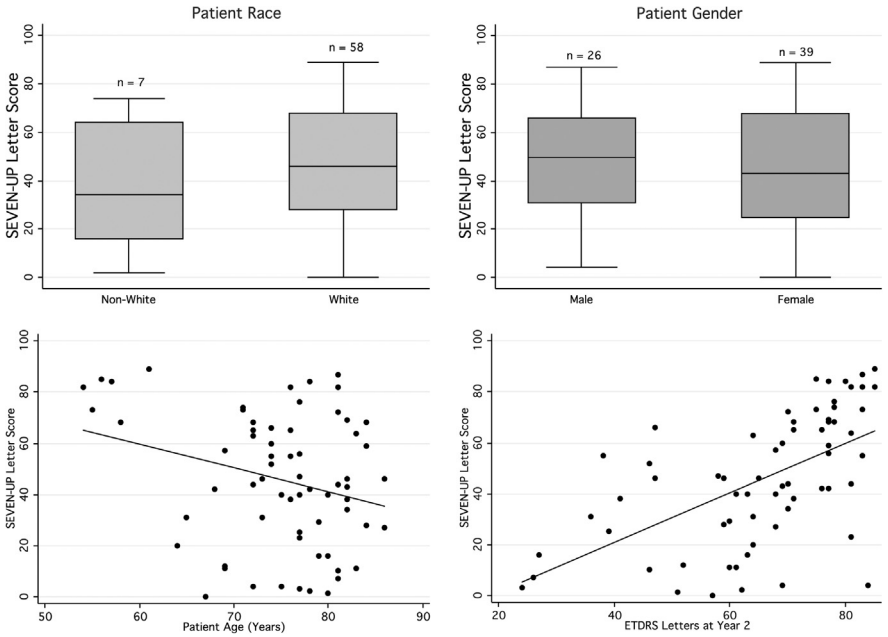

FIGURE 1. Long-term vision outcomes in subjects treated for exudative age-related macular degeneration are related to patient age and prior vision outcome, but not to patient gender or ethnicity. Box plots indicate seventy-fifth to twenty-fifth interquartile range (IQR), with median line; whiskers show highest and lowest values within a range of the twenty-fifth quartile minus 1.5 IQR and the seventy-fifth quartile plus 1.5 IQR. Comparable vision outcomes are seen among patients for (Top left) ethnicity and (Top right) gender. (Bottom left) Scatterplot showing visual acuity scores by age at study entry indicating an effect of poorer vision outcomes with increased age (coefficient, −0.93; $P = .027$). (Bottom right) Scatterplot showing year 7 vision score against year 2 vision score, indicating that higher baseline vision was associated with better final outcomes (coefficient, 0.97; $P < .001$). ETDRS = Early Treatment Diabetic Retinopathy Study.

images and FA. Interpretation and measurements were performed in a masked fashion by an experienced retinal specialist, with each study eye measured independently at least twice to reconcile disparities and determine a mean value. Macular atrophy was defined as a demarcated area of RPE defect or abnormal visibility of large choroidal vasculature, as an area of window defect without leakage on FA, and as an area of decreased autofluorescence on FAF imaging. Automated measurements were made by manually delineating the lesion borders using OIS integrated software (Ophthalmic Imaging Systems, Inc, Sacramento, California, USA). A minimum greatest linear dimension of 175 μm defined the presence of macular atrophy.

• **STATISTICAL METHODS:** All data were collected by clinical investigators in case report forms and forwarded for entry into an encrypted electronic database (REDCap) at the University of California, San Francisco. For statistical analysis, data were de-identified and analyzed using Stata software version 10.1 (Stata Corporation, College Station, Texas, USA). Linear regression models were used to identify clinical and anatomic factors that were associated with ETDRS letter score at the SEVEN-UP visit. All patients had only 1 eye in the study sample. Based on previous literature, initial vision score, patient age, gender, race, SD OCT indicators of leakage and macular thickness, submacular fibrotic scar formation, and macular atrophy were evaluated as potential predictors. These were chosen a priori, and the associations were evaluated for each in a preliminary bivariate regression analysis against vision outcomes. Subsequently, multivariate regression models were performed restricted to the 4 key anatomic variables, with the inclusion of prior baseline vision score where appropriate. Patient age, although found in the bivariate analysis to be associated significantly with vision outcomes, was not included so as to limit the number of variables in the statistical model given the sample size.

RESULTS

• **PATIENT DEMOGRAPHICS:** Figure 1 shows comparisons of vision outcomes for patient demographic factors and baseline vision, analyzed for independent associations to BCVA outcomes. For ethnicity, a minority of SEVEN-UP subjects were nonwhite (7, 11%); the white and nonwhite patient groups had comparable ETDRS letter scores (mean ± standard deviation ETDRS letter score, 46.6 ± 26.0 letters vs 39.0 ± 27.3 letters; $P = .51$). Male

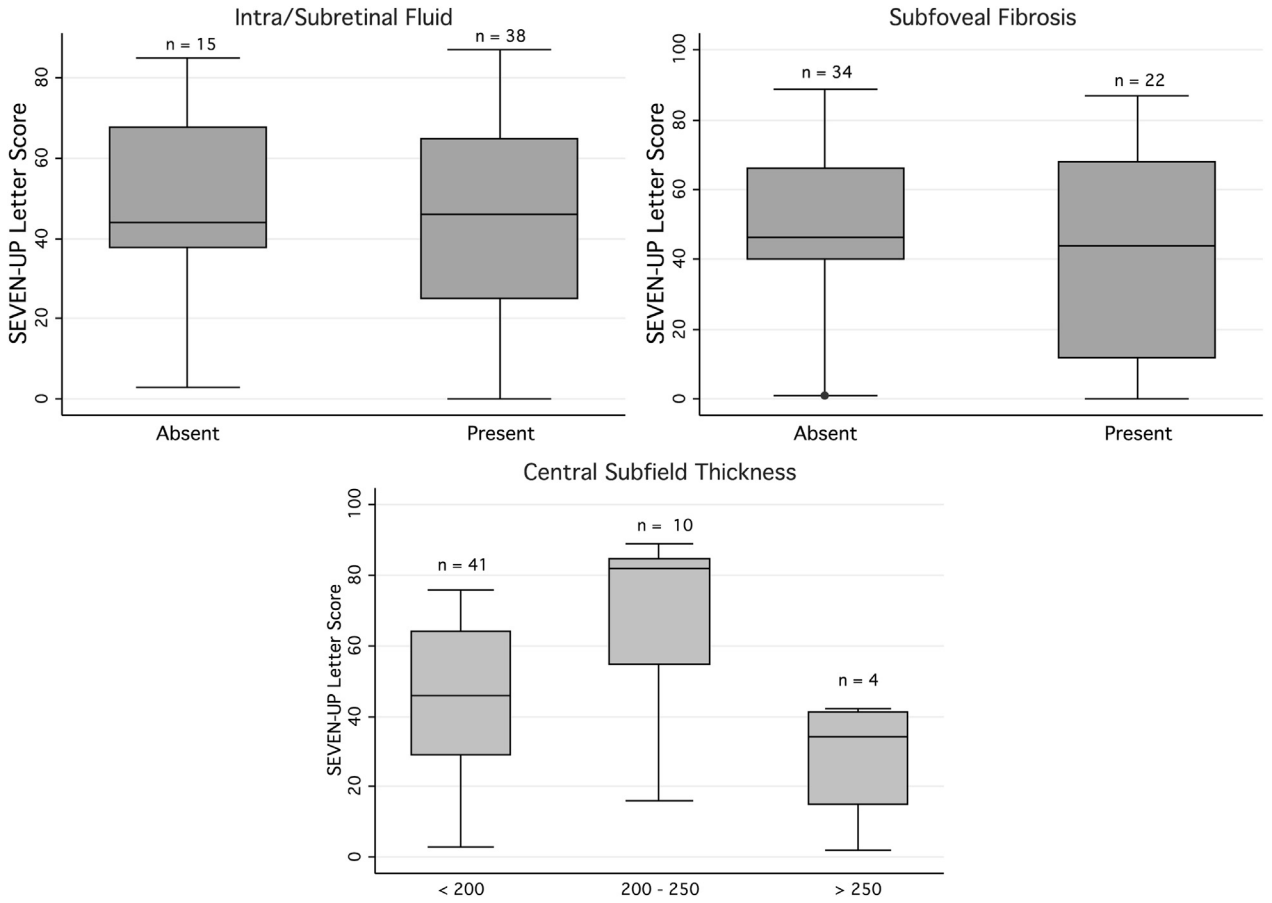

FIGURE 2. Macular atrophy is a determinant of long-term vision outcomes in subjects treated for exudative age-related macular degeneration. Box plots indicate seventy-fifth to twenty-fifth interquartile range (IQR), with median line; whiskers show the highest and lowest values within a range of the twenty-fifth quartile minus 1.5 IQR and the seventy-fifth quartile plus 1.5 IQR. Comparable vision outcomes at year 7 are seen in the presence or absence of (Top left) intraretinal or subretinal fluid, or both, and (Top right) subfoveal fibrosis. (Bottom) Macular thickness categories indicate reduced vision outcomes at year 7 for macular thinning (central subfield thickness [CST] < 200 μm) and for macular thickening (CST > 250 μm).

and female patient groups also had similar ETDRS vision score profiles (mean letter scores, 48.2 ± 26.7 vs 44.1 ± 25.2; $P = .55$). The mean patient age at the time of the SEVEN-UP visit was 82.1 years. The scatterplot of patient age against final ETDRS letter score indicates that older patients had significantly poorer visual outcomes (coefficient, −0.93; 95% confidence interval [CI], −1.75 to −0.11; $P = .027$).

Prior vision result at the completion of the ANCHOR or MARINA trials also was a significant predictor of final vision results at the SEVEN-UP visit approximately 5 years later. In Figure 1, ANCHOR or MARINA month 24 exit vision for each subject is plotted against the final SEVEN-UP vision; better prior vision score was associated significantly with better final vision score in a bivariate analysis (coefficient, 0.97; 95% CI, 0.62 to 1.32; $P < .001$; correlation coefficient, 0.58) and was confirmed in multivariate analysis that accounted for the effects of anatomic factors (coefficient, 0.52; 95% CI, 0.07 to 0.96; $P = .024$; Table 1).

• **ANATOMIC OUTCOMES:** SD OCT studies were available from 56 subjects at the SEVEN-UP visit; OCT imaging had not been obtained uniformly as part of ANCHOR, MARINA, and HORIZON, and for the purpose of these analyses, no OCT data were used from those previous clinical trials. In a preliminary bivariate analysis of 53 eyes with interpretable OCT images (Figure 2), the visual outcomes for eyes with the presence of intraretinal or subretinal fluid or both (72% of study eyes) corresponded closely to eyes without fluid (mean ETDRS scores, 44.1 ± 25.0 letters and 47.7 ± 22.7 letters, respectively; $P = .61$). There was a lack of a significant effect of intraretinal or subretinal fluid on final visual outcome while adjusting for other key anatomic factors in the multivariate regression analyses ($P = .97$; Table 1).

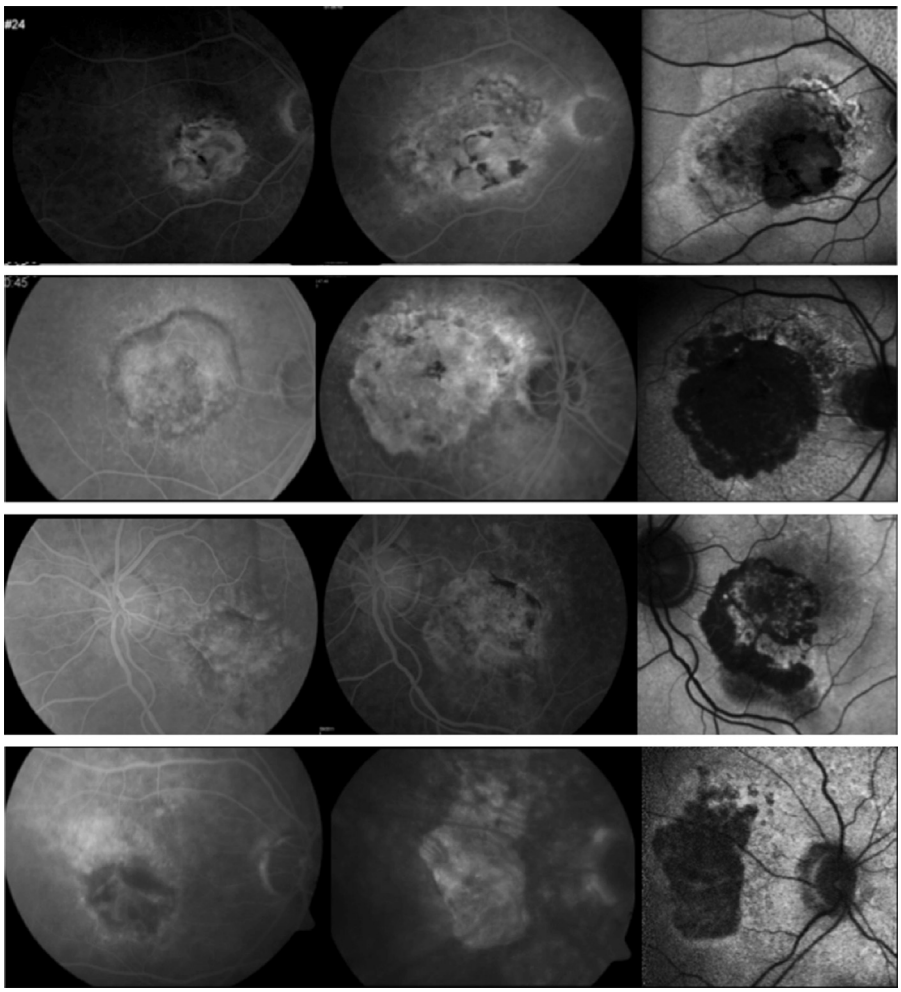

FIGURE 3. Cases of macular atrophy progression over an approximate 5-year period from subjects treated for exudative age-related macular degeneration. The following are shown for 4 patients: fluorescein angiograms (FAs) from (Left column) year 2 and (Center column) year 7, together with (Right column) fundus autofluorescence images from year 7. (Top row) Case 1: macular atrophy area increased from 0.97 mm^2 at year 2 (visual acuity, 20/50) to 2.45 mm^2 at year 7 (visual acuity, 20/80). (Second row) Case 2: macular atrophy area increased from 2.51 mm^2 (visual acuity, 20/400) to 3.10 mm^2 (visual acuity, 20/500). (Third row) Case 3: macular atrophy area increased from 0.53 mm^2 (visual acuity, 20/250) to 2.37mm^2 (visual acuity, 20/200). (Bottom row) Case 4: macular atrophy area increased from 1.05 mm^2 (visual acuity, 20/200) to 2.61 mm^2 (visual acuity, 20/250).

Submacular fibrosis, an end-stage characteristic of choroidal neovascularization and exudation, was present in 35 (61%) of 65 study eyes and was localized under the foveal center in 39%. In a bivariate analysis (Figure 2), comparable vision outcomes were found between the group with subfoveal fibrosis and the group without (mean ETDRS letter scores, 42.3 ± 29.3 vs 50.9 ± 20.7; coefficient, −8.58; 95% CI, −21.97 to 4.81; $P = .20$). Furthermore, in the multivariate regression analyses of the 4 key anatomic end points, no significant effect for subfoveal fibrosis was found in terms of final vision at SEVEN-UP ($P = .75$; Table 1).

On SD OCT measurements of macular thickness, the mean CST (average thickness of central 1 mm, measuring neurosensory retina only) was 170.0 μm. Seven percent of study eyes had macular thickening with CST of more than 250 μm. Macular thinning, defined as CST less than 200 μm, was seen in 75%. Although the isolated comparison of macular thickness categories against ETDRS letter score suggested reduced vision outcomes in both the group with macular thinning and in the group with macular thickening (mean ETDRS letter scores, 44.3 ± 21.7 and 28.0 ± 18.4, respectively, compared with normal group score of 67.9 ± 25.3; Figure 2), no significant effect was borne out when adjusting for the effects of other key anatomic factors in the multivariate regression analysis for final vision at SEVEN-UP visit (macular thinning, $P = .25$; macular thickening, $P = .06$; Table 1).

Multivariate regression analysis was performed to assess the independent effects of selected clinical and anatomic

TABLE 1. Multivariate Linear Regression Model in Patients Treated for Exudative Age-Related Macular Degeneration: Macular Atrophy Is the Key Anatomic Determinant of Long-Term Vision Outcomes (n = 46 Study Eyes)

Variable	Coefficient	Confidence Interval	*P* Value
Visual acuity at year 2 (letter score)	+0.52	0.07 to 0.96	.02
Intraretinal and/or subretinal fluid	−0.19	−11.65 to 11.26	.97
Macular thinning[a]	−9.12	−24.92 to 6.67	.25
Macular thickening[b]	−27.04	−55.51 to 1.43	.06
Subfoveal fibrosis	−1.84	−13.39 to 9.71	.75
Macular atrophy	−1.63	−2.45 to −0.81	<.001

[a]Central subfield thickness < 200 μm.
[b]Central subfield thickness > 250 μm.

factors. For the final visual outcome at the SEVEN-UP visit, Table 1 shows the results of a regression model on 46 study eyes with complete data available ($R^2 = 0.46$). The only macular anatomic variable demonstrating a significant association with final vision was macular atrophy lesion size, measured as area of definite decreased fundus autofluorescence (coefficient, −1.63; 95% CI, −2.45 to −0.81; $P < .001$), indicating that for each 1 mm^2 in area of macular atrophy, there was an associated vision decrement of 1.6 ETDRS letters.

• **MACULAR ATROPHY:** A predetermined subanalysis assessed the incidence, severity, and progression of macular atrophy, defined clinically as a demarcated area of absent RPE pigmentation, window defect on FA, and decreased autofluorescence on FAF imaging. Macular atrophy was nearly ubiquitous by the time of the SEVEN-UP visit, detected on FAF imaging in 98% of study eyes. Figure 3 shows examples of 4 patients. From the month 24 exit visit in the ANCHOR or MARINA trials (year 2) to the SEVEN-UP visit (year 7), the macular atrophy in each case increased in extent. To quantify macular atrophy progression over time, an analysis compared individual patients at their year 2 visit and their year 7 visit based on red-free images and FA (Table 2). Prior FA studies from ANCHOR or MARINA month 24 were available for 48 patients from the Wisconsin Reading Center dataset, 40 of which allowed accurate measurements. The progression analysis showed a visual decline of 21 letters over this mean 5.4-year interval. Every eye showed an increase in macular atrophy, with 57% increasing by 1 disc area or more. At year 2, in 22.5% of eyes the fovea was spared from macular atrophy, but by year 7, only 5% were fovea sparing.

The effect of final macular atrophy, as measured by definite decreased autofluorescence on FAF imaging, on final vision outcome at the SEVEN-UP visit is shown in the dichotomous comparison (Figure 4); in 56 study eyes with complete data, the group with area of macular atrophy higher than the median (8.01 mm^2) had reduced vision outcomes (mean ± standard deviation, 59.4 ± 20.6 letters vs 34.2 ± 22.0 letters). In the group with below-median macular atrophy areas, 11 (39%) of 28 eyes had final vision of 20/40 or better, compared with 1 (4%) of 28 eyes in the above-median group. The scatterplot shows a significant effect of worse final vision for study eyes with greater areas of macular atrophy (coefficient, −2.25; 95% CI, −2.92 to −1.59; $P < .001$). The progression of macular atrophy from year 2 (month 24 exit visit in ANCHOR or MARINA) to year 7 (SEVEN-UP visit) was assessed for its effect on vision change over the same period (Figure 4). Comparing 40 eyes with image data available at these time points, the group with above-median macular atrophy growth (≥ 1.25 mm^2 increase) had worse vision decline over approximately 5 years (mean ± standard deviation, −29.9 ± 24.3 letter change vs −13.3 ± 17.0 letter change). The scatterplot shows that progression of macular atrophy from years 2 to 7 was associated with the concomitant change in vision over this time in a bivariate model (coefficient, −11.0; 95% CI, −16.0 to −6.1; $P < .001$).

DISCUSSION

THE GOAL OF THESE ANALYSES WAS TO IDENTIFY LATE-stage anatomic characteristics associated with long-term vision outcomes in exudative AMD patients 7 to 8 years after initiation of anti-VEGF therapy. Macular atrophy, which had developed in nearly all of eyes, was found to be the primary anatomic correlate to vision outcomes: its progression over a 5-year period linearly associated with vision decline over that time, and final atrophy size was the key determinant of final vision score.

In the SEVEN-UP study,[9] 65 participants from the ranibizumab treatment arms of the ANCHOR, MARINA, and HORIZON trials were re-evaluated at a mean of 7.3 years after initiation of treatment. From the ANCHOR or MARINA baseline, half of study eyes had stable or improved vision, but half had declined, one third by 15 letters or more. Among the earliest to be treated with ranibizumab, the SEVEN-UP patients may reflect a specific chronologic juncture, because the period under study, 2003 through 2011, predated the establishment of current treatment frequency standards. After monthly ranibizumab treatment for 2 years in ANCHOR or MARINA, these subjects received much reduced treatment in the HORIZON study, 4.2 mean injections per year,[11] then even lower treatment frequency after exiting the study, a mean 1.6 injections per year from years 4 through 7. An update study on more recent phase 3 AMD trials could provide a better assessment of

TABLE 2. Macular Atrophy Progression Over Approximately 5 Years in Subjects Treated for Exudative Age-Related Macular Degeneration (n = 40 Study Eyes)

	Year 2	Year 7
Best-corrected visual acuity (letter score)	66.5 ± 14.75	44.92 ± 26.06
Macular atrophy present (% of eyes)	95	100
Subfoveal location	77.5	95 ($P = .02$)
Macular atrophy lesion size		
Mean area ± SD (mm^2)	0.83 ± 0.96	2.22 ± 1.59 ($P < .001$)
Mean disc area ± SD[a]	0.48 ± 0.55	1.25 ± 0.88
Mean greatest linear diameter ± SD (μm)	1116 ± 654	2015 ± 748
Macular atrophy area ≥1 disc area (%)	15	55 ($P < .001$)
Macular atrophy area ≥ 2 disc areas (%)	2.5	20 ($P = .012$)
Increase in area, years 2 to 7 (%)		
Any increase	100	
≥ 1 disc area increase	57	
Average rate of progression (range)		
Macular atrophy area (mm^2/y)	0.28 (0.01 to 5.01)	
Greatest linear diameter (μm/y)	169 (93.00 to 2706)	

SD = standard deviation.
[a]One disc area measures 1.77 mm^2 by Macular Photocoagulation Study standard.[37]

late-stage outcomes resulting from our current AMD management standards.

Active exudative disease was persistent in 72% of study eyes, but surprisingly this was not found to be associated with long-term vision outcomes in this subgroup of AMD patients, suggesting that the presence of macular leakage or thickening does not determine vision outcome, or perhaps does so only insofar as it contributes to macular atrophy. Indicators of chronic retinal damage were seen in most of these late-stage eyes, with central subretinal fibrosis in more than one third and macular thinning in 75%. But again, on multivariate regression analyses, neither macular thinning nor subfoveal fibrosis had a significant association with long-term vision outcomes.

Macular atrophy was the most prominent chronic effect observed, present in virtually all eyes at this stage. Macular atrophy progression over the late stage of these patients' course was associated with visual decline over this period. More than half of study eyes had an increase of 1 disc area or more in macular atrophy over a 5-year period since completing ANCHOR or MARINA, with the mean area growing from 0.8 to 2.2 mm^2, a rate of 0.28 mm^2 per year. In multivariate regression analyses, macular atrophy at year 7 was the only anatomic factor associated significantly with final vision ($P < .001$). For each 1 mm^2 of macular atrophy, there was an associated 1.6-letter deficit in ETDRS vision score at the SEVEN-UP visit. Good vision (20/40 or better) was achieved in 39% of eyes with macular atrophy area at the median or less, but in only 4% of above-median eyes. These findings indicate that the observed variability in long-term vision outcomes is determined to a large extent by the progression and severity of macular atrophy.

Rosenfeld and associates first associated the progression of geographic atrophy (GA) and RPE abnormalities with poor outcome groups at 2 years in ranibizumab-treated eyes within the ANCHOR and MARINA studies,[12] and the progression of GA over 2 years of treatment has been defined further in the Comparison of AMD Treatment Trials (CATT) study.[13,14] More recently, the incidence and pattern of macular atrophy development after choroidal neovascularization regression has been described in treated AMD eyes.[15] SEVEN-UP augments these studies in a long-duration patient cohort, but the mechanisms of macular atrophy formation and progression in the setting of treated exudative AMD remain inconclusive. In one hypothesis, atrophy could be explained by the progression of underlying GA, as would have occurred in the absence of choroidal neovascularization formation, or perhaps accelerated by factors in the neovascular process. But macular atrophy in exudative disease differs from nonneovascular GA. It often lacks the typical sharply demarcated, irregular borders for which the term *geographic* originally was applied. As seen in this study, macular atrophy is ubiquitous in late-stage exudative AMD and typically involves the central macula from the outset; in contrast, GA in nonexudative AMD occurs in a small fraction of patients,[16] with a tendency to form paracentrally around the fovea before spreading centripetally.[17–19] For the reasons above, we suggest the term *geographic atrophy* be reserved for eyes with nonneovascular AMD, to distinguish it from macular atrophy occurring through the course of exudative AMD.[15]

As a different hypothesis, anti-VEGF therapy itself has been proposed to promote macular atrophy, by counteracting the role of constitutively produced VEGF in neuronal

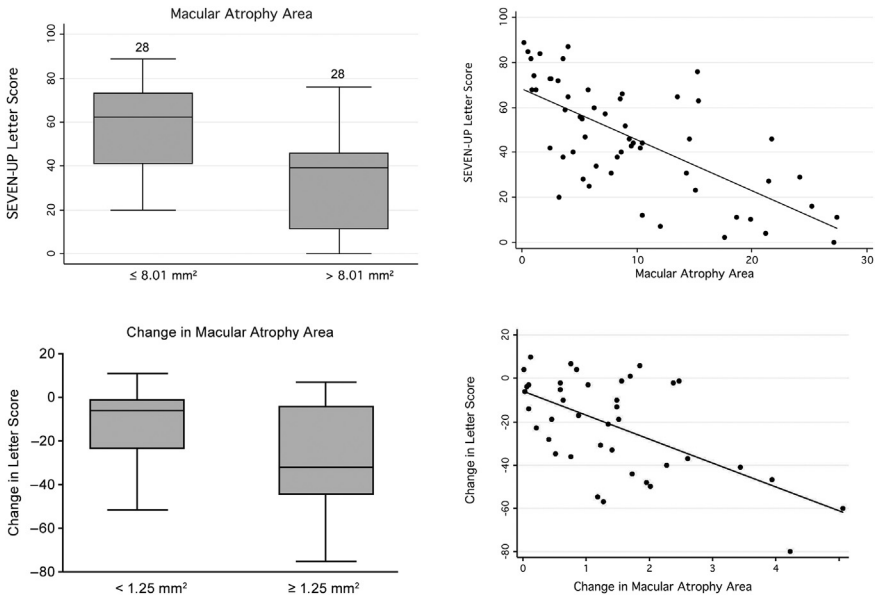

FIGURE 4. Macular atrophy severity is associated with poor long-term vision outcomes, and its progression over time correlates with visual decline in subjects treated for exudative macular degeneration. Box plots indicate seventy-fifth to twenty-fifth interquartile range (IQR), with median line; whiskers show highest and lowest values within a range of the twenty-fifth quartile minus 1.5 IQR and the seventy-fifth quartile plus 1.5 IQR. (Top left) For the final size of macular atrophy at year 7, the dichotomous comparison of the groups of eyes with area of macular atrophy below the median versus above the median (8.01 mm^2) shows reduced final vision outcomes for larger macular atrophy area; (Top right) scatterplot with regression line showing a significant effect of worse final vision with greater areas of macular atrophy (56 eyes; coefficient, −2.25; $P < .001$). For macular atrophy progression between years 2 and 7, (Bottom left) more visual decline over this period is seen for the group with above-median (1.25 mm^2) macular atrophy growth; (Bottom right) scatterplot showing that visual decline over 5 years is associated significantly with growth of macular atrophy area (40 eyes; coefficient, −11.0; $P < .001$).

or vascular maintenance. In both experimental models[20–26] and in human studies,[13,14,27] such off-target effects of VEGF blockade are under investigation. But in large controlled trials of anti-VEGF drugs in diabetic macular edema and retinal vein occlusion,[28–36] macular atrophy attributable to these agents has not been recognized, suggesting that its occurrence is particular to exudative AMD. Also, in treated AMD, RPE atrophy spares the retinal regions beyond the arcades, which are also exposed to VEGF inhibition by intravitreal agents. And as seen here in the SEVEN-UP study, macular atrophy progressed in the context of very low anti-VEGF injection frequency. Although conclusions on the pathogenesis of macular atrophy in treated AMD patients cannot be made from this or other available studies, a simple model would be that it arises secondary to exudation itself, with episodic leakage over a period of years subjecting the macula to serous fluid and blood; mechanical damage from angiogenic vessel outgrowth and contraction; and ischemic and inflammatory effects. Macular atrophy thus is seen as a nonspecific result of cumulative damage from exudative episodes over a patient's disease course, and therapeutic strategies to prevent these episodes may curtail macular atrophy and vision loss over the long term.

Limitations of the SEVEN-UP study have been discussed previously,[9] including the uncontrolled study design, partial recruitment and selection bias of eligible participants, the small number of patients, and the lack of a uniform treatment pattern in the off-study interim. Additionally, the current analyses, although predetermined, were not based on the primary end point, relied on retinal images obtained from the prior studies, and did not have complete retinal imaging data available for all subjects.

In summary, in treated AMD patients 7 years after entering the ANCHOR and MARINA studies, macular atrophy was progressive over the late disease stages, eventually affecting nearly all study eyes. Macular atrophy severity at year 7 was found to be the primary anatomic correlate to reduced final vision, and progression of macular atrophy from year 2 to year 7 had a linear relationship with vision decline over that period. Ongoing assessment of macular atrophy progression may be advisable in the management of exudative AMD patients, including FAF imaging. The findings may explain in part the disparate visual results that can be observed among treated AMD patients and underline the need for long-term studies to understand the therapeutic course of this and other chronic retinal diseases managed with intravitreal anti-VEGF agents.

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APPENDIX

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Biosketch

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Biosketch

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