Development and Course of Scars in the Comparison of Age-Related Macular Degeneration Treatments Trials

Ebenezer Daniel, MBBS, PhD,1 Wei Pan, MS,1 Gui-shuang Ying, PhD,1 Benjamin J. Kim, MD,1 Juan E. Grunwald, MD,1 Frederick L. Ferris III, MD,2 Glenn J. Jaffe, MD,3 Cynthia A. Toth, MD,3 Daniel F. Martin, MD,4 Stuart L. Fine, MD,5 Maureen G. Maguire, PhD,1 for the Comparison of Age-related Macular Degeneration Treatments Trials*

Purpose: To describe risk factors for scar formation and changes to fibrotic scar through 5 years in the Comparison of Age-related Macular Degeneration Treatments Trials (CATT).

Design: Multicenter, prospective cohort study.

Participants: A total of 1061 subjects in CATT.

Methods: Color photographic and fluorescein angiographic images from baseline and 1, 2, and 5 years were evaluated. Incidence of scar formation was estimated with Kaplan–Meier curves. Risk factors were assessed with Cox regression models.

Main Outcome Measures: Scar formation, fibrotic scar area, and macular atrophy associated with fibrotic scar (“atrophy”).

Results: Cumulative proportion of eyes with scar was 32%, 46%, and 56% at years 1, 2, and 5, respectively. Baseline factors associated with increased risk (adjusted hazards ratio [aHR] and 95% confidence interval [CI]) were classic choroidal neovascularization (CNV) (aHR, 4.49; 95% CI, 3.34–6.04) versus occult, hemorrhage >1 disc area (DA) (aHR, 2.28; 95% CI, 1.49–3.47) versus no hemorrhage, retinal thickness >212 μm (aHR, 2.58; 95% CI, 1.69–3.94) versus <120 μm, subretinal tissue complex thickness >275 μm (aHR, 2.64; 95% CI, 1.81–3.84) versus ≤75 μm, subretinal fluid thickness >25 μm (aHR, 1.31; 95% CI, 0.97–1.75) versus no fluid, visual acuity (VA) in fellow eye 20/20 (aHR, 1.72; 95% CI, 1.25–2.36) versus 20/50 or worse, retinal pigment epithelium elevation absence (aHR, 1.71; 95% CI, 1.21–2.41), and subretinal hyperreflective material (aHR, 1.72; 95% CI, 1.25–2.36). Among 68 eyes that developed fibrotic scar at year 1, VA decreased by a mean of additional 13 letters between years 1 and 5. Mean scar area was 1.2, 1.2, and 1.9 DA at 1, 2, and 5 years, respectively. Atrophy was present in 18%, 24%, and 54% of these eyes at years 1, 2, and 5, respectively; the mean areas were 1.6, 2.0, and 3.1 DA, respectively. Atrophy replaced fibrotic scar in 8 eyes at year 5. There was no significant correlation between scar growth and atrophy growth. The rate of growth for both was similar between the clinical trial and observation periods.

Conclusions: Several morphologic features, including classic CNV and large hemorrhage, are associated with scar formation. Rate of new scar formation declined after 2 years. Most fibrotic scars and accompanying macular atrophy expanded over time, reducing VA.

Supplemental material available at www.aaojournal.org.
the scar tissue. We have previously reported that both macular atrophy and foveal scar are the 2 foremost morphologic outcomes associated with poor VA in the Comparison of Age-related Macular Degeneration Treatments Trials (CATT). Although long-term follow-up of geographic atrophy after anti-VEGF therapy, more recently referred to as “macular atrophy,” has been described, long-term follow-up of scars after the initiation of anti-VEGF therapy has not received much attention.

The original CATT clinical trial was designed to assess differences between ranibizumab and bevacizumab, as well as differences between monthly and pro re nata dosing. At the end of the 2-year clinical trial period, the subjects were released from the systematic ocular examination and treatment specified by the study protocol. After providing consent, subjects received ocular examinations and imaging approximately 5 years after initiation of anti-VEGF treatment. The results of the follow-up study detailing the vision outcomes have been published. In this article, we report the incidence and risk factors of scar development through 5 years of follow-up, as well as the morphologic changes observed in and around fibrotic scars that had developed during the first year of the clinical trial.

**Methods**

**Enrollment and Follow-up of Subjects**

From 43 clinical centers in the United States, 1185 subjects who had untreated active (leakage on fluorescein angiogram [FA] and fluid on OCT) choroidal neovascularization (CNV) associated with age-related macular degeneration were enrolled in the CATT clinical trial between February 2008 and December 2009. The study eye was required to have CNV or fluid at the foveal center. Subjects were excluded if scar was located at the foveal center at enrollment, but study eyes with nonfoveal scars that were <50% of the total CNV lesions were included in the clinical trial. Additional eligibility criteria have been described previously. Subjects were randomly assigned to treatment with intravitreal injections of ranibizumab or bevacizumab and to 1 of 3 dosing regimens for the initial 2 years of the study: monthly injections, monthly evaluation with injection only when signs of active neovascularization were present (pro re nata), or monthly injections for 1 year followed by pro re nata injections for 1 year.

During the clinical trial, color fundus photographs (CFPs), FA, and OCT were obtained. The CFPs and FA were obtained at baseline and 1, 2, and 5 years. Additional evaluation was done only for images that also had year 2 and year 5 visit images to identify ablatively treated CNV lesions. The CNV area and the total CNV lesion area were measured using ImageJ (available at https://imagej.nih.gov/ij/). Grading of year 1, 2, and 5 visit images was performed applying the same methods. Each image set was dual-reader graded for the various morphologic outcomes by trained nonphysician readers and the CATT fundus photographic reading center director (E.D.), all of whom were masked to demographic and clinical details. Discrepancies were adjudicated between the graders and the director of the reading center, and unresolved discrepancies were reviewed by the principal investigator (J.E.G.) to complete a final consensus grading form. Likewise, OCT evaluation was performed at the Duke University Reading Center, where a reader team, composed of 2 independent readers and a senior reader, evaluated each scan. Grading included the CATT OCT end points of total thickness at the foveal center point and intraretinal fluid, subretinal fluid, and sub–retinal pigment epithelium (RPE) fluid. The director of grading (C.A.T.) and the reading center director (G.J.J.) remained masked to subject identifiers and made final decisions on reader disagreements that remained controversial after arbitration.

Scar was identified by CFP and FA as described previously. Fibrotic scars were defined as obvious white or yellow mounds of fibrous-appearing tissue that were well defined in shape and appeared solid on color stereo images. Hyperfluorescence due to tissue staining or blocked fluorescence of the underlying choroid was identified from FA. Nonfibrotic scars were typically flat, small, well-circumscribed areas of pigmentation with varying degrees of central hypopigmentation on CFP images. The hypopigmented area was flat, and choroidal vessels were not visible. Hyperfluorescence of the depigmented area appeared early on FA and persisted or increased in intensity in the late phase. Hypofluorescence on FA surrounding the hyperfluorescence corresponded to the pigmented borders apparent on CFPs.

**Assessment of the Fibrotic Scar at 1, 2, and 5 Years**

Additional evaluation was done only for fibrotic scars among eyes with images available for all visits (baseline and 1, 2, and 5 years). The reading center director assessed all year 1 CFPs and FA images that also had year 2 and year 5 visit images to identify fibrotic scars. Indeterminate or uncertain fibrotic scars were subjected to evaluation by a retina specialist and a senior reader, and consensus was obtained. With the use of ImageJ, measurements of area were obtained for the optic disc, fibrotic scar, and macular atrophy associated with fibrotic scar (atrophy) contiguous with or amidst the fibrotic scar. Atrophy had well-defined hypopigmented areas with exposed choroidal vessels observed on color images without visible fibrosis. The areas of fibrotic scar and atrophy were mutually exclusive, with fibrotic scar taking precedence over atrophy in instances when it was difficult to differentiate the 2 morphologic features. Hypopigmentation on the fibrotic scar was also documented. These measurements and assessments were performed on the 2- and 5-year images for eyes that had fibrotic scar identified at 1 year (Fig 1).
**Candidate Risk Factors**

Candidate risk factors for scar formation included baseline patient characteristics, such as age, gender, cigarette smoking, hypertension, diabetes, body mass index, dietary supplement use, cancers, hypercholesterolemia, and osteoarthritis. Ocular candidate risk factors were baseline VA in each eye; baseline morphologic features observed on color and fluorescein angiography, such as the type of CNV, hemorrhage, blocked fluorescence, nonfoveal scar and macular atrophy, and serous pigment epithelial detachment; baseline features observed on OCT images, such as intraretinal, subretinal, and sub-RPE fluid, vitreomacular adhesion and traction, subretinal hyper-reflective material, RPE elevation, subretinal tissue complex thickness (any combination of subretinal hyper-reflective material, pigment epithelium detachment, drusen material, and RPE), subretinal fluid thickness, and central retinal thickness; and the anti-VEGF drug and regimen used in the clinical trial period.

**Statistical Analysis**

We used Kaplan–Meier estimates for the cumulative incidence of scar through 5-year follow-up. Subjects who did not participate in the CATT Follow-Up study were censored at 2 years. For subjects missing images during the first 2 years, the previous scar status was carried forward. We used univariate and multivariate Cox proportional hazards models to identify the baseline risk factors for scar development.

Risk factors were first evaluated by univariate analysis (without adjustment for any other risk factors) using a discrete time Cox proportional hazard model for time to scar formation. The factors with a value 0.20 in the univariate analysis were included in a multivariate Cox proportional hazard model so that the independent effect of each risk factor could be assessed. The final multivariate model was created by applying a backward selection procedure that retained only those risk factors with a P value <0.05, with the exception of drug and regimen groups, which were included in all multivariate models. Adjusted hazard ratios (aHRs) for scar development during 5 years and their 95% confidence intervals (CIs) were calculated on the basis of the final multivariate models.

Among subjects who were identified with fibrotic scar at year 1 and followed up to year 5, we performed descriptive analysis for VA change over time, growth of fibrotic scar area over time, and hyperpigmentation changes over time, by using mean (standard deviation [SD]) for continuous measures and proportion for categoric measures. Fisher exact test was used for low-count frequency comparisons. All the statistical analyses were performed in SAS version 9.4 (SAS Institute Inc., Cary, NC), and P < 0.05 was considered to be statistically significant.

**Results**

After excluding eyes with scar at baseline, ungradable scar status at baseline, or no gradable images after baseline, there were 1061 patients with at least 1 gradable set of images during follow-up (Fig S2, available at www.aaojournal.org). After excluding subjects who had missing values in 1 or more variables cited in the footnote of Table 1, there were 1020, 965, and 510 complete image sets available for scar assessment at 1, 2, and 5 years, respectively. The Kaplan–Meier estimates of the cumulative rates of scar were 32.0% at 1 year, 46.3% at 2 years, and 56.4% at 5 years (Fig 3).

Several baseline characteristics were associated with the development of scar through 5 years (Table 1). The presence of predominantly classic CNV was associated with 4.5-fold risk (aHR, 4.49; 95% CI, 3.34–6.04; P < 0.001) compared with occult CNV. Good baseline VA (≥20/20) in the fellow eye was associated with increased risk of developing scar in the study eye (aHR, 1.34; 95% CI, 1.00–1.74; P = 0.04) compared with VA of 20/50 or worse. Large hemorrhages (>1 disc area [DA]) were associated with a more than 2-fold risk (aHR, 2.28; 95% CI, 1.49–3.47; P < 0.001) compared with no hemorrhages associated with the CNV. Eyes with central retinal thickness >212 μm had increased risk (aHR, 2.58; CI, 1.69–3.94; P < 0.001) compared with eyes with central retinal thickness <120 μm, and eyes with subretinal fluid thickness >0 to ≤25 μm had increased risk (aHR, 1.84; 95% CI, 1.21–2.80; P = 0.01) compared with eyes without any subretinal fluid. Risk increased with the thickness of the subretinal tissue complex at the foveal center with a more than 2.5-fold risk for thickness >275 μm (aHR, 2.64; 95% CI, 1.81–3.84; P < 0.001) compared with a thickness ≤75 μm. The absence of RPE elevation (aHR, 1.71; 95% CI, 1.21–2.41; P = 0.002) and subretinal hyper-reflective material (aHR, 1.72; 95% CI, 1.25–2.36; P < 0.001) increased the risk of scar by 70%. Incidence of scar was distributed similarly between the 2 drug groups and among the 3 dosing regimen groups (Table 1).

Photographic images at all 3 follow-up visits (1, 2, and 5 years) were available for 474 subjects, and 68 (14.3%) developed fibrotic scar in the study eye at 1 year. On average, the size of the scar changed slowly between years 1 and 5 (Fig 4). The change in size of fibrotic scars from year 1 to 2 and from year 2 to 5 is given in Table 2. The mean (SD) VA of these eyes was 61 [±20/63] (21) letters at 1 year, 63 [±20/50] (18) letters at 2 years, and 49 [±20/100] (26) at year 5. The mean (SD) VA was 38 [±20/160] (27) letters at year 5 in 8 eyes in which atrophy completely replaced the fibrotic scars (Table 3). The mean annual expansion rate of the fibrotic scar present in 68 eyes at year 1 was 0.02 (0.41) DA (range, −1.40 to 2.47; median, 0.004), whereas it was 0.20 (0.71) between year 2 and year 5 (range, −0.94 to 3.56; median, 0.01). The difference in the annual rate of expansion was not statistically significant (P = 0.33, Wilcoxon signed-rank test).

At 1 year, macular atrophy associated with fibrotic scar was observed in 12 eyes (18%), and the mean (SD) VA was 70 [±20/40] (15), whereas in eyes without macular atrophy associated with scar the mean (SD) VA was 59 [±20/63] (22) letters (P = 0.11). At 2 years, atrophy was observed in 16 eyes (24%) and the mean (SD) VA was 71 [±20/80] (15), whereas in eyes without atrophy the mean (SD) VA was 61 [±20/63] (19) letters (P = 0.04). At 5 years, atrophy was observed in 37 eyes (54%) and the mean (SD) VA was 44 [±20/125] (27), whereas in eyes without atrophy the mean (SD) VA was 53 [±20/80] (25) letters (P = 0.21). The average size of atrophy increased from 1.6 DA at year 1 to 2.0 DA in year 2 and to 3.1 DA in year 5 (Fig 5).

Among the 12 eyes with atrophy at year 1, the mean (SD) area increase was 0.73 (0.59) DA (range, 0.03–1.53 DA; median, 0.82 DA). Among the 16 eyes with atrophy at 2 years, the mean (SD) annual rate of area increase was 0.59 (0.53) DA (range, 0–1.53 DA; median, 0.51 DA). Among eyes that had both fibrotic scar and atrophy, there was no strong correlation between the area of the scar and the area of the atrophy, with correlation coefficients of 0.41 at year 1 (N = 12; P = 0.18), 0.35 at year 2 (N = 16; P = 0.18), and 0.01 at year 5 (N = 37 eyes; P = 0.96). The difference in the annual rate of expansion was −0.14 (0.7) DA (P = 0.79, Wilcoxon signed-rank test).

There were no significant associations with demographic or ocular characteristics between eyes with atrophy and eyes without atrophy in years 1, 2, or 5. Likewise, there were no significant associations with demographic or ocular characteristics between
Figure 1. Color images of fibrotic scar and macular atrophy associated with fibrotic scar (atrophy). A, Stable fibrotic scar: A1 shows a fibrotic scar that has developed at year 1 (black arrow). It remains stable at years 2 and 5. There is hyperpigmentation on the scar (green arrow). B, Scar increasing in size: B1 shows a fibrotic scar that shows no change in area from year 1 (B1) to year 2 (B2) but has a larger area in year 5 (B3) when there is growth superiorly (black arrow). There is also pigmentation on the scar (green arrow) at year 5. C, Scar with peripheral macular atrophy: C1 shows a fibrotic scar at year 1 that undergoes thinning at year 2 (B3, black arrow) with an area of macular atrophy associated with fibrotic scar (atrophy) surrounding it in year 5 (B3, green arrow). Increased hyperpigmentation is also seen at year 5 (B3, blue arrow). D, Macular atrophy associated with fibrotic scar: D1 shows a thick, round fibrotic scar at year 1 (black arrow). In year 5, the superior part of the fibrotic scar has been replaced by macular atrophy (D3, blue arrow). E, Scar completely replaced by macular atrophy: E1 shows a fibrotic scar (black arrow) that develops atrophy in year 2 (E2, blue arrow), and eventually at year 5 the area of the fibrotic scar is replaced by an expanding macular atrophy (E3, blue arrow).
eyes with expanding atrophy and those without such expansion in years 1, 2, or 5 (Tables S4 and S5, available at www.aaojournal.org). Pigmentation on the fibrotic scars was seen in 13% of eyes at year 1, in 22% of eyes at year 2, and in 53% of eyes at year 5 (Fig 6).

**Discussion**

Approximately one third of the CATT eyes developed retinal scar during the first year of treatment, and an additional 10% developed scar during the second year of treatment. At the completion of the 2-year clinical trial, the CATT subjects were released from their treatment protocol and were free to choose their ophthalmic care. Despite this change from the CATT clinical trial protocol and a longer follow-up period of 3 years, only an additional 10% of subjects developed scar, indicating that in eyes with nAMD treated with anti-VEGF therapy, the majority of scars occur within the first year of treatment.

We had shown earlier that during the first 2 years of treatment of nAMD with anti-VEGF drugs, the risk factors present at baseline for developing a scar included predominantly the classic type of CNV, blocked fluorescence, thicker retina, larger foveal subretinal tissue complex thickness, foveal subretinal fluid, and subretinal hyperreflective material. These risk factors, with the exception of blocked fluorescence, remained significantly associated with the development of scar through the additional 3 years of follow-up. However, 2 other baseline risk factors with a higher risk of scar were discovered: a better VA in the fellow eye and large hemorrhages. It is not entirely clear why a better VA in the fellow eye would be a risk factor for
development of scar in the study eye, but it is possible that it delayed the initial visit of the subject to an ophthalmologist and also might be less likely to be aggressively treated after the duration of the clinical trial.

The CATT study allowed recruitment of patients with nAMD having more than 50% hemorrhages relative to the total CNV lesion. Other major anti-VEGF clinical trials excluded such patients. Therefore, the CATT cohort presented a unique opportunity to study eyes with hemorrhages that were more than 50% of the total CNV lesion, and many of the hemorrhages were larger than 1 DA. The VA in these eyes at the end of the 2-year clinical trial was similar to the eyes that did not have such large hemorrhages at enrollment. However, the 5-year CATT Follow-Up study results show that relatively large hemorrhages present at enrollment, if observed over longer durations, more than double the risk of developing a scar. Apart from iron toxicity to the photoreceptors due to deposition of hemosiderin and the reduced nutrient flux, large hemorrhages promote the formation of scar and fibrin meshwork contraction that can further reduce vision by involving adjacent areas of the retina.

We also found the risk for developing a scar due to predominantly classic lesions at enrollment increased from 3-fold at 2 years to 4.5-fold through 5 years. It is possible that this increased risk is caused by treated quiescent classic CNV lesions that relapsed over time and subsequently developed a scar. It is also possible that some occult lesions converted to classic lesions and increased the risk of developing a scar. Once a fibrotic scar developed during the first year after initiation of anti-VEGF therapy, several changes were observed in and around the scar over a period of time. By 5 years, only 15% of the fibrotic scars at year 1 remained stable without any observable changes in the color images. There was little change in the average size of fibrotic scar between year 1 and 2, and the mean VA was maintained or slightly better at year 2 compared with year 1. However, over the time between the year 2 visit and the year 5 visit, the mean size of the fibrotic scar increased with a corresponding decrease in the mean VA in these eyes at year 5. The annualized rate of growth was similar from year 1 to 2 and year 2 to 5. The change due to difference in scar size and VA between the 2 periods could be attributed to a much longer time window in the second period and the difference in the type of care given during these 2 periods. During the first 2 years, the CATT clinical trial’s protocol required a monthly examination with anti-VEGF intravitreal injections given monthly or on a pro rata basis. At the end of 2 years, the CATT subjects were released from the protocol and were only seen after another 3 years. During this period, it is possible that reactivation of neovascularization occurred, resulting in extension of the scar area and reduction in vision.

Figure 3. Kaplan–Meier graph showing the cumulative incidence of scar through 5 years.

Figure 4. Box plot of fibrotic scar in disc areas over time among 68 eyes with fibrotic scar at year 1.
Macular atrophy associated with fibrotic scar develops within or adjacent to the scar and can encircle the scar partially or completely (Fig S2, available at www.aaojournal.org). Five years after enrollment, atrophy was observed in a little more than half of eyes that had developed a fibrotic scar at 1 year. As for fibrotic scar area expansion, the annualized increase in area was similar in the period of year 1 to year 2 and the period of year 2 to year 5. Mean VA in eyes that had atrophy at years 1 and 2 was good compared with eyes without atrophy but was reduced at 5 years. Expanding areas of atrophy are likely to produce scotomas and substantially affect vision when they involve the foveal center. Atrophy has been suggested to result from the remodeling of the choroidal vasculature producing reduced blood flow around the scar and the subsequent ischemia causing RPE cell death. It appears as though the expanding macular atrophy associated with nAMD have been shown to be present in high counts in eyes with subclinical CNV. The changes within the fibrotic scar and in areas adjacent to it, such as the pigment accumulation and expanding macular atrophy, may be due to an aberrant wound-healing process influenced by the initial anti-VEGF treatment. Myopic CNV treated with anti-VEGF has been shown to have similar development of fibrotic scars and associated progressive chorioretinal atrophy with poor visual outcome. However, even before the start of the anti-VEGF era, Sarks et al had described the expanding macular atrophy associated with fibrotic scars developing from nAMD. They suggested that the expansion of such atrophy was faster during the earlier periods of follow-up, but the study was limited by its retrospective nature, with only a small number of eyes (n = 20) that had undergone treatment with laser photocoagulation, radiotherapy, intravitreal triamcinolone injections, or combinations of these. Further, the measurements of atrophy in more than half of these commenced only after 2 years, unlike in our study that prospectively followed up fibrotic scars that had developed during the first year of therapy. It is not known whether the macular atrophy occurring as a result of nAMD without apparent fibrotic scar on color images is any different from this type of macular atrophy in terms of incidence, expansion, and association with VA. Reports on macular atrophy as a result of nAMD have not distinguished atrophy associated with fibrotic scar from macular atrophy without any preexisting fibrosis.

Our study had certain limitations. Although the follow-up at 2 years among living patients was high (93%), only 71% of living patients completed a follow-up study visit. The loss to follow-up may have resulted in inaccurate estimation of the incidence of scar from year 2 to year 5.

In our study, we were unable to find a strong correlation between scar area and atrophy area at all 3 follow-up time points when images were available for assessment. Also, limited by the small sample size, we were unable to identify any baseline demographic or ocular features that would predict the development and expansion of atrophy. It appears as though the expanding fibrotic scar and atrophy contribute to the decrease in VA in CATT study eyes at 5 years, even though they do not seem to substantially affect VA in year 2. Regular and long-term examinations of eyes to assess the development and progression of atrophy may be particularly important in clinical trials of antifibrotic agents to reduce the incidence of fibrotic scars after treatment of nAMD with anti-VEGF agents. In one tenth of eyes with fibrotic scar at year 1, atrophy appears to completely replace the fibrotic scar by year 5. It is possible that the collagen fibers are phagocytosed by Bruch’s membrane macrophages, which have been shown to be present in high counts in eyes with subclinical CNV.

Table 2. Change in Fibrotic Scar Change over Time

<table>
<thead>
<tr>
<th>Fibrotic Scar Size Change</th>
<th>N (%)</th>
<th>Mean (SD)</th>
<th>Median (Q1, Q3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>From year 1 to 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase</td>
<td>19 (27.9)</td>
<td>0.3 (0.6)</td>
<td>0.10 (0.07, 0.33)</td>
</tr>
<tr>
<td>Decrease</td>
<td>15 (22.1)</td>
<td>−0.3 (0.4)</td>
<td>−0.13 (−0.22, −0.08)</td>
</tr>
<tr>
<td>Same</td>
<td>34 (50.0)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>From year 2 to 5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase</td>
<td>33 (48.5)</td>
<td>1.8 (3.0)</td>
<td>0.94 (0.33, 1.48)</td>
</tr>
<tr>
<td>Decrease</td>
<td>23 (33.8)</td>
<td>−0.5 (0.6)</td>
<td>−0.37 (−0.65, −0.14)</td>
</tr>
<tr>
<td>Same</td>
<td>12 (17.6)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>From year 1 to 5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase</td>
<td>37 (54.4)</td>
<td>1.7 (2.8)</td>
<td>0.71 (0.21, 1.76)</td>
</tr>
<tr>
<td>Decrease</td>
<td>21 (30.9)</td>
<td>−0.7 (0.8)</td>
<td>−0.38 (−0.66, −0.13)</td>
</tr>
<tr>
<td>Same</td>
<td>10 (14.7)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Table 3. Scar and Macular Atrophy Area and Visual Acuity at Years 1, 2, and 5 among Study Eyes with Fibrotic Scar at Year 1 (N = 68)

<table>
<thead>
<tr>
<th>Year</th>
<th>N</th>
<th>Mean (SD)</th>
<th>Median (Min, Max)</th>
<th>Q1</th>
<th>Q3</th>
<th>Visual Acuity (Letters), Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrotic scar</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>68</td>
<td>1.2 (1.6)</td>
<td>0.54 (0.11, 10.18)</td>
<td>0.36, 1.19</td>
<td>61.1 (21.0)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>68</td>
<td>1.2 (1.5)</td>
<td>0.60 (0.13, 8.78)</td>
<td>0.34, 1.44</td>
<td>63.2 (18.3)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>68</td>
<td>1.9 (3.1)</td>
<td>0.77 (0.00, 19.74)</td>
<td>0.29, 2.06</td>
<td>48.1 (26.5)</td>
<td></td>
</tr>
<tr>
<td>Macular atrophy associated with fibrotic scar</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>12</td>
<td>1.6 (1.6)</td>
<td>0.82 (0.14, 4.27)</td>
<td>0.29, 3.07</td>
<td>69.9 (14.7)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>2.0 (2.0)</td>
<td>1.12 (0.18, 5.62)</td>
<td>0.68, 3.21</td>
<td>71.4 (13.0)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>37</td>
<td>3.1 (2.6)</td>
<td>2.30 (0.01, 9.66)</td>
<td>0.90, 4.76</td>
<td>44.4 (27.1)</td>
<td></td>
</tr>
</tbody>
</table>

Max = maximum; Min = minimum; N = number of eyes; Q = quartile; SD = standard deviation.
The number of treated eyes having pigmentation in or around the fibrotic scars was observed to increase proportionally with the years of follow-up, starting with 14% during the first year and involving more than half the subjects at year 5. This phenotypical presentation of pigmentation may be important, because it is believed that RPE cells undergo epithelial–mesenchymal transition and the melanotic cells that are unique to CNV are associated with atrophy with and without basal laminar deposits. This transdifferentiation of RPE cells from epithelial to mesenchymal phenotype can cause the RPE cells to adhere to and exert traction forces on the extracellular matrix and could be one of the factors contributing to the evolution of atrophy clinically. The atrophy process increases with time and is consistent with a shift in biologic activities observed during continued passage of RPE cells in vitro. The phenotypic diversity of RPE and its changing biological activity seen at a molecular level need to be understood clinically, and careful examination by different imaging modalities of the evolution of nAMD into a fibrotic scar and its gradual erosion by atrophy in eyes treated with anti-VEGF injections offers this opportunity.

In summary, a relatively small percentage of CATT subjects develop scar after 2 years compared with the first 2 years under anti-VEGF treatment. Large hemorrhages at enrollment appear to influence scar formation at later periods of follow-up. Fibrotic scars that developed at 1 year tended to change in size or be accompanied by atrophy and pigmentation, with only 15% remaining stable throughout the follow-up period. We observed a slow average increase in the area of fibrotic scar, probably due to ongoing organization of the collagen fibers or development of new areas of nAMD. Contiguous macular atrophy developed in an increasing number of eyes through 5 years, and the area expanded in size. We were unable to find any significant association with atrophy incidence or expansion with any of the baseline demographic or ocular characteristics.

References

Footnotes and Financial Disclosures

Originally received: October 25, 2017.
Final revision: December 22, 2017.
Accepted: January 7, 2018.

1 Scheie Eye Institute, University of Pennsylvania, Philadelphia, Pennsylvania.
2 National Eye Institute, Bethesda, Maryland.
3 Department of Ophthalmology, Duke University, Durham, North Carolina.
4 Cole Eye Institute, Cleveland Clinic, Cleveland, Ohio.
5 Department of Ophthalmology, University of Colorado School of Medicine, Aurora, Colorado.


*Members of the Comparison of Age-related Macular Degeneration Treatments Trials are available online at www.aaojournal.org.

Financial Disclosure(s):
The author(s) have made the following disclosure(s): G-s.Y.: Consultant — Janssen R & D; Personal fees — Chengdu Kanghong Biotech Co. Ltd., Ziemer Ophthalmic Systems AG.
B.J.K: Personal fees — Synergy Research.
G.J.J.: Consultancy relationship — Heidelberg Engineering, Alcon/Novartis, Genentech/Roche, Neurotech.
C.A.T.: Grants — Genentech; Personal fees — Alcon.
M.G.M.: Data and safety monitoring committee — Genentech/Roche.

Supported by cooperative agreements U10 EY017823, U10 EY017825, U10 EY017826, U10 EY017828, U10 EY023530, and R21EY023689 from the National Eye Institute, National Institutes of Health, and Department of Health and Human Services. ClinicalTrials.gov identifier NCT00593450.
The funding organization had no role in the design or conduct of this research.

HUMAN SUBJECTS: This study includes human subjects. No animal subjects were used in this study. The study was approved by the institutional review boards associated with each center, and all subjects provided written informed consent. The study was compliant with Health Insurance Portability and Accountability Act regulations.

Author Contributions:
Conception and design: Daniel, Maguire, Grunwald, Toth, Martin, Jaffe, Ferris
Data collection: Daniel, Maguire, Grunwald, Fine, Ying, Pan, Toth, Kim, Martin, Jaffe
Analysis and interpretation: Daniel, Maguire, Grunwald, Fine, Ying, Pan, Toth, Martin, Jaffe, Ferris
Obtained funding: N/A
Overall responsibility: Daniel, Maguire, Grunwald, Toth, Kim, Martin, Jaffe, Ferris

Obtained funding: N/A

Abbreviations and Acronyms:

aHR = adjusted hazard ratio; CATT = Comparison of Age-related Macular Degeneration Treatments Trials; CFP = color fundus photograph; CI = confidence interval; CNV = choroidal neovascularization; DA = disc area; FA = fluorescein angiogram; nAMD = neovascular age-related macular degeneration; RPE = retinal pigment epithelium; SD = standard deviation; VA = visual acuity; VEGF = vascular endothelial growth factor.

Correspondence:
Ebenezer Daniel, MBBS, PhD, Ophthalmology Reading Center, University of Pennsylvania, 3535 Market Street, Suite 700, Philadelphia, PA 19104.
E-mail: ebdaniel@mail.med.upenn.edu.