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

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***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. *Ophthalmology 2018;■:1–10 © 2018 by the American Academy of Ophthalmology*

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Intravitreal anti–vascular endothelial growth factor (VEGF) treatment for neovascular age-related macular degeneration (nAMD) has become the standard of care based on the results of several multicenter, randomized clinical trials with generally good visual and morphologic outcomes.[1,2] The results of treatment are derived mostly from clinical trials that have been capped at 2 years. Subjects who completed a 2-year clinical trial continue to receive care from ophthalmologists, unrestricted from the protocol of the clinical trial. Some investigators have collected follow-up data from these clinical trial subjects 5 to 8 years after initiation of anti-VEGF therapy, but their reports have been focused mainly on the visual status of these subjects.[3] A few studies have reported on the long-term outcomes of patients treated with anti-VEGF therapy in a real-world setting, but these too have dealt primarily with visual acuity (VA) outcomes.[4,5]

Scar and atrophy are the 2 most important morphologic features that influence visual outcomes in untreated nAMD, as well as in patients treated with anti-VEGF intravitreal injections.[6,7] Scars thicker than 0.2 mm have been associated with large-scale loss of the photoreceptors overlying



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the scar tissue.[8,9] 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).[9] 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.[10,11]

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.[12,13] 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.[14] 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.[12] 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 and 2 years, whereas OCT was obtained more frequently. 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. The CATT was registered with clinicaltrials.gov (NCT00593450). At the end of the 2-year follow-up period of the clinical trial, subjects were released from the study protocol and managed according to best medical judgment. All 1117 patients in CATT who were alive at the end of the clinical trial were invited to participate in the CATT Follow-up Study approximately 5 years after initiation of treatment with the anti-VEGF therapy. Among the invited patients, 203 had died by the time of the follow-up study, and among the remaining 914 living patients, 647 (71%) participated. Nonparticipating patients were on average 2 years older, had VA 5 letters worse by the end of the clinical trial, and had 2 fewer injections during the clinical trial when they had been assigned to treatment as needed.[14] The percentage of participants with scar at 2 years was 44% and was 38% among nonparticipants ($P = 0.10$).[14] Color fundus photographs, FA, and OCT were acquired at the time of the study visit.

### Assessment of Images

The methods used to grade the digital CFPs, FA images, and the OCT scans have been described previously.[15,16] At baseline, photographic images were evaluated at the fundus photograph reading center at the University of Pennsylvania for CNV type; contiguous hemorrhage, serous pigment epithelial detachment, or blocked fluorescence; and presence of scar or macular atrophy in both the study eye and the fellow eye. 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.[17]

Scar was identified by CFP and FA as described previously.[16] 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. Hyperpigmentation 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).