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Evolution of Geographic Atrophy in Participants Treated with Ranibizumab for Neovascular Age-Related Macular Degeneration

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Purpose: To evaluate the risk factors, incidence, and rate of progression of geographic atrophy (GA) in eyes with neovascular age-related macular degeneration (nAMD) treated with ranibizumab.

Design: Post hoc analysis of a prospective clinical study.

Participants: There were 69 participants with nAMD in ≥1 eye.

Methods: Participants were prospectively treated in the study eye with 0.5 mg intravitreal ranibizumab. Study eyes received 4 monthly injections followed by pro re nata injections until a fluid-free macula was achieved on optical coherence tomography. Risk factors assessed included baseline demographics, treatment, and ocular characteristics on imaging. Eyes were evaluated on fundus autofluorescence for GA. The rate of GA area growth in study and fellow eyes was analyzed by linear regression of square root transformed areas.

Main Outcome Measures: Development of new-onset GA and rate of GA area growth measured on ocular imaging, including fundus autofluorescence images of the study eyes.

Results: Sixty-nine participants (mean age, 78.8±7.8 years) with an average of 40.0±13.6 months of follow-up were analyzed. Twenty-two of the 69 study eyes (32%) were treatment naïve. During their first year of the study, participants received an average of 9.2±3.3 injections in the study eye. Of 63 study eyes with quality baseline images, 22 (35%) had preexisting GA. Of the remaining 41 eyes, 7 (17%) developed new-onset GA during study follow-up. Those who developed new GA were older (all ≥79 years old) and had received fewer study injections on average (6.9 vs. 10.4 injections at 1 year) compared with those who did not develop new GA. Of the 12 treatment-naïve study eyes without GA at baseline, 1 (8.3%) developed new GA during the study. In 21 study eyes with quantifiable GA area, eyes with GA present at baseline (16/21) enlarged by 0.34±0.26 mm/y, compared with 0.19±0.12 mm/y in eyes developing new-onset GA (5/21).

Conclusions: Although 17% of study eyes without GA present at baseline receiving ranibizumab developed new GA, the role of ranibizumab in the development of GA is unclear. Further prospective longitudinal studies are required to determine the eyes most at risk of developing GA in the setting of anti−vascular endothelial growth factor treatment. *Ophthalmology Retina 2017;1:34-41 Published by Elsevier Inc. on behalf of the American Academy of Ophthalmology*

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Age-related macular degeneration (AMD) is the leading cause of blindness in the United States.[1,2] Intravitreal injections of anti−vascular endothelial growth factor (VEGF) agents including ranibizumab have preserved vision in many patients affected by neovascular AMD (nAMD).[3,4] However, data from the Comparison of AMD Treatment Trials (CATT) study showing that approximately 18% of participants treated with anti-VEGF agents for 2 years developed geographic atrophy (GA) has led to increasing concern that anti-VEGF agents may increase the risk of GA development.[5] At this time, the superior visual outcomes of eyes with nAMD treated with anti-VEGF in clinical trials outweigh the potentially increased risk of GA development, but this risk should be further evaluated.

We previously reported on a study designed to image choroidal neovascularization (CNV) with high-speed indocyanine green (ICG) angiography to follow therapy with intravitreal ranibizumab.[6] In this post hoc analysis of these data, we evaluate factors affecting new GA development, incidence of GA, and GA growth rate in eyes undergoing ranibizumab therapy for nAMD. We determine the extent and expansion of GA based on fundus autofluorescence (FAF). The increased contrast sensitivity provided by autofluorescence images enables

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detection of small areas of atrophy in early disease compared with traditional color fundus photography.[7,8] This longitudinal, multimodal imaging study of participants with ICG-verified CNV provides a unique opportunity to evaluate the incidence and progression of GA in eyes with nAMD treated with ranibizumab.

Methods

This study was approved by the National Institutes of Health (NIH) Institutional Review Board and adhered to the tenets of the Declaration of Helsinki. All participants provided written informed consent. This work is compliant with the Health Insurance Portability and Accountability Act and is registered as clinical trial NCT00656903 on www.clinicaltrials.gov.

Study Participants

Participant selection and study intervention have been described previously.[9] Between March 2009 and August 2012, 75 participants with nAMD at the NIH Clinical Center in Bethesda, Maryland, were enrolled. Participants were ≥50 years old without medical conditions that might prevent consistent follow-up or contraindications for undergoing fluorescein and ICG angiography.

Each participant contributed 1 study eye to the protocol. If both eyes met the inclusion criteria, the study eye was chosen at the investigator's discretion. Inclusion criteria for the study eye included diagnosis of AMD defined by the presence of drusen ≥63 μm in size, CNV with associated exudation secondary to AMD, and visual acuity (VA) >20/400. Exclusion criteria included CNV or decreased vision not attributed to nAMD, subfoveal GA or fibrosis, myopic retinopathy, or a spherical equivalent refraction greater than −8.00 diopters. Eyes were also excluded for a history of CNV treatment using transpupillary thermotherapy, external beam radiation therapy, submacular surgery, and previous vitrectomy or scleral buckle. In this post hoc analysis, we included eyes with ≥1 year of follow-up and secondarily evaluated fellow eyes with ≥1 year of follow-up.

Study Intervention

Each study eye received induction therapy with intravitreal 0.5 mg ranibizumab (Lucentis, Genentech, Inc, San Francisco, CA) at baseline and at 1, 2, and 3 months, followed by pro re nata (PRN) treatment. The fellow eye received intravitreal ranibizumab at the investigator's discretion.

All participants were evaluated monthly for retreatment in the PRN phase until the conclusion of this study in April 2014 and received monthly injections in the study eye until a fluid-free macula was achieved on Cirrus optical coherence tomography (OCT; Carl Zeiss Meditec, Jena, Germany). A fluid-free macula was defined as complete resolution of subretinal and/or intraretinal fluid, which allowed for persistence of a retinal pigment epithelial detachment. If fluid or hemorrhage recurred, the study eye received intravitreal ranibizumab again following the PRN protocol without repeating the induction protocol. Best-corrected VA was evaluated with the Early Treatment Diabetic Retinopathy Study VA chart.

At each annual visit, participants underwent imaging with OCT, color fundus photography, FAF, fluorescein angiography (FA; Topcon Medical Systems, Inc, Oakland, NJ), and high-speed ICG (Heidelberg Engineering, Heidelberg, Germany). The ICG images were captured with a 30° view after injection with 1 mL of 8.3 mg/mL ICG dye. The FA images were obtained with a 50° view after injection with 5 mL of 10% fluorescein sodium.

Determination of Geographic Atrophy

For each participant's study eye, 1 photo each of color fundus photography, FAF, and late (10 min) FA from baseline and each subsequent year of enrollment were aligned to a color fundus photo using i2k Align software (DualAlign, Clifton, NY). This process created a stack of images for each eye across time and across the 3 imaging modalities aligned to a single photo. GA was defined on FAF as a region of hypo-autofluorescence ≥0.05 mm^2 in an area located within the vascular arcades that remained present across subsequent images and corresponded with ≥1 of the following criteria: (1) sharp margins and visible large choroidal vessels on color fundus photography; (2) sharp margins and uniform hyperfluorescence on FA; and/or (3) retinal pigment epithelium (RPE) and outer retinal loss on OCT.

Two trained graders (AT, JK) outlined the perimeter of all qualifying GA lesions on FAF images within stacks using the freehand drawing tool in ImageJ (NIH, Bethesda, MD). Homogenous contiguous areas of GA were traced manually. If multiple GA lesions existed, they were traced separately and summed. Pixel count was converted to area using the known 177 mm^2 area covered by the 50° Topcon color fundus photo.[9] Fellow eyes were similarly monitored and quantitated for GA excluding those with disciform lesions.

Potential Risk Factors for New Geographic Atrophy

Participant baseline information including age, sex, race, hypertension, and GA status in the fellow eye were evaluated and analyzed as potential risk factors for new GA development. Best-corrected VA, prior treatment for AMD, and number of intravitreal injections received during the study were also analyzed. Data on previous treatments were collected from a retrospective chart review.

Baseline FA and ICG imaging were used to characterize the CNV type (classic/minimally classic/occult/retinal angiomatous proliferation [RAP]/indeterminate) and the size of the lesion (mm^2) in the study eye, as previously published.[9] An OCT image was used to identify the presence of epiretinal membrane and foveal fluid in the study eye, defined as the presence of intraretinal fluid, subretinal fluid, or sub-RPE fluid within 500 μm of the foveal center. The presence of hemorrhage was identified on color fundus photography and the rate of GA development within an area of recorded hemorrhage was calculated.

For each study eye with quantifiable GA meeting the study definition of GA, we determined square root−transformed area (mm), shortest distance from lesion edge to fovea (mm), and whether the area of GA at any time point was completely outside the area of the baseline total CNV lesion on FA and ICG (GA location overlapping/nonoverlapping/unknown). On FA, total CNV lesion included CNV, exudation, contiguous hemorrhage, and serous pigment epithelial detachment. On ICG, total CNV lesion included the entire area of hyper-fluorescence on late (30 min) frames.

Analysis

Participants were classified into 3 study groups based on progression of the study eye: did not have any GA while enrolled in the study (never developed GA), developed GA while enrolled in the study (developed new GA), or had existing GA at baseline (GA present at baseline). For analysis of potential characteristics contributing to new GA in the setting of ranibizumab therapy, study eyes that developed new GA were compared with those that never developed GA. Because of the small number of participants in these groups, descriptive statistics are presented.

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