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Risk of Geographic Atrophy in the Comparison of Age-related Macular Degeneration Treatments Trials

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Abstract

Purpose—To describe risk factors for geographic atrophy (GA) in the Comparison of Age-related Macular Degeneration Treatments Trials (CATT).

Design—Cohort within a randomized clinical trial.

Participants—We analyzed 1024 CATT patients with no GA visible on color fundus photographs (CFPs) and/or fluorescein angiograms (FAs) at enrollment.

Methods—Eyes were assigned to ranibizumab (0.5 mg) or bevacizumab (1.25 mg) treatment and to a 2-year monthly or pro re nata (PRN) injection regimen, or monthly injections for 1 year and PRN for 1 year. Demographic, genetic, and baseline ocular characteristics and lesion features of CFP/FA and optical coherence tomography (OCT) were evaluated as risk factors for GA through 2 years of follow-up. Time-dependent Cox proportional hazard models were used to estimate adjusted hazard ratios (aHRs).

Main Outcome Measures—Development of GA.

Results—By 2 years, GA developed in 187 of 1024 patients (18.3%). Baseline risk factors for GA development included baseline visual acuity (VA) 20/200 (aHR, 2.65; 95% confidence interval [CI], 1.43–4.93), retinal angiomatous proliferation (RAP; aHR, 1.69; 95% CI, 1.16–2.47), GA in the fellow eye (aHR, 2.07; 95% CI, 1.40–3.08), and intraretinal fluid at the foveal center

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(aHR, 2.10; 95% CI, 1.34–3.31). Baseline factors associated with lower risk for GA development included blocked fluorescence (aHR, 0.49; 95% CI, 0.29–0.82), OCT measurements of subretinal fluid thickness of $>25\ \mu$ (aHR, 0.52; 95% CI, 0.35–0.78), subretinal tissue complex thickness of >275 compared with $75\ \mu$ (aHR, 0.31; 95% CI, 0.19–0.50), and vitreomacular attachment (aHR, 0.55; 95% CI, 0.31–0.97). Ranibizumab compared with bevacizumab had a higher risk (aHR, 1.43; 95% CI, 1.06–1.93), and monthly dosing had a higher risk (aHR, 1.59; 95% CI, 1.17–2.16) than PRN dosing. There were no strong associations between development of GA and the presence of risk alleles for *CFH*, *ARMS2*, *HTRA1*, *C3*, or *TLR3*.

Conclusions—Approximately one fifth of CATT patients developed GA within 2 years of treatment. Independent baseline risk factors included poor VA, RAP, foveal intraretinal fluid, monthly dosing, and treatment with ranibizumab. Anti-vascular endothelial growth factor therapy may have a role in the development of GA.

Age-related macular degeneration (AMD) is a leading cause of severe vision loss in people >65 years old in the United States. The prevalence of late AMD, defined as the development of neovascular AMD and/or geographic atrophy (GA), in the US population 40 years of age is estimated to be 1.47%.¹

Neovascular AMD is currently treated with intravitreal anti-vascular endothelial growth factor (VEGF) injections with excellent visual acuity (VA) response.^{2–6} Macular morphologic responses after anti-VEGF therapy are quite varied. One of the findings often observed in the area of the treated neo-vascular lesion is the development of retinal pigment epithelium (RPE) and choriocapillary atrophy that resembles the appearance of de novo GA.⁷ There are no long-term follow-up studies of these atrophic lesions, and it is not known whether their histology, growth patterns, and functional effects are similar to those of de novo GA lesions that develop in areas where no neovascularization was present previously. Because the atrophic lesions associated with treated neovascularization are clinically indistinguishable from de novo GA, they are referred to as GA throughout this article.

Patients in the Comparison of Age-related Macular Degeneration Treatments Trials (CATT) were treated for 2 years with the anti-VEGF agents ranibizumab or bevacizumab. As previously reported, the proportion of eyes at 2 years with GA not apparent at baseline was approximately 18%⁸ and when this type of lesion was present in the fovea, VA was markedly decreased.^{9,10} We now present an exploratory analysis of the 2-year cumulative incidence and the risk factors associated with the development of GA in CATT patients.

Methods

The CATT cohort and the methods used by the study have been described elsewhere.^{8–11} Briefly, the cohort consisted of 1185 patients with AMD and untreated choroidal/retinal neovascularization (CNV) with either the CNV or its sequelae, such as intraretinal fluid, subretinal fluid, serous pigment epithelial detachment, hemorrhage, or blocked fluorescence involving the foveal center. Patients enrolled in 43 clinical centers in the United States between February 2008 and December 2009. Inclusion criteria included age ≥ 50 years; active, untreated CNV secondary to AMD; and VA between 20/25 and 20/320 in the study eye. The study was approved by an institutional review board associated with each center. All patients provided written informed consent. This study was compliant with the Health Insurance Portability and Accountability Act regulations. The CATT study was registered with ClinicalTrials.gov (NCT00593450). At enrollment, patients were randomly assigned to 1 of 4 treatment groups defined by drug (ranibizumab or bevacizumab) and by dosing regimen (monthly or pro re nata [PRN]). At 1 year, patients initially assigned to monthly treatment retained their drug assignment but were reassigned randomly, with equal probability, to either monthly or PRN treatment. Patients initially assigned to PRN treatment

had no change in assignment and retained both their drug assignment and PRN dosing regimen for the second year.

At enrollment, patients provided a medical history and had bilateral color fundus photography (CFP), fluorescein angiography (FA), and time-domain optical coherence tomography (OCT).¹¹ Follow-up examinations were scheduled every 28 days for 2 years. We performed CFP and FA at 52 and 104 weeks. We scheduled OCT at every examination for patients assigned to PRN treatment and at selected time points for patients assigned monthly treatment. During the second year of follow-up, spectral-domain OCT could be used. Morphologic features of the study eyes at baseline were evaluated.^{8,9} Graders at the Photograph Reading Center were required to indicate whether there were signs of GA at the initial visit in the study eye as well as the fellow eye. Two trained and certified graders at the CATT Fundus Photograph Reading Center reviewed images acquired at the initial and follow-up visits. Discrepancies between the 2 graders were adjudicated.

At the CATT OCT Reading Center, 2 certified readers independently analyzed all scans for morphologic characteristics.¹¹ Readers identified intraretinal fluid, subretinal fluid, and fluid below the RPE (sub-RPE). When fluid was present, readers noted the location of fluid relative to the foveal center. They also identified the presence of subretinal hyperreflective material, epiretinal membrane, and vitreomacular attachment. Readers measured the thickness at the foveal center of the (1) retina, (2) subretinal fluid, and (3) subretinal tissue complex (defined as the distance from the outer photoreceptor border of the retina to Bruch's membrane, excluding subretinal fluid). A senior reader reconciled any grading disagreements between the initial reader pair.

Between July 2010 and September 2011, CATT patients were invited to provide blood samples for genetic studies. Blood samples from CATT patients were sent to the CATT Genetics Laboratory for DNA extraction. Five single nucleotide polymorphisms (SNPs) previously associated with AMD were evaluated.

Patients were considered to be at risk of incident GA if the reading center graders detected no evidence of GA in the study eye at enrollment. Both CFP and FA were used in assessing and characterizing GA. The diagnosis of GA required the presence within the macular vascular arcades of 1 patch $\geq 250 \mu$ in longest linear dimension of partial or complete depigmentation in the CFP that had 1 of these additional characteristics: sharply demarcated borders seen in CFP and/or FA, visibility of underlying choroidal vessels, excavated or punched out appearance on stereoscopy of CFP or FA, or uniform hyperfluorescence bounded by sharp borders on late-phase angiography. We did not use OCT scans for the determination of the presence of GA. Figure 1 shows 3 patients who developed GA in the CATT study.

Candidate risk factors for GA included demographic characteristics, cigarette smoking, hypertension, diabetes, dietary supplement use, cancer, hypercholesterolemia, anti-VEGF treatment group, and dosing regimen. Baseline ocular characteristics included VA in the study eye and fellow eye; CNV characteristics such as size, type, and location; and CNV lesion components (CNV, fibrotic or nonfibrotic scar, hemorrhage, blocked fluorescence [defined as hypofluorescence contiguous with CNV; Fig 2], and serous pigment epithelial detachment). Presence of retinal angiomatous proliferans (RAP) lesion was also noted.

Baseline OCT characteristics included retinal thickness, sub-retinal fluid thickness, and subretinal tissue complex thickness at the foveal center and presence of intraretinal fluid, subretinal fluid, sub-RPE fluid, RPE elevation, epiretinal membrane, vitreomacular attachment, and subretinal hyperreflective material.

Four SNPs previously associated with the risk of developing AMD were evaluated for association with incident GA: (1) complement factor H (*CFH*) Y402H (rs1061170), (2) age-related maculopathy susceptibility 2 (*ARMS2*, also called *LOC387715*) A69S (rs10490924), (3) high temperature requirement factor A1 (*HTRA1*) (rs11200638), and (4) complement component 3 (*C3*) R80G (rs2230199).^{12,13} One SNP previously associated with protection against GA, Toll-like receptor 3 (*TLR3*) (rs3775291), was also evaluated.¹⁴

Statistical Methods

Risk factors assessed as the presence or absence of a particular feature (such as lesion features, OCT fluid) were included as categorical variables. We classified risk factors measured on a continuous scale (e.g., VA, CNV area, OCT thickness) into categories for easier clinical interpretation. Categories for continuous variables were based on either the normal range (as for retinal thickness), quartiles of the distribution (as for subretinal tissue complex thickness), or clinically relevant cut-points (as for baseline VA). Subretinal fluid thickness was not divided into quartiles because the majority of the values were 0.

After excluding eyes with any GA at baseline, each risk factor was first evaluated by univariate analysis (without adjustment for other covariates), using the Cox proportional hazard models for GA that developed during 2 years of follow-up. Dosing regimen (monthly or PRN) was represented as a time-dependent covariate to accommodate the second randomization at 52 weeks for patients initially assigned monthly treatment. Risk factors with $P < 0.20$ in the univariate analysis were included in a multivariate analysis so that the independent effect of each predictor could be assessed. The final multivariate model was created by applying a backward selection procedure that retained only those predictors with $P < 0.05$, with the exception of drug and dosing regimen, which were included in all multivariate models. Adjusted hazard ratios (aHRs) and their 95% confidence intervals (CIs) were calculated from the final multivariate linear models.

For the assessment of association of 5 SNPs with incident GA, both univariate analysis and multivariate analysis (with adjustment by age, sex, and smoking status) were performed for each SNP. The linear trend P value was calculated from logistic regression by counting the number of risk alleles of the genotype (0, 1, or 2). The approach of controlling false discovery rate was used to correct P values for testing of multiple SNPs.¹⁵ All data analyses were performed using SAS (version 9.3, SAS Inc, Cary, NC).

Results

After excluding 82 subjects with GA at baseline and 79 subjects with missing or unknown GA, there were 1024 subjects at risk of developing GA in the CATT study (Fig 3). Among the 1024 subjects, 773 (75.5%) provided a blood sample for genotyping. Among the 1024 patients, 109 (10.6%) developed GA by the end of 1 year (Kaplan-Meier cumulative incidence rate, 0.11; 95% CI, 0.09–0.13), and 187 (18.3%) developed GA by the end of 2 years (Kaplan-Meier cumulative incidence rate, 0.19; 95% CI, 0.17–0.21). At 2 years of follow-up, the vast majority of patients with GA had extrafoveal GA (155; 83%), whereas 32 patients (17%) had foveal GA.

Tables 1, 2, and 3 show baseline characteristics and the risk of GA development identified by univariate analysis. Advancing age ($P = 0.0004$), monthly dosing regimen ($P = 0.001$; Table 1), worse vision at baseline in the study eye ($P = 0.03$) and the fellow eye ($P = 0.03$), subfoveal location of the total CNV lesion ($P = 0.003$), occult lesion type ($P = 0.03$), lesion composition ($P = 0.03$), RAP ($P < 0.0001$), presence of CNV/scar in the fellow eye ($P = 0.02$), presence of GA in the fellow eye ($P < 0.0001$; Table 2), greater retinal thickness in the

foveal center ($P < 0.0001$), less subretinal fluid thickness in the foveal center ($P = 0.03$), less subretinal tissue complex thickness in the foveal center ($P = 0.006$), presence of intraretinal fluid ($P < 0.0001$), and absence of subretinal fluid ($P < 0.0001$; Table 3) were all associated with GA development on univariate analysis. On the other hand, a decreased risk of GA development was observed in eyes with blocked fluorescence ($P = 0.02$) and vitreomacular attachment ($P = 0.009$).

The results of the final multivariate analysis for baseline predictors of GA are shown in Table 4. Relative to eyes with baseline VA of 20/25 to 20/40, eyes with worse VA had an increasingly greater risk of developing GA; VA of 20/200 to 20/320 was associated with an aHR of 2.65 (95% CI, 1.43, 4.93). When GA was present in the fellow eye, the study eye was more likely to develop GA (aHR, 2.07; 95% CI, 1.40–3.08). Eyes with RAP had a greater risk (aHR, 1.69; 95% CI, 1.16–2.47), whereas eyes with blocked fluorescence on angiography had a lesser risk (aHR, 0.49; 95% CI, 0.29–0.82). Eyes with any subretinal fluid in the foveal center were at lesser risk than eyes without subretinal fluid; when subretinal fluid thickness was $>25 \mu$, the aHR was 0.52 (95% CI, 0.35–0.78). Risk of GA decreased with increasing subretinal tissue complex thickness in the foveal center; relative to eyes with sub-RPE thickness $\leq 75 \mu$, eyes with a thickness of $> 275 \mu$ were associated with an aHR of 0.31 (95% CI, 0.19–0.50). Eyes with intraretinal fluid in the foveal center (aHR, 2.10; 95% CI, 1.34–3.31) or away from it (aHR, 1.80; 95% CI, 1.10–2.95) had a higher risk of developing GA compared with eyes with no intra-retinal fluid. Eyes with vitreomacular attachment on OCT had a lower risk of developing GA (aHR, 0.55; 95% CI, 0.31–0.97). Compared with eyes treated with bevacizumab, eyes treated with ranibizumab had a greater risk of developing GA (aHR, 1.43; 95% CI, 1.06–1.93). Eyes treated monthly had a greater risk (aHR, 1.59; 95% CI, 1.17–2.16) than eyes treated PRN.

Participants who received monthly injections throughout the study had a GA incidence of 15.0% during year 1 and 12.4% in year 2, whereas patients who received PRN injections throughout the study had a GA incidence of 8.3% during year 1 and 8.8% in year 2. Participants who received monthly injections in year 1 and were switched to PRN in year 2 had a GA incidence of 12.7 % in year 1 and 7% in year 2.

Each of the treatment arms had a different mean number of injections during the 2 years of the study. The 266 patients treated monthly for 2 years received a mean $\pm$ standard deviation of 22.5 ± 3.9 injections and had a cumulative incidence of GA of 64 (24.1%). The 247 patients treated monthly for 1 year and then PRN for another year received a mean $\pm$ standard deviation of 17.3 ± 4.5 injections and had a cumulative incidence of GA of 44 (17.8%). Finally, the 511 patients treated PRN for 2 years received a mean $\pm$ standard deviation of 13.1 ± 6.8 injections and had a cumulative incidence of GA of 79 (15.5%).

Table 5 displays the relationship between the genotype for 5 SNPs previously associated with AMD and GA in the study eyes. Incident GA was associated with the previously identified risk alleles in *ARMS2* (aHR for TT, 1.72; 95% CI, 1.07–2.76) and *HTRA1* (aHR for AA, 1.85; 95% CI, 1.16–2.97), although the association was not significant after adjustment for multiple comparisons by the false discovery rate method. There was no association of incident GA with SNPs in *CFH*, *C3*, or *TLR3*.

Discussion

Our study assessed lesions developing during 2 years of anti-VEGF therapy that have the characteristics of GA on color photography and FA. It is possible that the lesions that we describe in this article as GA developing in the area of total CNV lesion may not be histologically similar to the GA lesions that develop de novo in areas where no CNV lesion

was previously present. However, the lesions are clinically indistinguishable at 2 years. The GA associated with CNV has been described previously. A report from Sarks et al¹⁶ of a group of 20 eyes that had CNV before the advent of anti-VEGF therapy and developed GA suggested that the presence of a scar and the increasing age of the scar are risk factors for the development of GA. A histopathology study by Green¹⁷ in AMD eyes with disciform scars reported that 37% had areolar atrophy associated with the scar.

We identified a number of baseline risk factors associated with the development of GA in 18% of the CATT patients. One of the strongest risk factors identified was poor VA at baseline. Patients with VA between 20/200 and 20/320 had a 2.65 times greater risk of developing GA than patients with VA of 20/25 to 20/40. Because poor vision in AMD is probably a function of the extent of damage to the photo-receptors and the structures that support them, it is not surprising that poorer vision is associated with more GA. Presence of RAP was also associated with a 1.69 greater risk of development of GA, a finding that supports a previous report.¹⁸ This effect may be due to the presence of serous RPE detachments that resolve quickly with treatment, a process that could increase the risk of developing RPE atrophy. The presence of GA in the fellow eye at baseline was also associated with a doubling of the risk for the development of GA in the study eye, a finding similar to previous studies that have shown concordance in the development of GA between the 2 eyes.¹⁹

There were several anatomic findings identified on OCT or FA that seemed to influence the development of GA. Intraretinal fluid present in the fovea or outside the fovea on OCT was associated with a doubling of the risk of GA in comparison with patients who did not have fluid. On the other hand, increased subretinal fluid and sub-RPE tissue thickness were associated with a decreased risk for developing GA. Possibly the presence of fluid or tissue between the retina and the choriocapillaries may protect against the development of GA. The presence of blocked fluorescence was also associated with a decreased risk for developing GA. Blocked fluorescence on FA corresponds with a localized area of hypofluorescence that is contiguous with CNV and is not usually caused by visible hemorrhage, pigmentation, or other conditions observed on color photography that may decrease fluorescence.²⁰ The blocked fluorescence represents the advancing edge of a fibrovascular CNV, and further histopathologic and OCT studies are needed to better define the exact pathology that accounts for this feature on FA. The presence of fibrosis at the edge of the CNV could perhaps prevent the development of GA. Finally, the presence of vitreomacular attachment was associated with a 50% reduction in the risk for developing GA. This suggests that the physical attachment of the vitreous to the fovea may alter the diffusion of substances such as anti-VEGF agents in a way that may affect the mechanism, leading to GA development.

Treatment with ranibizumab, regardless of the dosing regimen, was associated with a 43% increase in risk of GA development ($P = 0.02$) in comparison with bevacizumab, suggesting that this medication may have a role in the formation of GA. The differences in the incidence of GA between the 2 medications could be because of differences in their effects on the RPE and choroid or because eyes treated with ranibizumab had more complete resolution of fluid. Although we found a greater incidence of GA in patients treated with ranibizumab, VA at 2 years was similar to acuities achieved in bevacizumab-treated patients,⁸ presumably because most of the GA that developed was extrafoveal.⁸ Data from the Age Related Eye Disease Study suggests that it takes a median of 2.5 years for extrafoveal GA to reach the center of the fovea.²¹ As such, the development and progression of GA may become a more visually important event with longer follow-up of CATT study patients. In contrast to our findings, 2-year results from the Alternative Treatments to Inhibit VEGF in Age-related Choroidal Neovascularization (IVAN) trial did not show a difference

between ranibizumab and bevacizumab in the rates for developing GA (28% for ranibizumab vs 31.2% of bevacizumab; odds ratio, 0.87; 95% CI, 0.61–1.25; $P = 0.46$).²²

Two years of treatment in CATT with monthly injections (mean of 22.5 injections), regardless of the type of anti-VEGF medication, was associated with a 59% increase in risk of GA development ($P = 0.003$) in comparison with PRN treatment (mean of 13.1 injections), suggesting that greater exposure to anti-VEGF medications may have a role in the development of this condition. The 2-year IVAN results confirmed our findings, with a higher rate of GA developing in eyes treated with continuous (monthly) therapy as opposed to discontinuous (PRN) treatment (33.3% continuous vs 25.7% discontinuous, odds ratio, 1.47; 95% CI, 1.03, 2.11; $P = 0.033$).²² Additional supporting evidence from CATT that dosing frequency may affect the development of GA may be found in an examination of the group who switched from monthly injections in year 1 to PRN treatment in year 2 (switched dosing group). The switched dosing group had a lesser incidence of GA during their second year under PRN treatment (7%) than during the first year of monthly injections (12.7%). This lower second year rate (7%) was similar to the second year rate of GA development in the group that had received PRN for 2 years (8.8%, PRN always group) and was lower than the second year rate of GA development in the patients who continued with monthly therapy in the second year of the study (12.4%, monthly always).

The relative incidence of GA among treatment groups was similar to the relative incidence of residual fluid on OCT; the higher the rate of residual fluid on OCT, the lower the rate of GA. This has led some to speculate that excessive drying of the retina may promote the development of GA. Others have speculated that the presence of residual fluid may have masked the assessment of GA, leading to lower rates of detection in eyes with residual fluid. The maximum difference in mean total thickness at the fovea between treatment groups was about 70 μ .^{6,8} The likelihood that this small amount of fluid or retinal thickness difference could affect GA detection rates by expert readers at the Fundus Photograph Reading Center assessing both color photos and FAs is extremely low. To investigate this issue, we reviewed all patients who had GA at year 1 and who had increases in total thickness at the fovea of >50 μ between years 1 and 2. We did not find evidence that the increased thickness precluded clear visualization of GA in any of the 16 patients reviewed.

Recent studies of mice have suggested that anti-VEGF drugs may interfere with maintenance of the normal retinal and choriocapillaries.²³ Because VEGF plays an important role in the normal function of the retina and the maintenance of the choriocapillaris by the RPE, therapies that block VEGF could have an effect on the development and progression of GA. Therefore, that more numerous and/or frequent injections and ranibizumab may be associated with more GA than bevacizumab support a potential effect of anti-VEGF medication on the development of this condition. These results have raised a number of important safety questions among clinicians using anti-VEGF therapy in AMD patients. Although the CATT results clearly show that these medications are highly effective in the treatment of exudative AMD, they also suggest that chronic use may have some undesirable side effects.

We found 2 AMD-associated SNPs in *ARMS2* and *HTRA1* that were weakly associated with the development of GA in patients receiving anti-VEGF therapy. However, this association was not significant when using a more conservative approach often used in genetic studies that adjust for multiple comparisons by the false discovery method. Our results are, therefore, consistent with the literature^{24–27} and do not confirm a relationship between specific AMD risk alleles and increased risk for developing GA while receiving anti-VEGF therapy. The SNP that we investigated in *TLR3* (rs3775291), which has been previously reported as protective for the development of GA,¹⁴ showed a trend in the direction of a

protective effect, and the magnitude of the effect was similar to what has previously been reported. The number of patients at risk who actually had this SNP was relatively small, and additional studies with a larger sample size are needed to confirm this relationship.

The strengths of this study are the relatively large sample size, the prospective design, and the masked assessment of the treatment outcomes using well-defined protocols. A relative weakness is that autofluorescence photography, a technique that is well suited to the assessment of GA,^{28,29} was not available. Our determinations of GA, however, were based on assessments of both CFP and FA, a combination that has been shown to better capture early stages of GA than color photography alone.³⁰

Our study has described a number of risk factors for the development of GA in AMD patients treated with anti-VEGF medications. The development of GA is a relatively slow process, with only 11% of patients at 1 year and 18% at 2 years having GA. Our results show that a monthly dosing regimen and ranibizumab treatment are associated with a higher risk of GA, suggesting a possible role for this type of dosing regimen and drug in the development of GA. These findings have important clinical implications and should be included in discussions with patients regarding the benefits and risks of the choice of treatment type and regimen. Although monthly injections may result in slightly better visual outcomes at 2 years, the increased risk of GA development may offset this benefit long term. Because of the tendency of de novo and, most likely, GA lesions after anti-VEGF to enlarge, the final effect of these lesions on central VA remains unknown. Follow-up of CATT patients beyond 2 years is essential to determine whether central VA will be maintained in these patients over time.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Development of geographic atrophy (GA) in eyes with neovascular age-related macular degeneration (AMD) after 2 years of anti-vascular endothelial growth factor therapy. **A1**, Choroidal neovascularization (CNV) at baseline on color fundus photography (CFP). **A2**, Classic CNV (white arrow) at baseline on fluorescein angiography (FA). **A3**, Optical coherence tomography (OCT) showing at baseline the CNV lesion with prominent intraretinal fluid (white arrow). **A4**, At 2 years of follow-up, CFP depicts a large GA lesion in the area of the previously active CNV (black arrow) and an additional small area of GA superior to the baseline CNV (white arrow). **A5**, At 2 years of follow-up, FA shows areas of hyperfluorescence with well-demarcated margins corresponding with the areas of GA in **A4**. **A6**, An OCT scan showing at 2-year follow-up increased choroidal signal penetration (white arrows) corresponding with the GA in **A4**. **B1**, Baseline CFP of active CNV. **B2**, Baseline FA shows active CNV with leakage. **B3**, Baseline OCT shows CNV with subretinal fluid (white arrow). **B4**, At 2 years, CFP shows a large area of central GA. **B5**, At 2 years, FA image shows a well-demarcated area of hyperfluorescence corresponding to the GA lesion in **B4**. **B6**, At 2 years, OCT shows attenuated retina overlying a well-demarcated area of

increased choroidal signal penetration in the central macula (white arrows) corresponding with the GA lesion. **C1**, Baseline CFP shows a peripapillary active CNV lesion surrounded by hemorrhage (white arrow). **C2**, Baseline FA shows hyperfluorescence and leakage in the area of active CNV (white arrow) seen in **C1**. **C3**, Baseline OCT shows subretinal hyperreflective material in the area of CNV (black arrow) and subretinal fluid under the fovea (white arrow). **C4**, At 2 years, CFP shows a well-defined area of GA adjacent to the area of CNV present in **C1**. **C5**, At 2 years FA shows hyperfluorescence corresponding to the area of GA seen in **C1**. **C6**, At 2 years, OCT shows outer retinal layer loss and areas of increased choroidal signal penetration (white arrows) corresponding with the GA seen in **C4**.

Figure 2.

Typical case of contiguous blocked fluorescence surrounding choroidal neovascularization.

A, Color fundus photography shows active choroidal neovascularization. **B**, Fluorescein angiography depicts an area of blocked fluorescence contiguous with the choroidal neovascularization (white arrows).

Figure 3.
Flow chart describing the patients of the study. GA = geographic atrophy.

Univariate Analysis of the Association between Baseline Patient Characteristics and Geographic Atrophy (GA) Incidence at 2 Years (n = 1024)

Table 1

Baseline Patient Characteristics	Patients at Risk, n	GA at Week 52 or 104, n (%)	P Value *	Hazard Ratio [†] (95% CI)	P Value [‡]
Age (yrs)					
50–69	128	12 (9.4)	<0.0001	1.00	0.0004
70–79	354	52 (14.7)		1.64 (0.87–3.07)	
80–89	476	106 (22.3)		2.66 (1.46–4.83)	
90	66	17 (25.8)		3.20 (1.53–6.71)	
Sex					
Female	634	120 (18.9)	0.51	1.00	0.56
Male	390	67 (17.2)		0.92 (0.68–1.23)	
Cigarette smoking					
Never	442	80 (18.1)	0.51	1.00	0.50
Quit	495	95 (19.2)		1.08 (0.80–1.45)	
Current	87	12 (13.8)		0.76 (0.41–1.39)	
Hypertension					
No	315	56 (17.8)	0.86	1.00	0.77
Yes	709	131 (18.5)		1.05 (0.77–1.43)	
Diabetes					
No	847	153 (18.1)	0.75	1.00	0.65
Yes	177	34 (19.2)		1.09 (0.75–1.58)	
Dietary supplement use					
No	106	14 (13.2)	0.28	1.00	0.21
β-Carotene, vitamins C, E, and zinc	642	117 (18.2)		1.42 (0.81–2.46)	
Other supplements	276	56 (20.3)		1.67 (0.93–3.00)	
Hypercholesterolemia					
No	434	69 (15.9)	0.10	1.00	0.13
Yes	590	118 (20.0)		1.26 (0.94–1.70)	
Drug group					
Bevacizumab	498	81 (16.3)	0.12	1.00	0.10
Ranibizumab	526	106 (20.2)		1.27 (0.95–1.70)	

Baseline Patient Characteristics	Patients at Risk, n	GA at Week 52 or 104, n (%)	P Value [*]	Hazard Ratio [†] (95% CI)	P Value [‡]
Regimen group [‡]					
PRN	511	79 (15.5)	0.013	1.00	0.001
Switched	247	44 (17.8)		–	
Monthly	266	64 (24.1)		1.64 (1.22–2.20)	

CI = confidence interval; PRN = pro re nata.

^{*} Fisher exact test.

[†] Univariate proportional hazard model.

[‡] Regimen group was modeled as a time-dependent variable with values of either PRN or monthly (for switched group, monthly in year 1 and PRN in year 2) used to calculate hazard ratios and P values from proportional hazard model.

Table 2

Univariate Analysis for the Association between Baseline Ocular Characteristics and Geographic Atrophy (GA) Incidence at 2 Years (n = 1024)

	Patients at Risk, n	GA at Week 52 or 104, n (%)	P Value *	Hazard Ratio [†] (95% CI)	P Value [‡]
Baseline VA in study eye					
20/25–40	377	52 (13.8)	0.03	1.00	0.03
20/50–80	375	74 (19.7)		1.49 (1.04–2.12)	
20/100–160	209	46 (22.0)		1.71 (1.15–2.54)	
20/200–320	63	15 (23.8)		1.89 (1.07–3.37)	
Baseline VA in fellow eye					
20/20	320	46 (14.4)	0.03	1.00	0.03
20/25–20/40	408	74 (18.1)		1.31 (0.91–1.89)	
20/50	296	67 (22.6)		1.65 (1.13–2.40)	
Baseline CNV area (DA)					
1	411	78 (19.0)	0.17	1.00	0.18
>1 to 2	208	29 (13.9)		0.70 (0.46–1.08)	
>2 to 4	193	35 (18.1)		0.97 (0.65–1.44)	
>4	97	25 (25.8)		1.39 (0.89–2.18)	
Missing	115	20 (17.4)		0.94 (0.57–1.53)	
Location of lesion					
Not subfoveal	266	65 (24.4)	0.004	1.00	0.003
Subfoveal	747	121 (16.2)		0.63 (0.47–0.86)	
Missing	11	1 (9.1)			
Lesion type					
Predominantly classic	235	31 (13.2)	0.02	1.00	0.03
Minimally classic	173	28 (16.2)		1.24 (0.75–2.07)	
Occult only	599	126 (21.0)		1.64 (1.11–2.43)	
Can't grade/no lesion	17	2 (11.8)			
Lesion composition					
CNV only	518	111 (21.4)	0.02	1.00	0.03
CNV and hemorrhage	259	49 (18.9)		0.90 (0.64–1.25)	
CNV and blocked fluorescence	74	9 (12.2)		0.55 (0.28–1.08)	

	Patients at Risk, n	GA at Week 52 or 104, n (%)	P Value*	Hazard Ratio [†] (95% CI)	P Value [‡]
CNV and SPED	46	5 (10.9)		0.48 (0.20–1.18)	
CNV and others	119	12 (10.1)		0.46 (0.25–0.83)	
No CNV/CG	8	1 (12.5)			
RAP lesion					
No	899	145 (16.1)	<0.0001	1.00	<0.0001
Yes	113	41 (36.3)		2.52 (1.78–3.57)	
No CNV/CG	12	1 (8.3)			
Blocked fluorescence					
No	863	169 (19.6)	0.009	1.00	0.02
Yes	155	17 (11.0)		0.54 (0.33–0.89)	
Missing	6	1 (16.7)			
SPED (proportion of total lesion)					
None	955	180 (18.8)	0.21	1.00	0.26
<50%	20	1 (5.0)		0.26 (0.04–1.85)	
50%	40	5 (12.5)		0.65 (0.27–1.58)	
No CNV/CG/missing	9	1 (11.1)			
Hemorrhage (associated with the lesion)					
None	654	127 (19.4)	0.52	1.00	0.58
2 DA	287	47 (16.4)		0.85 (0.61–1.18)	
>2 DA	73	12 (16.4)		0.86 (0.47–1.55)	
CD or CG or missing	10	1 (10.0)			
Atrophic or fibrotic scar					
None/questionable	976	182 (18.6)	0.21	1.00	0.19
Present	41	4 (9.)		0.52 (0.19–1.39)	
Glaucoma					
No	910	159 (17.5)	0.07	1.00	0.058
Yes	114	28 (24.6)		1.47 (0.99–2.20)	
CNV/scar in fellow eye					
None/questionable	692	113 (16.3)	0.03	1.00	0.02
Present	303	68 (22.4)		1.45 (1.08–1.97)	
Missing	29	6 (20.7)			

	Patients at Risk, n	GA at Week 52 or 104, n (%)	P Value*	Hazard Ratio [†] (95% CI)	P Value [‡]
GA in fellow eye					
None/questionable	926	151 (16.3)	<0.0001	1.00	<0.0001
Present	86	34 (39.5)		2.74 (1.89–3.98)	
Missing	12	2 (16.7)			

CD = cannot determine; CG = cannot grade; CI = confidence interval; CNV = choroidal/retinal neovascularization; DA = disc area; RAP = retinal angiomatous proliferans; SPED = serous pigment epithelial detachment; VA = visual acuity.

* Fisher exact test.

[†] Univariate proportional hazard model.

Univariate Analysis for the Association between Baseline Optical Coherence Tomography (OCT) Features and Geographic Atrophy (GA) Incidence at 2 Years (n = 1024)

Table 3

	Patients at Risk, n	GA at Week 52 or 104, n (%)	P Value*	Hazard Ratio [†] (95% CI)	P Value [‡]
Retinal thickness at foveal center (μ)					
<120	103	10 (9.7)	<0.0001	1.00	<0.0001
120–212	547	86 (15.7)		1.67 (0.87–3.22)	
>212	371	91 (24.5)		2.81 (1.46–5.41)	
Missing	3	0 (0.0)			
Subretinal fluid thickness at foveal center (μ)					
0	676	139 (20.6)	0.03	1.00	0.03
>0 to 25	83	13 (15.7)		0.74 (0.42–1.30)	
>25	262	35 (13.4)		0.62 (0.43–0.90)	
Missing	3	0 (0.0)			
Subretinal tissue complex thickness at foveal center (μ)					
>0 to 75	244	53 (21.7)	0.006	1.00	0.006
>75 to 160	237	55 (23.2)		1.05 (0.72–1.53)	
>160 to 275	263	45 (17.1)		0.75 (0.50–1.11)	
>275	277	34 (12.3)		0.53 (0.34–0.81)	
Missing	3	0 (0.0)			
Intraretinal fluid					
No fluid	261	26 (10.0)	<0.0001	1.00	<0.0001
Fluid not in foveal center	272	46 (16.9)		1.82 (1.13–2.95)	
Fluid in foveal center	478	114 (23.8)		2.62 (1.71–4.01)	
Missing	13	1 (7.7)			
Subretinal fluid					
No fluid	164	54 (32.9)	<0.0001	1.00	<0.0001
Fluid not in foveal center	492	81 (16.5)		0.45 (0.32–0.64)	
Fluid in foveal center	362	51 (14.1)		0.38 (0.26–0.56)	
Missing	6	1 (16.7)			
Sub-RPE fluid					
No fluid	445	80 (18.0)	0.49	1.00	0.46

	Patients at Risk, n	GA at Week 52 or 104, n (%)	P Value*	Hazard Ratio [†] (95% CI)	P Value [‡]
Fluid not in foveal center	175	39 (22.3)		1.27 (0.87–1.86)	
Fluid in foveal center	328	55 (16.8)		0.92 (0.65–1.29)	
Missing	76	13 (17.1)		0.95 (0.53–1.71)	
Epiretinal membrane					
No	843	155 (18.4)	0.48	1.00	0.53
Yes	139	29 (20.9)		1.14 (0.76–1.69)	
Missing	42	3 (7.1)		0.37 (0.12–1.16)	
Vitreomacular attachment					
No	842	169 (20.1)	0.007	1.00	0.009
Yes	128	13 (10.2)		0.47 (0.27–0.83)	
Missing	54	5 (9.3)		0.45 (0.18–1.09)	
RPE elevation					
No	136	21 (15.4)	0.41	1.00	0.29
Yes	874	165 (18.9)		1.28 (0.81–2.01)	
Missing	14	1 (7.1)			
Subretinal hyperreflective material					
No	226	45 (19.9)	0.50	1.00	0.63
Yes	785	141 (18.0)		0.92 (0.66–1.29)	
Missing	13	1 (7.7)			

CI = confidence interval; RPE = retinal pigment epithelium.

* Fisher exact test.

[‡] Univariate proportional hazard model.

Table 4

Multivariate Analysis for Factors Associated with Incidence of Geographic Atrophy (GA) at 2 Years*

Baseline Characteristics	No. of Subjects at Risk in the Final Model (n = 944)	Subjects with GA at Week 52 or 104, n (%)	Adjusted Hazard Ratio (95% CI) [†]	P Value [‡]
Baseline VA in study eye				
20/25–40	352	49 (13.9)	1.00	0.007
20/50–80	350	72 (20.6)	1.66 (1.14–2.44)	
20/100–160	189	43 (22.8)	1.70 (1.10–2.62)	
20/200–320	53	15 (28.3)	2.65 (1.43–4.93)	
RAP lesion				
No	839	140 (16.7)	1.00	0.007
Yes	105	39 (37.1)	1.69 (1.16–2.47)	
Blocked fluorescence lesion				
No	806	163 (20.2)	1.00	0.007
Yes	138	16 (11.6)	0.49 (0.29–0.82)	
GA in fellow eye				
None/questionable	864	147 (17.0)	1.00	0.0003
Present	80	32 (40.0)	2.07 (1.40–3.08)	
Subretinal fluid thickness at foveal center (μ)				
0	623	133 (21.4)	1.00	0.006
>0 to 25	75	12 (16.0)	0.69 (0.38–1.27)	
>25	246	34 (13.8)	0.52 (0.35–0.78)	
Subretinal tissue complex thickness at foveal center (μ)				
>0 to 75	228	52 (22.8)	1.00	<0.0001
>75 to 160	219	52 (23.7)	0.63 (0.42–0.95)	
>160 to 275	242	44 (18.2)	0.53 (0.34–0.82)	
>275	255	32 (12.2)	0.31 (0.19–0.50)	
Intraretinal fluid				
No fluid	255	26 (10.2)	1.00	0.006
Fluid not in foveal center	249	43 (17.3)	1.80 (1.10–2.95)	
Fluid in foveal center	440	110 (25.0)	2.10 (1.34–3.31)	
Vitreomacular attachment				
No	819	166 (20.3)	1.00	0.04
Yes	125	13 (10.4)	0.55 (0.31–0.97)	
Drug group				
Bevacizumab	455	77 (16.9)	1.00	0.02
Ranibizumab	489	102 (20.9)	1.43 (1.06–1.93)	
Regimen group [‡]				
PRN	470	75 (16.0)	1.00	0.003
Switched	236	44 (18.6)	–	
Monthly	238	60 (25.2)	1.59 (1.17–2.16)	

CI = confidence interval; CNV = choroidal neovascularization; RAP = retinal angiomatous proliferans; PRN = pro re nata; VA = visual acuity.

* Initial model includes age, baseline VA of the study eye, baseline VA of fellow eye, location of lesion, lesion type, blocked fluorescence, RAP lesion, CNV in fellow eye, GA in fellow eye, retinal thickness in the foveal center, subretinal thickness in the foveal center, subretinal tissue complex thickness in the foveal center, intraretinal fluid, subretinal fluid, vitreomacular attachment, drug, and regimen. The initial model went through backward selection, and the final multivariate model only included the significant variables listed in this table.

[†] Time-dependent proportional hazard model.

[‡] Regimen group was modeled as a time-dependent variable with values of either PRN or monthly (for switched group, monthly in year 1 and PRN in year 2) used for the calculation of hazard ratios and *P* values from proportional hazard model.

Table 5

Associations of Genotype with Geographic Atrophy (GA) Incidence at 2 Years (n = 773)

	Genotype	Patients at Risk, n	GA at Week 52 or 104, n (%) [†]	Univariate Analysis Hazard Ratio (95% CI) [‡]	Adjusted Analysis Hazard Ratio (95% CI) [§]
<i>CFH</i> rs1061170	CC	250	44 (17.6)	0.75 (0.48–1.16)	0.86 (0.55–1.34)
	TC	363	58 (16.0)	0.68 (0.45–1.03)	0.71 (0.47–1.08)
	TT	160	36 (22.5)	1.00	1.00
	Linear trend <i>P</i>		0.29	0.27	0.60
<i>ARMS2</i> rs10490924	Adjusted <i>P</i> //				0.60
	TT	153	34 (22.2)	1.52 (0.96–2.43)	1.72 (1.07–2.76)
	GT	377	67 (17.8)	1.18 (0.79–1.76)	1.18 (0.79–1.77)
	GG	243	37 (15.2)	1.00	1.00
<i>HTRA1</i> rs11200638	Linear trend <i>P</i>		0.08	0.08	0.031
	Adjusted <i>P</i> //				0.09
	AA	145	34 (23.5)	1.62 (1.02–2.58)	1.85 (1.16–2.97)
	AG	377	66 (17.5)	1.17 (0.78–1.74)	1.17 (0.78–1.74)
<i>C3</i> rs2230199	GG	251	38 (15.1)	1.00	1.00
	Linear trend <i>P</i>		0.048	0.046	0.015
	Adjusted <i>P</i> //				0.09
	GG	50	6 (12.0)	0.64 (0.28–1.46)	0.64 (0.28–1.49)
<i>TLR3</i> rs3775291	CG	295	53 (18.0)	0.96 (0.68–1.36)	1.00 (0.70–1.42)
	CC	428	79 (18.5)	1.00	1.00
	Linear trend <i>P</i>		0.40	0.40	0.49
	Adjusted <i>P</i> //				0.59
<i>TLR3</i> rs3775291	CC	377	73 (19.4)	1.82 (0.88–3.77)	1.70 (0.82–3.53)
	TC	323	57 (17.7)	1.63 (0.78–3.42)	1.58 (0.75–3.32)
	TT	73	8 (11.0)	1.00	1.00
	Linear trend <i>P</i>		0.12	0.13	0.21
No. of risk alleles	Adjusted <i>P</i> //				0.32
	0–2	80	11 (13.8)	1.00	1.00
	3	108	15 (13.9)	0.99 (0.46–2.16)	0.94 (0.43–2.04)
	4	146	29 (19.9)	1.45 (0.72–2.90)	1.40 (0.70–2.81)

Genotype	Patients at Risk, n	GA at Week 52 or 104, n (%) [†]	Univariate Analysis Hazard Ratio (95% CI) [‡]	Adjusted Analysis Hazard Ratio (95% CI) [§]
5	175	32 (18.3)	1.34 (0.68–2.66)	1.36 (0.69–2.70)
6	133	25 (18.8)	1.38 (0.68–2.81)	1.43 (0.70–2.92)
7	131	26 (19.9)	1.46 (0.72–2.96)	1.64 (0.80–3.33)
Linear trend <i>P</i>		0.18	0.19	0.06
Adjusted <i>P</i> ^{//}				0.12

CI = confidence interval; SNP = single nucleotide polymorphisms.

* The risk alleles are C for *CFH*, T for *ARMS2*, A for *HTRA1*, and G for *C3*. The protective allele is T for *TLR3*.

[†] Linear trend *P* value is from logistic regression model with genotype coded as 0, 1, 2 risk alleles.

[‡] Linear trend *P* value is from proportional hazard model with genotype coded as 0, 1, 2 risk alleles.

[§] Linear trend *P* value is from proportional hazard model adjusted for age, sex, and smoking status.

^{//} The multiple testing adjusted *P* values were calculated using the approach of false discovery rate.