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Systemic Complement Inhibition with Eculizumab for Geographic Atrophy in Age-Related Macular Degeneration: The COMPLETE Study

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Abstract

Purpose—To evaluate the effect of eculizumab, a systemic inhibitor of complement component (C5), on the growth of geographic atrophy (GA) in patients with age-related macular degeneration (AMD).

Design—Prospective, double-masked, randomized clinical trial.

Participants—Patients with GA measuring from 1.25 to 18 mm² based on spectral-domain optical coherence tomography imaging.

Methods—Patients were randomized 2:1 to receive intravenous eculizumab or placebo over 6 months. In the eculizumab treatment arm, the first 10 patients received a low-dose regimen of 600 mg weekly for 4 weeks followed by 900 mg every 2 weeks until week 24, and the next 10 patients

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received a high-dose regimen of 900 mg weekly for 4 weeks followed by 1200 mg every 2 weeks until week 24. The placebo group was infused with saline. Patients were observed off treatment for an additional 26 weeks. Both normal-luminance and lowluminance visual acuities were measured throughout the study, and the low-luminance deficits were calculated as the difference between the letter scores.

Main Outcome Measures—Change in area of GA at 26 weeks.

Results—Thirty eyes of 30 patients were enrolled. Eighteen fellow eyes also met inclusion criteria and were analyzed as a secondary endpoint. For the 30 study eyes, mean square root of GA area measurements $\pm$ standard deviation at baseline were 2.55 ± 0.94 and 2.02 ± 0.74 mm in the eculizumab and placebo groups, respectively ($P = 0.13$). At 26 weeks, GA enlarged by a mean of 0.19 ± 0.12 and 0.18 ± 0.15 mm in the eculizumab and placebo groups, respectively ($P = 0.96$). At 52 weeks of follow-up, GA enlarged by a mean of 0.37 ± 0.22 mm in the eculizumab-treated eyes and by a mean of 0.37 ± 0.21 mm in the placebo group ($P = 0.93$, 2 sample t test). None of the eyes converted to wet AMD. No drug-related adverse events were identified.

Conclusions—Systemic complement inhibition with eculizumab was well tolerated through 6 months but did not decrease the growth rate of GA significantly. However, there was a statistically significant correlation between the lowluminance deficit at baseline and the progression of GA over 6 months. *Ophthalmology* 2014;121:693-701 © 2014 by the American Academy of Ophthalmology.

The pathogenesis of age-related macular degeneration (AMD) is multifactorial, resulting from a combination of genetic and environmental risk factors.¹ Over the past decade, there has been growing evidence implicating a role for the complement system in AMD.² Histopathologic studies have identified various complement components in drusen, in Bruch's membrane, and in the inner choroid.^{3,4} Moreover, deposits similar in appearance to drusen in AMD have been found in eyes of patients with complement-mediated renal diseases.⁵ Genetic association studies using different populations have shown that genetic polymorphisms associated with AMD have been localized within or close to genes that encode complement proteins.⁶ In 2005, 4 groups identified a genetic polymorphism in complement factor H (*CFH*), which has been associated strongly with an increased risk of developing AMD.^{7–10} In addition, polymorphisms within other complement genes, such as complement component 3 (*C3*) genes¹¹ and the complement factor B (*CFB*)/complement component 2 (*C2*) locus,¹² have been associated with an increased risk of AMD. The most common risk-conferring *CFH* genetic variant for AMD is the Y402H polymorphism, resulting in a tyrosine-to-histidine substitution at amino acid position 402 within the *CFH* protein. Protective alleles associated with the complement pathway also have been reported. Two of the 5 *CFH*-related genes (*CFHR1–5*) that lie within the regulators of complement activation locus on chromosome 1q32, known as *CFHR1* and *CFHR3*, are considered to be protective against AMD.¹³

Currently, there is no proven therapy that stops the progression of dry AMD. The cessation of smoking along with vitamin and nutritional supplements combined with a healthy diet are considered the only options for slowing disease progression.^{14,15} Several treatment strategies that modulate the complement system in AMD are being investigated. These

treatments inhibit complement activation by targeting various effectors molecules, such as C3, C5, and factor D.^{15–17} The only inhibitor of terminal complement activation approved by the US Food and Drug Administration is eculizumab (Soliris; Alexion Pharmaceuticals, Cheshire, CT), a humanized monoclonal antibody derived from the murine anti-human C5 antibody. Eculizumab is approved for the systemic treatment of paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome. Both paroxysmal nocturnal hemoglobin-uria¹⁸ and atypical hemolytic uremic syndrome¹⁹ result from complement dysregulation, and eculizumab successfully controls these diseases by inhibiting C5 and preventing terminal complement activation and formation of membrane attack complex (C5b-9).²⁰

To investigate the role of systemic complement activation in AMD, we performed the Complement Inhibition with Eculizumab for the Treatment of Nonexudative Age-Related Macular Degeneration (COMPLETE) study, which was designed to evaluate the safety and efficacy of systemic eculizumab for the treatment of geographic atrophy (GA) in AMD.

Methods

Study Design

The COMPLETE study is an investigator-sponsored, randomized, double-masked, single-center study designed to evaluate the safety and efficacy of intravenous eculizumab for the treatment of patients with GA secondary to AMD. The study was performed with the approval of the Food and Drug Administration (investigational new drug application no. 104471). Before the initiation of the study, additional approval was obtained from the institutional review board at the University of Miami Miller School of Medicine. Informed consent was obtained from all patients before determination of full eligibility, and the study was performed in accordance with the Health Insurance Portability and Accountability Act. The COMPLETE study is registered at www.clinicaltrials.gov, and the clinical trial accession number is NCT00935883 (accessed September 18, 2013).

From November 2009 through March 2011, a total of 30 patients were enrolled. Eligibility criteria included age 50 years or older, total GA area of 1.25 to 18 mm², and visual acuity of 20/63 or better (Early Treatment Diabetic Retinopathy Study [ETDRS] letter score of at least 59). Exclusion criteria were visual acuity worse than 20/63, a total GA area of more than 18 mm² (7 disc areas), GA contiguous with any peripapillary atrophy, and any history of choroidal neovascularization in the study eye. If both eyes were eligible for the study, then 1 eye was chosen as the study eye at the discretion of the investigator. All patients enrolled in the study received a meningococcal vaccine at least 15 days before the initiation of treatment.

Treatment Protocol

Patients were randomized 2:1 to receive active treatment with eculizumab or placebo in a double-masked fashion. Randomization schedules were stratified with the use of a permuted-block strategy to insure balance. During the treatment period, patients received eculizumab for a period of 24 weeks with the primary endpoint at 26 weeks. The treatment

period was divided into an induction period and a maintenance period. The first 10 patients in the eculizumab group received the low dose of eculizumab (600 mg via intravenous infusion for 4 weeks followed by 900 mg every 2 weeks until week 24), whereas the next 10 patients received the high dose (900 mg eculizumab via intravenous infusion for 4 weeks followed by 1200 mg every 2 weeks until week 24). After 26 weeks, patients were followed up without treatment every 3 months for an additional 6 months.

Ophthalmologic Examination and Imaging Procedures

Ophthalmologic examination included best-corrected visual acuity measured using the ETDRS chart at 4 meters, low-luminance visual acuity testing at 4 meters using a 2.0-log unit neutral density filter (Wratten filter; Kodak, Rochester, NY),²¹ slit-lamp bio-microscopy, intraocular pressure measurement, and fundus examination. All imaging studies were performed at baseline, 12 weeks, 26 weeks, and 52 weeks of follow-up. These studies included color and autofluorescence (AF) imaging with a fundus camera-based flash system (TRC-50DX; Topcon Medical Systems, Oakland, NJ; AF excitation λ , 535–585 nm; detection λ , 605–715 nm), AF and fluorescein angiographic imaging with a confocal scanning laser ophthalmoscopy system (Spectralis; Heidelberg Engineering, Heidelberg, Germany; AF excitation λ , 488 nm; detection λ , >500 nm), and spectral-domain (SD) optical coherence tomography (OCT) imaging with both the Cirrus (Carl Zeiss Meditec, Inc., Dublin, CA) and Spectralis (Heidelberg Engineering) instruments.

The Cirrus SD OCT system was used to acquire 200 200 cubes centered at the fovea. From these datasets, one can generate en face OCT fundus images (OFIs) and en face OCT partial fundus images derived from a slab beneath the retinal pigment epithelium (sub-RPE slab).²² The OFIs represent virtual fundus images resulting from the en face summation of the reflected light from each A-scan.

The areas of GA observed in the OFI and the sub-RPE slab image were outlined manually by 2 independent graders (C.A.A.G.F., Z.Y.) at the Bascom Palmer Eye Institute using a CintiQ WACOM digitizing tablet (WACOM Corp., Vancouver, WA) and image analysis software (Adobe Photoshop CS2; Adobe Systems, Inc., San Jose, CA) as previously described.²³ A consensus image was used for measurements. In the cases in which the 2 graders could not reach an agreement on the outlines of the GA, a third senior grader (P.J.R.) outlined the lesion and his measurement was used for the analysis. The Topcon flash AF images were registered to the OFI using custom-built retinal image registration software based on the blood vessel ridges.²⁴ These registered flash-AF images, the confocal scanning laser ophthalmoscopy AF images, and the fluorescein angiography images were outlined manually by 2 certified graders at the Doheny Eye Institute Reading Center, and one consensus measurement was used for the analysis. The area measurements of GA underwent a square root transformation. This approach eliminated the influence of lesion size on test–retest variability and growth rates.²³ The growth of GA was defined as the difference of the square root of the area measurements at the suitable time points.

Choroidal imaging was performed with the Spectralis instrument (Heidelberg Engineering) and the enhanced depth imaging protocol. Two independent graders (Z.Y. and C.A.A.G.F.)

manually measured choroidal thickness at the foveal center, and a consensus image was used for quantitation.

Outcome Measures

The primary outcome of the study was to evaluate the effect of inhibiting C5 on the growth of GA in patients randomized to receive eculizumab treatment (including low-dose and high-dose regimens) versus placebo. The primary outcome was to be determined from the measurements of GA area obtained using SD OCT sub-RPE slab images. Growth rates were expressed as differences in the square root area measurements (in millimeters). Fellow eyes that met inclusion criteria were used for secondary outcome analysis. Secondary outcomes included the change in area of GA in study eyes measured with autofluorescence and fluorescein angiographic imaging; the change in area of GA in fellow eyes measured with SD OCT, AF, and fluorescein angiographic imaging; the change from baseline in normal-luminance and lowluminance ETDRS visual acuity in both study and fellow eyes; and conversion rate from dry AMD to wet AMD in both study and fellow eyes. Changes in renal function, C-reactive protein (CRP) levels, and complement protein levels were assessed as well.

Safety was assessed through the summary of ocular and nonocular adverse events, serious adverse events, ocular assessments, deaths, laboratory test results, and vital signs. Safety analyses included subjects who received at least 1 eculizumab infusion. Adverse events leading to discontinuation from the study were documented. After being enrolled, all subjects were vaccinated against *Neisseria meningitides*, and the first infusion was performed at least 2 weeks after the vaccination.

Statistical Analysis

Previous studies have demonstrated that taking the square root of area measurements before calculation of enlargement rates of GA removed the dependence of growth on baseline area and resulted in a homogeneous test–retest variance across the range of lesion sizes. Enlargement rates were compared between actively treated and placebo groups with the 2-sample *t* test. An ancillary analysis conducted with analysis of variance compared enlargement rates between eyes treated with placebo, a low-dose regimen, and a high-dose regimen. The primary study analysis included only 1 eye per patient; however, a secondary analysis included fellow eyes that would have been eligible for the study.

Sample Size Determination

The study was designed with 80% power to detect a 75% reduction in mean enlargement rate at 26 weeks based on previously published natural history data.²³

Pharmacokinetic and Complement Factors Analysis

During the study, blood samples for pharmacokinetic and complement factor screening were drawn and analyzed in a masked fashion at baseline and at every planned visit at weeks 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 38, and 52. Alexion Pharmaceuticals laboratory measured soluble C5b-9 and performed a hemolytic assay for C5 activity. Levels of factor H and C3 also were measured.

Renal Function and C-Reactive Protein Levels

Renal function, as assessed by serum creatinine levels and glomerular filtration rate, and CRP levels were evaluated at baseline and at weeks 26 and 52. Glomerular filtration rate and CRP were evaluated at baseline and at weeks 26 and 52.

Genetic Analysis

Genetic testing for 7 single nucleotide polymorphisms was performed in all patients as previously described,²⁵ and the prevalence of the following [alleles] was assessed: C5, rs17611 [G]; CFH, rs1061170 [C]; C3, rs2230199 [G]; CFH, rs2274700 [C]; HTRA1, rs10490924 [T]; CFB, rs641153-R32Q [G]; and C2, rs9332739-E318D [G].

Results

Baseline Characteristics

A total of 30 patients were enrolled in the study and were randomized 2:1 to receive eculizumab or placebo. The first 10 patients who received eculizumab received the low-dose regimen, and the next 10 patients received the high-dose regimen. Eighteen fellow eyes met inclusion criteria and were analyzed as a secondary endpoint. The mean age $\pm$ standard deviation was 79 ± 7 years in the eculizumab group and 81 ± 6 years in the placebo groups. The mean age of patients in the low-dose regimen was 79 ± 7 years and 80 ± 7 years for those receiving the high-dose regimen. For the 30 study eyes, the mean area at baseline in the eculizumab group was 7.3 ± 4.8 mm² and that in the placebo group was 4.6 ± 3.6 mm² ($P = 0.12$). On the square root scale, which was used to determine the growth of GA, the mean standard $\pm$ deviation area measurements were 2.55 ± 0.94 and 2.02 ± 0.74 mm the placebo groups, in eculizumab and respectively ($P = 0.13$). Low- and high-dose eculizumab groups had similar square root area measurements at baseline ($P = 0.44$). Mean visual acuity at baseline was 71.3 ± 7.8 EDTRS letters in the eculizumab group and 78.6 ± 5.2 letters in the placebo group ($P = 0.012$). The mean visual acuity in the high-dose group was 67.8 ± 7.4 EDTRS letters, 7 letters fewer than in the low-dose group, which was 74.8 ± 6.7 EDTRS letters ($P = 0.040$).

Primary Outcome: Enlargement Rate of Geographic Atrophy at 26 Weeks

All the patients completed 26 weeks of follow-up. Table 1 and Figure 1 show the growth at week 26 for the eculizumab and placebo groups. There was no difference between any of the groups. At 26 weeks, the mean changes in GA were 0.19 ± 0.12 and 0.18 ± 0.15 mm in the eculizumab and placebo groups, respectively ($P = 0.96$). This outcome ruled out a treatment-related reduction in the enlargement rate of 55% or more based on the 95% confidence interval of the difference in growth rates between active and placebo groups, which ranged from -0.10 to $+0.10$ mm. When we stratified the growth of GA according to the dose of eculizumab, there was no difference in growth rate, either (Table 1). The mean GA enlargement rates were not significantly different ($P = 0.40$), with the low-dose group having a change of 0.16 ± 0.07 mm and the high-dose group having a change of 0.21 ± 0.15 mm over 26 weeks (Table 1). As expected, there was no correlation between baseline lesion

size and enlargement rates using the square root area scale, either within treatment groups or with treatment groups combined (all $|r| < 0.4$; all $P > 0.29$).

Secondary Outcomes

Fellow Eyes at 26 Weeks. Eighteen fellow eyes met inclusion criteria to enter the study and were analyzed as a secondary end point (Fig 1; Table 1). Evaluation of the enlargement rate for 48 eyes (30 study eyes plus 18 fellow eyes) showed no difference ($P = 0.70$) between the eculizumab-treated group (mean, 0.17; standard deviation, 0.10) and the placebo group (mean, 0.16; standard deviation, 0.10) or between the low-dose eculizumab group (mean, 0.16; standard deviation, 0.06) and the high-dose eculizumab group (mean, 0.17; standard deviation, 0.13; $P = 0.82$).

52-Week Follow-up. Although the primary outcome was considered to be the enlargement rate at the 26-week visit, the patients were followed up through 52 weeks to determine if there was any delayed treatment effect. At 52 weeks, there was no difference between the enlargement rates of the study eyes in the eculizumab and placebo groups ($P = 0.93$). The annual enlargement rate was 0.37 ± 0.21 and 0.37 ± 0.22 in the eculizumab and placebo groups, respectively. Similarly, there was no difference between the low- and high-dose eculizumab groups ($P = 0.55$). Evaluation of the enlargement rate for all 48 eyes (30 study eyes and 18 fellow eyes) showed no difference at 52 weeks between the eculizumab and placebo groups ($P = 0.83$).

Comparison of enlargement in study eyes during the first 26 weeks with that during the following 26 weeks (weeks 26 to 52) did not find a change in enlargement rate between these periods ($P = 0.92$, repeated measures analysis of variance) nor an interaction between period and treatment group ($P = 0.97$, repeated measures analysis of variance). Changes in the size of GA from weeks 26 to 52 were 0.19 ± 0.11 mm in the eculizumab group and 0.18 ± 0.14 mm in the placebo group. Figure 2 and Figure 3 (available online at www.aaojournal.org) show examples of GA lesions that grew over the 52 weeks of follow-up. None of the eyes demonstrated macular neovascularization during the 52 weeks of follow-up.

Visual Acuity. Table 2 (available online at www.aaojournal.org) displays changes in ETDRS visual acuity in placebo and control groups at 26 and 52 weeks of follow-up. In the study eyes, the average change in ETDRS acuity in the placebo group at week 26 was -2.6 ± 7.2 compared with $+2.5 \pm 4.1$ in the eculizumab group ($P = 0.019$). The significance of this difference was largely the result of a single placebo eye that lost 22 letters of visual acuity when this eye's GA affected the fovea. At 52 weeks, the average change in ETDRS visual acuity in the placebo group was 2.9 ± 7.0 compared with 0.7 ± 7.2 in the eculizumab group ($P = 0.43$).

Low-Luminance Acuity Deficit. At 26 and 52 weeks, the enlargement of GA was not associated with either the baseline normal luminance ETDRS visual acuity letter score or the baseline low-luminance ETDRS visual acuity letter score (all $|r| < 0.18$; all $P > 0.23$), as presented in Figure 4. However, the baseline low-luminance visual acuity deficit, which is defined as the difference between the normal luminance letter score and the low-luminance

visual acuity letter score, was shown to correlate with the enlargement rate of GA over 52 weeks. A statistically significant association existed between the lowluminance visual acuity deficit at baseline and the enlargement rate of GA at 26 and 52 weeks (Pearson correlation for 26 weeks: $r = 0.38$, $P = 0.008$; Pearson correlation for 52 weeks: $r = 0.4$, $P = 0.004$).

Choroidal Thickness. No correlation was found between choroidal thickness and the baseline square root area of GA or the growth of GA at 26 and 52 weeks, with or without including fellow eyes in the analysis (all $P > 0.25$) as presented in Figure 5 (available at www.aajournal.org). After adjustment for age and axial length, there was modest correlation between choroidal thickness and square root baseline area (study eyes, $r = -0.37$, $P = 0.056$; study eyes and fellow eyes, $r = -0.34$, $P = 0.022$). After adjusting for age and axial length, baseline choroidal thickness was not correlated with growth of square root area at 26 weeks ($P > 0.10$) or 52 weeks (study eyes, $P = 0.12$; study eyes and fellow eyes, $P = 0.085$).

Genetic Analysis

There were no differences in baseline areas of GA and the number of copies of the at-risk alleles studied (Table 3, available at www.aajournal.org). All patients carried at least 1 at-risk allele. For the CFB rs641153 and C2 rs9332739 single nucleotide polymorphisms, all but 1 participant had 2 copies of the at-risk alleles. Moreover, there was no evidence of an effect of the number of at-risk alleles at a particular locus on the enlargement rate of GA and there was no evidence of an interaction between the total number of alleles on the enlargement rate of GA.

Pharmacokinetics

During the study, blood samples were collected to assay for eculizumab (enzyme-linked immunosorbent assay in micrograms per milliliter) and C5 activity. Among patients receiving eculizumab, all samples collected between onset of treatment and week 26 showed measurable levels of drug. Eculizumab levels rose rapidly during treatment weeks 1 to 4, with the low-dose cohort averaging 65 to 189 $\mu\text{g/ml}$ and the high-dose cohort averaging 122 to 259 $\mu\text{g/ml}$. Between weeks 6 and 26, eculizumab levels continued to increase minimally by 2 $\mu\text{g/ml}$ weekly in actively treated patients. On average, C5 activity decreased to less than 9% of normal levels by week 1 after treatment and to less than 1% by week 2. Among the patients receiving placebo injections, circulating levels of eculizumab were undetectable and C5 activity was normal.

Renal Function and C-Reactive Protein Levels

Renal function, as assessed by serum creatinine levels and glomerular filtration rate, and CRP levels were evaluated at baseline and through week 26. When all randomized treatment groups were compared, there were no differences in renal function and CRP levels at baseline and at week 26 (all $P > 0.1$). Baseline renal function (Pearson's $r = 0.11$ [$P = 0.58$], Spearman's $\rho = 0.02$ [$P = 0.90$]) and CRP levels (Pearson's $r = -0.05$ [$P = 0.80$], Spearman's $\rho = 0.12$ [$P = 0.54$]) did not correlate with disease progression.

Safety Outcome

Systemic complement inhibition with eculizumab was well tolerated through 52 weeks, and no drug-related adverse events were identified in the patients included in the study.

Discussion

The COMPLETE study was the first prospective, randomized, placebo-controlled investigation of complement inhibition for the treatment of AMD. This phase 2 clinical trial was performed to evaluate the clinical efficacy and safety of C5 inhibition using a systemically administered Food and Drug Administration–approved drug known as eculizumab. The study had an 80% power to detect a 75% reduction in the mean growth rate of GA over 26 weeks, and after 26 weeks we can say definitively that the treatment failed to meet this endpoint. Based on the 95% confidence interval of the difference in growth rates between active and placebo groups, we effectively can rule out a treatment effect of 55% or more for the slowing of the GA enlargement rate. Moreover, there was no apparent treatment effect when comparing the low-dose eculizumab regimen and high-dose regimen. However, we did detect a statistically significant correlation between the low-luminance deficit at baseline and the progression of GA over 6 months. Previously, Sunness et al²¹ reported that low-luminance visual acuity deficits were correlated with the loss of visual acuity over 2 years. If we assume that the growth of GA eventually results in the loss of visual acuity over 2 years, then our results support their findings and demonstrate that this lowluminance visual acuity deficit correlates with the short-term expansion of GA. Moreover, our results suggest that the low-luminance deficit, a simple test of visual function, can detect central photoreceptor dysfunction even before the edge of GA extends through the foveal center and that this dysfunction correlates with the growth rate of GA. In clinical trials, this may serve as a useful way of identifying and stratifying eyes into groups at baseline that are more likely to progress. It is entirely possible that an experimental drug may have a different onset of action in eyes in which the GA is more likely to progress rapidly compared with the effect the drug might have in eyes that are progressing more slowly. Unfortunately, the COMPLETE study was powered inadequately to perform the type of subgroup analysis to detect such a differential treatment effect if one existed. However, we suggest that low-luminance deficit testing should be used in all future clinical trials of dry AMD.

Although our study may have been too small to detect a treatment effect that reduced the growth rate of GA to 55% or less of the normal growth rate, it is also possible that the drug had no effect on the growth rate because complement activation has no role in the growth of GA. We showed that there was no association between the number of at-risk genetic alleles and the growth of GA, and this result is consistent with recent publications showing no association between the progression rates of GA and these same at-risk alleles.^{26,27} Although the genetics of AMD suggest a role for complement in the pathogenesis of AMD, it is entirely possible that complement plays a role in the earlier stages of the disease, rather than in the progression of GA, which is classified as an advanced form of AMD.²⁸

Other possible explanations for the lack of a treatment effect could be that the dose of eculizumab was too low or the drug should have been delivered as a direct intravitreal

injection to achieve an adequate level of drug in the retina or the RPE. If complement inhibition was needed in the choroid to stop the growth of GA, then the dose of eculizumab should have been adequate; however, if the complement inhibition was needed in the eye, then the amount of drug delivered systemically was probably inadequate to penetrate the RPE. The rationale for using a systemic drug was based on the belief that complement activation in the choroid played an important role in the progression of dry AMD. Moreover, eculizumab already has been approved for systemic delivery, so systemic delivery of eculizumab was possible without additional safety studies. In contrast, the use of intravitreal eculizumab would have required extensive animal testing and a human, phase 1, dose-escalation safety study. Moreover, systemic delivery had certain advantages over frequent monthly injections of a drug into the eye. Because AMD is a bilateral disease, systemic therapy would be able to deliver the drug to both eyes with a single infusion. Based on previous studies of patients with paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome, we also knew that these dosing regimens of eculizumab achieved drug concentrations of more than 35 µg/ml in the peripheral blood, and at this concentration, systemic complement C5 is completely inhibited.^{18,29,30} This was confirmed by the pharmacokinetic studies of our patients who received the drug. In particular, C5 activity decreased to less than 1% of the pretreatment average by week 2, demonstrating that therapeutic blood levels were reached and inhibition of C5 activity was achieved. Of note, the drug has systemic risks, most notably meningococcal meningitis, which can be prevented with the use of the meningococcal vaccine. However, now that this systemic approach has failed to show a dramatic treatment effect in our study, it is entirely possible that an intravitreal dosing strategy with eculizumab might have resulted in a different outcome.

Another possible explanation for why systemic C5 inhibition failed to show a treatment effect could be that C5 was the wrong complement target. C5 inhibition prevents only terminal complement activation, and by preserving more proximal complement function, such as production of C3a anaphylotoxin and C3b, complement-mediated damage could have continued. After all, polymorphisms in C3 have been associated with AMD, whereas there is no clear association between genetic variants in the C5 gene and AMD.^{11,31,32}

Two additional shortcomings of the study include the small sample size and its short duration. The sample size shortcoming would be even more of an issue if eculizumab was effective only in the smaller genetic subgroup of patients, such as the patients carrying the at-risk alleles in the CFH locus. In addition, it is possible that there may be a lag in the onset of a treatment effect, so studies would need to be run for at least 2 years to appreciate a treatment effect. However, this exploratory study was designed as a pilot investigation to determine if systemic therapy showed any suggestion of a treatment benefit. Based on the linearity of the growth rates and the lack of any suggestion of a treatment effect, it is unlikely that further systemic investigations with this drug will be undertaken to determine whether a smaller treatment effect could be observed because of the cost and the intensity of the treatment regimen.

It is possible that a different endpoint might have shown a treatment effect. Such an endpoint could be the ability of a treatment to decrease the conversion rates from dry to wet

AMD or the effect of the drug on the GA margins. These kinds of endpoint would require many more patients and a longer study duration. We chose lesion growth rate as the outcome variable for this trial because our goal was to use a Food and Drug Administration–approved endpoint to serve as a surrogate for the preservation of visual acuity, and the Food and Drug Administration agreed with our choice. Lesion area is a straightforward measurement that can be obtained with commercially available OCT software and can be performed easily with current imaging techniques. If we had demonstrated an effect of eculizumab on GA growth, that would have justified a large phase 3 study with acuity preservation as an outcome variable. In such a study, the imbalance in acuity we saw between our small randomized groups could have confounded interpretation; however, in the current study, with lesion growth as the outcome, it is immaterial. In addition to SD OCT measurements, we also assessed lesion area growth with Heidelberg and Topcon AF imaging and fluorescein angiography. These other methods did not suggest a different conclusion; however, presenting these data is outside the scope of this article and is the subject of one currently in preparation.

In summary, C5 inhibition with systemic eculizumab did not slow the growth rate of GA in the COMPLETE study. However, we did detect a statistically significant correlation between the low-luminance visual acuity deficit at baseline and the progression of GA over 6 months. Ongoing clinical trials using other intravitreal drugs that target C5 and factor D will determine whether complement inhibition for the treatment of GA is a viable treatment strategy in AMD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Graphs showing the growth of geographic atrophy over 52 weeks in patients receiving the eculizumab versus placebo. Outcomes (A and C) for the study eyes and (B and D) the pooled study eyes and fellow eyes, outcomes for (A and B) the placebo and all the active treatment arms, outcomes for (C and D) the low-dose and high-dose treatment arms, as well as the placebo arms, for study eyes and fellow eyes that met inclusion criteria.

Figure 2.

Images from the left eye of a 73-year-old woman included in the low-dose group with growth in the area of geographic atrophy over 52 weeks. (A,D,G) Color fundus images obtained at baseline, 26 weeks, and 52 weeks, respectively. (B,E,H) Fundus autofluorescence images (Heidelberg Spectralis) obtained at baseline, 26 weeks, and 52 weeks, respectively. (C,F,I) Sub-retinal pigment epithelium slab en face image generated from spectral-domain optical coherence tomography datasets (Zeiss Cirrus) at baseline, 26

weeks, and 52 weeks, respectively. Area measurements were (C) 8.26 mm² at baseline, (F) 9.47 mm² at 26 weeks, and (I) 10.88 mm² at 52 weeks.

Figure 4.

Graph showing the relationship between low-luminance visual acuity deficit at baseline and growth of the square root of the area of geographic atrophy over (A) 26 weeks and (B) 52 weeks. Both study eyes (30 eyes) and fellow eyes (18 eyes) that met inclusion criteria are shown. For 26 weeks, $r = 0.38$ and $P = 0.008$; for 52 weeks, $r = 0.41$ and $P = 0.004$.

Table 1

Mean (Standard Deviation) Geographic Atrophy Enlargement (in Millimeters) by Treatment Group and Length of Follow-up

Follow-up (wks)	Study Eyes				Study and Fellow Eyes			
	Only Eyes Randomized to Active Treatment				Only Eyes Randomized to Active Treatment			
	Placebo (n = 10)	Active (n = 20)	P Value *	Low Dose (n = 10)	High Dose (n = 10)	P Value *	Placebo (n = 16)	Active (n = 32)
26	0.18 (0.15)	0.19 (0.12)	0.96	0.16 (0.07)	0.21 (0.15)	0.40	0.16 (0.13)	0.17 (0.10)
52	0.37 (0.22)	0.37 (0.21)	0.93	0.35 (0.10)	0.40 (0.28)	0.55	0.32 (0.20)	0.33 (0.18)
							Low Dose (n = 15)	High Dose (n = 17)
							0.16 (0.06)	0.17 (0.13)
							0.33 (0.09)	0.33 (0.23)
								P Value *
								0.70
								0.72
								0.82
								0.95

* Two-sample *t* test.