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Treatment of Geographic Atrophy with Intravitreal Sirolimus

The Age-Related Eye Disease Study 2 Ancillary Study

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Purpose: To evaluate the efficacy and safety of sirolimus, an immunosuppressive drug, for the treatment of age-related macular degeneration (AMD)–associated geographic atrophy (GA).

Design: Randomized, controlled, single-masked multicenter phase II clinical trial of intravitreal sirolimus versus sham therapy in Age-Related Eye Disease Study 2 (AREDS2) clinical centers.

Participants: Patients with GA.

Methods: Participants were assigned randomly to a monthly intravitreal injection of sirolimus (20 μL [440 μg]) or sham treatment. Best-corrected visual acuity (BVCA), spectral-domain OCT, fundus color photography, and fundus autofluorescence (FAF) images were obtained at baseline and every 6 months until visit month 24.

Main Outcome Measures: Rate of progression of GA (square millimeters per year) measured on color fundus photographs from baseline to 24 months. Secondary outcome measures include change in BVCA, worsening of vision by 3 lines or more, and changes in area of GA measured on FAF and OCT.

Results: Fifty-two participants (mean age, 79 years) were enrolled, with 27 study eyes assigned to sirolimus from May 2012 through March 2014. The baseline median area of GA was 4.73 disc areas (DA; 12.01 mm^2). The mean growth rates of GA detected on color fundus photographs were 2.27 mm^2 (standard deviation [SD], 2.17 mm^2) and 1.91 mm^2 (SD, 2.27 mm^2) at month 12 and 4.94 mm^2 (SD, 2.96 mm^2) and 5.72 mm^2 (SD, 3.97 mm^2) at month 24 for the sirolimus and sham groups, respectively. There was no statistically significant difference in the GA growth rates between the 2 treatment groups ($P = 0.33$). Median visual acuity changes and incidence of 15-letter loss from baseline were not different between the 2 treatment groups ($P = 0.19$). The intervention was stopped early because of sterile endophthalmitis that occurred in 3 participants in the sirolimus group. Participants were followed up for safety until the study was closed in May 2015 because of lack of efficacy.

Conclusions: Sirolimus did not result in different rates of GA growth in this phase II study. Immunosuppression may be important for some stages of the AMD process, but may not necessarily be the main pathway for the development of GA. *Ophthalmology Retina 2017;■:1–10 Published by Elsevier 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] and the developed world. Geographic atrophy (GA) associated with AMD is 1 of the 2 forms of late AMD characterized often by the development and regression of large drusen, followed by the progressive loss of the outer retinal layers and the retinal pigment epithelium (RPE).[2] This process may start at the center of the macula (the fovea) or eventually involve the fovea, leading to central visual loss. Geographic atrophy accounts for approximately 80% of all cases of late AMD. There is no proven effective therapy for preventing the onset or retarding the progression of GA, despite numerous agents tested previously. This remains an unmet medical need as the number of individuals affected with AMD is predicted to double by 2020 from numbers estimated in 2004 to be 1.75 million with late AMD.[3]

Although the pathogenesis of AMD is unknown, several pathways have been hypothesized as potentially causal, including chronic inflammation.[4–6] Genetic association studies implicate the complement pathway of the immune system in the pathogenesis of late AMD, including GA.[7–9] Dysregulated expression of the complement regulatory proteins as well as the presence of activated microglia[10] and macrophages[11] in the outer retina in eyes with AMD are demonstrated in histopathologic studies. Immunoglobins,

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activated complement factors, and activated microglia also are found in large drusen, the precursors to GA.[12–14] These findings suggest that agents that reduce immune responses may be reasonable to test for the treatment of GA. One such agent is sirolimus, an immunosuppressive drug.[15] It is known as an inhibitor of the mammalian target of rapamycin, a multifunctional serine-threonine kinase. The inhibition of mammalian target of rapamycin can result in a variety of changes in cellular function, including cell survival, growth, and proliferation.[16] Mammalian target of rapamycin inhibition also results in immunosuppression as T-cell and B-cell proliferation and antibody production are markedly suppressed.[17] In a study of mice that had postnatal ablation of RPE mitochondrial oxidative phosphorylation, there was gradual dedifferentiation of the RPE that lead to photoreceptor degeneration and reduced electrical responses of the retina to light.[18] Administration of sirolimus (or rapamycin) reduced the RPE dedifferentiation and preserved the photoreceptors. Inhibition of the mammalian target of the rapamycin pathway may be a potential therapy for degenerative diseases of the RPE such as GA associated with AMD.

Sirolimus is approved by United States Food and Drug Administration as an immunosuppressive drug after renal transplantation[19] and after stent placement for balloon angioplasty.[20] A proprietary formulation of a nonaqueous solution of sirolimus has been tested for ocular diseases including diabetic retinopathy,[21] GA,[22,23] and uveitis.[24] After success in phase I and II trials for noninfectious uveitis,[25] sirolimus currently is being evaluated in a phase III trial. In this study, we report the results of a multicenter randomized controlled clinical trial of sirolimus for the treatment of GA conducted as an ancillary study of the Age-Related Eye Disease Study 2 (AREDS2).

Methods

This was an ancillary study of a National Institutes of Health–supported study, the AREDS2, a clinical trial of oral supplements of omega-3 long-chain polyunsaturated fatty acids and lutein plus zeaxanthin for the treatment of AMD.[26] This ancillary study was a multicenter, randomized, single-masked phase II clinical trial conducted in 13 AREDS2 clinical centers. This AREDS2 ancillary study of sirolimus for GA was reviewed and approved by each of the institutional review boards and written informed consent was obtained from all participants. The research was conducted according to the tenets of the Declaration of Helsinki and in compliance with the Health Insurance Portability and Accountability Act. This study was registered at clinicaltrials.gov (identifier, NCT01675947).

To be eligible, AREDS2 participants had to be at least 55 years of age or older with sufficiently clear media for quality fundus photography and had to have GA area between 0.75 and 8 disc areas (DA) in at least 1 eye. As part of the AREDS2 ancillary study, the GA initially had to involve the center of the fovea and had to demonstrate a progression rate of at least 2 mm^2/year, as determined by the AREDS2 reading center. We began enrollment in September 2012. In 2013, when AREDS2 terminated and to increase the pace of recruitment, non-AREDS2 participants with GA not involving the center of the fovea were recruited. These non-AREDS2 participants did not have consistent previous fundus photographs to measure the progression rate of GA.

Exclusion criteria included those unlikely to comply with study procedures, follow-up visits, or both and those who had a poor 2-year survival prognosis. Presence of confounding ocular diseases such as glaucoma, significant diabetic retinopathy, uveitis, high myopia, and neovascular AMD requiring therapies such as macular laser photocoagulation, photodynamic therapy, anti–vascular endothelial growth factor (VEGF) agents, and other therapies also rendered the eye ineligible. Prior surgery with vitrectomy ever or cataract surgery or yttrium–aluminum–garnet capsulotomy within the previous 3 months also rendered the patient ineligible.

Participants eligible in 1 eye were assigned randomly either to intravitreal injection of sirolimus (20 μL [440 μg]) or a sham treatment consisting of subconjunctival injection of lidocaine. Participants with both eyes eligible were assigned intravitreal injection of sirolimus in 1 randomly selected eye and sham treatment in the fellow eye. Treatments were scheduled monthly for 24 months. Standardized study procedures, including best-corrected visual acuity (BCVA), stereoscopic color fundus photography, fundus autofluorescence (FAF) images, and spectral-domain OCT, were performed at baseline and every 6 months after enrollment for the 24-month duration of the study. For safety, BCVA also was measured at the month 2 and 3 study visits and FAF also was added to the month 2 visit.

The imaging was conducted at each clinical site on equipment that was certified by the reading center. Spectral-domain OCT images were acquired by either using a Spectralis (Heidelberg Engineering, Heidelberg, Germany) or Cirrus (Zeiss Meditec, Dublin, CA) device according to reading center protocols. The FAF images were acquired with either blue light scanning laser ophthalmoscopy (Spectralis, Franklin, MA) or optical camera flash photography using the manufacturer's supplied autofluorescence filters with green light (Zeiss, Topcon, Oakland, NJ).

The study medication (DE-109), a proprietary formulation of a nonaqueous solution of sirolimus, in a vehicle composed of polyethylene glycol 400 and 4% ethanol (200 proof), was provided as a clear solution by the company (Santen Pharmaceutical Co., Ltd., Osaka, Japan) for the study as a frozen 0.5-mL sterile injectable solution. The dose of 440 μg was chosen based on prior studies that evaluated other doses. This dose was considered to be safe and bioavailable. The medication was thawed immediately before injection and drawn into a 0.3-mL syringe (Becton Dickinson, Frankling Lakes, NJ) with a 30-gauge, 0.5-inch-long needle. A 20-μL volume (440-μg) injection was given intravitreally after topical anesthesia with 0.5% proparacaine and topical povidone–iodine. Similar preparation of the injection site was performed on the sham treatment group, but subconjunctival injection of lidocaine was given instead of the intravitreal injection.

Investigators who were administering the therapies were not masked to the treatment assignment. The research team, including those obtaining BCVA, ocular images, and OCT, was masked to the treatment group allocation. The certified graders at the fundus photograph reading center also were masked to the treatment assignment, and they determined the primary outcome for this study, namely the measurement of the area of GA as documented by fundus photographs over the course of the study.

Outcome Measurements

The primary outcome was the rate of change from baseline over time (24 months) in the area of GA based on masked gradings of the digital color fundus photographs using manual computer planimetry by certified graders at a centralized fundus photography reading center. Secondary outcomes include change in BCVA, worsening of BCVA of 3 lines or more (15 letters or more) compared with baseline, change in area of GA as measured on FAF, change in central subfoveal thickness measured on OCT, and