Treatment of Geographic Atrophy by the Topical Administration of OT-551: Results of a Phase II Clinical Trial

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PURPOSE. To investigate the safety and preliminary efficacy of OT-551, a disubstituted hydroxylamine with antioxidant properties, for the treatment of geographic atrophy (GA), the advanced atrophic form of age-related macular degeneration (AMD).

METHODS. The study was a single-center, open-label phase II trial, enrolling 10 participants with bilateral GA. Topical 0.45% OT-551 was administered in one randomly assigned eye three times daily for 2 years. Safety measures were assessed by complete ophthalmic examination, fundus photography, and review of symptoms. The primary efficacy outcome measure was the change in best corrected visual acuity at 24 months. Secondary efficacy measures included changes in area of GA, contrast sensitivity, microperimetry measurements, and total drusen area from baseline.

RESULTS. Study drug was well tolerated and was associated with few adverse events. The mean change in BCVA at 2 years was $+0.2 \pm 13.3$ letters in the study eyes and -11.3 ± 7.6 letters in fellow eyes ($P = 0.0259$). However, no statistically significant differences were found between the study and fellow eyes for all other secondary outcome measures.

CONCLUSIONS. OT-551 was well tolerated by study participants and was not associated with any serious adverse effects. Efficacy measurements in this small study indicate a possible effect in maintaining visual acuity. However, the absence of significant effects on other outcomes measures in this study suggests that OT-551, in the current concentration and mode of delivery, may have limited or no benefit as a treatment for GA (ClinicalTrials.gov number, NCT00306488). (*Invest Ophthalmol Vis Sci.* 2010;51:6131–6139) DOI:10.1167/iov.10-5637

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Geographic atrophy (GA) is the advanced atrophic form of age-related macular degeneration (AMD) that increases in prevalence with age^{1–3} and results in progressive moderate and severe visual loss over time.⁴ GA is characterized anatomically by the development and progressive enlargement of areas of retinal atrophy that extend through the outer neuroretina, retinal pigment epithelium (RPE), and choroid,^{5,6} effectively depriving affected areas of light sensitivity.⁷ There is currently no treatment that has been demonstrated to effectively prevent the onset of GA⁸ or to retard lesion enlargement and/or vision loss.^{9,10} Given the size and significance of this unmet need, clinical trials that further our knowledge of investigational methods and therapeutic strategies are of public health significance.

Although the pathogenic mechanisms underlying GA are largely unknown, oxidative stress, associated also with aging¹¹ and smoking,¹² has been implicated as a potential etiologic factor.^{13,14} In this purported mechanism, reactive oxygen species in the retina exert cumulative cellular damage, leading to eventual retinal and retinal pigment epithelial cell atrophy and death. The presence of oxidized lipids in drusen^{15,16} and the deleterious effects associated with oxidized derivatives of retinal molecules^{17,18} suggest the etiologic relevance of oxidative stress and indicate a possible benefit in reducing free radicals in the AMD retina.¹³ Piperidine nitroxides, exemplified by compounds such as Tempol, are capable of reacting directly with free radicals and exert potential antioxidant effects.^{19–21} This information provided a scientific rationale to investigate the therapeutic significance of OT-551, a disubstituted hydroxylamine compound that is converted to the piperidine Tempol-H, for the treatment of GA. Tempol-H has been reported to protect RPE cells from oxidative damage in vitro²² and photoreceptors from acute light-induced damage in experimental animals.²³

The main objective of the present pilot study was to determine the safety and efficacy of topical OT-551 in the treatment of bilateral GA. Other objectives of the study were to develop and evaluate anatomic and functional outcome measures for the interventional studies of GA, in a unilateral treatment study design.²⁴

METHODS

Study Design

This single-center, open-label, phase II study of OT-551 (0.45% eye drop) was conducted at the National Eye Institute (NEI), National Institutes of Health (NIH) in participants with bilateral GA. The research was supported by the Intramural Research Program of the Division of Epidemiology and Clinical Applications, NEI (contract N01-EY-7-0001). The study protocol and informed consent forms were

reviewed and approved by an institutional review board and an investigational new drug application number (66882; Othera Pharmaceuticals, Inc., West Conshohocken, PA) was obtained from the U.S. Food and Drug Administration (FDA) for the study. An independent data and safety monitoring committee provided study oversight. The study adhered to the tenets of the Declaration of Helsinki.

Study Medication

OT-551, synthesized by Othera Pharmaceuticals, is a lipophilic, disubstituted hydroxylamine that, when administered as an eye drop, may be able to access the retina by passage through the cornea and subsequent diffusion through aqueous and vitreous humors and/or by passage via a scleral route. Nonclinical pharmacokinetic studies (Othera Pharmaceuticals, Investigator's Brochure, unpublished data, 2005) have indicated that OT-551 is converted by intraocular esterases to its active metabolite, Tempol-H (TP-H). OT-551 and TP-H both contain active hydroxylamine groups, and can interact, directly or indirectly, with the free radicals within the eye, terminating free radical reactions and exerting antioxidant effects. The pharmacologic activity of this investigational agent is thought to relate to its ability to limit the oxidative damage implicated in the pathogenesis of AMD.^{17,25}

Study Population

Eligible participants were at least 60 years old and had a diagnosis of bilateral GA related to AMD. The primary eligibility criteria were (1) an area of GA in each eye that was not contiguous with areas of peripapillary atrophy and (2) the absence of evidence or history of exudative forms of AMD. A complete listing of inclusion and exclusion criteria is found in Table 1.

Eligibility for participation was determined during a screening and a baseline visit to the clinic. Clinical evaluation included a brief physical examination, an ophthalmic history assessment, measurement of visual acuity and intraocular pressure, dilated fundus examination, and fundus photography. After suitable participants were identified and informed consent obtained for participation, the investigator assessed tol-

erability to the study medication by placing a drop in each eye and assessing the subjective participant response and clinical evaluation 15 minutes after drop instillation. Enrollment in the study would be considered if the participant reported good subjective tolerance and displayed no signs of an allergic response (prominent conjunctival redness or swelling, periocular swelling or excessive tearing). All assessed participants ($n = 11$) tolerated the study medication well and were enrolled in the study.

Study Objectives

The overall study objective was to provide pilot data on the 2-year effects of the study medication on visual function and the progression of GA. The primary objectives were to establish the ocular and systemic safety of the investigational agent and to investigate the effect of the study medication on changes in best corrected visual acuity. The secondary objectives were to evaluate the effect of the study medication on the following: (1) the change in area of GA as evaluated by the grading of digital color fundus photographs (CFPs) and fundus autofluorescence (FAF) images, (2) the progression to neovascular AMD, (3) change in drusen area as measured on fundus photography, (4) change in contrast sensitivity, and (5) change in perimetric assessment as measured by a microperimeter (MP-1; Nidek, Gamagori, Japan).

Study Design

One eye in each participant was randomly assigned to receive the study medication (referred to hereafter as the study eye). The contralateral eye (referred to hereafter as the fellow eye) was assigned to observation. Participants were instructed to place 1 drop (40 μ L) of study medication into the study eye three times daily for the duration of the study and to refrain from placing any medication into the fellow eye. The rationale for monocular treatment in a setting of bilateral disease was based on the observed correlation in the rate of GA enlargement between fellow eyes of patients with bilateral GA.²⁶ In this monocular treatment study, the fellow eye provided a control for the study eye. Participants were instructed to take the study medica-

TABLE 1. Eligibility and Exclusion Criteria

Subject-level inclusion criteria	
Age ≥ 60 years	
Clinical diagnosis of advanced atrophic age-related macular degeneration	
Able to understand and sign protocol's informed consent document	
Ability to administer study eye drops or has a caretaker who can administer treatment	
Subject-level exclusion criteria	
Inability to undergo study procedures or attend follow-up visits	
Enrollment in another investigational study and actively receiving study therapy	
Female participants of child-bearing potential who are lactating or who are not using birth control	
Actively receiving chemotherapy treatment	
History of malignancy that would compromise the 2-year study survival	
History of or demonstration of allergy to benzalkonium chloride	
Present use of ocular or systemic medications known to be toxic to the lens, retina, or optic nerve	
Ocular inclusion criteria (to be fulfilled by both eyes)	
Geographic atrophy present in both eyes	
Area of GA can be imaged in its entirety and is not contiguous with any areas of peripapillary atrophy	
Able to maintain steady fixation in the foveal or parafoveal area	
Adequate media clarity for quality fundus photographs	
Ocular exclusion criteria (applies to either eye)	
History of other ocular disease that can confound the outcome of the study (e.g., diabetic retinopathy, uveitis)	
Chronic requirement for ocular medications for diseases that may affect the outcome of the study	
Evidence of pseudovitelliform macular degeneration	
Evidence of vitreoretinal traction maculopathy	
History of laser, photodynamic therapy (PDT)	
History of intravitreal injection of any agent (e.g., anti-VEGF, triamcinolone)	
History of any previous treatment for AMD other than AREDS or equivalent supplement formulation	
History of vitrectomy, penetrating keratoplasty, trabeculectomy, or trabeculoplasty	
History of ocular herpes simplex virus	
Surgical lens removal (cataract extraction) in the previous 3 months	

tion over a minimum period of 24 months. After the 24-month time point, participants would be given the option of stopping the study medication or continuing treatment in the study eye until a common termination date. Participants would undergo an additional final safety visit 1 month after the cessation of the study medication.

Participants were examined in the clinic every 3 months between baseline and 12 months and every 6 months thereafter. The ETDRS method was used to measure best corrected visual acuity (BCVA) at 4 m at baseline and every 6 months thereafter. A standardized manifest refraction was performed at baseline and 1 and 2 years, as well as any other study visits when VA testing revealed a ≥ 10 -letter decrease from baseline values. A review of ocular and systemic symptoms or adverse events was conducted at each visit. An ophthalmoscopic examination (comprising applanation tonometry, a dilated slit lamp examination, and indirect ophthalmoscopy) was conducted at each visit, and ocular changes, not consistent with the natural history of GA, were recorded. Progression to advanced neovascular AMD was also assessed by ophthalmic examination. In cases in which exudative activity was suspected, ancillary testing with fluorescein angiography and/or optical coherence tomography was performed. Laboratory evaluations, including serum chemistry, hematology, urinalysis, and urine chemistry were performed at baseline and at yearly intervals. All untoward medical occurrences were recorded as adverse events, regardless of their relation to the study medication.

Examination Procedures

The following examination procedures were performed in both the study and fellow eyes between baseline and 12 months and at every 6-month visit thereafter: (1) stereoscopic CFPs, (2) FAF imaging with a confocal scanning ophthalmoscope (HRA FAF; HRA2; Heidelberg Engineering, Vista, CA), and (3) microperimetry (MP-1 microperimeter, Nidek). Contrast sensitivity measurement with a Pelli-Robson chart was performed at baseline and at 12 and 24 months.

CFPs and HRA FAF images were sent to the Doheny Image Reading Center at the University of Southern California for digital manual grading by masked graders. The area of GA and the total area of drusen in field 2 (30° photographic field centered on the fovea) were determined by planimetry from color stereoscopic fundus images. For drusen area quantification, borders of all drusen were manually delineated by graders. FAF images were graded according to a standardized protocol, by scoring the areas of decreased, increased, and abnormal FAF in the macula. The location of GA was scored on FAF images as (1) subfoveal, (2) probably subfoveal, or (3) not subfoveal and the distance of the nearest GA boundary to the foveal center was measured. Color and FAF images were graded and quantified independently. Microperimetry was performed with a 68-loci circular grid centered on the center of the macula covering the central 20° field (10-2 program). The Goldmann III test stimulus of 200-ms duration was used and the evaluation conducted by using

TABLE 2. Baseline Demographic and Ocular Data for Participants Completing 24 Months of Follow-up

Number of participants	10
Age, y, mean $\pm$ SD (range)	76.8 $\pm$ 8.27 (65–88)
Sex, female, <i>n</i> (%)	6 (60)
Race, white, <i>n</i> (%)	10 (100)
Assignment of study eye, right <i>n</i> (%)	4 (40)
Lens status of study eye, pseudophakic, <i>n</i> (%)	
Study eye	4 (40)
Fellow eye	4 (40)
Baseline best-corrected visual acuity, letters, mean $\pm$ SD (range)	
Study eye	46.1 $\pm$ 20.8 (9–71)
Fellow eye	57.1 $\pm$ 12.0 (40–79)
Contrast sensitivity, log values, mean $\pm$ SD (range)	
Study eye	0.9 $\pm$ 0.339 (0.3–1.35)
Fellow eye	1.04 $\pm$ 0.180 (0.75–1.35)
Location of geographic atrophy lesion	
Subfoveal (involving center of fovea)	16 eyes of 8 participants
Nonsubfoveal (not involving center of fovea)	4 eyes of 2 participants
Mean distance of lesion to center of fovea (nonsubfoveal lesions only), mm	
Study eye, <i>n</i> = 2	0.36
Fellow eye, <i>n</i> = 2	0.26
Area of GA (measured from fundus photography), mm ² , mean $\pm$ SD (range)	
Study eye	6.87 $\pm$ 3.35 (1–13.5)
Fellow eye	6.80 $\pm$ 3.28 (3.44–13.8)
Measured from HRA autofluorescence imaging, mm ² , mean $\pm$ SD (range)	
Study eye	7.15 $\pm$ 3.16 (1.03–13.4)
Fellow eye	7.01 $\pm$ 3.47 (3.54–14.5)
Mean total drusen area, mm ² , mean $\pm$ SD (range)	
Study eye	0.454 $\pm$ 0.476 (0.05–1.5)
Fellow eye	0.415 $\pm$ 0.445 (0.07–1.61)
Microperimetry measurements, number of scotomatous points (i.e., sensitivity, <0 dB)	
Study eye	34.1 $\pm$ 12.8 (22–62)
Fellow eye	32 $\pm$ 17.1 (13–61)
Mean overall sensitivity of all points, dB, mean $\pm$ SD (range)	
Study eye	4.62 $\pm$ 2.72 (0.265–8.62)
Fellow eye	5.10 $\pm$ 3.65 (0.441–11.2)
Mean overall sensitivity of nonscotomatous points, dB, mean $\pm$ SD (range)	
Study eye	8.44 $\pm$ 3.80 (3–14)
Fellow eye	8.65 $\pm$ 3.46 (4.29–15)

a 4-to-2 staircase strategy. The following test parameters were tallied: (1) number of scotomatous loci (loci with sensitivity of <0 dB), and (2) macular mean sensitivity (dB).

Statistical Analysis

Commercial software (Prism, ver. 5.0; GraphPad, La Jolla, CA) was used to calculate summary statistics (mean and SD or SEM) for demographic, visual acuity, fundus image data, and microperimetry performance data. Paired *t*-tests were used to compare these parameters between study and fellow eyes. Correlations between study and fellow eyes and between HRA FAF and CFP imaging modalities were computed with the Spearman correlation coefficient. All *P* values are two-tailed; *P* < 0.05 denoted statistical significance.

RESULTS

Baseline Patient Demographics and Ocular Characteristics

Between December 12, 2006, and October 17, 2007, 11 participants were enrolled in the study. Of these, 10 completed at least 24 months of follow-up, and 1 (participant P6) was lost to follow-up after 3 months. Enrollment was closed after the original target of 10 evaluable participants was met. Treatment effect outcomes are limited to the 10 participants completing the 2-year follow-up. The analysis of safety data includes all 11 enrolled participants. Table 2 summarizes the baseline demographic and ocular information of the 10 participants who completed the follow-up. Statistical analyses (paired *t*-tests) did not reveal any significant differences at baseline between the study and fellow eyes for all the ocular parameters examined (*P* > 0.05 for all comparisons). GA area at baseline, as measured on CFPs and HRA FAF images, correlated highly between the eyes (Spearman *r* = 0.903 for CFPs and 0.915 for FAF images; *P* < 0.005 ; Figs. 1A, 1B, respectively). However, the visual acuities of the study and fellow eyes at baseline did not demonstrate a similar high correlation (Spearman *r* = -0.092 , *P* = 0.811; Fig. 1C).

Ocular and Systemic Safety of the Investigational Agent

No serious adverse events were noted in the 11 participants. A total of 36 adverse events were recorded during the study, all of which were either mild or moderate in severity, and the majority (32/36) were judged to be either not related to or remotely related to the study treatment. The study drug was withheld for a period in four participants during the following occurrences: a hip injury, blurry vision and thrush, a sore eye and decreased visual acuity, and shingles. One participant declined to return after 3 months of study treatment and was lost to follow-up. All the remaining 10 participants who were observed up to the 2-year time point reported compliance with the thrice-daily monocular application of the study drug. Adverse events and severity are summarized by category in Table 3.

Ocular adverse events constituted about one third of all events (15/36) and are listed for study and fellow eyes in Table 4. In four participants, episodes of small subretinal and intraretinal hemorrhages were noted in the peripapillary region. In one participant, the episodes recurred twice in the same eye. Of all five episodes, four occurred in the study eye and one in the fellow eye. All episodes were asymptomatic and were typically present for 3 to 6 months before resolving. These were judged not to be related to the formation of choroidal neovascularization and resembled the asymptomatic peripapillary hemorrhages previously described.²⁷

FIGURE 1. Baseline GA lesion area and visual acuity in the study and fellow eyes. Baseline GA areas, as measured on CFPs (A) and HRA FAF (B) correlated positively between the study and fellow eyes. Baseline visual acuity in the study and fellow eyes did not show a similar correlation (C).

Effect of Study Treatment on Visual Acuity

The primary objective of the study was to investigate the effect of the study medication on changes in BCVA. Figure 2A shows the overall change in visual acuity in the study and fellow eyes from baseline for all 10 participants at the 2-year (104-week) time point. Eight of 10 participants lost fewer letters or gained more letters in the study eye compared with the fellow eye. Figure 2B shows the mean change in BCVA from baseline (in ETDRS letters) at weeks 24, 52, 76, and 104. At the 104-week time point, the mean BCVA in the study eyes increased by 0.2 ± 13.3 letters, whereas that in the fellow eyes decreased by

TABLE 3. Summary of All Adverse Events by Category and Severity for All Enrolled Participants

Adverse Event Category	Severity					
	Mild/Grade 1		Moderate/ Grade 2		Total	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Allergic, immunologic	4	12.5	0	0	4	11.1
Infection	3	9.4	0	0	3	8.3
Musculoskeletal	1	3.1	2	50.0	3	8.3
Neurologic	1	3.1	0	0	1	2.8
Ocular	12	37.5	0	0	12	33.3
Cardiovascular	2	6.3	0	0	2	5.6
Dermatologic	4	12.5	1	25.0	5	13.9
Endocrine	1	3.1	0	0	1	2.8
Other	4	12.5	1	25.0	5	13.9
Total	32	100.0	4	100.0	36	100.0

n = 11.

11.3 ± 7.6 letters (*n* = 10; *P* = 0.0259). The proportions of participants losing ≥5 or ≥10 letters compared with baseline were lower in the study eye than in the fellow eye at all time points (Figs. 2C, 2D, respectively). At 2 years, 1 study eye and 3 fellow eyes (of 10) lost ≥15 letters compared with baseline. No participant developed advanced exudative neovascular AMD in either eye during the study period. Pseudophakia was equally distributed between study and fellow eyes at baseline (Table 2), and no participants underwent cataract surgery during the study period.

Effect of Study Treatment on Contrast Sensitivity and Microperimetry

Changes in contrast sensitivity and microperimetry were also designated as secondary functional outcome measures. Contrast sensitivity evaluations assessed the participants' ability to distinguish different levels of luminances and to discern objects against a background with low contrast. The natural history of contrast sensitivity change in GA, as measured by the Pelli-Robson chart, has not been analyzed. Considering only the fellow eyes, changes in contrast sensitivity scores were generally small and inconsistent; at the 2-year time point, of 10 fellow eyes, 6 had the same baseline score, with two eyes having a decrease and two eyes an increase in sensitivity scores from baseline values. Figure 3 shows the mean change in contrast sensitivity for study and fellow eyes at the 1- and 2-year time points. At 2 years, the mean contrast sensitivity decreased marginally and nonsignificantly from baseline scores (-0.075 ± 0.33 in the study eyes and -0.15 ± 0.27 in the fellow eyes; *P* = 0.6059, paired *t*-test). These results indicate that changes in contrast sensitivity, as measured by the Pelli-Robson method, do not

progress sufficiently over a 2-year period in the natural history of GA to be useful in evaluating treatment effect.

Bilateral microperimetry (MP-1) data at baseline, 1- and 2-year time points were available for 8 of 10 participants; 2 participants were unable to sufficiently complete testing to contribute results for analysis. Microperimetry measurements were used to calculate (1) the changes in the number of scotomatous points (i.e., testing points centered on the macula reporting a lack of retinal sensitivity within the range tested) from baseline values and (2) the changes in the mean sensitivity (in dB, on a scale from 0 to 20 dB) among nonscotomatous points. Figure 4A shows the change at week 104 in the number of scotomatous points in the eight participants for whom data were available. Of 16 available eyes (study and fellow eyes), 14 demonstrated an increase in the total number of scotomatous points over 2 years. Five of eight participants showed a smaller increase (or greater decrease) in scotomatous points in the study eye compared with the fellow eye at 2 years (Fig. 4A). The mean changes in the number of scotomatous points at different time points between study and fellow eyes were not significantly distinct at any point during the 2-year study (*P* > 0.05 for all comparisons; Fig. 4B). All 16 eyes tested demonstrated decreases in mean retinal sensitivity (in nonscotomatous points) over the 2-year period (Fig. 4C), but differences between study and fellow eyes were also not significant at any point during the study (*P* > 0.05 for all comparisons; Fig. 4D).

Effect of Treatment on Area of Geographic Atrophy

Changes in the total area of atrophy in the study and fellow eyes were designated as a secondary outcome of the study. The

TABLE 4. Summary of Ocular Adverse Events in Study and Fellow Eyes for All Enrolled Participants

Ocular Event	Study Eye	Fellow Eye	Total
Small subretinal/intraretinal hemorrhages	4	1	5
Elevated IOP	0	2	2
Blurry vision	1	1	2
Increase in posterior subcapsular cataract	1	0	1
Decreased visual acuity	1	1	2
Sore eye	1	0	1
Dry skin on eyelid	1	1	2
Total	9	6	15

n = 11.

FIGURE 2. Change in visual acuity measurements in the study and fellow eyes from baseline in all participants completing 104 weeks (2 years) of study follow-up ($n = 10$). (A) Change in visual acuity from baseline for each participant (indicated by P1, P2, and so forth) at 104 weeks for the study and fellow eyes. The study eyes in P5 and P11 maintained baseline acuity. (B) Mean change in visual acuity at 24, 52, 76, and 104 weeks after baseline (P values indicate results of a two-tailed paired t -tests). (C) Proportion of the study and fellow eyes experiencing a 5-letter or greater vision loss from baseline at 104 weeks. (D) Proportion of the study and fellow eyes experiencing a 10-letter or greater vision loss from baseline at 104 weeks.

growth in the area of the GA lesion was monitored with both CFPs and HRA FAF imaging and quantified by masked readers at a reading center. There was excellent agreement between the areas of GA, as quantified by the two imaging modalities (Spearman correlation, $r = 0.986$), with areas measured from HRA FAF images being slightly but significantly larger than those measured from CFPs (mean difference [HRA FAF – CFP] $\pm$ SD = 0.178 ± 0.45 mm²; $P = 0.0001$, paired t -test). Figures 5A and 5B show the percentage increases in GA area in all participants ($n = 10$) at the 2-year time point, as measured from CFPs and HRA FAF images respectively. All study and fellow eyes demonstrated an increase in total GA area from that at baseline, as measured from both imaging modalities. The mean total GA area increased monotonically with time in both the study and fellow eyes, in terms of both mean total GA area (in square millimeters; Figs. 5C, 5D) and the percentage change of GA area from baseline values (Figs. 5E, 5F). As

measured from CFPs, the mean 2-year increase in GA area was 2.46 ± 1.25 mm² (or 1.23 mm²/y) in the study eyes and 2.47 ± 0.73 mm² (or 1.24 mm²/y) in the fellow eyes. As measured from HRA FAF images, the mean 2-year increase in GA area was 2.17 ± 0.83 mm² (or 1.08 mm²/y) in the study eyes and 2.24 ± 0.91 mm² (or 1.12 mm²/y) in the fellow eyes. Pair-wise comparisons on parameters of (1) change of GA area from baseline at week 104, and (2) percentage change in GA area from baseline at week 104, as determined from both CFP and HRA FAF images, did not reveal any significant differences between the study and fellow eyes ($P > 0.05$ for all comparisons). Analysis of differences in 2-year changes in GA area between study and fellow eyes in each participant similarly did not reveal systematic differences (data not shown).

In the 10 participants (20 eyes; 10 study eyes and 10 fellow eyes) analyzed in the study, the location of GA in 4 eyes of 2 participants (participant 9 and 10) were scored as nonsubfoveal at baseline. In participant 9, GA lesions in both the study and fellow eyes remained nonsubfoveal in location by 2 years. In participant 10, GA lesions in both the study and fellow eyes progressed into the center of the fovea by 2 years. In all the remaining eyes (16/20 eyes), the location of GA was subfoveal (i.e., involving the center of the fovea) at baseline.

Effect of Treatment on Total Drusen Area

Total drusen area, manually quantified from CFP images by reading center grading, was also studied as a secondary outcome measure. Figure 6A shows the percentage change in drusen area at week 104 relative to baseline for all eyes; 14 of 16 eyes demonstrated a decrease in total drusen area. This general decrease in total drusen area was also observed in the mean total drusen area (Fig. 6B), mean change in total drusen area (Fig. 6C), and percentage change in total drusen area (Fig. 6D). Although mean decreases in drusen area are greater in the study eyes than in the fellow eyes, these were not statistically significant ($P > 0.05$ for all comparisons).

FIGURE 3. Mean change in contrast sensitivity from baseline as measured by the Pelli-Robson chart in the study and fellow eyes at 52 and 104 weeks.

DISCUSSION

The study, enrolling 10 participants with bilateral GA without evidence or history of neovascular AMD, was designed to administer unilateral study treatment to only one randomly selected study eye in each participant, with the fellow untreated eye serving as its control. The symmetry in GA lesion areas, configuration, and enlargement rates between fellow eyes in bilateral GA increased the statistical likelihood, given the size and duration of the study, that therapeutic effects on lesion size would be detectable.²⁴

For the primary efficacy outcome measure, the change of visual acuity from baseline, a significantly lower mean decrease in visual acuity was noted in the study eyes compared with the fellow eyes. The proportions of eyes losing ≥ 5 letters, ≥ 10 letters, or ≥ 15 letters were also all lower in the study eye group than in the fellow eye group. This apparent benefit of the study treatment may be confounded by several factors: (1) The lower mean baseline visual acuity among study eyes than in fellow eyes (46 ± 21 letters vs. 57 ± 12 letters), (2) the lack of a strong correlation between lesion expansion and visual acuity decline,⁴ and (3) the phenomenon of spontaneous improvement of visual acuity, related to the deterioration of vision in the better-seeing fellow eye.²⁸ The higher mean visual acuity in fellow eyes relative to study eyes at baseline may have increased the chance that the same degree of anatomic progression of a GA lesion would result in relatively greater declines of visual acuity in fellow eyes. In addition, as only two participants in the study had GA lesions that were nonsubfoveal in location at baseline, of which only one had GA lesions progressing to involve the center of the fovea during the study, differential progression of GA lesions into the fovea are unlikely to account for the difference in mean visual acuity change between study and fellow eyes.

In addition to changes in visual acuity, the natural history of functional decline in GA has also been found for other functional measures such as low luminance visual dysfunction and reading rates.^{29,30} In this study, we investigated contrast sen-

sitivity measurement (with the Pelli-Robson chart) and microperimetry as functional outcome measures. Although 2-year changes in contrast sensitivity measurements did not progress consistently or sufficiently to be useful as an outcome measure, increases in scotoma size and decreases in overall retinal sensitivity, as measured by microperimetry, were significant and progressive over the course of the 2-year study. These two microperimetric measures however were not statistically distinct between study and fellow eyes at the 2-year time point and thus did not reflect a beneficial effect of the study drug on the basis of microperimetry.

Enlargement of GA lesions, as indicated by increases in the total area of atrophy, was evaluated using two imaging modalities, CFPs and HRA FAF, and quantified by a reading center using planimetric methods. Despite potential differences in the measurement of GA area between modalities in individual cases,^{31,32} the mean differences between modalities were small ($0.178 \pm 0.45 \text{ mm}^2$) as previously found.³³ Increases in mean change in area and mean percentage in area were not statistically distinct between study and fellow eyes from both imaging modalities and, as such, did not indicate a detectable treatment effect of the study drug on lesion growth. Overall rates of lesion expansion over the 2-year period ($1.23 \text{ mm}^2/\text{y}$ for study eyes [median baseline area = 6.80 mm^2]; and $1.24 \text{ mm}^2/\text{y}$ for the fellow eyes [median baseline area = 7.09 mm^2], as measured from CFPs) were similar to those reported by Klein et al.³⁴ ($1.3 \text{ mm}^2/\text{y}$), but lower than those found in two other studies ($1.8\text{--}2.6 \text{ mm}^2/\text{y}$).^{4,35}

Changes in total drusen area were also monitored in the study and fellow eyes. Of note, change in mean drusen area and percentage change in drusen area decreased from baseline in both the study and fellow eyes and did not differ significantly between the two groups. Decreases in total drusen area may be related to the overall natural history of GA and can potentially reflect treatment effects on GA progression.^{36,37}

The features of the study design that may have limited study conclusions include: (1) small number of participants, (2) rel-

FIGURE 5. Change in GA area measurements in the study and fellow eyes from baseline for all participants completing 104 weeks (2 years) of study follow-up ($n = 10$). (A, B) Change in GA area from baseline in each participant (indicated by P1, P2, and so forth) at 104 weeks in the study and fellow eyes, as measured from CFPs (A) and HRA FAF (B). (C, D) Mean increase in GA area at 24, 52, 76, and 104 weeks after baseline as measured from CFPs (C) and HRA FAF (D). (E, F) Mean percentage increase in GA area at 24, 52, 76, and 104 weeks after baseline as measured from CFPs (E) and HRA FAF (F). P values indicate results of two-tailed paired t -tests.

actively short duration of study, (3) possible unreported participant noncompliance in daily topical drug administration, and (4) a lack of pharmacologic data on drug distribution systemically and to the contralateral eye. With respect to GA outcome measures, our results support the use of CFPs and HRA FAF imaging in observing GA lesion enlargement, the use of microperimetry in monitoring functional progression, but not the

measurement of contrast sensitivity using the Pelli-Robson chart.

In conclusion, our results indicate that topical OT-551 is well-tolerated by study participants from ocular and systemic standpoints. Administration of the investigational drug in the study eye did not exert a significant effect on lesion enlargement, retinal sensitivity, or area of total drusen relative to the

FIGURE 6. Change in total drusen area in the study and fellow eyes from baseline for all participants completing 104 weeks (2 years) of study follow-up ($n = 10$). (A) Percentage change in visual acuity from baseline for each participant (indicated by P1, P2, and so forth) at 104 weeks for study and fellow eyes. (B) Mean total drusen area at 24, 52, 76, and 104 weeks after baseline. (C) Mean and (D) percentage changes in total drusen at 24, 52, 76, and 104 weeks after baseline. P values indicate results of a two-tailed paired t -test.

control fellow eye. The detection of a significant difference in visual acuity change favoring the study eye may suggest a treatment effect, but this warrants further substantiation. In a concurrent but separate phase II clinical trial of OT-551 employing a different study design (randomized, parallel-group, placebo-controlled trial) and involving 137 participants, no significant differences in GA areal progression were found between treated and placebo groups at 18 months (Sternberg et al., IOVS 2010;51:ARVO E-Abstract 6416). Also, no benefits with respect to BCVA were discernable in treated participants in this trial. It is possible that suboptimal drug delivery to the retina may have limited the therapeutic effects observed. It is also possible that the lack of a placebo drop for the fellow eye influenced compliance and diminished the relative therapeutic effect of the drug. The absence of significant effects on outcomes measures other than visual acuity in our study and the failure to replicate the visual acuity effect in a larger study suggest that OT-551, in the current concentration and mode of delivery, has limited or no benefit as a treatment for GA.

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