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Real-World Geographic Atrophy Growth Before and After Intravitreal Avacincaptad Pegol Treatment: A Retrospective Cohort Study

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Abstract

Background/Objectives:

To evaluate whether intravitreal avacincaptad pegol (ACP) slows geographic atrophy (GA) progression in routine clinical practice.

Subjects/Methods:

This single-centre retrospective cohort study included eyes with GA or macular atrophy secondary to age-related macular degeneration (AMD) treated with ACP. Near-infrared reflectance (NIR) and optical coherence tomography (OCT) imaging were obtained at ACP initiation and approximately 1 year before and after treatment. GA was manually delineated on NIR images using OCT B-scans as reference. Annualised square-root and perimeter-adjusted growth rates were compared using linear mixed-effects models.

Results

We included 114 eyes from 74 patients (mean (SD) age 80.9 (8.0) years) who received 7.0 (3.9) injections. Mean pre- and post-ACP follow-up was 0.99 (0.22) and 0.91 (0.20) years. Square-root GA growth was 22.7% lower after ACP initiation (0.37 ± 0.24 vs 0.29 ± 0.21 mm/year; $P < 0.001$), and perimeter-adjusted growth was 23.1% lower (0.115 ± 0.073 vs 0.088 ± 0.063 mm/year; $P < 0.001$). Square-root growth was reduced in non-exudative AMD (22.2%; $P = 0.002$; $n = 89$), exudative AMD (24.7%; $P = 0.10$; $n = 25$), foveal GA (25.1%; $P = 0.003$; $n = 50$), and extrafoveal GA (21.2%; $P = 0.02$; $n = 64$). Visual acuity decline did not differ before versus after ACP initiation ($P = 0.32$).

Conclusions

GA growth was significantly slower after ACP initiation in the real-world cohort over approximately 1 year. The magnitude of GA growth slowing was comparable across foveal and extrafoveal GA and non-exudative and exudative AMD subgroups.

INTRODUCTION

Geographic atrophy (GA) is the atrophic late stage of age-related macular degeneration (AMD) and a major cause of irreversible central vision loss worldwide.(1) In 2023, the U.S. Food and Drug Administration approved the intravitreal complement inhibitors pegcetacoplan and avacincaptad pegol (ACP) for the treatment of GA secondary to AMD, representing the first approved therapies shown to slow GA progression.(2, 3) However, ongoing debate regarding treatment versus observation, divergent

regulatory decisions outside the United States, and the absence of a demonstrated visual acuity benefit underscore the need for additional evidence on real-world treatment efficacy.(2–8)

In the pivotal GATHER1 and GATHER2 trials, monthly intravitreal ACP reduced the mean rate of GA area growth by approximately 14% to 35% relative to sham over 12 months in eyes with extrafoveal GA secondary to non-exudative AMD.(3, 9) However, the anatomic efficacy of ACP in routine clinical practice remains poorly characterised. Real-world patients differ from pivotal-trial participants in injection adherence, lesion morphology, and the prevalence of concurrent or prior anti-vascular endothelial growth factor (anti-VEGF) therapy for exudative AMD. Notably, the phase 3 trials excluded eyes with GA involving the foveal centre or exudative AMD.(2, 3) In addition, prior GA clinical trials have largely relied on fundus autofluorescence (FAF) imaging, which is not consistently obtained in routine clinical practice. By contrast, near-infrared reflectance (NIR) and optical coherence tomography (OCT) imaging are widely available and frequently acquired during routine retina visits, but whether the anatomic treatment effect of ACP can be detected using these clinically obtained imaging modalities remains unclear. Thus, additional real-world evidence is needed to evaluate whether ACP slows GA progression in broader clinical populations and using imaging modalities that reflect routine clinical practice.

In addition to real-world efficacy, the conventional GA area-based endpoints used in GA trials have limited sensitivity for detecting individual treatment response. GA area growth rate, the most common trial endpoint, varies several-fold across eyes and is strongly influenced by lesion morphology, obscuring treatment effects and increasing required sample sizes.(2, 3, 10) The square-root transformation reduces the dependence of growth rate on baseline lesion size(11–13) and enlarges linearly over approximately 30 years,(10) but it still does not capture the full spectrum of GA lesion characteristics, including lesion number, perimeter, circularity, and topographic distribution of atrophy, which vary widely across patients.(11, 13–19) We previously developed a perimeter-adjusted GA growth rate endpoint, which normalises area growth by lesion perimeter and unifies the effects of lesion area, number, and circularity while improving statistical power.(13, 20, 21)

In the present study, we evaluated the real-world effect of intravitreal ACP on GA progression at the Duke Eye Center using a pre- versus post-treatment design.(22) We quantified treatment response with square-root–transformed and perimeter-adjusted GA growth rates, assessed consistency across foveal and extrafoveal GA and non-exudative and exudative AMD, and examined factors associated with treatment response.

SUBJECTS AND METHODS

Study Design and Participants

We conducted a retrospective cohort study of patients with GA secondary to non-exudative AMD or macular atrophy secondary to exudative AMD who received their first intravitreal ACP injection at the Duke Eye Center on or before August 9, 2025. This study was approved by the Duke University Health

System Institutional Review Board for Clinical Investigations (Protocol ID Pro00118634), which determined it to be exempt from further review as secondary research for which informed consent is not required. The study complied with the Health Insurance Portability and Accountability Act, conformed to all applicable federal and state laws, and adhered to the tenets of the Declaration of Helsinki. Eyes were eligible if they had (1) a clinical diagnosis of GA secondary to non-exudative AMD or macular atrophy secondary to exudative AMD, as determined by a retina specialist from the electronic health record; (2) at least one intravitreal injection of ACP (2 mg), with ACP as the first complement inhibitor received; (3) gradable NIR and OCT imaging (Heidelberg Spectralis HRA + OCT, Heidelberg Engineering, Heidelberg, Germany) at the visit of treatment initiation, as well as 6–24 months before and 6–24 months after the first ACP injection. When multiple visits were eligible, the visit closest to 12 months from the first injection was selected. Eyes were excluded if the GA lesion was contiguous with peripapillary atrophy, extended beyond the imaging field of view, had poor image registration, or had no GA lesion at the pre-treatment visit. Macular atrophy secondary to exudative AMD was defined as GA in an eye with concurrent or prior neovascular AMD, as documented by a retina specialist. Patient and eye flow through the study is summarised in Fig. 1.

Imaging Method, Image Registration, and GA Grading

Clinical data, including age, sex, visual acuity, number of ACP injections, and treatment complications, were extracted from the electronic health record. If OCT imaging was not available on the exact date of a selected visit, an OCT scan from within one month before or after the visit was used; the NIR imaging date served as the timepoint for all progression analyses. GA lesions were manually delineated on NIR images in Heidelberg Eye Explorer software (Heidelberg Engineering, Heidelberg, Germany) at each visit, with reference to corresponding OCT B-scans to improve border accuracy (Supplementary Fig. 1). GA area was measured directly in Heidelberg Eye Explorer. Prior studies have shown strong agreement in GA area and progression rate measurements between FAF and NIR imaging.(23) The foveal centre was identified on the NIR image with reference to the horizontal OCT B-scan through the fovea.

Intergrader reproducibility and intermodality agreement were evaluated before grading the full cohort. A subset of 30 randomly selected eyes was independently graded by 2 graders who were masked to each other’s measurements. One eye was excluded because the GA lesion extended beyond the imaging field of view, leaving 29 eyes in the reproducibility analysis. After excellent intergrader reproducibility was established, the full dataset was graded by the primary grader (RA) using prespecified delineation criteria. Because longitudinal grading of co-registered images in Heidelberg Eye Explorer displays acquisition dates and visit sequence, masking to pre- versus post-ACP timepoint was not possible. To minimise potential measurement bias, the same grading criteria were applied consistently across all visits, lesion borders were verified using corresponding OCT B-scans, and all delineations were subsequently reviewed and adjudicated by a senior grader (LLS). To validate NIR imaging, the delineations used in the intergrader test were compared against fundus autofluorescence (FAF) imaging.

For perimeter-based analyses, the GA contours, image scale, and 3 corresponding retinal vessel bifurcations were annotated using custom MATLAB software (The MathWorks, Natick, MA). All visits were displayed simultaneously, and three corresponding vessel bifurcations visible across the complete image series were selected to co-register follow-up images to the treatment-initiation visit, correcting for translation, rotation, and scaling.(24) Registered images were overlaid and visually inspected to confirm alignment. This manual registration approach was previously validated, demonstrating a mean residual registration error of 28.6 µm, comparable to that of the deep learning based EyeLiner method.(25) GA perimeter,(13) and GA circularity index (GACI)(17) were computed from the registered delineations. We calculated GACI as $\frac{4\times \pi \times Total\ Area}{Total\ Perimeter^2}$.(17)

Outcome Measures

The study evaluated GA area across three timepoints: the pre-treatment, treatment-initiation, and post-treatment visits. The primary outcome was the annualized growth rate of square-root transformed GA area (mm/year), defined as the change in the square root of the GA area divided by the interval duration in years. The prespecified secondary outcomes were the annualized growth rate of GA area (mm^2/year), defined as the change in the GA area divided by the interval duration in years, and the perimeter-adjusted GA growth rate (mm/year), defined as the change in GA area divided by the product of the interval duration and the mean GA perimeter across the interval. Each GA growth metric was calculated separately for the pre-treatment and post-treatment intervals for each eye. Visual acuity change was also evaluated as a secondary outcome.

Statistical Analysis of Conventional Endpoints

All statistical analyses were performed in R software (version 4.4.3). Pre- versus post-treatment comparisons of the square-root and perimeter-adjusted growth rates were performed using linear mixed-effects models (“lme4” package(26) in R) with random intercepts for patient and eye to account for within-patient and within-eye correlation. Subgroup analyses were performed separately for eyes with non-exudative AMD and eyes with exudative AMD. To identify factors associated with ACP treatment effect, univariable linear mixed-effects models were performed with the post-minus-pre difference in the square-root and perimeter-adjusted growth rates as the outcomes and 10 factors evaluated one at a time: age, visual acuity, GA area, GA perimeter, lesion focality (unifocal vs. multifocal), foveal centre point involvement (foveal vs. extrafoveal GA), GACI, number of GA lesions at the time of ACP initiation, the total number of injections, and the injection frequency during follow-up. Injection frequency was calculated for each eye as the total number of ACP injections divided by the duration of post-treatment follow-up, expressed as injections per year. Each univariable model included a random intercept for participant. Longitudinal changes in visual acuity were modelled using linear mixed-effects models with separate pre- and post-ACP slopes.

RESULTS

Participant Characteristics

Of 152 patients who received intravitreal ACP as their first complement inhibitor during the study period, 72 were excluded prior to grading. An additional 6 patients were excluded during grading for absent GA at the pre-treatment visit (n = 3) or GA extending beyond the imaging field of view (n = 3). The final analytic sample comprised 114 eyes from 74 patients with both pre- and post-ACP follow-up (Fig. 1). Baseline characteristics of the 74 included and 78 excluded patients are compared in Supplementary Table 1; the groups did not differ significantly in age, sex, exudative AMD status, visual acuity, GA area, lesion multifocality, or foveal centre point involvement.

Baseline characteristics are summarised in Table 1. Mean (SD) age at ACP initiation was 80.9 (8.0) years, and 48 (64.9%) patients were female. At treatment initiation, mean (SD) GA area was 9.09 (8.07) mm^2, GA perimeter 17.7 (9.2) mm, and GACI 0.42 (0.23), indicating substantial variability in lesion morphology. Seventy-five eyes (65.8%) had multifocal GA, and 50 eyes (43.9%) had GA involving the foveal centre. Of the 114 eligible eyes, 89 (from 61 patients) had non-exudative AMD and 25 (from 17 patients) had concurrent or prior exudative AMD. Of these 25 eyes, 24 had prior anti-VEGF treatment; the median interval from the last anti-VEGF injection to ACP initiation was 2.0 months (interquartile range, 1.1–3.7; available in 22 eyes), and no eye had subretinal or intraretinal fluid on OCT at initiation. Eyes received a mean (SD) of 7.0 (3.9) ACP injections, with pre- and post-treatment follow-up of 0.99 (0.22) and 0.91 (0.20) years.

Table 1
Characteristics of Eligible Patients and Eyes

Number of eligible patients (eyes), n	**74 (114)**
Age at ACP initiation, yrs, mean (SD)	80.9 (8.0)
Sex, female, n (%)	48 (64.9%)
Number of eligible patients (eyes) with non-exudative AMD, n	61 (89)
Number of eligible patients (eyes) with exudative AMD, n	17 (25)
Number of ACP treatment, mean (SD)	7.0 (3.9)
Characteristics of eligible eyes at ACP Initiation	
Visual acuity, ETDRS letters, mean (SD)	54.7 (23.3); Snellen equivalent 6/24
GA area, mm^2, mean (SD)	9.09 (8.07)
Multifocal lesion, n (%)	75 (65.8%)
Mean number of GA lesions, n (SD)	2.67 (1.81)
GA circularity index	0.42 (0.23)
Lesion perimeter (mm)	17.7 (9.2)
Foveal centre point involvement, n (%)	50 (43.9%)

ACP = avacincaptad pegol; AMD = age-related macular degeneration; ETDRS = Early Treatment Diabetic Retinopathy Study; GA = geographic atrophy; SD = standard deviation.

Intergrader and Intermodality Reproducibility of GA Grading

Reproducibility was assessed in 84 visits from 29 eyes (Supplementary Fig. 2). Between the 2 graders, the mean difference in NIR GA area was 0.54 mm^2 (95% limits of agreement, − 1.53 to 2.61) and the intraclass correlation coefficient was 0.99. NIR and FAF measurements agreed closely, with a mean difference of − 0.51 mm^2 (95% limits of agreement, − 2.40 to 1.37) and a Pearson correlation coefficient of 0.99.

ACP Significantly Reduced GA Growth Rates

Across all 114 eyes, the annualised square-root GA growth rate decreased from 0.37 (0.24) mm/year before ACP initiation to 0.29 (0.21) mm/year after initiation, a 22.7% reduction ($P < 0.001$; Fig. 2A, Table 2). One eye developed new-onset exudative AMD requiring bevacizumab; no other complications were documented. This eye was retained in the primary analysis; in a sensitivity analysis excluding it, the

square-root GA growth rate decreased from 0.37 (0.24) to 0.29 (0.21) mm/year (P < 0.001; 113 eyes from 73 patients).

Table 2
Geographic Atrophy Growth Rate Before and After Avacincaptad Pegol Initiation

Cohort	Pre-ACP (mean ± SD)	Post-ACP (mean ± SD)	Mean % change	Eyes with decreased growth rate post-ACP, %	P value for GA growth rate, pre- vs. post-ACP*
Endpoint 1: Square root transformed area growth rate, mm/year†					
All eyes (n = 114)	0.37 (0.24)	0.29 (0.21)	22.7%	73.7%	< 0.001
Non-exudative AMD (n = 89)	0.39 (0.25)	0.30 (0.22)	22.2%	74.2%	0.002
Exudative AMD (n = 25)	0.31 (0.22)	0.24 (0.18)	24.7%	72.0%	0.10
Endpoint 2: Perimeter-adjusted growth rate, mm/year‡					
All eyes (n = 114)	0.115 (0.073)	0.088 (0.063)	23.1%	75.4%	< 0.001
Non-exudative AMD (n = 89)	0.119 (0.074)	0.092 (0.065)	23.2%	77.5%	0.001
Exudative AMD (n = 25)	0.099 (0.067)	0.076 (0.058)	22.4%	68.0%	0.17

ACP = avacincaptad pegol; AMD = age-related macular degeneration; GA = geographic atrophy; SD = standard deviation.

*P values are from a linear mixed-effects model with random intercepts for patient and eye.

†GA square root area growth rate (mm/year) = $\frac{\sqrt{GAareaatlastvisit(mm^2)}-\sqrt{GAareaatfirstvisit(mm^2)}}{Timeinterval(year)}$

‡GA perimeter-adjusted growth rate $= \frac{\text{GAareagrowthrate}(mm^2/year)}{MeanGAperimeterbetweenthefirstandlastvisits(mm)}$

The treatment effect was consistent in the non-exudative AMD subgroup (n = 89), in which the square-root growth rate decreased from 0.39 (0.25) mm/year to 0.30 (0.22) mm/year, a 22.2% reduction (P = 0.002; Fig. 2B). In the exudative AMD subgroup (n = 25), the square-root growth rate decreased from 0.31 (0.22) mm/year to 0.24 (0.18) mm/year, a 24.7% reduction that did not reach statistical significance (P = 0.10; Fig. 2C). Eighty-four of the 114 eyes (73.7%) had a slower square-root growth rate after ACP initiation than before (Table 2).

Results were concordant for the prespecified perimeter-adjusted endpoint (Table 2). Across all 114 eyes, the perimeter-adjusted growth rate decreased from 0.115 (0.073) mm/year before ACP initiation to

0.088 (0.063) mm/year after initiation, a 23.1% reduction (P < 0.001), with 86 of 114 eyes (75.4%) showing a lower post-treatment rate. The perimeter-adjusted growth rate decreased by 23.2% in the non-exudative AMD subgroup (0.119 (0.074) to 0.092 (0.065) mm/year; P = 0.001) and by 22.4% in the exudative AMD subgroup (0.099 (0.067) to 0.076 (0.058) mm/year; P = 0.17).

Using unadjusted raw metrics, the annualised growth rate of total GA area was 1.82 (1.43) mm^2/year before ACP and 1.67 (1.38) mm^2/year after initiation (P = 0.27). This is expected, as unadjusted GA area expansion is a quadratic function(10, 18) and the rate is strongly dependent on lesion area and perimeter.(12, 13)

ACP Significantly Reduced GA Growth Rates in Both Foveal and Extrafoveal GA

Of the 114 eyes included in the analysis, 50 eyes from 37 patients had foveal-involving GA and 64 eyes from 47 patients had extrafoveal GA. ACP significantly reduced the square-root GA growth rate in both subgroups: by 21.2% in extrafoveal GA (0.42 (0.25) to 0.33 (0.24) mm/year; P = 0.02) and by 25.1% in foveal GA (0.31 (0.22) to 0.24 (0.16) mm/year; P = 0.003). Results were concordant for the perimeter-adjusted endpoint, with significant reductions of 22.9% in extrafoveal GA (0.124 (0.076) to 0.095 (0.068) mm/year; P = 0.01) and 23.3% in foveal GA (0.103 (0.07) to 0.079 (0.056) mm/year; P = 0.02).

Factors Associated with the Magnitude of the Treatment Effect

Eyes received a mean (SD) of 7.0 (3.9) ACP injections during post-treatment follow-up, an injection frequency of 7.7 (4.0) injections per year (median 8.5, interquartile range 5.1–11.0). In univariable linear mixed-effects models, none of the 10 evaluated factors (age, visual acuity, total number of injections, injection frequency, GA area, GA perimeter, lesion focality, foveal centre involvement, GACI, and number of GA lesions) was significantly associated with the reduction in square-root-transformed or perimeter-adjusted growth rate (Table 3). The estimates for injection frequency were directionally consistent across both endpoints, each additional injection per year being associated with a greater reduction in the growth rate (square-root endpoint, -0.0046 mm/year per injection/year, 95% CI -0.0166 to 0.0075, P = 0.46; perimeter-adjusted endpoint, -0.0017 mm/year per injection/year, 95% CI -0.0055 to 0.0022, P = 0.40).

Table 3
Univariable Associations of Participant and Ocular Characteristics with the Change in GA Growth Rate After ACP Initiation

Factors*	Effect estimate [95% CI] in square-root GA area growth rate, mm/yr	P value in sqrt GA area growth rate	Effect estimate [95% CI] in perimeter-adjusted growth rate,† mm/yr	P value in perimeter-adjusted growth rate
Age, per 1 year	0.0013 [-0.0048, 0.0074]	0.67	0.0005 [-0.0014, 0.0025]	0.60
Visual acuity, per 1 ETDRS letter	-0.0008 [-0.0029, 0.0013]	0.45	-0.0002 [-0.0009 to 0.0004]	0.49
Total number of injections, per 1 injection	-0.0053 [-0.0177, 0.0072]	0.40	-0.0015 [-0.0055 to 0.0025]	0.46
Injection frequency, per 1 injection/year	-0.0046 [-0.0166, 0.0075]	0.46	-0.0017 [-0.0055, 0.0022]	0.40
GA area, per 1 mm^2	0.0023 [-0.0027, 0.0074]	0.36	0.0010 [-0.0006 to 0.0026]	0.20
GA perimeter, per 1 mm	0.0007 [-0.0047, 0.0060]	0.80	0.0008 [-0.0009 to 0.0025]	0.33
Lesion focality, multifocal vs. unifocal	0.0033 [-0.0998, 0.1064]	0.95	0.0100 [-0.0227 to 0.0427]	0.55
Foveal center involvement, present vs. absent	0.0093 [-0.0892, 0.1078]	0.85	0.0044 [-0.0271 to 0.0359]	0.78
GA circularity index, per 1-unit	0.0290 [-0.1866, 0.2447]	0.79	-0.0208 [-0.0901 to 0.0485]	0.55
Number of GA lesions, per 1 lesion	-0.0164 [-0.0434, 0.0106]	0.23	-0.0021 [-0.0105 to 0.0063]	0.62

ACP = avacincaptad pegol; CI = confidence interval; ETDRS = Early Treatment Diabetic Retinopathy Study; GA = geographic atrophy.

* Each factor was evaluated separately in a univariable linear mixed-effects model, with the change in growth rate (post-ACP minus pre-ACP) as the dependent variable and a participant-level random intercept to account for correlation between fellow eyes. Negative coefficients indicate a greater reduction in growth rate after ACP initiation. Factors were measured at ACP initiation except that total number of injections and injection frequency were measured during the post-ACP follow-up period.

Factors*	Effect estimate [95% CI] in square-root GA area growth rate, mm/yr	P value in sqrt GA area growth rate	Effect estimate [95% CI] in perimeter-adjusted growth rate,† mm/yr	P value in perimeter-adjusted growth rate

† GA perimeter-adjusted growth rate $= \frac{\mathrm{GAareagrowthrate}(mm^2/year)}{MeanGAperimeterbetweenthe2visits(mm)}$

Visual Acuity

Among 92 eyes from 61 patients with complete pre- and post-ACP visual acuity data, mean (SD) best-corrected visual acuity was 54.9 (23.7) Early Treatment Diabetic Retinopathy Study letters at ACP initiation. Visual acuity declined at an estimated − 4.39 letters/year (95% CI, − 7.68 to − 1.10) before ACP initiation and − 7.36 letters/year (95% CI, − 10.9 to − 3.82) after ACP initiation, without statistically significant difference between slopes (P = 0.32). Visual acuity is not routinely measured at injection-only visits at our centre, accounting for the missing data in the remaining 22 eyes.

DISCUSSION

In this real-world cohort of 114 eyes from 74 patients treated at a single academic retina centre, intravitreal ACP was associated with a 22.7% reduction in square-root-transformed GA growth rate and a 23.1% reduction in perimeter-adjusted GA growth rate over approximately 1 year of treatment, using each eye as its own pre-treatment control. Eyes received a mean (SD) of 7.0 (3.9) injections, reflecting real-world dosing rather than the fixed monthly dosing of the phase 3 trials,(3) yet significant anatomic slowing was still observed. The treatment effect was consistent across clinically relevant subgroups, including non-exudative and exudative AMD along with foveal and extrafoveal GA. These findings support the real-world anatomic efficacy of ACP in slowing GA progression.

The magnitude of the treatment effect observed in this real-world cohort is consistent with the 14% to 35% reductions in GA area growth rate reported in the GATHER1 and GATHER2 phase 3 trials over 12 months.(3, 9) This suggests that ACP retains its anatomic efficacy when delivered in routine clinical practice, where adherence, concomitant therapies, and lesion morphology differ from the tightly controlled trial setting. The treatment effect was consistent across the non-exudative and exudative AMD subgroups (22.2% and 24.7% reductions in square-root growth rate, respectively). Although not statistically significant in the smaller exudative subgroup (25 eyes from 17 patients), the consistent direction and magnitude suggest that exudative AMD may not preclude an anatomic response to ACP.

The findings in foveal and extrafoveal GA are also clinically important. The GATHER trials demonstrated efficacy in extrafoveal GA and excluded foveal-involving GA.(3, 9) In contrast, we found significant reductions in both, concordant across both endpoints. These results are consistent with a recent real-world pegcetacoplan report, which found similar treatment effects in foveal and nonfoveal GA.(22) Because foveal GA carries a disproportionate burden of visual dysfunction, and eyes with foveal GA continue to lose visual acuity at comparable or faster rates than eyes with extrafoveal GA,(6, 7) evidence

of an anatomic treatment effect in this subgroup supports the clinical rationale for ACP treatment in patients with foveal centre involvement. Prospective studies with prespecified subgroup analyses are needed to confirm these findings and to evaluate ACP in macular atrophy secondary to exudative AMD.

The lack of significance for unadjusted total GA area growth warrants consideration. GA area growth is strongly influenced by lesion size and perimeter,(11, 13, 18, 19) and accelerates as lesions enlarge because a larger lesion has a greater border across which new atrophy can accrue. In a pre- versus post-treatment design this biases against detecting benefit: post-treatment lesions are by definition larger and would be expected to grow faster in absolute area. The square-root transformation reduces this size dependence by approximately linearizing GA growth,(10, 18) whereas the perimeter-adjusted endpoint normalises area expansion by lesion perimeter.(13, 20, 21) Raw GA area growth may therefore underestimate treatment efficacy, whereas square-root-transformed and perimeter-adjusted growth rates provide more appropriate endpoints for real-world pre-post designs.

In contrast to the anatomic findings, visual acuity declined at comparable rates before and after ACP initiation, with no statistically significant difference in slope. This is consistent with GATHER1, GATHER2, OAKS, and DERBY, which similarly demonstrated anatomic slowing without a clear visual acuity benefit over the trial follow-up periods.(2, 3, 9) This dissociation likely reflects limited follow-up, the insensitivity of visual acuity to localised GA progression outside the fovea, and irreversible damage in regions already atrophied before treatment. Longer follow-up and more spatially resolved functional measures, such as microperimetry, will be needed to better characterise the visual implications of ACP treatment in routine practice.

This study has several strengths. The pre- versus post-treatment design(22) allowed each eye to serve as its own control, reducing confounding from stable inter-eye differences in lesion morphology and natural history. Both square-root–transformed and perimeter-adjusted endpoints were evaluated and yielded concordant evidence of treatment effect. Because NIR imaging is acquired routinely as part of OCT and more commonly than FAF, this study shows that clinically available NIR/OCT imaging can detect the anatomic response to ACP over approximately 1 year. Reproducibility was excellent (intraclass correlation coefficient 0.99 for NIR; Pearson r = 0.99 for NIR vs. FAF), supporting the validity of the measurements.

The study has several limitations. First, the study was retrospective and lacked a randomised concurrent control group. Although the pre-post design controls for stable eye-level characteristics, regression to the mean and treatment-selection bias could contribute. However, included and excluded patients did not differ significantly in any measured baseline characteristic (Supplementary Table 1), supporting the representativeness of the cohort. Second, eyes received a mean of 7 injections rather than protocolised monthly treatment, which may affect generalisability but allowed us to examine dosing intensity as a determinant of response. Injection frequency was not significantly associated with the treatment effect, but estimates for both endpoints were directionally consistent with greater slowing at higher dosing frequency, as would be expected if complement inhibition is time-limited between doses. This is

hypothesis-generating: the confidence intervals included no effect, the analysis was exploratory and unadjusted for multiple comparisons, and more frequent treatment may suggest greater adherence. A prospective study with protocolised dosing would be needed to test for a dose-response relationship. Third, the exudative AMD subgroup was modest in size, limiting statistical power for subgroup-specific inference. Fourth, manual delineation is time-consuming and may limit scalability, although reproducibility and FAF correlation were excellent. Fifth, visual acuity data were obtained from routine clinical care rather than standardised research refraction. Finally, longer follow-up is needed to assess the durability of the treatment effect and to determine whether anatomic slowing translates into functional benefit.

In conclusion, intravitreal ACP was associated with a 22.7% reduction in square-root-transformed GA growth and a 23.1% reduction in perimeter-adjusted growth in a real-world cohort. The treatment effect was consistent in non-exudative and exudative AMD and in foveal and extrafoveal GA. Visual acuity declined at comparable rates before and after ACP initiation, consistent with findings from the pivotal trials. These findings support the real-world anatomic efficacy of ACP and support further investigation of its use in patients with concurrent exudative AMD.

Declarations

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Figures

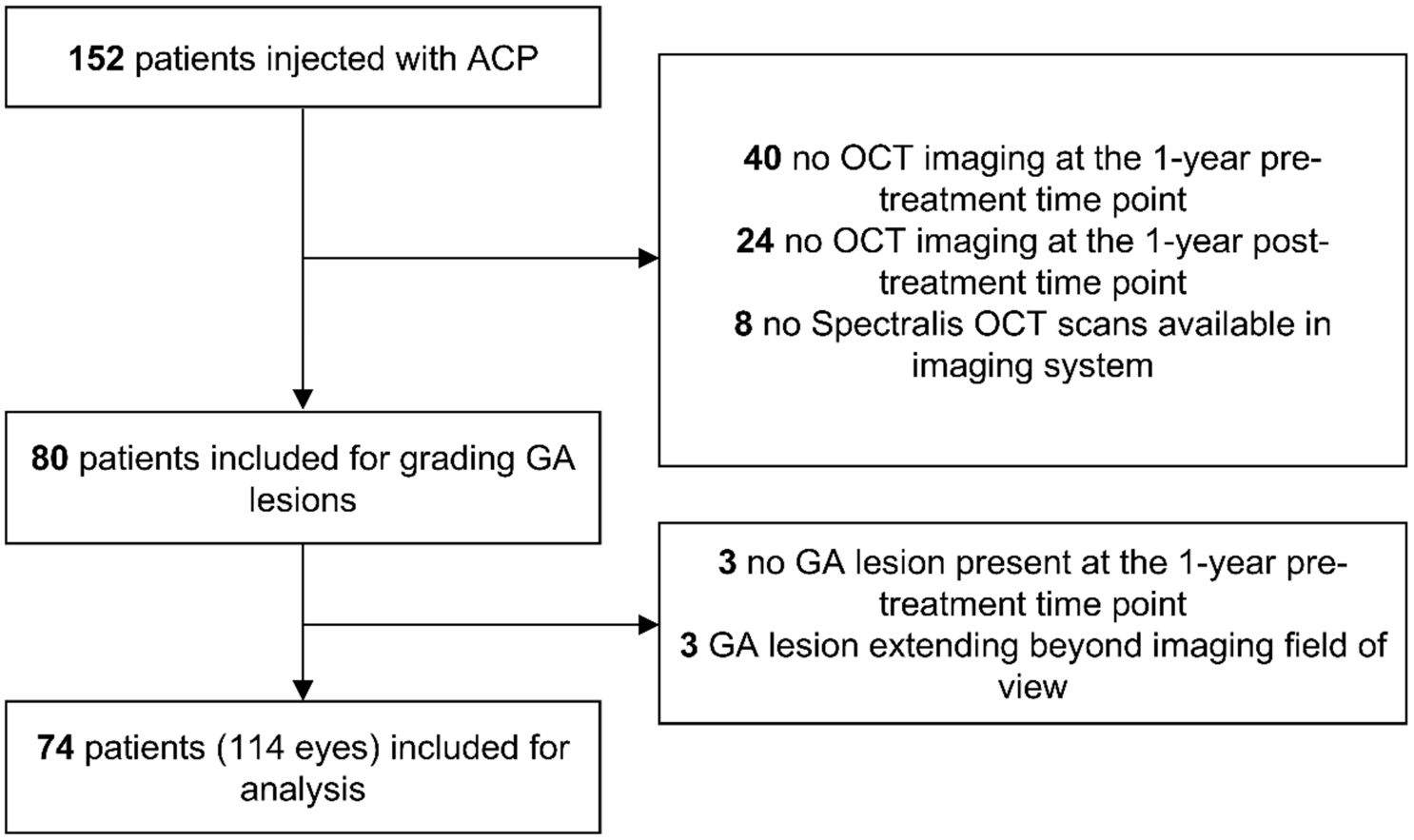

Figure 1

Flowchart of patient inclusion in the study. ACP = avacincaptad pegol; GA = geographic atrophy; OCT = optical coherence tomography.

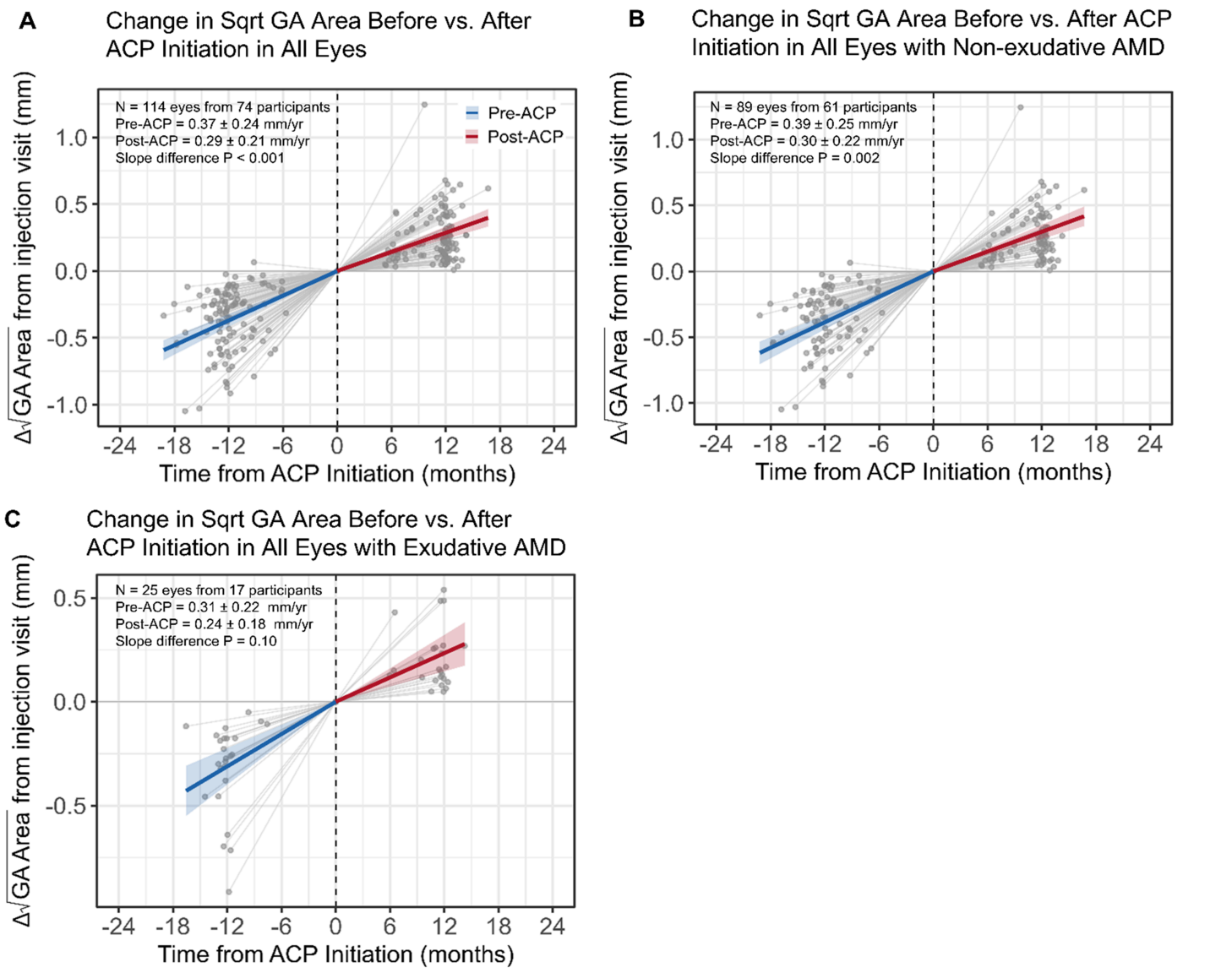

Figure 2

Change in square-root-transformed geographic atrophy (GA) area as a function of time from avacincaptad pegol (ACP) initiation in (**A**) all eyes (N = 114 eyes from 74 participants), (**B**) eyes with non-exudative age-related macular degeneration (AMD) at baseline (N = 89 eyes from 61 participants), and (**C**) eyes with exudative AMD at baseline (N = 25 eyes from 17 participants). Individual eyes' data are represented by grey circles connected by grey lines. The blue and red lines represent the mean linear fits for the pre- and post-ACP periods, respectively, with shaded bands showing the 95% confidence intervals (CIs). The vertical dashed line indicates the ACP initiation visit. **A**, Among all eyes, the growth rate of square-root-transformed GA area decreased from 0.37 (0.24) mm/year pre-ACP to 0.29 (0.21) mm/year post-ACP (slope difference P < 0.001). **B**, Among eyes with non-exudative AMD at baseline, the growth rate decreased from 0.39 (0.25) mm/year pre-ACP to 0.30 (0.22) mm/year post-ACP (slope difference P = 0.002). **C**, Among eyes with exudative AMD at baseline, the growth rate decreased from 0.31 (0.22) mm/year pre-ACP to 0.24 (0.18) mm/year post-ACP (slope difference P = 0.10). P values are from linear

mixed-effects models with random intercepts for patient and eye. ACP = avacincaptad pegol; AMD = age-related macular degeneration; GA = geographic atrophy.

Supplementary Files

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