Abstract

Purpose: To perform an optical coherence tomography (OCT)-based analysis of atrophy progression in patients treated with pegcetacoplan.

Design: Post-hoc analysis of the phase 2 multicenter, randomized, sham-controlled FILLY trial of intravitreal pegcetacoplan for the treatment of geographic atrophy (GA).

Methods: Manual annotation of absence of retinal pigment epithelium (RPE), ellipsoid zone (EZ) and external limiting membrane (ELM) was performed on OCT volumes from baseline and month 12 from the FILLY trial.

Main Outcome Measures: Correlation of GA areas measured on fundus autofluorescence (FAF) and OCT. Difference in square root transformed growth areas of RPE, EZ and ELM loss between treatment groups (monthly injection (AM), injection every other month (AEOM), and sham (SM)).

Results: OCT volumes from 113 eyes of 113 patients (38 AM, 36 AEOM, 39 SM) were included, resulting in 11,074 B-Scans. Median growth of RPE loss was significantly slower in the AM group (0.158 [0.057 – 0.296]) than the SM group (0.255 [0.188 – 0.359]), p = 0.014). Importantly, growth of EZ loss was also significantly slower in the AM group (0.127 [0.041 – 0.247]) than the SM group (0.232 [0.130 – 0.349], p = 0.017). There was no significant difference in growth of ELM loss between the treatment groups (p = 0.114).

Conclusions: OCT imaging provided consistent results for GA growth compared to FAF. Additionally to slower RPE atrophy progression in patients treated with pegcetacoplan, a significant reduction in EZ impairment was also identified by OCT, suggesting the use of OCT as a more sensitive monitoring tool in GA therapy.

Comparison of FAF versus OCT-based evaluation of the therapeutic response to pegcetacoplan in Geographic Atrophy

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Introduction

In a recent breakthrough advance, promising results have been reported for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD) from phase 2 and 3 trials investigating the efficacy and safety of intravitreal pegcetacoplan, a complement C3 inhibitor. The trials demonstrated a significantly reduced GA growth rate measured on fundus autofluorescence (FAF) in treated patients compared to patients receiving sham injections. (1, 2)

GA is the advanced stage of non-neovascular AMD, which is a leading cause of blindness in developed countries. (3) Of all AMD patients, 85-90% are affected by the non-neovascular AMD type which results in at least 1 million patients in the US and 8 million patients worldwide. (4-7) Severe vision loss, however, occurs at a late stage of the disease when the fovea is involved. (8, 9) Therefore, functional parameters like best corrected visual acuity (BCVA) do not reflect disease severity in GA. In the absence of reliable functional markers, clinical studies have used GA growth, an anatomical endpoint, to investigate disease progression and therapeutic efficacy. (10)

With the advent of therapeutic proof-of-principle comes a strong need for identifying optimal imaging methods for patients receiving treatment in clinical trials as well as routine practice. Conventionally, FAF has been considered the standard imaging modality used in clinical trials to assess GA growth. (11) FAF provides a two-dimensional *en face* representation of the atrophic area, with hypoautofluorescence indicating retinal pigment epithelium (RPE) loss. (12) Compared to two-dimensional FAF imaging, OCT, acquired as a volume of cross-sectional scans, provides three-dimensional and therefore more detailed information about the morphology of the affected retinal layers. (13) Previous studies showed that measurements of GA areas by OCT and FAF correlate well, (14) however, the definite RPE loss on OCT did not entirely correspond to the hypoautofluorescent areas on FAF. (15) More importantly, the photoreceptor status cannot be assessed by FAF and, due to masking macular pigment, the fovea cannot be identified easily. (11)

Based on histology, several OCT biomarkers in GA have been proposed, such as RPE loss and loss of the photoreceptor-related ellipsoid zone (EZ) and external

limiting membrane (ELM), (16) with the ELM descent towards the Bruch membrane having been described as the border of atrophy. (17, 18) Unfortunately, RPE loss already represents an irreversible stage of the disease. Therefore, earlier indicators of GA progression are of high interest for clinical trials. The so-called junctional zone surrounding the atrophy, which is the transition zone between healthy and atrophic retina, shows different morphologic alterations demarcating the subsequent area that is likely to become atrophic. (19) In particular, photoreceptor degeneration in the junctional zone has been associated with future GA progression rates. (20) Furthermore, retinal function depends on photoreceptor integrity (20, 21). Consequently, the photoreceptor layers as visualized on OCT are a promising biomarker for earlier treatment intervention and monitoring of GA treatment.

In this study, we comprehensively evaluated the OCT-based measurement of GA progression under complement inhibition treatment for the very first time by expert manual assessment. The purpose of this exploratory post-hoc analysis was to evaluate whether the efficacy of pegcetacoplan in slowing RPE atrophy, measured on FAF, is reproducible on OCT-based analysis. Simultaneously, growth of photoreceptor atrophy was analysed on OCT images.

Methods

Study Design and Participants

This study is a post-hoc analysis of the prospective, multicenter, randomized, sham-controlled phase 2 FILLY trial of intravitreal pegcetacoplan, an investigational therapy for GA secondary to AMD targeting complement C3 (ClinicalTrials.gov identifier: NCT02503332). The primary endpoint was the square root transformed GA growth area imaged on FAF between baseline and 12 months, assessed by a centralized reading center. A detailed description of the FILLY trial has been published previously. (1) In brief, patients enrolled in the FILLY trial had to be at least 50 years of age with a diagnosis of GA secondary to AMD based on FAF imaging. Further major criteria for inclusion were best corrected visual acuity (BCVA) of 24 letters or better using Early Treatment Diabetic Retinopathy Study (ETDRS) charts (20/320 Snellen equivalent), GA area size measured on FAF of 2.5mm^2 or more and 17.5mm^2 or less, presence of any pattern of hyperautofluorescence in the junctional zone of GA, and in case of multifocal GA at least one focal lesion of 1.25 mm^2 or more. Patients were excluded if the study eye showed GA secondary to other causes than AMD, history or current evidence of exudative AMD, and retinal disease other than AMD. 246 patients from 46 sites were randomized in a 2:2:1:1 manner to receive 15mg intravitreal pegcetacoplan monthly (AM), pegcetacoplan every other month (AEOM), sham injection monthly (SM) or sham injection every other month (SEOM) for 12 months.

All patients provided written informed consent. The study was performed in accordance with the tenets of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. This post-hoc analysis was approved by the ethics committee at the Medical University of Vienna.

Image analysis

Patients imaged using Spectralis SD-OCT (Heidelberg Engineering, Heidelberg, Germany) with data available at baseline and month 12 were included in this analysis. SD-OCT volumes were acquired as volumes of 49 B-Scans of each 512 A-Scans, with a pixel area of approximately 120 x 11.25 µm^2, covering the central 20 degrees of the macula. The exact pixel values depended on the axial length. All

annotations were performed on an A-scan basis on every B-scan, using an in-house software tool. Manual annotation of complete RPE loss was performed. The absence of EZ and ELM was manually annotated, if it occurred within or adjacent to the RPE loss area. RPE loss was defined as the complete absence of RPE in combination with hypertransmission in the underlying choriocapillaris. EZ loss was defined as the complete absence of the ellipsoid zone and ELM loss was defined as the complete absence of the external limiting membrane. **Figure 1** shows an example annotation of the three atrophic areas on OCT with the en-face contours on the respective SLO image.

Images with insufficient image quality to perform a reliable annotation as well as images from patients that did not complete the 12 month follow-up were excluded from this analysis. All OCT scans were annotated by a trained image annotator from a group of four and supervised by an experienced clinician.

Statistical analysis

Descriptive statistics were used to summarize demographics and baseline characteristics of the study population. Normal distribution was assessed by means of Shapiro-Wilk-test and data was reported as mean ± standard deviation (SD) for normally distributed data and median ± interquartile range (IQR) for non-normally distributed data, respectively. All statistical analyses were performed using SPSS® version 26 and 28.

OCT-FAF comparison

The RPE loss measured on OCT was compared to the hypoautofluorescent GA area measured on FAF by the centralized reading center of the FILLY trial. The OCT-based atrophy area was calculated by multiplying the number of respectively annotated A-scans with the pixel area reported by the OCT device. The correlation between the GA areas in mm^2 measured on OCT vs. on FAF was reported using Pearson's correlation coefficient (r) and coefficient of determination (R^2) for baseline and month 12. In addition, the limits of agreement were evaluated with a Bland-Altman plot.

OCT-based assessment of atrophy growth under therapy

Baseline RPE loss was compared to both EZ loss as well as ELM loss using the Wilcoxon rank sum test for paired samples.

The month 12 growth area of the three different biomarkers was calculated. To adjust for baseline lesion size the previously established square root transformation was performed by calculating the difference between the square root of the baseline and the square root of the month 12 areas. (22) The resulting growth areas were compared between the treatment groups AM, AEOM and pooled SM using the Kruskal-Wallis-test. Post-hoc pairwise testing was performed using the Mann-Whitney-U-test and the correction for multiple testing was performed with the Bonferroni method.

Results

Study population

OCT volumes from baseline and month 12 of 113 eyes from 113 patients were included in this analysis, resulting in a total of 11,074 manually annotated B-scans. Depending on the treatment assignment, 38 OCT volumes were included from the AM group, 36 from the AEOM group and 39 from the pooled SM group. 65.5% of the study population were female. Mean patient age was 78.9 ± 7.2 years. Of a total of 195 baseline Spectralis scans from the FILLY trial, 40 patients were excluded because of insufficient follow-up data and 42 patients were excluded because of insufficient OCT quality for manual annotation at baseline or month 12.

OCT-FAF comparison

The comparison of GA areas measured on FAF and the area of RPE loss measured on OCT revealed a correlation coefficient of r = 0.97 with an R^2 = 0.86 at baseline and r = 0.97 with an R^2 = 0.81 at month 12. The Bland-Altman-Plot comparing the GA areas assessed on both imaging modalities showed a bias towards higher GA area measurements assessed by FAF as compared to OCT, especially in larger lesions at month 12. Mean difference in measured GA areas between the two imaging modalities was 0.91 ± 0.95mm^2 at baseline and 1.28 ± 1.23mm^2 at month 12 (**Figure 2**).

OCT-based assessment of atrophy growth under therapy

The results from the annotated RPE loss, EZ loss and ELM loss on OCT at baseline are summarized in **Table 1**. At baseline, the area of EZ loss was consistently larger than the RPE loss in all cases ($p < 0.001$). There was no significant difference in RPE loss and ELM loss at baseline ($p = 0.46$).

Comparison of RPE, EZ and ELM loss growth between treatment groups is shown in **Figure 3**, with the statistics summarized in **Table 2**. Results showed statistically significant less median growth of RPE loss at month 12 in the AM group compared to the SM group (0.158mm [0.057 – 0.296] vs. 0.255mm [0.188 – 0.359], $p = 0.014$). Median growth in the AEOM group was 0.190mm [0.106 – 0.336] and showed a trend but no significant difference compared to the other study groups.

According to RPE loss, median growth of the EZ loss at month 12 was also statistically significantly lower in the AM group compared to the SM group (0.127mm [0.041 – 0.247] vs. 0.232mm [0.130 – 0.349], p = 0.017). Median EZ loss growth in the AEOM group was 0.179mm [0.101 – 0.293] and showed no significant difference compared to the other treatment groups.

The median growth of ELM loss showed a trend, but no statistically significant difference between the treatment groups at month 12 (p = 0.114).

Discussion

This analysis provides the first ground truth OCT measurements of human expertise on GA patients receiving intravitreal complement inhibitory treatment. Most importantly, the treatment effects on RPE atrophy, measured on FAF in the FILLY trial, are proven to be accurately reflected on OCT imaging. Interestingly, our results showed that the progression of photoreceptor atrophy, measurable only on OCT, is also slowed in patients treated with pegcetacoplan compared to non-treated patients. As areas with photoreceptor loss have been demonstrated to predict subsequent RPE loss (20), this is an essential finding for understanding the mechanisms of disease in GA and the therapeutic response pattern of complement inhibition. Overall, the results of this extensive effort in human expert annotation provide evidence that FAF may be replaced by routine OCT imaging in clinical practice and that OCT may provide more relevant guidance for disease management.

Regarding the reliability of FAF imaging in GA, our results revealed a bias towards smaller GA areas measured on OCT compared to FAF. Previous studies by our group showed that the definite RPE loss graded on OCT was only weakly correlated with hypoautofluorescent GA areas delineated on FAF, reporting a correlation coefficient of 40%. When adding the areas of uncertain RPE alteration and moderate RPE loss on OCT the correlation increased to 97%. This indicates the discrepancies between OCT and FAF with respect to the visualized morphologic structures. (15)

Our results, based on A-scan level expert grader assessment of the RPE on OCT clearly confirm a positive treatment effect of pegcetacoplan on RPE atrophy progression. Although the bimonthly treated group showed no statistically significant difference, a trend towards slower RPE loss growth was observed compared to sham. In addition to assessment of RPE disruption, we also performed an A-scan based evaluation of relevant neurosensory layers. In our study, the areas of EZ loss at baseline were consistently larger than the areas of RPE loss, suggesting that photoreceptor degeneration precedes RPE loss in GA. This is in line with previous studies investigating the junctional zone of GA lesions on OCT. (23-27) Morphological analyses demonstrated that the photoreceptor loss, indicated by the EZ loss on OCT, reaches outside the GA margin in the majority of cases. (23, 28)

Subsequent studies revealed that the photoreceptor loss in the junctional zone correlated well with future GA progression, both globally and locally. (20, 26) Functional testing with microperimetry provided a significant correlation of the photoreceptor status in the junctional zone with retinal sensitivity, represented by a significantly lower sensitivity in areas with photoreceptor damage. (21, 29-31) In multiple regression analysis the photoreceptor damage was the only predictor of decreased retinal sensitivity, while RPE loss was not found to be a predictor. (21) Consequently, OCT-based measurement of photoreceptor loss in patients with GA is essential in disease monitoring, as this level of detail cannot be reached by FAF. Our results prove a treatment effect of pegcetacoplan not only on RPE atrophy progression, but more importantly also on progression of photoreceptor atrophy. Liao et al. raised the hypothesis that an imbalance in deposition and removal of C3 fragments at the level of RPE, photoreceptors and capillary endothelium adds to the pathomechanisms in the development of GA. C3 fragment accumulation would then lead to phagocytosis of the affected cells. (1) This phenomenon could explain a treatment effect by complement C3 inhibition on both RPE and photoreceptor cells. At the level of the ELM we found a trend, but no significant treatment effect. As we focused on complete absence of the ELM, we might have missed some changes in areas of an ELM descent. This could be subject of further studies evaluating the treatment effect of pegcetacoplan in a multilayer approach.

Monitoring of the photoreceptor condition is of highest relevance as this is the correlate for retinal function. In respect to the dynamics of GA starting at the photoreceptor layer, OCT could also identify patients at risk for clinically relevant GA progression and enable earlier interventions. GA is responsible for severe vision loss in approximately 20% of all AMD patients and more than 8 million individuals are affected worldwide. (7) As the prevalence of AMD increases with age, these numbers are expected to grow further due to an increased life expectancy. (6, 32) In the light of such a huge unmet medical need, there is currently an extensive research effort ongoing in finding an effective treatment for slowing disease progression in GA secondary to AMD with several phase 2 to phase 3 trials. (33) Subsequently to the FILLY trial, the results from the confirmatory phase 3 trials DERBY and OAKS have been revealed recently, where pegcetacoplan met the primary endpoint in OAKS and narrowly missed the primary endpoint in DERBY. (2) Other phase 2/3 trials like

Zimura, a complement C5 inhibitor also showed promising results in inhibiting disease progression in GA secondary to AMD. (34) With the prospect of treatments for GA to be authorized soon and potentially administered on a regular basis, there is a strong need to identify the optimal method to monitor disease progression and therapeutic response in GA patients. Intravitreal treatment is burdensome and identification of patients that will benefit from treatment is essential. Similar to neovascular AMD, where OCT has become the standard of care in screening and monitoring of patients receiving anti-VEGF injections regularly, (35) OCT-based monitoring can also provide precise measurement of disease activity and progression in GA patients. As central vision is only affected in advanced stages, there is no easily obtainable functional parameter to assess disease progression and therapeutic response in GA. (8, 9) Therefore, the main focus for evaluating the therapeutic response in GA patients, especially in earlier stages of extrafoveal disease where loss of visual acuity can still be prevented, relies on morphologic parameters. Knowledge of OCT-based assessment of treatment response, as performed in this analysis, provides the basis for identification of possible responders and non-responders to minimize treatment burden and to offer personalized treatment in one of the most abundant diseases in medicine.

Limitations of our analyses include the limited population size of a phase 2 trial, which will require confirmation in larger phase 3 data sets. There may also be a potential selection bias related to the post-hoc nature of the analysis, as a non-random subset of FILLY patients with Spectralis scans of sufficient image quality were included. This subgroup was selected as Spectralis scans offer superior signal-to-noise ratio needed for reliable manual annotations.
Moreover, as the primary clinical trial was planned with regard to FAF measurements, the data was not statistically predetermined for post-hoc OCT-based analysis. Although manual grading was performed with certified human expertise, a subjective aspect is inherent to annotations of ambiguous cases, specifically in cases with variable image quality throughout follow-up. However, this error is assumed to affect all study arms equally in only a minority of cases, shown by the low number of outliers.

In summary, our study provides the first evidence of equivalence of FAF and OCT imaging in a successful complement inhibition trial. Proof-of-principle relies on human expert grader-based analysis of RPE and photoreceptor loss and maintenance on OCT imaging of GA patients receiving complement inhibitory treatment. Results clearly show a positive treatment effect of pegcetacoplan on both RPE and photoreceptors and its manifestation on OCT-based morphologic monitoring of GA. In the future, such image-based approaches are expected to gain even more relevance due to the availability of automated feature quantification, which may efficiently replace the time consuming and resource-intensive task of manually grading. (36)

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Figure Legends

Figure 1: Example baseline scan with manual annotation
Manual annotation of RPE loss (blue), EZ loss (green), ELM loss (red) on SLO (left) and OCT B-scan (right).

Figure 2: Comparison between geographic atrophy areas on fundus autofluorescence and optical coherence tomography
Comparison of geographic atrophy areas in mm^2 by scatterplot (left) and Bland-Altman plot (right) from baseline (upper row) and month 12 (lower row). The 95% limits of agreement (mean difference ±1.96 SD of the difference) are plotted with orange (positive values) and green (negative values) lines. The blue line denotes the mean difference between the measurements in mm^2.

Figure 3: Boxplots of square root transformed growth areas between the treatment groups for each of the three biomarkers
Black dots denote outliers (1.5 to > 3 x IQR). EZ = ellipsoid zone, ELM = external limiting membrane, RPE = retinal pigment epithelium, AM = monthly injection, AEOM = bimonthly injection, SM = sham.

Table 1: Baseline optical coherence tomography measurements between treatment groups

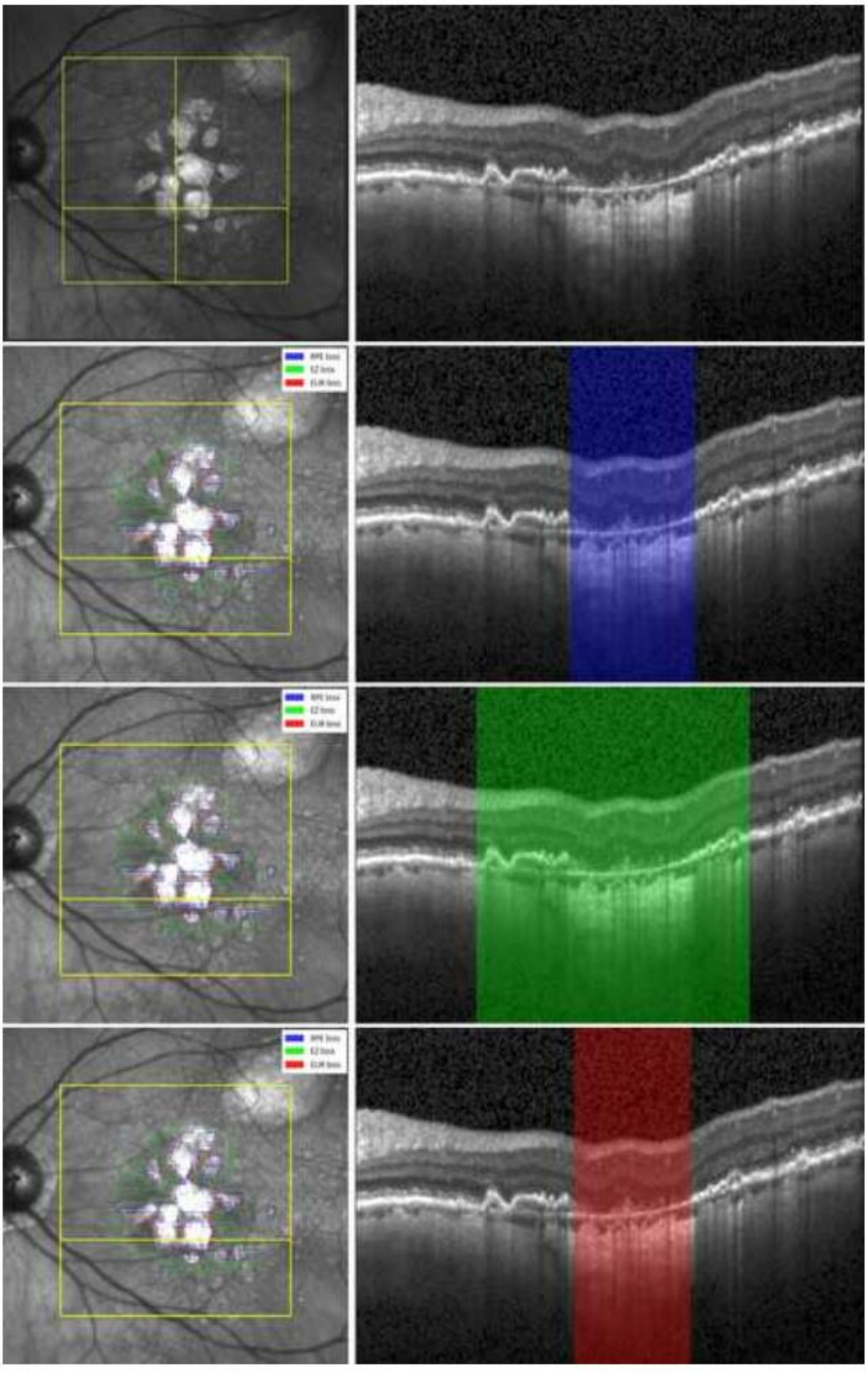
Biomarker	Median [IQR] baseline area (mm^2) per treatment group		
	AM	AEOM	SM
RPE loss	5.37 [3.861 – 9.304]	7.779 [4.009 – 10.794]	6.647 [4.449 – 10.694]
ELM loss	5.308 [3.516 – 9.193]	7.153 [4.044 – 10.821]	8.003 [4.644 – 10.433]
EZ loss	8.238 [5.88 – 13.046]	11.079 [5.516 – 15.242]	10.092 [6.086 – 14.323]

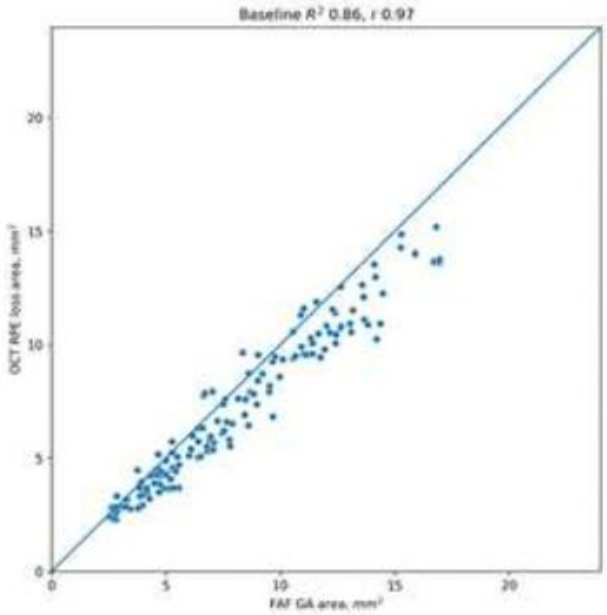
Data are presented as median [interquartile range]. IQR = interquarile range, RPE = retinal pigment epithelium, ELM = external limiting membrane, EZ = ellipsoid zone, AM = monthly injection, AEOM = bimonthly injection, SM = sham.

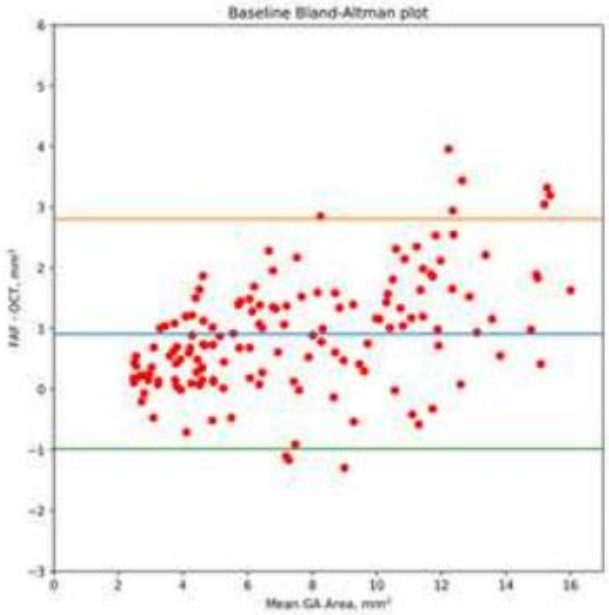
Table 2: Growth areas (square root) at month 12 between treatment groups

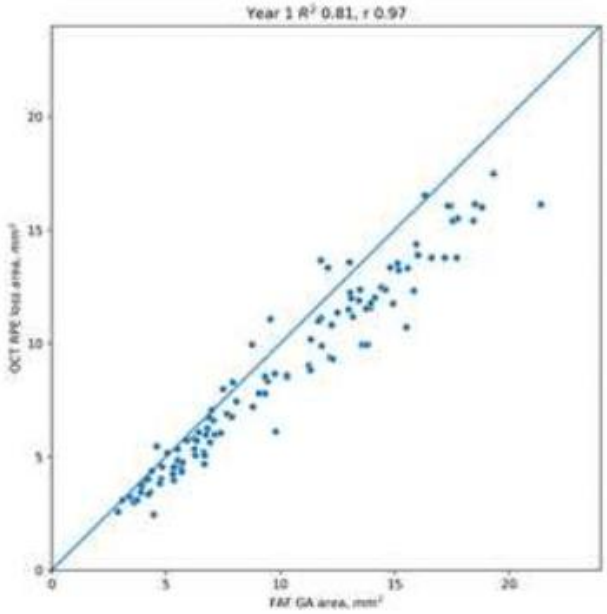
Biomarker	Meidan [IQR] growth area (mm/year) per treatment group			p-value
	AM	AEOM	SM	
RPE loss	0.158 [0.057 – 0.296]	0.190 [0.106 – 0.336]	0.255 [0.188 – 0.359]	0.018* (AM - SM 0.014*)
ELM loss	0.054 [-0.049 – 0.169]	0.085 [-0.026 – 0.225]	0.166 [0.056 – 0.252]	0.114
EZ loss	0.127 [0.041 – 0.247]	0.179 [0.101 – 0.293]	0.232 [0.130 – 0.349]	0.022* (AM - SM 0.017*)

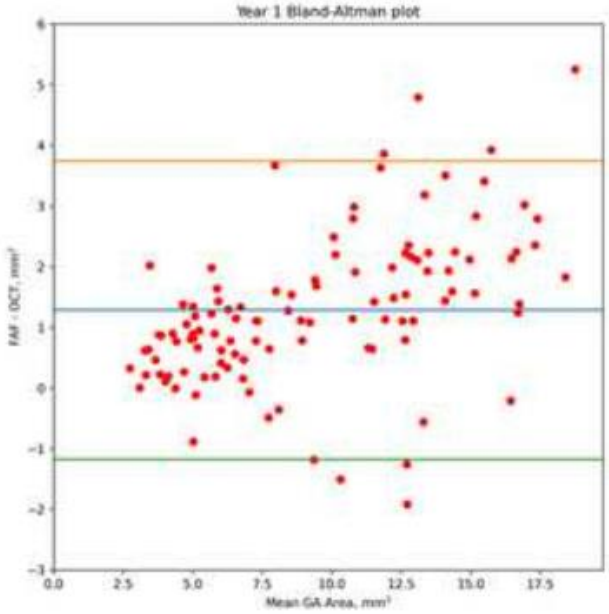
Data are presented as square root transformed median [interquartile range]. IQR = interquarile range, RPE = retinal pigment epithelium, ELM = external limiting membrane, EZ = ellipsoid zone, AM = monthly injection, AEOM = bimonthly injection, SM = sham injection. P-values in brackets denote post-hoc pairwise comparison between AM and SM group.

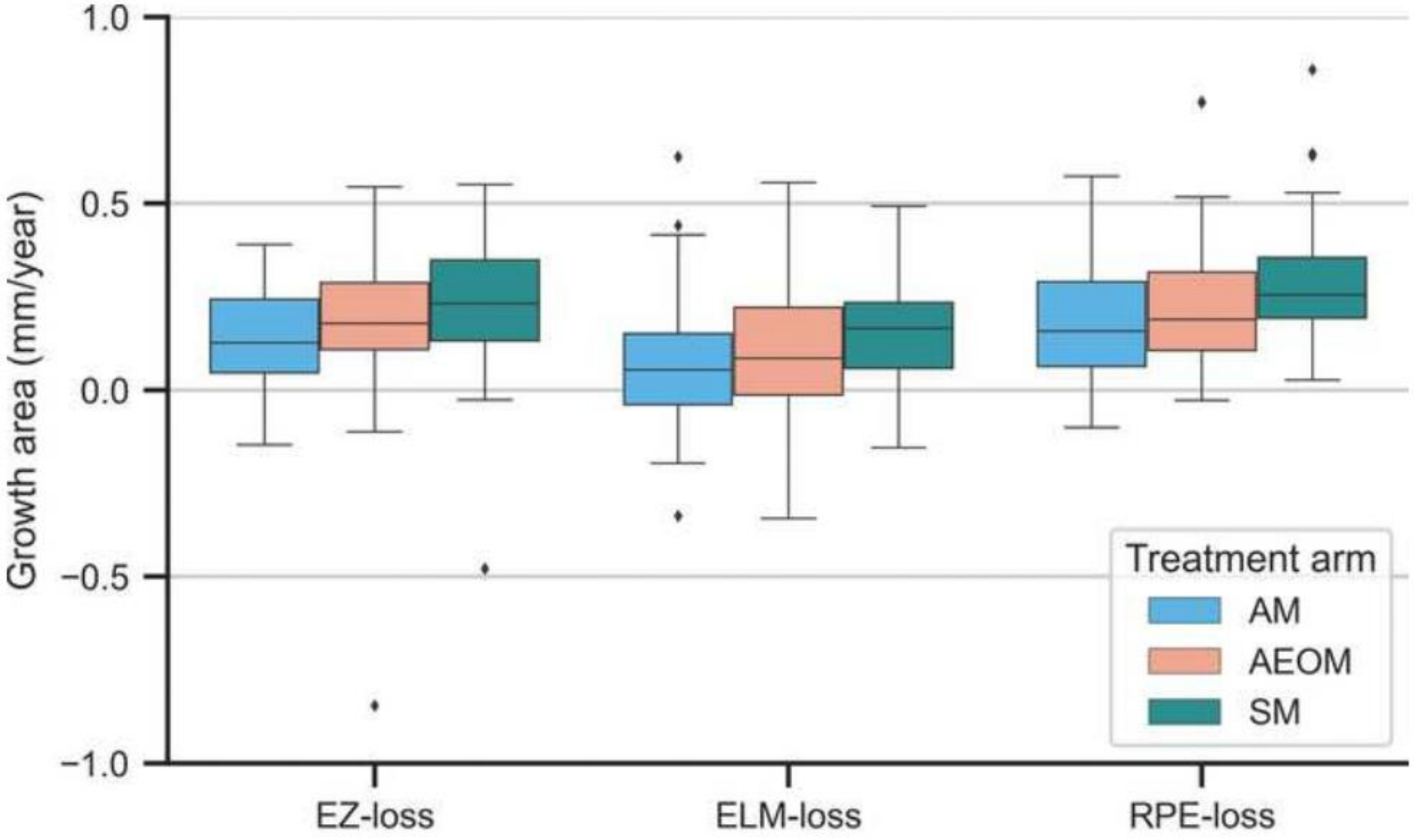



Baseline R^2 0.86, r 0.97
OCT RPE loss area, mm^2
FAF GA area, mm^2


Baseline Bland-Altman plot
FAF - OCT, mm^2
Mean GA Area, mm^2


Year 1 R^2 0.81, r 0.97
OCT RPE loss area, mm^2
FAF GA area, mm^2


Year 1 Bland-Altman plot
FAF - OCT, mm^2
Mean GA Area, mm^2


1.0
0.5
0.0
−0.5
−1.0
Growth area (mm/year)
EZ-loss
ELM-loss
RPE-loss
Treatment arm
AM
AEOM
SM