Analysis of Peripapillary Atrophy in Relation to Macular Geographic Atrophy in Age-Related Macular Degeneration

Petrus Chang, Anna Tan, Glenn J. Jaffe, Monika Fleckenstein, Frank G. Holz, and Steffen Schmitz-Valckenberg; for the GAP Study Group

1Department of Ophthalmology, University of Bonn, Bonn, Germany
2Ophthalmology, Duke University Eye Center, Durham, North Carolina, United States

Correspondence: Steffen Schmitz-Valckenberg, Department of Ophthalmology, University of Bonn, Ernst-Abbe-Str. 2, 53127 Bonn, Germany; steffen.schmitz-valckenberg@ukb.uni-bonn.de.

See the appendix for the members of the Geographic Atrophy Progression (GAP) Study Group.

Submitted: November 11, 2015
Accepted: February 28, 2016

Purpose. The purpose of this study was to investigate the presence, configuration, and progression of peripapillary atrophy (PPA) relative to macular geographic atrophy (GA) in AMD.

Methods. Confocal scanning laser ophthalmoscopy images of 413 eyes of 413 patients with GA secondary to AMD (median age, 77.0 years) were evaluated for the presence and configuration of PPA at baseline. In addition, the progression of PPA and the regression of the shortest linear dimension between PPA and GA (“buffer zone”) were assessed in 164 eyes that had completed 12 months of follow-up.

Results. At baseline, PPA was present in 357 (86.4%) of 413 eyes, of which 330 eyes (79.9%) were classified as nonconfluent and 27 eyes (6.5%) as confluent PPA. At month 12, eight eyes had transformed from nonconfluent to confluent PPA. The median buffer zone at baseline was significantly smaller in these latter eyes than in eyes where the PPA remained nonconfluent (168.46 vs. 1451.64 μm; P < 0.001). The mean regression rate of the buffer zone was 163.0 μm/y (interquartile range, 77.2–281.3).

Conclusions. Peripapillary atrophy is highly prevalent in eyes with GA due to AMD. Assessment of the buffer zone in eyes with nonconfluent PPA at baseline may be helpful to identify subjects at risk for the progression to confluent PPA. In future interventional clinical trials, it may be useful to exclude any eyes both with confluent PPA at baseline and at risk for development of confluent PPA over time to improve the accuracy of GA lesion size quantification and its enlargement over time.

Keywords: age-related macular degeneration, geographic atrophy, fundus autofluorescence, scanning laser ophthalmoscopy

Geographic atrophy (GA) may develop in eyes with exudative AMD, as well as those with concurrent exudative phenotypes that include choroidal neovascularization (CNV) and flattened pigment epithelial detachments.1,3 Geographic atrophy is responsible for severe visual loss in approximately 20% of all patients with AMD.4,5 It is characterized by the progressive enlargement of areas with outer retinal atrophy, which are associated with corresponding absolute scotoma.6-9 In eyes with exudative AMD, unlike those with neovascular AMD, there is no effective therapy to halt or slow the progression of GA and subsequent vision loss.10,11

Fundus autofluorescence (FAF) imaging is a noninvasive imaging method that allows topographic mapping of lipofuscin distribution in the RPE cell monolayer in vivo.12 Photoreceptor degeneration and RPE cell death in areas of GA exhibit a severely reduced FAF signal.13,14 Because of the contrast between hypo-autofluorescent areas and normal retina, it is possible to determine lesion boundaries accurately, particularly compared with conventional fundus photography. Using customized image analysis software, atrophic patches can be quantified, and the spread of the total atrophy size can be determined over time.15 These quantified lesion areas can then serve as an anatomic outcome parameter in interventional clinical GA trials.10,16

Previous studies suggest that there may be some association between peripapillary atrophy (PPA) and late-stage AMD.17,18 In cases where the boundaries of the GA lesion are confluent with PPA, it may be difficult to assess the exact extent of GA lesions, because it may be unclear where GA ends and PPA begins.17 Furthermore, it may be even more difficult to monitor the spread of atrophy over time, because one must differentiate between progression of GA and PPA, an assessment that is especially challenging in eyes that progress from nonconfluent to confluent PPA during the observation period. This issue is of special importance in the context of interventional trials that rely on accurate quantification of the change in total GA lesion size as an outcome measure.

Different strategies have been used to address the measurement of GA lesion area in eyes with PPA. One method is to include only areas of atrophy within the standard ETDRS (Early Treatment Diabetic Retinopathy Study) grid. Another approach is to draw a perpendicular demarcation line at the confluence (or "bridge") between GA and PPA and to then disregard any atrophy nasal to this demarcation line to quantify total GA lesion size. In this latter case, the exact location of the demarcation line can be set either at the most narrow part of the confluence or, alternatively, as a tangential line to the most temporal border of the optic nerve head.15 Regardless of where...
the demarcation line is placed, this approach would always result in a loss of precision, as GA and PPA may have different growth rates. Another strategy would be to exclude any eyes with PPA from studies.

The main aim of the present study was to develop an improved method to quantify total GA lesion size and its enlargement over time in eyes that transform from non-confluent to confluent PPA over the duration of a typical clinical study. To achieve this goal, we used data from a large natural history study in subjects with GA secondary to AMD. The first step was to determine the prevalence of PPA at baseline. Second, progression of atrophy over time with a particular focus on the confluence rates between GA and PPA was analyzed. The final aim was to define a minimum buffer zone between GA and PPA that would potentially allow us to identify eyes at baseline in which confluence over time between PPA and GA would be unlikely during a predefined observational period. At the same time, those eyes that were determined at baseline as having a high risk for transforming from nonconfluent to confluent PPA could then be excluded during the screening process. We hypothesized that this approach would allow for a more accurate quantification of atrophy and its progression over time in interventional studies.

**METHODS**

**Population**

Subjects were recruited from the natural history of Geographic Atrophy Progression (GAP) study (www.clinicaltrials.gov, #NCT00599846). This was a prospective, multicenter, non-interventional, observational study with no masking or randomization. It was originally designed to identify risk factors and to quantify atrophic lesion growth in patients with GA secondary to AMD. Participation sites included centers in the United States, Europe, Israel, and Australia. The study followed the tenets of the Declaration of Helsinki and was approved by the local ethics committees. Informed consent was obtained from each subject after explanation of the nature and possible consequences of the study. Scheduled study visits were at baseline and every 6 months for up to 18 months. The primary and secondary study outcomes have been reported elsewhere.19

To be included into the GAP study, subjects had to be at least 50 years of age with a well-demarcated area of GA secondary to AMD in the study eye. The total GA lesion size had to be \( \leq 17.5 \text{ mm}^2 \) (approximately 7 disc areas [DAs]) with one single lesion of \( \geq 1.25 \text{ mm}^2 \) (0.5 DA). Best-corrected visual acuity (BCVA) in the study eye had to be \( \geq 35 \) letters. In the fellow eye, drusen \( \geq 63 \mu m \) or GA had to be present. Patients who were not eligible for the study if any signs of CNV were observed in either eye. At the baseline visit, all subjects underwent a complete ophthalmic examination including a dilated fundus examination; retinal images were collected using confocal scanning laser ophthalmoscopy (cSLO) imaging and fundus photography. Eligibility was initially determined by the investigator at each participating clinical center. Imaging data were sent to a central reading center (Duke Reading Center, Durham, NC, USA, in collaboration with the GRADE Reading Center, Bonn, Germany) for analysis.

**Imaging Protocol**

Retinal imaging and data submission were performed according to standardized Reading Center operating procedures. These procedures included certification of each photographer prior to the initiation of the study at his/her clinical site. All patients underwent cSLO retinal imaging (Heidelberg Retina Angiograph, HRA classic, HRA2, or Spectralis; Heidelberg Engineering, Heidelberg, Germany) and included acquisition of near-infrared reflectance (IR, 820 nm), blue reflectance (BR, 488 [HRA2 and Spectralis] or 512 nm [HRA classic]), and FAF (excitation [exc], 488 nm; emission [em], 500–700 nm). Images were recorded with a minimum resolution of 512 \( \times \) 512 pixels. The field of view was set at 30 degrees (°) and centered on the macula. For the FAF modality, two additional fields were obtained: one temporal to the macula and the other one nasal to the macula with the temporal aspect of the optic disc in the center.

Retinal imaging data were uploaded by each clinical site through a secure website to an electronic database. Images were then assigned to readers who analyzed the images according to predefined grading parameters, including FAF pattern classification and atrophy configuration (unifocal/multifocal).19,20 The total size of GA was assessed by semi-automated customized image analysis software according to standard operation procedures, as previously described.15,21 These included image alignment of follow-up images to each baseline image and using the individual scaling factor of the baseline image for all images of the same eye to determine the total size of atrophy in square millimeters at each visit.

When there was confluent PPA, a straight white line at the most narrow part (or bridge) of the confluent atrophy was drawn perpendicular to the general orientation of the bridge as

**FIGURE 1.** Illustration of the original strategy used in the GAP Study to quantify total atrophy size in the presence of PPA. A perpendicular white line was positioned at the “bridge” between macular GA and PPA. The same reference line was drawn at the identical position on every follow-up visit image. (A) Color fundus image. (B) Processed FAF image at baseline. (C) Processed FAF image at month 6 (which was also the early exit visit of this subject).
the demarcation reference line (Fig. 1). Any atrophy nasal to the demarcation line was disregarded for GA quantification. In subsequent visits, the demarcation line was drawn at this exact same position before atrophy quantification. For each visit, a grading report was generated, signed, and archived. Additionally, the processed images with GA lesion boundaries that were automatically outlined in white were saved electronically.

### Image Grading

Using the baseline cSLO images, the presence (yes/no) and the configuration (confluent/nonconfluent) of PPA were analyzed in all eyes. For the 164 study eyes with retinal imaging data available at month 12, the smallest linear dimension (SLD) of the buffer zone both at the baseline and month 12 visits was determined by a single reader using the central FAF image (field 2). The SLD was defined as the shortest linear distance between the most nasal GA area and PPA. Analysis followed a multistep process (Fig. 2). (1) The boundaries of the PPA on the central FAF image (the initially processed image from the primary study analysis that showed the boundaries of the central atrophic lesion) were outlined using the pencil-function of Adobe Photoshop CS4 (Adobe Systems, Inc., San Jose, CA, USA) (Fig. 2A). Near-infrared and BR images were additionally available to discriminate the PPA borders for the measurement on the FAF image (Figs. 2B, 2C). (2) The SLD of the buffer zone was drawn as a line using the line function (Fig. 2D). (3) Pixel values were then converted into micrometers using the individual scaling factor of the baseline image as given by the Heidelberg Eye Explorer software.

### Statistical Analysis

Data were compiled in Microsoft Access and analyzed using SPSS 18 (IBM SPSS Statistics, Chicago, IL, USA). Statistical analysis included both frequency and descriptive statistics. Regression of the buffer zone SLD was determined by analysis included both frequency and descriptive statistics. The length of the buffer zone at baseline (visit 1) and subsequent normalization of the SLD of the buffer zone both at the baseline and month 12 visits was calculated by subtracting the measurement at 12 months (visit 3) from the measurement at baseline (visit 1) and subsequent normalization of the SLD of the buffer zone both at the baseline and month 12 visits was determined by a single reader using the central FAF image (field 2). The SLD was defined as the shortest linear distance between the most nasal GA area and PPA. Analysis followed a multistep process (Fig. 2). (1) The boundaries of the PPA on the central FAF image (the initially processed image from the primary study analysis that showed the boundaries of the central atrophic lesion) were outlined using the pencil-function of Adobe Photoshop CS4 (Adobe Systems, Inc., San Jose, CA, USA) (Fig. 2A). Near-infrared and BR images were additionally available to discriminate the PPA borders for the measurement on the FAF image (Figs. 2B, 2C). (2) The SLD of the buffer zone was drawn as a line using the line function (Fig. 2D). (3) Pixel values were then converted into micrometers using the individual scaling factor of the baseline image as given by the Heidelberg Eye Explorer software.

### RESULTS

#### Patient Characteristics

All 413 study eyes of the 413 GA patients in the baseline GAP Study cohort were included in the current analysis. The demographic data and the primary and secondary end points have been published elsewhere. In brief, the median age was 77 years (interquartile range [IQR], 72–82). There were 245 (59%) women. The median total GA size for all eyes at baseline was 6.13 mm² (IQR, 2.95–10.11), with a median progression rate of 1.49 mm²/y (IQR, 0.06–7.33). At the month 12 visit, imaging data of 164 GA patients were available for analysis. For this latter subgroup, the median age was 77 years (69 male, 95 female), and the median GA size at baseline was 6.14 mm². The limited follow-up data are mainly due to the early termination of the GAP Study with initiation of the Geography Atrophy Treatment Evaluation (GATE) Study (NCT00890097) and subsequent enrollment of patients in this treatment study.

#### Presence, Configuration, and Changes of PPA Over Time

At baseline, 357 (86.4%) of 413 study eyes had PPA, of which 350 (79.9%) were classified as nonconfluent PPA and 27 (6.5%) as confluent PPA (Fig. 3A). In the subset of 164 study eyes for which follow-up data were available for at least 12 months, PPA was present at baseline in 141 (86%) eyes. In this group, 10 (7.1%) of 141 eyes had baseline confluent PPA (Fig. 3B). Of the remaining 131 (92.9%) of 141 eyes with nonconfluent PPA at baseline, there were 8 (6.1%) eyes that progressed to confluent PPA within 12 months (transforming PPA) (Fig. 3C). In the group of eyes with no PPA at baseline, 10 (6.1% of 164 eyes) eyes developed PPA during the observation period. None of these eyes progressed to confluent PPA.

#### Association Between Total GA Lesion Size at Baseline and the Configuration of PPA

Figure 4A shows the distribution of total GA area in square millimeters at baseline for different configurations of PPA in the subgroup of patients for which 12-month follow-up data were available (n = 164). There was a significantly greater size of GA at baseline for transforming PPA (median, 7.8 mm²) and confluent PPA (median, 12.7 mm²) in comparison to eyes...
classified as nonconfluent PPA (median, 5.7 mm²) and no PPA (median, 4.7 mm²; P < 0.001).

Quantitative Assessment of the Buffer Zone SLD

The median SLD of the buffer zone at baseline was 1368.0 lm (IQR, 690.8–1916.0; range, 45.9–3500.0). The length was significantly smaller (Mann-Whitney U, P < 0.001) in eyes classified as transforming PPA (n = 8; median, 168.5 lm; IQR, 134.5–300.0) in comparison to eyes that did not transform to confluent PPA at month 12 (nonconfluent PPA; n = 132; median, 1452.0 lm; IQR, 893.6–1918.0; Fig. 4B).

The SLD of the buffer zone was significantly smaller in eyes with multifocal GA (n = 111; median, 1249.46 lm; IQR, 671.8–1799.0) than in eyes with unifocal GA (n = 29; median, 1917.0 lm; IQR, 1070.0–2321.0; P < 0.01; Fig. 4C). Multivariate analysis showed that multifocal GA had a smaller SLD of the buffer zone compared with unifocal GA, when adjusted for the macular GA size at baseline (P < 0.05).

The majority of eyes had the previously defined diffuse FAF pattern (n = 94; median, 1296.0 lm; IQR, 655.9–1906.0). There were too few eyes in each category with the other FAF patterns for a detailed analysis. There was no statistically significant association with the SLD of the buffer zone in all eyes with the diffuse FAF pattern to all eyes with other FAF patterns (P = 0.22).

The median regression of the buffer zone SLD was 163 μm/y (IQR, 77.2–281.3; range, 3.4–1769.2; Fig. 5). Regression of the SLD of the buffer zone was neither significantly affected by the number of GA spots (P = 0.09) nor the FAF patterns (diffuse versus all other patterns) at baseline (P = 0.65).
would propose a length of at least 300 intended observational period. For a 12-month study, we those eyes with nonconfluent or no PPA. This result is eyes with confluent and transforming PPA compared with nonconfluent to confluent PPA in this study.

third quartile out of the eight eyes that transformed from the assumption that transforming eyes compared with non-confluent PPA at baseline and by minimizing the inclusion of eyes with nonconfluent PPA at baseline that may transform to confluent PPA at follow-up visits. We recommend that this approach should be used in interventional GA trials to refine outcome parameters that are based on the assessment of change in GA lesion size over time. This approach would allow a more precise assessment of new therapeutic strategies that aim to reduce further lesion enlargement.

ACKNOWLEDGMENTS

The GAP Study was sponsored by Alcon Research Ltd. The following Alcon Research Ltd. employees contributed to this study as Clinical Trial Managers: Alberta Davis, Petra Kozma-Wiebe, and Miguel Martinez.

Supported by Alcon Laboratories, Inc. (Fort Worth, TX, USA). The GAP Study was funded, designed, and conducted by the sponsor. The primary and secondary study objects are not the aim of the current publication and have been reported elsewhere. The data presented are additional analyses that were conducted without extra funding by the sponsor. The manuscript was reviewed and approved by the sponsor.

Disclosure: P. Chang, Heidelberg Engineering (F), Carl Zeiss Meditec AG (F), Optos (F); A. Tan, Heidelberg Engineering (F), Carl Zeiss Meditec AG (F), Optos (F); G. Jaffe, Alcon/Novartis

DISCUSSION

The current analysis demonstrates dynamic changes in atrophy progression over time with regards to macular GA lesions and PPA in subjects with GA secondary to AMD. It confirms that nonconfluent PPA (79.1%) is highly prevalent, whereas confluent PPA (6.1%) is rather uncommon in subjects with a total lesion \( \leq 17.5 \) mm\(^2\) (approximately 7 DAs).\(^7\) Over time, there was an increase in the total number of eyes showing PPA (86%-92%). In addition, only a small proportion of eyes (6.1%; \( n = 8 \)) with nonconfluent PPA at baseline changed into confluent PPA (transforming PPA) during the 12-month observational period.

Accurate assessment of the total GA lesion area is challenging in the presence of confluent and particularly transforming PPA.\(^8\)\(^9\)\(^17\) The precise measurement of the macular GA area is especially important in interventional studies that aim to reduce GA enlargement rates over time and that use change in lesion size as the primary efficacy outcome parameter.\(^10\) We had initially hypothesized that if one excluded eyes with confluent PPA at the baseline visit and those that developed confluent PPA at any follow-up visit (transforming eyes), it would be possible to more accurately quantify lesion variation over time. Given the presence and distribution of the configuration of PPA at baseline in the current analysis, we believe that it would be prudent and practical to exclude eyes with baseline confluent PPA, particularly because the proportion of such eyes is small. However, given the high number of eyes with nonconfluent PPA at baseline and the low number of eyes transforming from nonconfluent to confluent PPA within 12 months, it would be impractical to also exclude any eye with PPA at baseline.

Herein, a detailed analysis focused on the quantification of the SLD between PPA and GA (so-called “buffer zone”). Although SLD regression rate in the buffer zone was highly variable among eyes, the quantitative analysis clearly confirms the assumption that transforming eyes compared with non-transforming eyes and eyes with nonconfluent PPA at baseline have a much smaller baseline buffer zone. Based on these results, we would suggest not only to exclude eyes with confluent PPA at baseline, but also to consider limiting the inclusion of eyes with nonconfluent PPA at baseline to those eyes with a certain minimal SLD between PPA and the most nasal part of macular GA. The minimal buffer zone length that would qualify as a “safety zone” would depend on the intended observational period. For a 12-month study, we would propose a length of at least 300 \( \mu \)m, which would be the third quartile out of the eight eyes that transformed from nonconfluent to confluent PPA in this study.

The baseline area of macular GA was significantly larger in eyes with confluent and transforming PPA compared with those eyes with nonconfluent or no PPA. This result is expected, as the buffer zone dimensions in our study are inversely affected by the combination of the PPA area and the area of macular GA. Geographic atrophy presents in a variety of different patterns: the lesion can be unifocal or multifocal and also further classified in to various abnormal FAF patterns.\(^7\)\(^-\)\(^9\)\(^22\) Significantly lower buffer zone dimensions were found to be associated with multifocal GA, whereas an association to previously defined FAF patterns was not seen. Further studies to identify other risk factors for transforming into confluent PPA could also help to refine patient selection in future trials.

The strengths of this study include the use of data from a large-scale, multicenter, natural history study; standardized submission of imaging data to a reading center that certified study site imaging technicians; and prospective data collection according to a predefined standardized image acquisition protocol. Limitations of this study include relative high rates of patient dropouts, mainly due to the rollover into a prospective, interventional study (GATE Study). However, 164 patients completed a 12-month follow-up, allowing for a meaningful analysis. There may also have been a general selection bias of included patients who completed the 12-month follow-up due to the specific GAP Study inclusion and exclusion criteria, particularly with regard to the morphologic criteria (e.g., total lesion size).\(^19\)

In conclusion, this study suggests that buffer zone SLD is a potential useful parameter to identify subjects at risk to transform over time from nonconfluent to confluent PPA. Our study data would suggest that the accuracy of lesion size quantification can be improved by excluding eyes with confluent PPA at baseline and by minimizing the inclusion of eyes with nonconfluent PPA at baseline that may transform to confluent PPA at follow-up visits. We recommend that this approach should be used in interventional GA trials to refine outcome parameters that are based on the assessment of change in GA lesion size over time. This approach would allow a more precise assessment of new therapeutic strategies that aim to reduce further lesion enlargement.

FIGURE 5. Regression over time of the buffer zone SLD between PPA and macular GA (A, color fundus photography at baseline; B, corresponding FAF image at baseline with SLD measurement; C, FAF image at month 6 with SLD measurement; D, FAF image at month 12 with SLD measurement).
References


APPENDIX

The following principal investigators were members of the GAP Study Group: H. J. Agostini (Freiburg, Germany), R. Anand (Dallas, TX, USA), J. Arnold (Sydney, Australia), F. Bandello (Udine, Italy), D. S. Boyer (Beverly Hills, CA, USA), D. M. Brown (Houston, TX, USA), D. Callanan (Arlington, TX, USA), U. Chakravarty (Belfast, Ireland), G. Cowan (Fort Worth, TX, USA), S. Downes (Oxford, United Kingdom), R. Gruymer (Melbourne, Australia), L. S. Halperin (Ft. Lauderdale, FL, USA), Y. G. He (Dallas, TX, USA), J. S. Heier (Boston, MA, USA), F. G. Holz (Bonn, Germany), A. Leys (Leuven, Belgium), A. Loewenstein (Tel Aviv, Israel), E. Midena (Padova, Italy), S. Patel (Abitene, TX, USA), D. Pauleikhoff (Münster, Germany), A. Pollock (Rehovot, Israel), C. Pruente/M. Georgoulis (Vienna, Austria), S. R. Russell (Iowa City, IA, USA), S. V. Sadda (Los Angeles, CA, USA), L. Singerman (Cleveland, OH, USA), J. A. Sahel/S. Mohnand-Said (Paris, France), G. Staurenghi (Milan, Italy), M. P. Teske (Salt Lake City, UT, USA), A. Tufail (London, United Kingdom), C. Von Strachwitz (Würzburg, Germany), J. A. Wells III (West Columbia, SC, USA), P. Wiedemann (Leipzig, Germany), and S. Wolf/U. Wolf-Schnurrbusch (Bern, Switzerland).