Type-1 choroidal neovascularization is associated with reduced localized progression of atrophy in age-related macular degeneration

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Abstract

Purpose: To investigate the association between the presence of type-1 choroidal neovascularization (CNV) and the localized progression of atrophy in age-related macular degeneration (AMD).

Design: Analysis of patients' data collected in the context of two non-interventional, prospective studies conducted at the Department of Ophthalmology, University of Bonn, Germany.

Subjects: A total of 98 eyes diagnosed with AMD of 59 patients (40 female, 19 male) with a mean (± SD) age at baseline of 76.60±6.65 years and a median [IQR] review period of 1.17 years [1.01, 1.55] were included. Eyes were subdivided into three categories based on multimodal imaging and on ocular history: RPE-atrophy with treatment-naïve quiescent CNV (n=7), RPE-atrophy with a history of exudative CNV (n=10), and RPE-atrophy without evidence of co-existing CNV (n=81)

Methods: RPE-atrophy was delineated based on serial fundus-autofluorescence and infrared-reflectance images using the RegionFinder software. If CNV was detected by optical coherence tomography angiography (OCTA), its location and dimension was spatially mapped to RPE-atrophy. The *localized* progression of RPE-atrophy in topographic relation to the CNV lesion was than analyzed using mixed-effects logistic regression. The spatial overlap (Dice coefficient) between predicted and observed RPE-atrophy progression was evaluated to estimate the model accuracy.

Main Outcome Measures: Odds ratio (OR) for localized RPE-atrophy progression in areas overlying type 1 CNV.

Result: The prediction model achieved a high overlap between predicted and observed RPE-atrophy progression with a cross-validated Dice coefficient [95 % CI] of 0.87 [0.85, 0.89] reflecting a high accuracy. The odds for future RPE-atrophy involvement were reduced by a factor of (odds ratio [95% CI]) 0.21 [0.19, 0.24] in the presence of treatment-naïve quiescent

type 1 CNV and by the factor of 0.46 [0.41, 0.51] in presence of exudative type 1 CNV, respectively.

Conclusion: The results indicate that there is markedly reduced RPE-atrophy progression in areas co-localizing with quiescent and exudative type 1 CNV. This observation is compatible with a potential protective effect of type 1 CNV on the RPE and overlying neurosensory retina. These results may have relevant clinical implications for the management of CNV and may further lead to new therapeutic strategies to prevent atrophy progression.

Introduction

Age-related macular degeneration (AMD) is a major cause of legal blindness in industrial countries.[1–3] The late-stages of AMD are characterized by the development of macular neovascularization and/or atrophy of the photoreceptors, the retinal pigment epithelium (RPE), and of the choriocapillaris (ChC). The current concept is to treat macular neovascularization with anti-VEGF therapy to prevent or decrease exudation from these neovascular membranes into the surrounding retinal tissue. While anti-VEGF therapy has been proven to be safe and effective to significantly delay vision loss due to neovascular AMD,[4] there is no treatment available to stop or halt the progression of atrophy in late-stage AMD. Hence, atrophic AMD is characterized by progressive visual loss,[5] that severely impacts activities of daily living,[6] and quality of life.[7]

Various pathogenic factors have been implicated in the progression of atrophy in AMD.[8,9] The surrounding non-atrophic junctional zone is characterized by degenerative alterations affecting the photoreceptors, the retinal pigment epithelium (RPE) as well as Bruch's membrane (BrM) and the choriocapillaris (ChC).[10–15] However, it is not yet known, what exact events lead to development and progression of compete atrophy of the RPE and outer retina. While the main focus of clinical research in atrophic AMD was to identify the relevant risk factors for *increased* atrophy development and/or progression,[8] sporadic clinical observations were reported that the presence of subtypes of macular neovascularization might be associated with *decreased* atrophy progression. [16–18] Hypothetically, development of type 1 choroidal neovascularization (CNV), that originates from the choroid and breaks through BrM to be localized directly beneath the RPE may represent a protective mechanism to prevent RPE and photoreceptor degeneration. This view is contrary to therapeutic approaches aiming to achieve complete regression of the abnormal vessel complex..

To prove the hypothesis that type 1 CNV prevents RPE-atrophy progression would therefore have relevant clinical implications for the management of macular neovascularization and may further lead to new therapeutic strategies to prevent atrophy progression.

With this aim, we use longitudinal data of patients with RPE-atrophy to develop predictive models for the *localized* disease progression in topographic relation to type 1 CNV presence. These models allowed us to reliably predict the spatio-temporal disease progression, which can be applied to formally test the aforementioned hypothesis in a quantitative manner. With this approach, we demonstrate that presence of type 1 CNV is indeed associated with a slower directional progression of RPE-atrophy.

Methods

Patients

Patients included in this analysis participated in two longitudinal studies with the same basic imaging protocol: (1.) the non-interventional, prospective natural history Directional Spread in Geographic Atrophy 2 study (DSGA 2, NCT02051998, PI: M. Fleckenstein),[19,20] (2.) or the prospective cohort Structure-Function-Correlation in CNV secondary to AMD study (PI: S. Schmitz-Valckenberg).[21,22] Both of these longitudinal studies were conducted at the Department of Ophthalmology, University of Bonn, Germany, adhered to the tenets of the Declaration of Helsinki and were approved by the institutional review board (Institutional Review Board of the University of Bonn, approval ID: 197/12 and 191/16, respectively). Written informed consent was obtained from all participants in these studies. The inclusion criteria have been described previously in detail.[19–22] Briefly, for the DSGA 2 study, patients needed to be older than 55 years at the time of inclusion and had to exhibit geographic atrophy (GA) secondary to AMD in at least one eye.[23] The diagnosis of AMD was based on the presence of drusen and hyperpigmentary changes and a compatible FAF phenotype, while excluding FAF phenotypes of mimicking diseases such as late-onset Stargardt disease.[24] For the Structure-Function-Correlation in CNV secondary to AMD study, patients needed to show CNV secondary to AMD defined by drusen and by exclusion of other causes of CNV (e.g., angioid streaks, pathologic myopia). In this study, eyes could receive anti-VEGF therapy as the standard of care. For both studies, exclusion criteria were any history of retinal surgery, laser photocoagulation, and radiation therapy or other retinal disease in the study eye such as diabetic retinopathy.[23] Patients were seen for up to 24 months at 6 month or 12 month intervals, respectively. In both studies, according to the protocols, retinal imaging was also performed in the fellow-eyes, regardless of the AMD stage. Therefore, in the DSGA study, follow-up data also for eyes with exudative CNV undergoing anti-VEGF therapy (as the standard of care) were available.

To be included in the current analysis, patients had to exhibit well-demarcated RPE-atrophy, defined by a region of hypertransmission in SD-OCT with disruption of the RPE of at least 250 µm in diameter, evidence of overlying photoreceptor degeneration and absence of signs of an RPE tear.[25] Moreover, only patients with longitudinal follow-up data ≥6 months after the initial Optical Coherence Tomography Angiography (OCTA) exam were included in the analysis. Presence of type 1 CNV was not an exclusion criterion (see 'Categorization of eyes'),
To illustrate long-term association between CNV and reduced localized RPE-atrophy progression, imaging data that had been collected in the context of the DSGA study prior to the baseline of this analysis was also used (prior to the availability of OCTA imaging).

Imaging protocol

Following pupil dilatation with 0.5% tropicamide and 2.5% phenylephrine, patients underwent 30° x 30° fundus autofluorescence imaging (λ excitation 488 nm, λ emission 500 - 700 nm), 30° x 30° infrared reflectance (λ 815 nm) imaging, and 30° x 25° SD-OCT imaging (121 B-scans, ART 25) using a Spectralis HRA+OCT2 (Heidelberg Engineering, Germany). OCTA imaging was performed with the PLEX Elite 9000 including a 6x6 mm and 9x9 mm scan (Carl Zeiss Meditec, Germany). Additional fluorescein angiography (FA) and/or indocyanine green angiography (ICGA) was performed at the discretion of the investigator e.g., if there was suspicion of CNV.

Categorization of eyes:

The categorization of eyes was performed by two readers based on serial multimodal imaging and on the patients' ocular history that had been collected in the context of the DSGA/Structure-Function-Correlation studies. In case of discrepancies, the final decision was made through joint image re-evaluation.

Eyes were subdivided into three categories:

1. RPE-atrophy with treatment-naïve quiescent CNV: The term "treatment-naïve quiescent type 1 CNV" here refers to type 1 CNV lesions visible on OCTA, that have

not been treated previously and that had no signs of exudation (defined by intra- or subretinal fluid and/or retinal hemorrhage) during the course of the study similar to the definition by Querques and coworkers [26]. Typically, in these eye, there is a dense vascular network between BrM and the RPE on OCTA,[27,28] and there is the previously described diagnostic 'double-layer sign' on structural OCT [29,30] in absence of signs of exudation (Figure 1).

2. RPE-atrophy with a history of exudative type 1 CNV: The term "exudative type 1 CNV" here refers to type 1 CNV lesions that had been treated by anti-VEGF due to signs of exudation (cf. above). This group may therefore include eyes with inactive CNV (i.e., cessation of exudative activity after anti-VEGF therapy).

3. RPE-atrophy without evidence of CNV: Eyes were categorized into this group if there was no evidence of CNV (as defined by OCTA and the absence of the 'double-layer sign' on structural OCT) in the setting of RPE-atrophy. These eyes could also be referred to 'geographic atrophy' (GA) according to the CAM consensus.[25]

Eyes that exhibited any type of the following clinical entities were excluded from this analysis: treatment-naïve quiescent type 1 CNV without RPE-atrophy, exudative type 1 CNV without RPE-atrophy, fibrotic lesions and/or type 2 CNV [including minimally classic CNV] as well as intermediate AMD.

Image grading

RPE-atrophy was semi-automatically annotated using the RegionFinder software (Heidelberg Engineering, Germany) based on FAF and IR images as previously described.[31,32] The grading task was randomly split among three experienced readers to obtain unbiased annotations. In eyes with RPE-atrophy and treatment-naïve quiescent type 1 CNV or exudative type 1 CNV, the area of CNV was delineated on the OCTA outer retina to choriocapillaris (ORCC) slab (6x6 mm scan). The segmentation of the RPE-Fit boundary, which defines the outer boundary of the ORCC slab (RPE Fit + 37 µm offset) was adjusted, if necessary.

Imaging features and feature engineering

For the prediction of localized progression, the labeled OCTA images were registered to the FAF images using vessel bifurcations as landmarks (Figure 2). Hereby, a superficial OCTA slab was utilized to define the point selections instead of the ORCC slab, since vessel bifurcations for retinal vessels were better visible in the superficial slab. Similarly, the fovea was labeled on the structural SD-OCT volume by selecting the central B-scan and then mapped to the co-acquired confocal scanning laser ophthalmoscopy (cSLO) infrared reflection (IR) image, which was also registered to the FAF images. To reduce the computational complexity, the imaging data was down-sampled from an en-face resolution of 768×768 px to 300x300 px. For the first and last visits of each eye, the X-Y coordinates, the distance to the fovea, distance to the boundary of atrophy and the localized presence of CNV (presence/absence) were recorded for each pixel. In consideration of the fovea position, the laterality (temporal versus nasal) and vertical position (superior versus inferior) were determined for each pixel. Since the eccentricity revealed a non-monotonic effect on atrophy development based on visual analysis (i.e., atrophy development was less likely at both, small [<2°] and large eccentricities [>8°]), the eccentricity was transformed into a categorical predictor (0°-2°, 2°-4°, 4°-6°, 6°-8°, >8°).

Predictive modeling and statistical analyses

Statistical analyses were performed using the software environment R and the add-on packages lme4 and caret. To determine the potential localized effect of CNV on RPE-atrophy progression, a mixed-effects logistic regression model was fitted to the data. This model served to predict future presence of atrophy on a localized, pixel-wise basis and considered the hierarchical nature of the data (eyes nested within patients). The model considered global predictors (i.e., affecting every location in the eye) such as the diagnostic group (treatment-naïve quiescent type 1 CNV with RPE-atrophy, exudative type 1 CNV with RPE-atrophy, RPE-atrophy without evidence of CNV) and the follow-up time as well as localized predictors (i.e.,

specific to each pixel-wise location) including the distance to the prior atrophy boundary (in degree), distance to the foveal center (eccentricity in degree), the vertical (superior vs. inferior) and horizontal (temporal vs. nasal) position as well as the localized presence of treatment-naïve quiescent CNV (absence/presence) or exudative type 1 CNV (absence/presence). The odds ratio obtained from mixed-effects logistic regression for the association between the localized future development of RPE-atrophy and the localized presence of treatment-naïve quiescent CNV served as primary outcome.

Further, to estimate the spatial prediction accuracy of the model, the Dice coefficient was calculated using 5-fold cross-validation (considering the patients as grouping factor). The Dice coefficient is a spatial overlap index ranging from 0 (indicating no spatial overlap between predicted and observed RPE-atrophy progression) to 1 (indicating complete overlap).[33] The optimal classification threshold for the predicted probabilities was hereby obtained from the training sets and applied to each respective test set.

Last, to estimate the association between “global” (i.e., overall) RPE-atrophy progression and the presence of treatment-naïve quiescent type 1 CNV and or exudative type 1 CNV, we applied the point-wise model to predicted future localized RPE-atrophy progression, while setting the variable “presence of localized CNV” to “absent” for all locations and the diagnosis to “RPE-atrophy without CNV” for all eyes. All of the remaining predictors were not altered. A mixed-effects model considering the hierarchical nature of the data (eyes nested within patients) was applied to determine the difference between predicted progression rates based on all predictors versus predicted progression rates after concealing the presence of CNV.

Results

Baseline data

A total of 98 eyes of 59 patients with a mean age (± SD) of 76.60 ± 6.65 years with a median [IQR] review period of 1.17 years [1.01, 1.55] were included in this analysis. These eyes were categorized as follows: a total of seven eyes with RPE-atrophy and treatment naïve quiescent CNV; at total of ten eyes with RPE-atrophy and exudative type 1 CNV; and a total of 81 eyes with RPE-atrophy but no evidence of CNV.

A total of 20 eyes of the overall 118 eyes of the 59 patients had been excluded due to absence of RPE-atrophy (n=7), presence of fibrotic lesions and/or type 2 CNV (n=7) or due to insufficient image quality (n=6). Table 1 provides a detailed overview of the eye-level diagnoses.

In terms of topographic relationship, for eyes with treatment-naïve quiescent type 1 CNV, the area of RPE-atrophy was fully embedded in the type 1 CNV lesion in one eye (e.g., Figure 4, upper patient), while it was adjacent to the treatment-naïve quiescent CNV in the other six eyes (e.g., Figure 2 and Figure 4, lower patient). For eyes with RPE-atrophy with exudative type 1 CNV, RPE-atrophy was fully embedded in the CNV lesion in 3 eyes (e.g., Figure 5) and adjacent to the CNV lesion in 7 eyes. The overall RPE-atrophy progression rates tended to be smaller for eyes with treatment-naïve quiescent type 1 CNV (estimate [95% CI] 0.95 mm^2/year [0.35 – 1.56]) and eyes with exudative type CNV (1.15 mm^2/year [0.50 – 1.80]) as compared to eyes without evidence of CNV (1.56 mm^2/year [1.27 – 1.85]). The same tendency was observed for the square-root transformed progression rates (Table 2).

Association of CNV presence and localized RPE-atrophy progression

RPE-atrophy area and age at baseline did not differ significantly in dependence of the diagnostic subgroup (i.e., RPE-atrophy with treatment-naïve quiescent type 1 CNV, RPE-atrophy with exudative type 1 CNV, or RPE-atrophy without evidence of CNV; Table 2).

The point-wise (mixed-effects) logistic regression revealed that the follow-up time, distance to the atrophy boundary, eccentricity from the fovea as well as the horizontal position (temporal versus nasal retina) were significantly associated with the localized future development of RPE-atrophy (Table 3)

Notably, the localized presence of treatment-naïve quiescent type 1 CNV was associated with markedly reduced odds for the localized future progression of RPE-atrophy (odds ratio [95% CI] of 0.21 [0.19, 0.24]; P<0.001). For eyes with treatment-naïve quiescent type 1 CNV, no additional global (i.e., spatially unspecific) association with localized future RPE-atrophy progression was observed (0.89 [0.53, 1.49]; P=0.658). Similarly, the localized presence of exudative type 1 CNV was associated with markedly reduced odds for the localized future progression of RPE-atrophy (0.46 [0.41, 0.51]; P<0.001). The diagnosis of exudative type 1 CNV was also associated with a reduced progression of RPE-atrophy in a global (i.e., spatially unspecific) manner (0.31 [0.18, 0.53]; P<0.001). A marginal effects plot - limited to the immediate junctional-zone surrounding the RPE-atrophy (0.5° [approx. 145 µm], in view of the nature of the disease) - illustrated this pronounced association of treatment-naïve quiescent and exudative type 1 CNV with a reduced localized progression probability (Figure 3).

The cross-validated spatial overlap between predicted RPE-atrophy and observed RPE-atrophy at follow-up was (Dice coefficient, mean [95 % CI]) 0.51 [0.47, 0.55] when considering only regions not previously affected by RPE-atrophy and 0.87 [0.85, 0.89] when considering all topographic locations, underscoring the model accuracy.

To estimate the association between “global” (i.e., overall) RPE-atrophy progression and the presence of treatment-naïve quiescent type 1 CNV and or exudative type 1 CNV, we applied the point-wise model to predicted future localized RPE-atrophy progression, while concealing the presence of CNV. All of the remaining point-wise prognostic variables were not altered. The then predicted progression rates of RPE-atrophy for the assumption of absence of CNV were higher by a mean [95 % CI] of +1.07 mm^2/year [0.44, 1.71] for eyes with treatment-naïve quiescent type 1 CNV and +0.89 mm^2/year [0.20, 1.58] for eyes with exudative type 1 CNV.

Long-term association between CNV and reduced localized RPE-atrophy progression

For the following four eyes (three patients) with RPE-atrophy and CNV long-term imaging data was available that had been collected in the context of the DSGA 1-study prior to the baseline of this analysis (P1: 7 years and 6 month, P2: 4 years and 6 months, P3: 5 years). Although, no OCTA data was available for these earlier study visits, there was evidence of the presence of quiescent type 1 CNV (Figure 4) or exudative type 1 CNV (Figure 5) based on SD-OCT ('double layer sign') and FA (stippled hyperfluorescence). There was markedly slower RPE-atrophy progression in areas with quiescent type 1 CNV or exudative type 1 CNV. These long-term observations further underscore the aforementioned quantitative analyses with reduced odds for RPE-progression in areas overlying CNV lesions (Figure 4 and 5).

Discussion

This analysis demonstrates that in eyes with RPE-atrophy, there is slower atrophy progression in areas overlying type 1 CNV as compared to areas without evidence of co-localized CNV.

Although, a causal association, i.e., a potential protective effect of type 1 CNV on RPE and photoreceptors, is not proven by our data, the following criteria and observations support this hypothesis: the relationship between the presence of type 1 CNV and reduced localized odds for future RPE-atrophy progression in this analysis was significant and distinct (i.e., odds ratios of 0.21 [0.19, 0.24] and 0.46 [0.41, 0.51], respectively), consistent among eyes with treatment-naïve quiescent CNV as well as with exudative type 1 CNV, spatially specific and temporally plausible (i.e., reduced odds for future RPE-atrophy progression follow the prior presence of type 1 CNV). Our findings are also compatible with the previous qualitative observations that the sub-foveal presence of treatment-naïve quiescent type 1 CNV or exudative type 1 CNV may be associated with a preservation of the fovea.[16,17]

With regard to biological plausibility, two potentially synergistic mechanisms may underlie a potential protective effect of type 1 CNV with regard to RPE-atrophy enlargement. Since alterations of BrM and ChC were previously identified beyond the boundary (i.e., outside) of RPE-atrophy, these alterations might precede the development of RPE-atrophy and constitute potential therapeutic targets.[10,34] Type 1 CNV could potentially influence RPE-atrophy progression by reducing the effect of both of these alterations. Type 1 CNV may enhance the interchange between the RPE and choroid by increasing the sub-RPE capillary density and thereby the sub-RPE blood flow to compensate for ChC breakdown as observed in histopathologic studies and *in vivo* by OCTA.[10,24,34–38] In addition, type 1 CNV also obviates the interchange barrier due to an age-associated BrM change, which is characterized by an increased calcification of elastic fibers and accumulation of lipid rich extracellular deposits between the RPE basal lamina and the inner collagenous layer of BrM including basal linear deposits (BLinD) and soft drusen.[11–13,39–42]

Potential therapeutic implications

The results of this study suggest that there might be a protective component of CNV evolution and that pharmaceutical regression of a CNV lesion - when it appears quiescent, without exudation - may not necessarily represent an optimal treatment target. Hence, anti-VEGF therapy of such lesions without exudative activity has to be carefully studied before being a recommended intervention. Notably, it was recently demonstrated that even tolerating some exudative activity as presented by subtle subretinal fluid (SRF) can achieve similar visual acuity outcomes as a treatment aimed at resolving all SRF.[43] Accordingly, instead of aiming for complete CNV regression, control of exudative activity might prove beneficial for patients. However, a better understanding of signaling pathways involved in the transition from quiescent to exudative CNV to prevent severe complications would be a prerequisite.[46]

Implications for clinical trials in GA

Homogeneity of patients in clinical trials is a prerequisite to obtain reliable outcomes. The current study clearly demonstrates that eyes with RPE-atrophy with treatment-naïve quiescent type 1 CNV show a slower progression as compared to eyes with RPE-atrophy without evidence for CNV. Accordingly, stratification or systematic exclusion of eyes exhibiting type 1 CNV in OCTA seems warranted in the context of future clinical trials investigating RPE-atrophy progression.

Limitations and strengths

Several limitations of the reported analysis need to be considered. In terms of methodology, the accuracy for the localized prediction of future RPE-atrophy could have been most likely enhanced using a more complex model (e.g., random forest regression). However, we deliberately chose a simpler model in consideration of interpretability and the ability to perform of statistical inference. More importantly, our prediction accuracy for future RPE-atrophy was with a (cross-validated) Dice coefficient of 0.87 for an unknown patient similar to the Dice coefficient (0.84) obtained in a previous study in the setting of RPE-atrophy, which used a

more complex model, which was much more challenging to interpret.[47] Further, currently available OCTA devices most likely do not allow for detection of all CNV lesions in eyes with RPE-atrophy (i.e., CNV lesions thinner than the optical resolution of the device [6.3 µm] or with a blood flow below the the detection limit). Notably, *Sarks* reported in 1976 in a histopathologic study the presence of neovascularization from the choroid in 10 of 24 eyes (41.7 %) with the clinical diagnosis of RPE atrophy, which markedly exceeds the rate of identified treatment-naïve quiescent CNV among all eyes with RPE-atrophy in this analysis or as previously reported by *Capuano* and coworkers (11.3 %).[16,48] Moreover, we do not report any functional data to underscore that prevention of RPE-atrophy progression is also associated with a preservation of retinal sensitivity. This relevant aspect will be addressed in the ongoing study.

Notable strengths of this study are the large sample of eyes with RPE-atrophy without evidence of CNV and the thorough quantitative analysis to account for a large variety of potential confounders that may affect the localized progression of atrophy. It must be noted, that the number of eyes with RPE-atrophy and treatment-naïve quiescent type 1 CNV as well as with RPE-atrophy and exudative type 1 CNV is rather small. Yet, the association strength is marked and most importantly, the high number of eyes with RPE-atrophy without CNV with longitudinal data allowed for differential analysis between common factors associated with reduced RPE-atrophy progression and type 1 CNV. Our observed progression rates were similar to previously reported progression rates of RPE-atrophy.[20,38,49,50]

In summary, this analysis demonstrates that presence of type 1 CNV is associated with reduced localized RPE-atrophy progression. While our data do not prove a causal relation, i.e., protection of RPE and photoreceptors by type 1 CNV, it certainly supports this hypothesis. The results may lead to critical consideration of therapeutic approaches aiming for complete regression of CNV or prevention of CNV development in AMD.

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522

Figures

Figure 1. Eye with RPE-atrophy and treatment-naïve quiescent choroidal neovascularization (CNV). The figure shows the fundus autofluorescence (FAF), infrared reflection (IR), fluorescein angiography (FA) and indocyanine green angiography (ICGA) images of a patient with RPE-atrophy and treatment-naïve quiescent CNV. The quiescent CNV lesion is characterized by stippled hyperfluorescence by FA and a placoide appearance by ICGA. Both spectral domain optical coherence tomography (SD-OCT) scans show the marked double-layer sign, a flat separation between the retinal pigment epithelium (RPE) and Bruch's membrane (BrM). In the superior SD-OCT scan (position indicated by the green arrow in the IR image), the break of BrM, where putatively the feeding arterioles and draining venules enter the sub-RPE space, is visible (white arrowhead). The CNV lesion is clearly visible in the optical coherence tomography angiography (OCTA) outer retina to choriocapillaris (ORCC) slab.

Figure 2. Localized progression model for RPE-atrophy in presence of choroidal neovascularization (CNV). (A) Modeling of retinal pigment epithelium (RPE)-atrophy progression. Areas of RPE-atrophy were annotated using the RegionFinder software (Heidelberg Engineering, Germany) based on fundus autofluorescence (FAF) and infrared reflection (IR)confocal scanning laser ophthalmoscopy images. CNV was delineated based on optical coherence tomography angiography using the outer retina to choriocapillaris (ORCC) slab. Subsequently, these annotations were registered to the FAF images based on retinal vessel bifurcation. Ad-hoc software was used to extract the listed imaging biomarkers, which were then used to predict future development of atrophy in a point-wise manner. (B) Exemplary patient with RPE-atrophy and treatment-naïve quiescent type 1 CNV. Notably, the observed atrophy progression at follow-up as well as the (cross-validated) predicted probability for atrophy progression in this patient were lower for the region with the underlying treatment-naïve quiescent type 1 CNV lesion as compared to other regions along the atrophy boundary (i.e., 'green' versus 'red' proportion of the peri-lesional halo). The orthogonal representation of the atrophy boundary, which visualizes the lateral spread of atrophy (LSGA)[51] further underscores this observation.

Figure 3. Probability of localized retinal pigment epithelium (RPE) atrophy progression within the 0.5° (145 µm) boundary of RPE-atrophy. The marginal effects plot shows the predicted marginal probabilities and 95% confidence intervals for the localized progression of RPE-atrophy within the immediate junctional-zone of RPE-atrophy (defined as 0.5° [approx. 145 µm for an emmetropic eye]) in dependence of the diagnosis of the eye (RPE-atrophy without evidence of coexisting CNV [i.e., 'geographic atrophy'], RPE-atrophy with treatment-naïve quiescent type 1 choroidal neovascularization,or RPE-atrophy with exudative type 1 CNV) and in dependence of the localized absence or presence of treatment-naïve quiescent CNV or exudative CNV, respectively. The predicted marginal probabilities for RPE-atrophy progression for eyes without evidence of CNV and eyes with treatment-naïve quiescent CNV, respectively, are compatible with the previously published lateral spread of RPE-atrophy (i.e., 'LSGA', median of 106.9 µm/year).[51] The localized presence of treatment-naïve quiescent CNV was associated with a markedly lower probability for localized RPE-atrophy progression. In eyes with exudative type 1 CNV, the diagnosis was overall associated with a lower probability of RPE-atrophy progression. Moreover, the localized presence of exudative CNV was associated with a further reduced probability of RPE-atrophy progression.

Figure 4. Long-term effect of treatment-naïve quiescent type 1 choroidal neovascularization (CNV) on RPE-atrophy progression. For these two patients with treatment-naïve quiescent CNV, multimodal long-term imaging data was available that had been collected in the context of the DSGA 1-study prior to the baseline of this analysis. Please note, these prior study visits were not used for the quantitative analyses. For the patient in the top two images, the diagnosis of treatment-naïve quiescent CNV was established in 2011 based on the double-layer sign on spectral-domain optical coherence tomography (SD-OCT) and the stippled hyperfluorescence in the fluorescein angiography (FA). The white dashed overlay indicates the area exhibiting the double-layer sign. The area of RPE-atrophy, as seen in the fundus autofluorescence (FAF) images, enlarged only minimally within 7 years (red versus orange dashed hull). The treatment-naïve quiescent CNV lesion appears to have enlarged based on optical coherence tomography angiography (OCTA). In the patient in the bottom two images, the diagnosis treatment-naïve quiescent CNV could be established in 2014 based on the above-mentioned criteria. The treatment-naïve quiescent CNV lesion in this patient was located nasally to the GA focus. The 4-year follow-up shows definite progression of RPE-atrophy away from the CNV lesion, while the progression towards the CNV lesion was only minimal.

Figure 5. Long-term effect of exudative type 1 choroidal neovascularization (CNV) on retinal pigment epithelium (RPE) atrophy progression. For these two patients with exudative CNV, multimodal imaging data prior to the baseline of this study were available. Please note, these prior study visits were not used for the quantitative analyses. For the patient in the top two images, the diagnosis of exudative CNV was established in 2011 based on the double-layer sign in spectral-domain optical coherence tomography (SD-OCT) and the stippled hyperfluorescence in the fluorescein angiography (FA). The white dashed overlay indicates the area exhibiting the double-layer sign. The area of RPE-atrophy, as seen in the fundus autofluorescence (FAF) images, enlarged only minimally within the 7.5 years (red versus orange dashed hull). The exudative CNV lesion appears to have enlarged based on optical coherence tomography angiography (OCTA). For the patient in the bottom two images, the diagnosis exudative CNV could be established in 2012 based on the above-mentioned criteria. The 6.5-year follow-up shows only minimal progression of the RPE-atrophy. Both patients received anti-VEGF therapy during the shown time-interval (the patient on top received a total of 28 intravitreal anti-VEGF injections, the patient on the bottom receive a total of 3 intravitreal anti-VEGF injections).