Long-term Follow-Up and Regeneration of Retinal Pigment Epithelium (RPE) after Tears of the Epithelium in Exudative Age-Related Macular Degeneration (AMD)

Langzeit Follow-up und Regeneration des retinalen Pigmentepithels (RPE) nach Rupturen des retinalen Pigmentepithels bei exsudativer altersbedingter Makuladegeneration (AMD)

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ABSTRACT

Background The goals of this study are to evaluate potential long-term visual deterioration associated with retinal pigment epithelial (RPE) tears in patients with neovascular age-related macular degeneration (nAMD) and to find treatment-related and morphological factors that might influence the outcomes.

Patients and Methods This retrospective study enrolled 21 eyes of 21 patients from the database of Vista Eye Clinic Binningen, Switzerland, diagnosed with RPE tears, as confirmed by spectral domain optical coherence tomography (SD-OCT), with a minimum follow-up period of 12 months. Treatment history before and after RPE rupture with anti-VEGF therapy, visual acuity, and imaging (SD-OCT) were analyzed and statistically evaluated for possible correlations.

Results Mean patient age was 80.5 ± 6.2 years. The mean length of total follow-up was 39.7 ± 13.9 months. The mean pigment epithelial detachment (PED) height increased by 363.8 ± 355.5 µm from the first consultation to 562.8 ± 251.5 µm at the last consultation prior to rupture. Therefore, a higher risk of RPE rupture is implied as a result of an increase in PED height ($p = 0.004$, $n = 14$). The mean visual acuity before rupture was 66.2 ± 16.0 letters. Mean visual acuity deteriorated to 60.8 ± 18.6 letters at the first consultation after rupture ($p = 0.052$, $n = 21$). A statistically nonsignificant decrease in vision was noted in the follow-up period. After 2 years, the mean BCVA decreased by 10.5 ± 23.7 ETDRS letters ($p = 0.23$, $n = 19$). PED characteristics before rupture and amount of anti-VEGF injections after rupture did not affect the visual outcome. None of the 21 patients included in our study showed a visual improvement in the long-term follow-up. RPE atrophy increased significantly from 3.35 ± 2.94 mm^2 (baseline) to 6.81 ± 6.25 mm^2 over the course of 2 years ($p = 0.000\,013$, $n = 20$).

Conclusions The overall mean vision decrease after rupture was without statistical significance. There was no significant change in BCVA at the 2-year follow-up, independent of the

amount of anti-VEGF injections provided. In this study, there was a significant increase in RPE defect over a follow-up of 2 years, implying progression of contraction of RPE and/or macular atrophy.

ZUSAMMENFASSUNG

Hintergrund Ziel der Studie war es, die langfristige Sehverschlechterung bei Rupturen des retinalen Pigmentepithels (RPE) bei Patienten mit exsudativer altersbedingter Makuladegeneration (AMD) zu untersuchen und behandlungsbedingte und morphologische Faktoren zu ermitteln, die die Visusprognose beeinflussen können.

Patienten und Methoden In diese retrospektive Studie wurden 21 Augen von 21 Patienten aus der Datenbank der Vista Augenklinik Binningen, Schweiz, aufgenommen, bei denen mittels optischer Kohärenztomografie (SD-OCT) eine Ruptur des RPE diagnostiziert wurde und eine Follow-up-Periode von mindestens 12 Monaten bestand. Der Behandlungsverlauf vor und nach der RPE-Ruptur mit Anti-VEGF-Injektionen, die Sehschärfe und bildgebende Verfahren (SD-OCT) wurden analysiert und auf mögliche Korrelationen untersucht.

Ergebnisse Das Durchschnittsalter der Patienten betrug 80,5 ± 6,2 Jahre. Die durchschnittliche Dauer der Nachbeobachtung betrug 39,7 ± 13,9 Monate. Die mittlere Zunahme der PED-Höhe lag bei 363,8 ± 355,5 µm von der ersten Konsultation auf 562,8 ± 251,5 µm bei der letzten Konsultation vor dem Auftreten der Ruptur. Entsprechend kann ein höheres Risiko einer RPE-Ruptur als Folge einer Zunahme der PED-Höhe mit statistischer Signifikanz nachgewiesen werden (p = 0,004, n = 14). Die mittlere Sehschärfe vor der Ruptur lag bei 66,2 ± 16,0 ETDRS-Letters. Eine Verschlechterung bei der ersten Konsultation nach der Ruptur auf 60,8 ± 18,6 ETDRS-Letters konnte gemessen werden (p = 0,052, n = 21). In der Nachbeobachtungszeit konnte eine weitere statistisch nicht signifikante Abnahme der Sehkraft festgestellt werden. Innerhalb von 2 Jahren nahm der mittlere korrigierte Visus um 10,5 ± 23,7 ETDRS-Letters ab (p = 0,23, n = 19). Die Charakteristika der PED vor der Ruptur und die Menge der nach der Ruptur verabreichten Anti-VEGF-Injektionen hatten keinen Einfluss auf die Visusprognose. Keiner der 21 Patienten, die in unsere Studie aufgenommen wurden, zeigte in der langfristigen Nachbeobachtung eine Sehverbesserung. Die RPE-Atrophie vergrößerte sich jedoch statistisch signifikant von 3,35 ± 2,94 mm^2 (Baseline) auf 6,81 ± 6,25 mm^2 im Laufe von 2 Jahren (p = 0,000 013, n = 20).

Schlussfolgerungen Der Mittelwert des Sehvermögens nahm nach der Ruptur ab. Auch in der Nachbeobachtungszeit bis zu 2 Jahren konnte ein weiterer nicht signifikanter Trend zur Abnahme des mittleren korrigierten Visus festgestellt werden, unabhängig von der Anzahl der verabreichten Anti-VEGF-Injektionen. In unserer Studie wurde ein signifikanter Anstieg des RPE-Defekts über einen Nachbeobachtungszeitraum von 2 Jahren festgestellt, was auf eine fortschreitende Kontraktion des RPE und/oder eine Makulaatrophie schließen lässt.

Background

Age-related macular degeneration (AMD) is one of the main causes for vision impairment in industrialized countries [1]. Pigment epithelial detachment (PED) is a common finding, which, in its serous form, is associated with neovascular AMD (nAMD) [2]. Enlargement of a PED can lead to a retinal pigment epithelial (RPE) tear, which can result in further loss in vision [3, 4]. Overall occurrence of RPE tears in patients with nAMD is estimated to be between 2 and 6% [5]. More recent studies suggest that the risk increases to 12–25% with preexisting PEDs [5]. Casswell et al. reported in 1985 that 10% of patients with PEDs develop RPE tears [6].

RPE tears in nAMD have been described in the natural course of disease [7] as well as various treatments such as with intravitreal anti-vascular growth factors (anti-VEGF) [8–11], intravitreal triamcinolone [12], and verteporfin photodynamic therapy [13]. Spaide observed that a choroidal neovascular membrane contraction can be seen in spectral domain optical coherence tomography (SD-OCT) in a fibrovascular PED 1 week after ranibizumab injection [14]. The consecutive tangential traction is believed to be the reason for RPE tear development after anti-VEGF treatment, especially as the rupture mostly occurs on the contralateral side [11]. While the risk of RPE tears caused by anti-VEGF treatment is still a matter of controversy, several other risk factors have been identified.

Chan et al. reported that PED height can be used as a predictor of RPE tears [8]. Moroz et al. [15] found wavy RPE indentations and small interruptions in the elevated RPE to be predictors for RPE tears in nAMD patients treated with bevacizumab. Using fluorescein angiography, Coscas et al. [16] found uneven filling to be a predictive marker. Bastian et al. [17] suggested that increased reflectance signals on near-infrared (NIR) imaging using confocal scanning laser ophthalmoscopy (cSLO) may act as a prognostic marker for RPE tears. They proposed that these signals should be prospectively evaluated in a larger cohort of PED patients.

Since the introduction of anti-VEGF treatment, a growing number of RPE tears have been reported [18]. For example, the PED tear rate after pegaptanib injections was mentioned to be 27% in a small study [8]. Sarraf et al. [9] found a much smaller rupture rate of 4.7% under ranibizumab treatment in an analysis of the HARBOR study. The subgroup with extra-large PED (≥ 352 µm) showed a rupture rate of 14% [9]. Ruptures often occurred within 2 months after the first injection [10].

The aim of our study was to analyze factors in clinical and imaging data (SD-OCT) that could predict the further outcome of vision in patients with RPE tears in a clinical routine setting. Additionally, the impact and benefits of continued anti-VEGF injections were evaluated.

Patients and Methods

This retrospective, non-interventional, single-center study was conducted at Vista Klinik Binningen, Switzerland. The study was approved by the local ethics committee (Ethics Committee Northwestern Switzerland – EKNZ, EKNZ No 2021–00 898). The research was pursued in accordance with the tenets of the Declaration of Helsinki and Good Clinical Practice (ICH-GCP).

All patients in the database of Vista Augenklinik Binningen, Switzerland, diagnosed with RPE tears confirmed by SD-OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany) with a minimum follow-up period of 12 months and best-corrected visual acuity (BVCA) of 0.1 standard Snellen (35 ETDRS letters) were included (21 eyes of 21 patients). Standard Snellen BVCA measurements were performed during each consultation and converted to ETDRS letter scores for the purpose of the study [19].

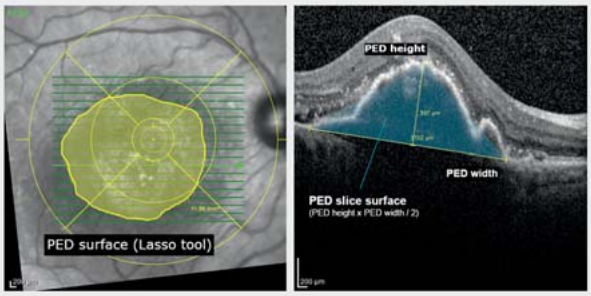
Both morphological factors in imaging (SD-OCT) as well as the history of anti-VEGF injections prior and after the RPE tear occurred were retrospectively analyzed. PED height, PED width, PED slice surface in OCT (defined by PED height × PED width/2) and PED horizontal surface (Lasso tool) were evaluated as described in ▶ **Fig. 1**. PED location was evaluated using the ETDRS grid. RPE defect area was measured in SD-OCT combined with infrared imaging using the method described in Cedro et al. [20], which has been shown to correlate with fundus autofluorescence imaging measurements.

Due to the small sample size, we did not perform a correlation analysis but compared different parameters and formed subgroups separated by their respective median for illustration purposes. We calculated the difference in visual outcome regarding PED height, PED width, PED slice surface in OCT, PED horizontal surface (Lasso tool), and PED location before rupture, amount of anti-VEGF injections before and after the RPE tear occurred, and the medication used for anti-VEGF injections.

Data are presented as the mean ± standard deviation or percentage. Differences between groups were tested for statistical significance with the Wilcoxon test (paired and unpaired, respectively). Statistical analyses were performed with RStudio, version 2023.09.1 (RStudio: Integrated Development Environment for R. Posit Software, PBC, Boston, MA, USA). P values (two-sided) were determined; differences between groups were considered to be of statistical significance if the p value was < 0.05.

Results

From 21 patients, 21 eyes were included. Mean patient age was 80.5 ± 6.2 years (median: 80.4, range: 66.1–94.5), with 71.4 % females. The mean total follow-up was 39.7 ± 13.9 months (median: 38.5, range: 14–60). For all patients included in this study, pre-RPE rupture records are available. Seventeen eyes received intravitreal anti-VEGF treatment before the rupture occurred. PED before rupture involved the central mm ETDRS subfield in 19 patients and in 2 patients, the inner ETDRS ring without the central mm. The rupture affected the central mm ETDRS subfield in 3 patients, the inner ETDRS ring in 17, and the outer ETDRS ring in 1 patient. Before the RPE tear occurred, the mean PED height increased by 363.8 ± 355.5 µm (median: 423.5, n = 14) from the first consultation to 562.8 ± 251.5 µm (median: 526.0; n = 21) at the last consultation just before the rupture occurred (p = 0.004, n = 14). The mean interval between these 2 consultations was 210.0 ± 413.0 days (median: 34.0, range: 7–1314). Seven patients had only one consultation before the RPE tear.



▶ **Fig. 1** PED measurements of the last OCT imaging before RPE rupture.

Baseline (first visit with RPE tear) BCVA was 60.8 ± 18.6 ETDRS letters (median: 60.0) for all eyes. There was a decrease in BCVA from 66.2 ± 16.0 letters (median: 70.0) at the last visit before rupture by 5.4 ± 12.9 letters (median: 0 letters) (p = 0.052). The mean interval between these 2 consultations was 114 ± 335 days (median: 32, range: 10–1609). For all eyes with a follow-up of 24 months (n = 19), an average decrease in BCVA of 10.5 ± 23.7 ETDRS letters was noted compared to baseline (p = 0.23). Among subgroups regarding different baseline characteristics, we compared the mean BCVA and the mean change in BCVA at 2 years (▶ **Table 1**). A surprise finding revealed less elevated PEDs before rupture had a lower mean BCVA at baseline. This can be explained by the observation that the increase in PED height tended to be higher before rupture for these patients. Therefore, a stronger disease activity can be assumed. None of the PED's characteristics before rupture showed any statistical significance within their subanalysis for PED height, PED width, and PED surface (Lasso tool and slice surface). However, the loss of ETDRS letters in higher PEDs was three times the amount of the group with lower PEDs (− 16.2 vs. − 5.3 ETDRS letters, p = 0.41).

After 2 years, there was a nearly equal loss of BCVA in the group that received less than 19 anti-VEGF injections compared to the group that received 19 or more (− 10.3 letters vs. − 10.6 letters, p = 0.90). None of the subjects showed a visual improvement in the long-term follow-up within the scope of our study post-rupture.

Mean RPE atrophy at baseline was 3.35 ± 2.94 mm^2 (median: 3.04). Over the course of 2 years, a statistically significant increase of 3.47 ± 4.25 mm^2 (median: 1.89) could be seen (p = 0.000 013, n = 20). After 2 years, mean RPE atrophy was 6.81 ± 6.25 mm^2 (median: 5.41). There were no cases of RPE regeneration in our population.

▶ **Table 1** Morphological and therapeutic factors with their respective functional outcome (BCVA).

Baseline characteristics of patients with 2 years of follow-up (n = 19)					
		BVCA BL (letters)	**BCVA 2Y (letters)**	**Mean change (letters)**	**P value (BL to 2Y)**
PED height before rupture, n (range in µm)					
▪ < 598 µm	10 (226–526 µm)	55.2	49.9	− 5.3	0.94
▪ ≥ 598 µm	9 (598–1044 µm)	64.4	48.2	− 16.2	0.18
				p = 0.41	
PED width before rupture, n (range in µm)					
▪ < 3705 µm	10 (1983–3218 µm)	63.5	54.2	− 9.3	0.57
▪ ≥ 3705 µm	9 (3705–8118 µm)	55.2	43.4	− 11.7	0.29
				p = 0.74	
PED surface (horizontal, Lasso tool)					
▪ < 9.76 mm^2	10 (3.23–9.46 mm^2)	62.5	54.2	− 8.3	0.73
▪ ≥ 9.76 mm^2	9 (9.76–31.81 mm^2)	56.3	43.4	− 12.9	0.16
				p = 0.41	
PED slice surface (vertical width × height/2)					
▪ < 1.05 mm^2	10 (0.22–0.94 mm^2)	57.2	47.9	− 9.3	0.57
▪ ≥ 1.05 mm^2	9 (1.05–8.43 mm^2)	62.2	50.4	− 11.8	0.29
				p = 0.74	
Amount of anti-VEGF injections before rupture					
▪ 0	3 (0)	66.7	55.0	− 11,6	1.00
▪ 1–3	13 (1–3)	57.07	50.5	− 6.6	0.62
▪ > 3	3 (7–55)	63.3	37.3	− 26.0	0.50
				0 vs. 1–3: p = 0.79 0 vs. > 3: p = 1.00 1–3 vs. > 3: p = 0.38	
Amount of anti-VEGF injections after rupture					
▪ < 19	9 (1–14)	53.6	43.2	− 10.3	0.53
▪ ≥ 19	10 (19–51)	65.0	54.4	− 10.6	0.36
				p = 0.90	
Type of anti-VEGF injections					
▪ Ranibizumab	4	58.8	56.3	− 2.5	1.00
▪ Aflibercept	10	59.2	46.1	− 13.1	0.29
▪ Crossover (ranibizumab to aflibercept)	5	61.0	49.4	− 11.6	0.50

Discussion

Visual acuity outcome in nAMD is related to the short- [21] and long-term [22, 23] health of the outer retina and the RPE layers. Severe RPE destroying events like RPE tears lead to an initial loss in visual acuity. This has been shown by several colleagues [3, 4] and was also found in this study's evaluations. Our study showed a high standard deviation in all mean BCVA values, which reflects the high variability in visual outcomes. In this study, a nonsignificant trend (p = 0.23) towards decreased visual acuity had occurred [from right after the RPE tear (baseline) compared to the 2-year follow-up] independent of the number of anti-VEGF treatments. Persistent neovascular activity leading to progressive scarring could be an explanation for this latter finding.

In addition to the acute pigment epithelial defect, progressive macular atrophy may occur. One possible mechanism of progressive macular atrophy could be from a further rolling of the pigment epithelium. The significant increase in RPE defect area in

our study over 2 years supports this suggestion. In contrast to our findings, Heimes et al. [24] showed an increased recovery of autofluorescence at the RPE-free area in patients with a stabilized or improved BCVA at year 2. In patients with worsened BCVA at year 2, a continued expansion of the neovascular complex in the area of the RPE tear was found. This resulted in larger fibrovascular scars. Romano et al. [25] were also able to show an increased recovery of autofluorescence in several patients, combined with less BCVA deterioration. In this study, there were no cases of RPE regeneration at the 2-year follow-up.

PED height is a known risk factor for RPE tears. This study showed a statistically significant increase in PED height before RPE tears. Multiple authors found thresholds between 400 and 580 µm to be significant for high RPE tear risk [8, 26 – 28]. This study did not show a statistically significant impact concerning PED height, PED width, or PED surface (Lasso tool and slice surface; ▶ **Fig. 1**) on functional outcome (BCVA) 2 years following a tear.

To reduce the mechanical stress on the RPE monolayer and associated risk of tear after anti-VEGF therapy, treating eyes with elevated PEDs with either half-dose aflibercept [29] or bimonthly half-dose ranibizumab [30] may be advantageous. For now, it remains unclear if new bispecific or higher concentrated drugs might result in different incidences of RPE tears.

Eyes with high-risk PEDs are typically not included in pivotal and regulatory nAMD studies and RPE tears are still rare events. It is important to monitor these patients in real-world analyses regarding the incidence and follow-up of RPE tears. Patients at risk for RPE tears and receiving anti-VEGF therapy should be clearly informed of this associated risk. We recommend that anti-VEGF treatment not be stopped in most patients with RPE tear and active disease [31]. However, the decision must be made depending on the situation. If the residual visual acuity is good and there is a residual RPE below the fovea, treatment should definitely be continued. In other cases, discontinuation of treatment can be discussed in consultation with the patient.

Conflict of Interest

Nicolas Skalicky: No financial contributions or personal relationships in the aforementioned sense.
Katja Hatz: Consultating Fees: Bayer, Novartis Switzerland, Allergan/Abbvie, Roche;
Financial Research Contributions: Bayer, Novartis Switzerland, Allergan/Abbvie, Roche, Zeiss.
None of the contributions is of relevance regarding this study.

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