RANIBIZUMAB IN PIGMENT EPITHELIAL TEARS SECONDARY TO AGE-RELATED MACULAR DEGENERATION

A Prospective Study

PETRA P. LARSEN, MD,* AKIO OISHI, MD, PhD,* MOHAMMAD SELEMAN BEDAR, MD, FEBO,* PHILIPP K. R. HEYMER, MD,* CHRISTOPH R. CLEMENS, MD, FEBO,† SUSANNA KÖNIG, MD,‡ MATTHIAS GUTFLEISCH, MD,§ DANIEL PAULEIKHOFF, MD,§ NICOLE ETER, MD,† ARMIN WOLF, MD,‡ FRANK G. HOLZ, MD, FEBO,* TIM U. KROHNE, MD, FEBO*

Purpose: To assess efficacy of intravitreal ranibizumab in retinal pigment epithelium tears secondary to neovascular age-related macular degeneration.

Methods: The Ranibizumab In Pigment epithelial tears secondary to age-related macular degeneration (RIP) study is a prospective, single-arm, multicenter, investigator-initiated trial. Twenty four eyes of 24 patients with a retinal pigment epithelium tear secondary to age-related macular degeneration received monthly intravitreal injection of 0.5mg ranibizumab for 12 months, together with monthly assessments of morphologic and functional efficacy parameters. Primary outcome measure was mean best-corrected visual acuity at final visit compared with baseline.

Results: Mean best-corrected visual acuity remained stable over the 12-month study period with 50.3 Early Treatment of Diabetic Retinopathy Study letters (±18.7; Snellen equivalent 20/100) at baseline and 52.9 letters (±19.7; Snellen equivalent 20/100) at final visit ($P = 0.39$). One eye (4%) experienced a vision loss of ≥15 letters, and 2 eyes (8%) gained ≥15 letters. Mean central retinal thickness decreased from 571 μm (±185 μm) to 436 μm (±171 μm; $P = 0.0001$). Vision-related quality of life was stable with a mean VFQ-25 score of 79.0 (±10.8) at baseline and 74.3 (±13.9) at final visit ($P = 0.12$).

Conclusion: In retinal pigment epithelium tears secondary to age-related macular degeneration, monthly intravitreal ranibizumab therapy results in stabilization of visual acuity over 12 months.

RETINA 00:1–9, 2018

Retinal pigment epithelium (RPE) tears are a complication of neovascular age-related macular degeneration (AMD).[1] Retinal pigment epithelium tears may occur spontaneously or after treatment including laser photocoagulation, photodynamic therapy, and intravitreal injections of vascular endothelial growth factor (VEGF)-inhibitory agents.[2–4] In AMD, RPE tears are most commonly associated with pigment epithelial detachments (PEDs).[1] During the natural course of PEDs, spontaneous regression, geographic atrophy, scarring, or RPE tears may occur.[5] Contraction of choroidal neovascularization (CNV) with traction to the RPE is considered to be a cause of RPE tears.[6,7] The main risk factors for the development of RPE tears under anti-VEGF treatment include the presence of a vascularized PED, a small ratio of CNV size to PED size, as well as the PED's area and height.[8–11] Retinal pigment epithelium tears occur in approximately 12% to 20% of vascularized PEDs treated with anti-VEGF therapy,[12] including pegaptanib,[13] bevacizumab,[14,15] ranibizumab,[16] and aflibercept.[17,18] Although the incidence of RPE tears after anti-VEGF treatment is similar to that reported for untreated PEDs, a temporal correlation between the start of anti-VEGF therapy and the development of the tears has been observed.[19,20]

Although anti-VEGF treatment may potentially accelerate the development of RPE tears, the treatment may have beneficial effects in RPE tears with underlying CNV. Retrospective studies show that continuous treatment with anti-VEGF agents is effective in improving or stabilizing visual function in RPE tears.[21–23]

However, because the presence of an RPE tear constituted an exclusion criterion in all prospective large-scale clinical trials studying the efficacy of anti-VEGF in neovascular AMD (e.g. ANCHOR, MARINA, CATT, VIEW 1/2), prospective data for the efficacy of anti-VEGF therapy in this AMD subtype are currently lacking, thus hindering the development of treatment recommendations for RPE tears.

We conducted a prospective, multicenter, investigator-initiated trial to evaluate the efficacy of monthly ranibizumab in RPE tears over a period of 12 months.

Patients and Methods

Patient Selection

The Ranibizumab In Pigment epithelial tears secondary to AMD (RIP) study is a prospective, interventional, single-arm, multicenter, investigator-initiated trial (eudract.ema.europa.eu, EudraCT no. 2011-005807-33; clinicaltrials.gov, registration no. NCT01914159) in patients diagnosed with an RPE tear secondary to neovascular AMD in the study eye. The study followed the tenets of the Declaration of Helsinki and was approved by the institutional review boards of the participating study centers: University of Bonn, University of Münster, and Ludwig Maximilian University Munich. Written informed consent was obtained from each patient before study inclusion. Study patients were recruited over a period of 27 months (February 2013 to April 2015) at the Departments of Ophthalmology of University of Bonn, University of Münster, and Ludwig Maximilian University Munich. Only patients with neovascular activity of the AMD were included into the study, whereas patients with subretinal fibrosis, central geographic atrophy, or who were otherwise deemed by the investigator as unlikely to benefit from the study treatment were excluded from the study. Because neither the efficacy nor potential adverse effects of anti-VEGF therapy in RPE tears are known yet, we excluded eyes with a best-corrected visual acuity (BCVA) of the contralateral eye of below 20/200 as a safety measure. Further ocular exclusion criteria included uncontrolled glaucoma, active ocular inflammation, any diseases resulting in visual impairment including retinal diseases such as previous retinal detachment, other diseases that required ocular surgery within 1 month before screening, and pronounced lens opacity precluding retinal imaging. A total of 29 patients were screened for this study during the recruitment period, and 5 of them did not meet the eligibility criteria. Thus, 24 eyes of 24 patients were included in this study.

Study Treatment and Investigations

All patients received monthly intravitreal injections of ranibizumab (0.5 mg) into the study eye over the study period of 12 months. Before each injection, patients were examined by standardized BCVA assessment according to the Early Treatment of Diabetic Retinopathy Study (ETDRS) protocol,[24] dilated fundus examination, spectral-domain optical coherence tomography (OCT), and fundus autofluorescence imaging (Figure 1). At baseline, in addition, color fundus photography, fluorescein angiography, and indocyanine green angiography were performed to establish and document the diagnosis. Vision-related quality of life was assessed at baseline and final visit using the National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25).[25] The primary outcome measure of the study was mean BCVA at final visit as compared to baseline. Secondary outcome measures included mean change of central retinal thickness (CRT) as measured by OCT and mean change of patient-reported vision-related quality of life as assessed by NEI VFQ-25.

Statistical Analysis

Statistical analysis was performed using the software SPSS Statistics 23 (SPSS, Chicago, IL) and Excel 2013 (Microsoft, Redmond, WA). Study results were analyzed according to the intention-to-treat principle, and no last-observation-carried-forward approach was applied to dropouts. All results are expressed as mean ± SD. For statistical analyses, we used paired Student's *t*-test and Pearson correlation coefficient. *P* values below 0.05 were considered statistically significant.

From the *Department of Ophthalmology, University of Bonn, Bonn, Germany; †Department of Ophthalmology, University of Münster, Münster, Germany; ‡Department of Ophthalmology, Ludwig Maximilian University, Munich, Germany; and §Department of Ophthalmology, St. Franziskus Hospital, Münster, Germany.

P. P. Larsen, Novartis: F; A. Oishi, Alcon: F; Bayer: R; Novartis: R; P. K. R. Heymer, Novartis: F; C. R. Clemens, Novartis: F; S. König, Novartis: F; M. Gutfleisch, Alcon: F; Novartis: F; Ophthotech: F; Pfizer: F; Roche: F; D. Pauleikhoff, Alcon: F; Allergan: F; Acucela: F; Bayer: F; Genetech: F; Novartis: F; Ophthotech: F; Pfizer: F; Roche: F; N. Eter, Novartis: F; A. Wolf, Bayer: F; DORC: R; GenSight: F; Novartis: C, F, R; Oertli: R; Ophthotech: F; Optos: C, R; Roche: F; F. G. Holz, Acucela: C, F; Allergan: F, R; Bayer: C, F, R; Bioeq: C, F; Boehringer-Ingelheim: C; Carl Zeiss MediTec: F, R; Genentech: C, F, R; Heidelberg Engineering: C, F, R; Merz: C, F; NightstarX: F; Novartis: C, F, R; Optos: F; Pixium: F; Roche: C, F; Thea: C; T. U. Krohne, Alimera Sciences: C, R; Bayer: C, F, R; Heidelberg Engineering: R; Novartis: C, F, R. The remaining author have no financial/conflicting interests to disclose.

Reprint requests: Tim U. Krohne, MD, FEBO, Department of Ophthalmology, University of Bonn, Ernst-Abbe-Straße 2, Bonn D-53127, Germany; e-mail: krohne@uni-bonn.de

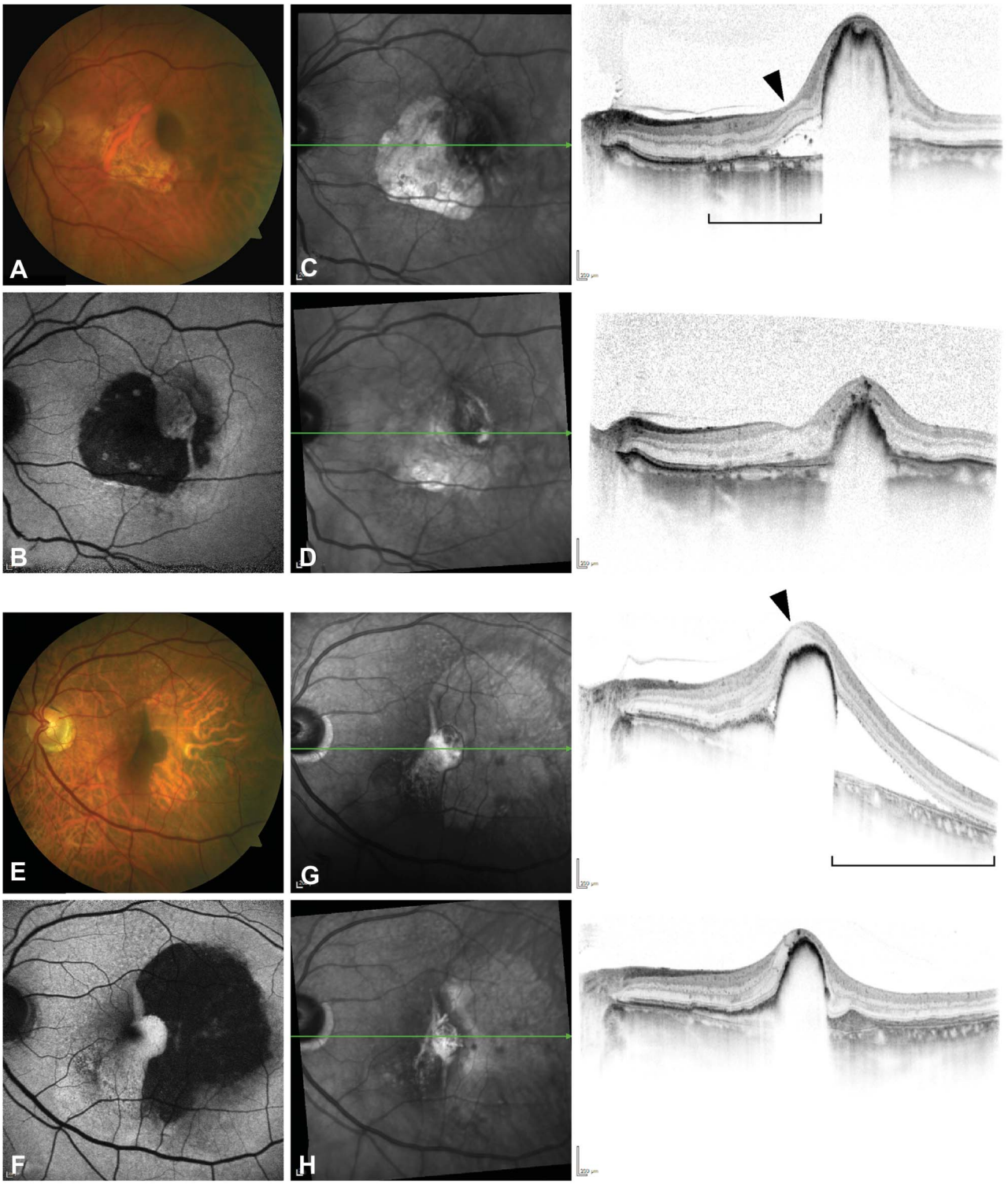

Fig. 1. Retinal imaging in two representative study patients. **A.** Baseline color fundus photography, (**B**) baseline fundus autofluorescence imaging, and (**C**) baseline OCT imaging of a study eye whose fovea (arrowhead) is located above the RPE-free area (bracket) of the RPE tear. **D.** Optical coherence tomography imaging at the final study visit demonstrates resolution of subretinal fluid and height reduction of the contracted RPE. **E–G.** By contrast, baseline retinal imaging of another study eye reveals an RPE tear with the fovea (arrowhead) located on the contracted RPE. **H.** Again, subretinal fluid is resolved and height of the contracted RPE is reduced at the final study visit.

Results

In this prospective study, 24 eyes of 24 consecutive patients with an RPE tear secondary to AMD were included (mean age, 76.8 years; age range, 67–92 years; 10 women, 14 men; Table 1). Of these, 22 eyes (91.6%) had already been treated with anti-VEGF agents for neovascular AMD before study recruitment. Three patients (12.5%) dropped out before completing the study due to reasons unrelated to the study treatment.

Nineteen of 24 eyes (79.2%) had acute RPE tears, defined as tears that had developed within 2 months before recruitment. For all these 19 eyes, OCT imaging within 2 months before the first study treatment was available that confirmed the absence of an RPE tear at that time. All these eyes had received anti-VEGF therapy before development of the RPE tear. The mean interval between diagnosis of the RPE tear and start of study treatment in these eyes was 25.0 days (±17.9 days; range, 4–62 days).

The remaining 5 of 24 study eyes (20.8%) had long-standing RPE tears that had developed more than 2 months (range, 3 months–3 years) before study recruitment but still exhibited signs of exudative activity of the AMD in funduscopy, OCT, and angiography, warranting treatment. Three of these 5 eyes had previous retinal imaging confirming the time point of RPE tear occurrence 2, 3, and 3 years before study recruitment. All these three eyes had already received anti-VEGF therapy before study recruitment. For the remaining 2 eyes, the patients described a sudden visual decline in the study eye 3 months and 6 months before study recruitment, respectively, but no ophthalmologic examinations had been performed since. Both these eyes did also not receive any previous anti-VEGF therapy. In the absence of previous retinal imaging, we considered the time point of perceived sudden visual loss as the most likely time the RPE tear had occurred and, thus, graded these 2 eyes as long-standing tears.

Complete previous treatment records were not available for all study patients, for example, due to referral from another institution; however, according to those records available, no study patient had received intravitreal corticosteroid injections or photodynamic therapy before enrollment in the study. For those 22 eyes that had received anti-VEGF therapy before study inclusion, the average number of previous anti-VEGF injections was 8.9 (±8.0; range, 1–27). Of these eyes, 13 had received ranibizumab, 4 aflibercept, 3 bevacizumab, and 2 both ranibizumab and aflibercept.

Despite multimodal retinal imaging at study baseline (i.e. after occurrence of the RPE tear), the lack of availability of fluorescein angiographic records before RPE tear development for a substantial proportion of the study patients (e.g. those referred to the study centers from other institutions) did not allow us to accurately classify the preexisting type of CNV lesions at baseline in all enrolled patients in our study. Morphologic assessment by multimodal retinal imaging at baseline revealed that the fovea was located above the RPE-devoid area of the tear in 1 of 23 gradable eyes (4.3%; Figure 1, A–D), was located on the contracted RPE of the tear in 19 eyes (82.6%; Figure 1, E–H), and was unaffected by the tear (either the contracted RPE or the RPE-free area) in 3 eyes (13.0%). Over the course of the study, mean CRT as measured by OCT from internal limiting membrane to Bruch membrane decreased significantly from 571 μm (±185 μm) at baseline to 436 μm (±171 μm) at final visit ($P = 0.0001$). In the 3 patients who dropped out

Table 1. Baseline Characteristics of the RIP Study Cohort and a Comparable Historical Control Cohort[19]

	RIP Study, All Eyes	RIP Study, Tears <2 Months	Historical Control Cohort, All Eyes	Historical Control Cohort, Untreated Tears
Eyes, n (patients, n)	24 (24)	19 (19)	37 (37)	12 (12)
Age, years (±SD)	76.8 (±5.2)	77.7 (±4.8)	78.8 (±6.0)	79.6 (±4.6)
Eyes with acute tear <2 months, n (%)	19 (79%)	19 (100%)	37 (100%)	12 (100%)
Eyes with anti-VEGF therapy before study, n (%)	22 (92%)	19 (100%)	37 (100%)	12 (100%)
Baseline BCVA, mean logMAR (±SD; Snellen equivalent)	0.69 (±0.37; 20/100)	0.64 (±0.32; 20/100)	0.88 (±0.43; 20/160)	1.06 (±0.51; 20/250)
Eyes with any anti-VEGF therapy over the 12-month study period, n (%)	24 (100%)	19 (100%)	25 (68%)	0 (0%)
Anti-VEGF treatments over the 12-month study period, mean number (±SD; range)	12 (±0; 12–12)	12 (±0; 12–12)	2.08 (±1.9; 0–7)	0 (±0; 0–0)

before completing the study, mean CRT in the study eye decreased from 723 μm (±508 μm) at baseline to 647 μm (±327 μm) at the last visit before dropout. Thus, mean CRT of these 3 eyes was somewhat higher than and their mean reduction in CRT was somewhat less than the 21 eyes that remained in the study.

According to the grading system proposed by Sarraf et al,[26] no study eye exhibited an RPE tear size of Grade 1 (<200 μm greatest diameter of the RPE-free area in the vector direction of the tear), 3 eyes (13.0%) of Grade 2 (200 μm to 1 disk diameter), 19 eyes (82.6%) of Grade 3 (>1 disk diameter), one eye (4.3%) of Grade 4 (>1 disk diameter and fovea over RPE-free area), and one eye was not gradable. At baseline, the mean greatest diameter of the RPE-free area in the vector direction of the tear was 1982.0 μm (±654.0 μm; range, 851–3,256 μm).

Mean baseline BCVA for all 24 eyes was 50.3 ETDRS letters (±18.7; Snellen equivalent 20/100; 0.69 logarithm of the minimum angle of resolution [logMAR] ± 0.37). Mean BCVA at final study visit was 52.9 letters (±19.7; Snellen equivalent 20/100; 0.64 logMAR ± 0.39). There was no significant difference between these values ($P = 0.39$; Figure 2). When the 5 eyes with long-standing RPE tears (>2 months) were excluded from the analysis, mean BCVA for the remaining 19 eyes with acute RPE tears was 52.8 letters (±16.2; Snellen equivalent 20/80; 0.64 logMAR ± 0.32) at baseline and 54.5 letters (±17.6; Snellen equivalent 20/100; 0.61 logMAR ± 0.35) at final visit, again without significant difference ($P = 0.38$). Mean BCVA at baseline, mean BCVA at final visit, and mean BCVA change were not significantly different between the subgroups of eyes with acute and long-standing RPE tears ($P = 0.64$, $P = 0.21$, and $P = 0.48$, respectively). In the 3 patients who dropped out before completing the study, mean BCVA was 46.7 letters (±24.4; Snellen equivalent 20/125) at baseline and 45.0 letters (±30.0; Snellen equivalent 20/125) at the last attended study visit before dropout.

Stratification of functional results by RPE tear characteristics confirmed BCVA stabilization for each of the analyzed subgroups (Table 2). In particular, BCVA did not change significantly over the study period in the subgroups of eyes with long-standing RPE tears (n = 5; $P = 0.82$), with the fovea located on the retracted RPE (n = 19; $P = 0.27$), with a tear not affecting the fovea (n = 3; $P = 0.16$), with a tear size of Grade 2 (n = 3; $P = 0.80$), and with a tear size of Grade 3 (n = 19; $P = 0.33$).

Two of 24 eyes (8%) exhibited a significant improvement in BCVA by at least 15 ETDRS letters, one eye (4%) lost significantly in BCVA by at least 15 letters, and in 21 eyes (88%) BCVA remained stable within a range of ± 15 letters. Both eyes with significant BCVA improvement were affected by an acute tear (≤2 months) of Grade 3 size (>1 disk diameter) with the fovea on the contracted RPE. The one eye with significant BCVA loss had a long-standing tear of likewise Grade 3 size with the fovea on the contracted RPE. Change in visual acuity did not correlate with the change of CRT in OCT (r = −0.104; $P = 0.663$).

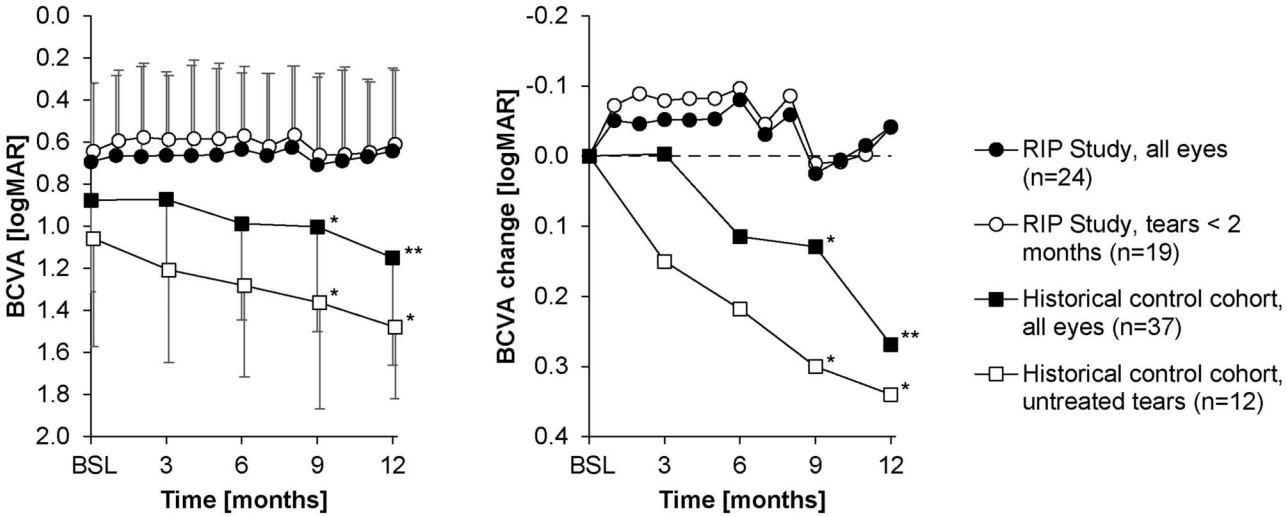

Fig. 2. Mean BVCA (left) and mean BCVA change (right) over the 12-month study period. In the study cohort of 24 eyes (●), mean BCVA after 12 months remained stable compared with baseline ($P = 0.39$). Likewise, the subgroup of 19 eyes with acute RPE tears (less than 2 months between tear diagnosis and first study treatment; ○) exhibited stabilization of BCVA ($P = 0.38$). By contrast, a comparable historical control cohort[19] of 37 eyes (■) with acute RPE tears treated by a mean number of 2.08 anti-VEGF injections (range, 0–7) demonstrated a significant decline of mean BCVA ($P = 0.0012$). Within this historical control cohort, the subgroup of untreated eyes (□; n = 12) suffered an even more pronounced loss of mean BCVA ($P = 0.013$). BSL, baseline.

Table 2. Functional and Morphologic Treatment Results Stratified by RPE Tear Characteristics

RPE Tear Characteristics		Eyes, n	BCVA at BSL, Mean ETDRS Letters (±SD; Snellen Equivalent)	BCVA at Final Visit, Mean ETDRS Letters (±SD; Snellen Equivalent)	Significance of Difference, *P*	CRT at BSL, Mean μm (±SD)	CRT at Final Visit, Mean μm (±SD)	Significance of Difference, *P*
Duration	Acute	19	52.8 (±16.7; 20/100)	54.5 (±18.2; 20/80)	0.40	565 (±206)	449 (±194)	0.0009
	Long-standing	5	40.6 (±26.4; 20/160)	46.3 (±29.7; 20/125)	0.82	594 (±116)	382 (±48)	0.057
Location	RPE-free area under fovea	1	51 (±0; 20/100)	52 (±0; 20/100)		406 (±0)	279 (±0)	
	Retracted RPE under fovea	19	50.0 (±19.8; 20/100)	53.8 (±21.2; 20/100)	0.27	619 (±156)	471 (±166)	0.0002
	Extrafoveal tear	3	52.3 (±21.2; 20/100)	48.3 (±14.2; 20/125)	0.16	244 (±100)	215 (±57)	0.51
Size	Grade 2	3	53.3 (±12.1; 20/100)	51.3 (±16.1; 20/100)	0.80	563 (±44)	365 (±113)	0.27
	Grade 3	19	49.8 (±20.6; 20/100)	53.2 (±21.8; 20/100)	0.33	583 (±208)	459 (±185)	0.0013
	Grade 4	1	51 (±0; 20/100)	52 (±0; 20/100)		406 (±0)	279 (±0)	
Total		24	50.3 (±18.7; 20/100)	52.9 (±19.7; 20/100)	0.39	571 (±185)	436 (±171)	0.0001

Duration of RPE tear existence before start of study treatment was classified as acute (≤2 months) or long-standing (>2 months). Retinal pigment epithelium tear size was categorized according to the greatest diameter of the RPE-free area in the vector direction of the tear as Grade 2 (200 μm−one disk diameter), Grade 3 (>1 disk diameter), or Grade 4 (>1 disk diameter and fovea over RPE-free area) as proposed by Sarraf et al.[26] One eye was not gradable regarding RPE tear location and size.
BSL, baseline.

Patient-reported vision-related quality of life remained stable over the course of the study with mean NEI VFQ-25 scores at baseline and final visit of 79.0 (±10.8) and 74.3 (±13.9; $P = 0.12$), respectively.

Systematic assessment of morphologic treatment effects was challenging due to the often gross structural alterations of the retina secondary to the RPE tear. However, most study eyes exhibited a reduction of intraretinal/subretinal fluid over the study period, and four eyes even had complete resolution of intraretinal/subretinal fluid at the last study visit. By contrast, three eyes were nonresponsive to study treatment as assessed by significant persistence or even increase of intraretinal or subretinal fluid over the study period. All these three nonresponsive eyes had acute tears of size Grade 3 with the fovea on the contracted RPE.

At study baseline, RPE tears in 23 study eyes were unilobular, whereas one study eye exhibited a multilobular tear configuration that may represent a risk factor for subsequent lesion enlargement.[27] However, total RPE tear area in this eye did not increase over the study period.

No case of endophthalmitis occurred over the course of the study. One study eye experienced an increase of a preexisting subretinal hemorrhage between the second study visit (BCVA, 22 ETDRS letters; Snellen equivalent, 20/400) and third study visit (BCVA, 4 letters; Snellen equivalent, 20/800) that resolved without additional intervention. This study eye was also the only one that exhibited an increase in total RPE tear area over the study period, resulting from a second tear in the area of the former hemorrhage between the fourth study visit (BCVA, 7 letters; Snellen equivalent, 20/800) and fifth study visit (BCVA, 14 letters; Snellen equivalent, 20/500). Study treatment was continued in this eye despite these events but BCVA decreased by 11 ETDRS letters between baseline and the last study visit. No other ocular serious adverse events were reported during the study. All reported systemic serious adverse events (e.g. bradycardia, rib fracture, and kidney stone) were classified as likely not study intervention–related.

Discussion

The efficacy of intravitreal anti-VEGF therapy in neovascular AMD has been demonstrated in several prospective large-scale clinical trials, but the presence of an RPE tear constituted an exclusion criterion in all these trials.[28–31] Thus, the efficacy of anti-VEGF therapy in this AMD subtype is unclear. To the best of our knowledge, the RIP study provides the first prospective

efficacy data for anti-VEGF therapy in RPE tears secondary to AMD, demonstrating a stabilization of visual acuity under monthly ranibizumab therapy over 12 months. Corresponding to the stabilization of vision within the 12-month follow-up time, patient-reported vision-related quality of life as assessed by NEI VFQ-25 score likewise was stable in the study cohort. However, the patient number of our study allows only for a descriptive analysis of this variable parameter.

To relate the RIP study results with the natural history of RPE tears, we used data of one of our own previous studies to generate a historical control cohort of untreated RPE tears. Similar to the RIP study, this previous study included eyes with RPE tears secondary to AMD (37 eyes of 37 patients; mean age, 78.8 years; age range, 63–90 years).[19] All eyes in this cohort suffered from an acute RPE tear that had developed under anti-VEGF therapy, similar to the RIP study subgroup of acute RPE tears (Table 1). Within the first 12 months of follow-up, these eyes received a mean of only 2.1 anti-VEGF treatments (range, 0–7), thus significantly less than the eyes in the RIP study. During this period, mean BCVA of the control cohort declined significantly from 0.88 logMAR (±0.43; Snellen equivalent, 20/160) at baseline to 1.15 logMAR (±0.51; Snellen equivalent, 20/320) after 12 months ($P = 0.0012$; Figure 2). Post hoc analysis of the subgroup of eyes that did not receive any treatment within the first 12 months after the RPE tear (n = 12; mean age 79.6; age range 72–88) revealed an even more pronounced loss of visual acuity. In this untreated subgroup, mean BCVA declined from 1.06 logMAR (±0.51; Snellen equivalent, 20/250) at baseline to 1.48 logMAR (±0.34; Snellen equivalent, 20/640) after 12 months ($P = 0.013$). Thus, despite the lower baseline mean BCVA compared with our study cohort, this historical control cohort experienced a further significant decline of mean BCVA over 12 months without treatment, whereas our study cohort exhibited a stabilization of mean BCVA over 12 months under ranibizumab therapy. Although many relevant patient parameters of the historical control cohort and its untreated subgroup are similar to the RIP study cohort, direct comparability of results derived from different studies in general remains limited due to potential differences in study design and baseline characteristics.

Several retrospective studies of anti-VEGF therapy in RPE tears secondary to AMD have been conducted.[32–34] Rouvas et al[33] reported retrospectively a beneficial effect of intravitreal ranibizumab in the majority of 21 eyes of 20 patients with RPE tears with a median of 7 injections and 12-month follow-up time. Coco et al found a statistically significant difference in visual acuity comparing 12 anti-VEGF–treated and 9 anti-VEGF–untreated eyes with RPE tears in a retrospective study. Mean number of injections in the treated group was 6, and 15 eyes presented with a Grade 3 tear, 3 eyes with a Grade 2 tear, and 3 eyes with a Grade 4 tear according to the classification by Sarraf et al.[26] Follow-up period varied between 6 months and 48 months.[34] In another retrospective study by Durkin et al, anti-VEGF treatment after RPE tear resulted in all 14 patients at least maintaining their BCVA within the mean follow-up time of 14.3 months. The average number of injections given after the tear was 7.[22] Heimes et al retrospectively analyzed the long-term BCVA outcome of 22 eyes with an RPE tear of 21 patients. The eyes were divided into two groups with comparable baseline BCVA and tear size, and the group (n = 11) receiving a significantly higher number of injections during the first year after development of the RPE tear had also a better BCVA outcome than the other (n = 11).[23] Similarly, Sarraf et al[35] concluded in a retrospective analysis of 56 eyes with an average follow-up of 42 months that a greater number of injections correlated with a better visual acuity and was associated with lower risk of subretinal fibrosis. Moreira et al retrospectively analyzed a cohort of 5 patients with RPE tears without foveal involvement, demonstrating an improvement in visual acuity under anti-VEGF treatment (mean number of injections, 4.2) over a mean follow-up period of 52 months. By contrast, using a retrospective study design with 10 eyes of 10 patients, Asao et al showed that despite continuous anti-VEGF treatment, mean visual acuity deteriorated over the course of the follow-up period with a mean of 27.3 months. However, the mean number of treatments in this study was comparatively low with only 3.3 injections over 12 months.[36]

The question whether anti-VEGF therapy in AMD increases the long-term risk of developing RPE tears or whether it only accelerates RPE tear development has not yet been resolved. In a combined analysis of the prospective, randomized ANCHOR, MARINA, and PIER studies, the incidence of RPE tears over 2 years was not different between ranibizumab-treated eyes and those that received control treatment (sham injection or photodynamic therapy); however, most RPE tears in the ranibizumab group occurred shortly after the initiation of anti-VEGF therapy.[21] Moreover, in the HARBOR study, there was no difference in the incidence of RPE tears between the groups treated with 0.5 mg and 2.0 mg of ranibizumab.[37] In our study cohort, 22 eyes had received anti-VEGF therapy before study inclusion with an average number of previous anti-VEGF injections of 8.9. Although the effect of anti-VEGF therapy on RPE tear development remains

unclear, the high number of previous anti-VEGF treatments in some of our study eyes may have predisposed these eyes for the formation of RPE tears.

As a potential risk of continuous anti-VEGF therapy after the occurrence of an RPE tear, Asao et al and Clemens et al reported RPE tear enlargement during anti-VEGF therapy, possibly due to further CNV contraction.[27,36] We observed such an enlargement during therapy in 1 of 24 study eyes but without negative effect on visual acuity in this eye. Whether the risk of RPE tear enlargement increases under anti-VEGF therapy as compared to untreated tears and how this affects visual acuity need to be evaluated in future studies.

In our study, most eyes (82.6%) presented with a tear of Grade 3 tear according to the grading system suggested by Sarraf et al.[26] It has been suggested that visual prognosis may be determined by size and location of the RPE tear and that outcome may be particularly poor in Grade 4 tears (diameter >1 disk diameter and RPE-free area including the fovea) regardless of continuation of anti-VEGF therapy.[26,35] Interestingly, the one patient in our cohort with a Grade 4 tear exhibited stable BCVA over the 12-month study period (baseline BCVA, 51 ETDRS letters; Snellen equivalent, 20/100; BCVA at last visit, 52 letters; Snellen equivalent, 20/100) despite complete resolution of subretinal fluid under the study therapy and subsequent location of the fovea on the bare Bruch membrane devoid of RPE (Figure 1, A–D). This observation is in line with case reports by other groups,[38,39] as well as our own previous finding that after an RPE tear, outer nuclear layer thickness may remain stable even within the RPE-free area.[40] These findings suggest that subfoveal RPE loss by an RPE tear may not necessarily lead to loss of foveal function and that in selected cases, Grade 4 tears may also profit from anti-VEGF therapy.

In a retrospective case series of 10 eyes of 10 patients, Mukai et al described 2 types of repair mechanisms after RPE tear development, that is, early and complete resolution of subretinal fluid with direct attachment of the outer retina to Bruch membrane and persistent subretinal fluid for more than 6 months with development of thickened proliferative tissue at the area of RPE loss. As fibrovascular scarring may further impair visual acuity, this observation supports the application of continuous anti-VEGF therapy after RPE tear development to reduce subretinal fluid.[41]

Our study has several limitations including lack of a control group, small sample size, and a short follow-up period of 12 months. Moreover, the study cohort varied widely regarding tear morphology and topography, anti-VEGF pretreatment, and time between diagnosis of tear and start of study treatment. As we analyzed fixed monthly treatment regimen, further studies are needed to evaluate pro re nata (PRN) or treat and extend (T&E) therapy regimens and to define retreatment criteria for eyes with RPE tears under such treatment regimens. Despite these limitations, our study provides the first prospective morphologic and functional efficacy data for anti-VEGF therapy in RPE tears secondary to AMD.

The results of our study, together with those of previous retrospective studies, suggest an advantageous effect of frequent anti-VEGF therapy on stabilization of visual acuity after occurrence of an RPE tear secondary to AMD.

Key words: RPE rip, neovascular AMD, IIT, anti-VEGF therapy.

Acknowledgments

Funding for this investigator-initiated trial was provided by Novartis Pharma GmbH, Germany. The authors acknowledge the support by the Study Center Bonn (SZB; Christoph Coch, MD), University Hospital Bonn, and the Institute of Medical Biometry, Informatics, and Epidemiology (IMBIE; Rolf Fimmers, PhD), University Hospital Bonn.

References

1. Hoskin A, Bird AC, Sehmi K. Tears of detached retinal pigment epithelium. Br J Ophthalmol 1981;65:417–422.
2. Chang LK, Sarraf D. Tears of the retinal pigment epithelium: an old problem in a new era. Retina 2007;27:523–534.
3. Gass JD. Retinal pigment epithelial rip during krypton red laser photocoagulation. Am J Ophthalmol 1984;98:700–706.
4. Gelisken F, Inhoffen W, Partsch M, et al. Retinal pigment epithelial tear after photodynamic therapy for choroidal neovascularization. Am J Ophthalmol 2001;131:518–520.
5. Wolf A, Rüping J, Neubauer AS, et al. Alterations of vascular pigment epithelium detachments associated with age-related macular degeneration during upload with intravitreal ranibizumab. Retina 2013;33:1843–1849.
6. Nagiel A, Freund KB, Spaide RF, et al. Mechanism of retinal pigment epithelium tear formation following intravitreal anti–vascular endothelial growth factor therapy revealed by spectral-domain optical coherence tomography. Am J Ophthalmol 2013; 156:981–988.
7. Clemens CR, Eter N. Retinal pigment epithelium tears: risk factors, mechanism and therapeutic. Ophthalmologica 2016;235:1–9.
8. Sarraf D, Chan C, Rahimy E, Abraham P. Prospective evaluation of the incidence and risk factors for the development of RPE tears after high-and low-dose ranibizumab therapy. Retina 2013;33:1551–1557.
9. Chan CK, Abraham P, Meyer CH, et al. Optical coherence tomography–measured pigment epithelial detachment height as a predictor for retinal pigment epithelial tears associated with intravitreal bevacizumab injections. Retina 2010;30:203–211.
10. Chiang A, Chang LK, Sarraf D. Predictors of anti-VEGF-associated retinal pigment epithelial tear using fa and OCT analysis. Retina 2008;28:1265–1269.

11. Clemens CR, Bastian N, Alten F, et al. Prediction of retinal pigment epithelial tear in serous vascularized pigment epithelium detachment. Acta Ophthalmologica 2014;92:50–56.
12. Doguizi S, Ozdek S. Pigment epithelial tears associated with anti-VEGF therapy: incidence, long-term visual outcome, and relationship with pigment epithelial detachment in age-related macular degeneration. Retina 2014;34:1156–1162.
13. Singh RP, Sears JE. Retinal pigment epithelial tears after pegaptanib injection for exudative age-related macular degeneration. Am J Ophthalmol 2006;142:160–162.
14. Ronan SM, Yoganathan P, Chien FY, et al. Retinal pigment epithelium tears after intravitreal injection of bevacizumab (avastin) for neovascular age-related macular degeneration. Retina 2007;27:535–540.
15. Chan CK, Meyer CH, Gross JG, et al. Retinal pigment epithelial tears after intravitreal bevacizumab injection for neovascular age-related macular degeneration. Retina 2007;27:541–551.
16. Cho HJ, Kim HS, Yoo SG, et al. Retinal pigment epithelial tear after intravitreal ranibizumab treatment for retinal angiomatous proliferation. Am J Ophthalmol 2015;160:1000–1005.
17. Saito M, Kano M, Itagaki K, et al. Retinal pigment epithelium tear after intravitreal aflibercept injection. Clin Ophthalmol 2013;7:1287–1289.
18. Hata M, Oishi A, Yamashiro K, et al. Incidence and causes of vision loss during aflibercept treatment for neovascular age-related macular degeneration. Retina 2017;37:1320–1328.
19. Gutfleisch M, Heimes B, Schumacher M, et al. Long-term visual outcome of pigment epithelial tears in association with anti-VEGF therapy of pigment epithelial detachment in AMD. Eye 2011;25:1181–1186.
20. Pauleikhoff D, Löffert D, Spital G, et al. Pigment epithelial detachment in the elderly. Clinical differentiation, natural course and pathogenetic implications. Graefes Arch Clin Exp Ophthalmol 2002;240:533–538.
21. Cunningham ET, Feiner L, Chung C, et al. Incidence of retinal pigment epithelial tears after intravitreal ranibizumab injection for neovascular age-related macular degeneration. Ophthalmology 2011;118:2447–2452.
22. Durkin SR, Farmer LD, Kulasekara S, Gilhotra J. Change in vision after retinal pigment epithelium tear following the use of anti-VEGF therapy for age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol 2016;254:1–6.
23. Heimes B, Farecki ML, Bartels S, et al. Retinal pigment epithelial tear and anti-vascular endothelial growth factor therapy in exudative age-related macular degeneration: clinical Course and Long-Term Prognosis. Retina 2016;36:868–874.
24. Ferris FL, Bailey I. Standardizing the measurement of visual acuity for clinical research studies: guidelines from the eye care technology forum. Ophthalmology 1996;103:181–182.
25. Mangione CM, Lee PP, Gutierrez PR, et al. Development of the 25-item National Eye Institute visual function questionnaire. Arch Ophthalmol 2001;119:1050–1058.
26. Sarraf D, Reddy S, Chiang A, et al. A new grading system for retinal pigment epithelial tears. Retina 2010;30:1039–1045.
27. Clemens CR, Alten F, Baumgart C, et al. Quantification of retinal pigment epithelium tear area in age- related macular degeneration. Retina 2014;34:24–31.
28. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. New Engl J Med 2006;355:1419–1431.
29. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. New Engl J Med 2006;355:1432–1444.
30. Heier JS, Brown DM, Chong V, et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. Ophthalmology 2012;119:2537–2548.
31. Martin DF, Maguire MG, Ying G, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. New Engl J Med 2011;364:1897–1908.
32. Lesniak SP, Fine HF, Prenner JL, Roth DB. Long-term follow-up of spontaneous retinal pigment epithelium tears in age-related macular degeneration treated with anti-VEGF therapy. Eur J Ophthalmol 2010;21:73–76.
33. Rouvas A, Ladas I, Georgalas I, et al. Ranibizumab for the treatment of exudative age-related macular degeneration associated with retinal pigment epithelial tear. Retina 2011;31:1083–1088.
34. Coco RM, Sanabria MR, Hernandez AG, Fernández Muñoz M. Retinal pigment epithelium tears in age-related macular degeneration treated with antiangiogenic drugs: a controlled study with long follow-up. Ophthalmologica 2012;228:78–83.
35. Sarraf D, Joseph A, Rahimy E. Retinal pigment epithelial tears in the era of intravitreal pharmacotherapy: risk factors, pathogenesis, prognosis and treatment (an American ophthalmological society thesis). Trans Am Ophthalmological Soc 2014; 112:142–159.
36. Asao K, Gomi F, Sawa M, Nishida K. Additional anti-vascular endothelial growth factor therapy for eyes with a retinal pigment epithelial tear after the initial therapy. Retina 2014;34:512–518.
37. Sarraf D, London NJS, Khurana RN, et al. Ranibizumab treatment for pigment epithelial detachment secondary to neovascular age-related macular degeneration: post hoc analysis of the HARBOR study. Ophthalmology 2016;123:2213–2224.
38. Yoshitani S, Katsura M, Minamoto A, et al. Retinal pigment epithelial tear involving the fovea with preserved visual function. Ophthalmic Surg Lasers Imaging 2003;34:217–220.
39. Krøyer K, la Cour M, Larsen M. Dissociation of rod and cone sensitivity by acute localized retinal pigment epithelium loss. Acta Ophthalmol 2008;86:338–340.
40. Oishi A, Fang PP, Thiele S, et al. Longitudinal change of outer nuclear layer after retinal pigment epithelial tear secondary to age-related macular degeneration. Retina 2018;38:1331–1337.
41. Mukai R, Sato T, Kishi S. Repair mechanism of retinal pigment epithelial tears in age-related macular degeneration. Retina 2015;35:473–480.