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Review

MANAGEMENT OF RETINAL PIGMENT EPITHELIUM TEAR DURING ANTI–VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY

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Purpose: This article aims to review current evidence on the development, diagnosis, and management of retinal pigment epithelium (RPE) tear during anti–vascular endothelial growth factor (VEGF) therapy.

Methods: Literature searches were performed using MEDLINE/PubMed databases (cut-off date: August 2019).

Results: Three key recommendations were made based on existing literature and clinical experience: 1) Multimodal imaging with color fundus photography, optical coherence tomography, near-infrared reflectance imaging, fundus autofluorescence imaging, optical coherence tomography-angiography, and/or fluorescein angiography are recommended to diagnose RPE tear and assess risk factors. Retinal pigment epithelium tears can be graded by size and foveal involvement. 2) Patients at high risk of developing RPE tear should be monitored after each anti-VEGF injection. If risk factors worsen, it is not yet definitively known whether anti-VEGF administration should be more frequent, or alternatively stopped in such patients. Prospective research into high-risk characteristics is needed. 3) After RPE tear develops, anti-VEGF treatment should be continued in patients with active disease (as indicated by presence of intraretinal or subretinal fluid), although cessation of therapy should be considered in eyes with multilobular tears.

Conclusion: Although evidence to support the assumption that anti-VEGF treatment contributes to development of RPE tear is not definitive, some data suggest this link.

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The Vision Academy is an international group of ophthalmic specialists who work together to share existing skills and knowledge and build best practice in the management of retinal disease, particularly in areas with insufficient conclusive evidence. Selected members of the Vision Academy met in October 2017 to discuss the current literature on retinal pigment epithelium (RPE) tear in patients with age-related macular degeneration (AMD).

Age-related macular degeneration is a chronic degenerative condition[1] that can lead to irreversible loss of vision.[2] Neovascular AMD (nAMD) is characterized by growth of abnormal blood vessels beneath the macula (choroidal neovascularization [CNV]), and is usually treated with anti–vascular endothelial growth factor (VEGF) agents.

Retinal pigment epithelium tears are a relatively frequent occurrence in patients with nAMD and associated pigment epithelial detachment (PED), with reported incidence rates of 10% to 12% of eyes.[3] In the longer term, visual acuity is frequently poor for these patients, particularly in the case of larger tears and if the foveal center is affected.[4] In this review, we provide an overview of the current evidence for the development of RPE tear during anti-VEGF therapy, and advice on how best to manage this condition. Specifically, we aim to address whether RPE tear development is attributable to injection dosing, frequency, or drug choice, rather than the natural history of PED in nAMD, and we explore how to identify patients at greatest risk. We also aim to

evaluate the most appropriate imaging techniques for documenting RPE tears, appropriate diagnostic criteria, and optimal management of patients with RPE tear.

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Pathogenesis, Predictors, and Risk Factors for Retinal Pigment Epithelium Tear

Retinal pigment epithelium tears were first described in 1981[5] as a complication of PED in patients with nAMD. They also occur in other conditions and nAMD variants such as polypoidal choroidal vasculopathy and retinal angiomatous proliferation[6]; however, RPE tears in these conditions will not be covered in this review. Although the pathogenesis of RPE tear has not been fully elucidated, several mechanisms have been proposed.[7,8] One such hypothesis is that in patients with nAMD and PED, subretinal fluid applies hydrostatic pressure to the RPE, causing it to stretch, and contraction of the choroidal neovascular membrane adds tractional forces to the already delicate RPE layer.[6] Thus, it has been suggested that anti-VEGF treatment could increase the likelihood of RPE tear, because it could augment contraction of the choroidal neovascular membrane. However, older treatments such as photodynamic therapy with verteporfin were also associated with RPE tear,[6] and tears may occur as a spontaneous complication of PED.

Despite the lack of detailed insight into the disease mechanism, several predictors and risk factors for RPE tear development have been identified to date, such as greater height and basal diameter of the PED, a smaller

Table 1. Predictors and Risk Factors for RPE Tear Development

Predictors and Risk Factors for RPE Tear Development	Reference
Increased surface area and a large linear diameter of the subfoveal PED In particular, a large PED basal diameter and PED height $\geq$400 μm	4,8–10
A small ratio of CNV size to PED size In a study of RPE tear in eyes following bevacizumab* injection, a CNV to PED ratio of $<$50% was identified as a risk factor	11
Serous vascularized PED (compared with fibrovascular PED) As identified by areas of stippled hyperfluorescence and signs of leakage in the later phases	8,12
Presence of radial hyperreflective lines in patients with PED lesions	8
Recent PED PED duration of $\leq$4.5 months was a significant risk factor for RPE tear formation (odds ratio = 166.7; 95% CI 15.2–1,000)	13
Microrips in the RPE	14

*Bevacizumab is not licensed for the treatment of retinal diseases.

CI, confidence interval.

ratio of CNV to PED size, fibrovascular PED, and more recent PED (Table 1).

Recommendations for the Diagnosis and Monitoring of Patients With Retinal Pigment Epithelium Tear

Although a range of retinal imaging modalities are recommended for the diagnosis and monitoring of RPE tear, there are currently no officially recognized guidelines, and a multimodal approach provides the most complete information. These modalities include color fundus photography, optical coherence tomography (OCT), fluorescein angiography (FA), OCT-angiography (OCT-A), near-infrared reflectance imaging, and fundus autofluorescence. Examples of RPE tear are provided in Figures 1–3. These examples show signs indicating a higher risk of RPE tear, including RPE wrinkling, radial lines on near-infrared imaging, and multilobular RPE detachment.

Color fundus photography is used to document subretinal blood and follow its resorption. Optical coherence tomography should be used both to detect the presence of RPE tear and to assess risk; for example, in patients with large serous PED or irregular choroidal thickness.[15] Fluorescein angiography is commonly used and can provide information on PED diameter and fluid leakage due to CNV.[10,11,16] Optical coherence tomography-angiography has the added benefit over FA in that a more accurate CNV/PED ratio can be calculated, because it is less affected by dye leakage,[17] although there may be difficulties with the interpretation of OCT-A in the presence of PED because of segmentation errors. In addition, near-

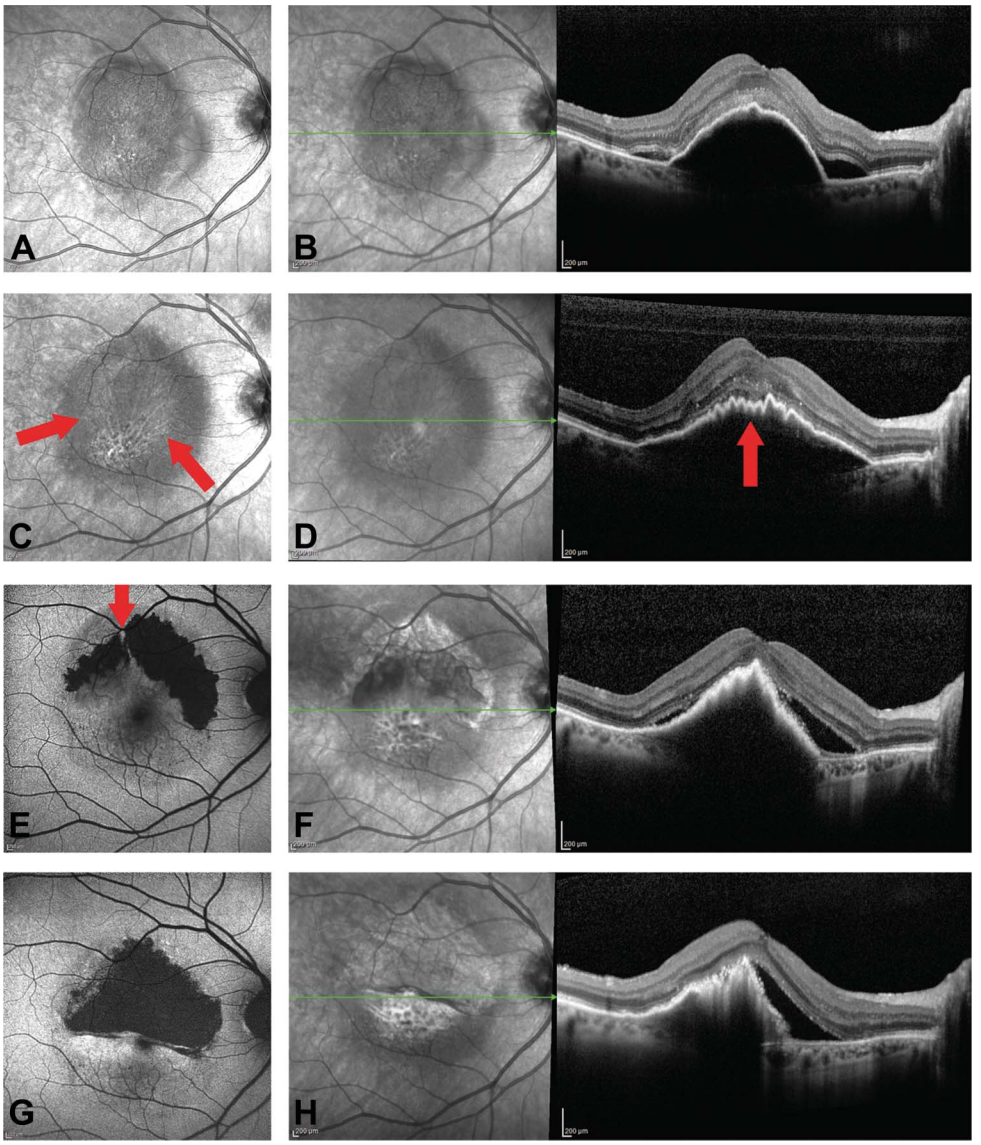

Fig. 1. Development of RPE tear in a patient with large, elevated PED with associated subretinal fluid. Transition from multilobular to unilobular tear. **A.** NIR/(**B**) infrared & OCT: A 79-year-old female patient presented with large, elevated PED with associated subretinal fluid. Treatment with anti-VEGF was initiated. **C.** NIR/(**D**) infrared & OCT: 5 weeks later following one injection, wrinkling and radial lines were visible in the upper sector of the PED (arrows). **E.** FAF/(**F**) infrared & OCT: 4 weeks later, following one further injection, development of an RPE tear was observed superiorly (arrow). **G.** FAF/(**H**) infrared & OCT: 4 weeks later, following another injection, further progression of the RPE tear with retraction of the RPE tear to the edge of the fovea was observed. FAF, fundus autofluorescence; NIR, confocal near-infrared fundus reflectance.

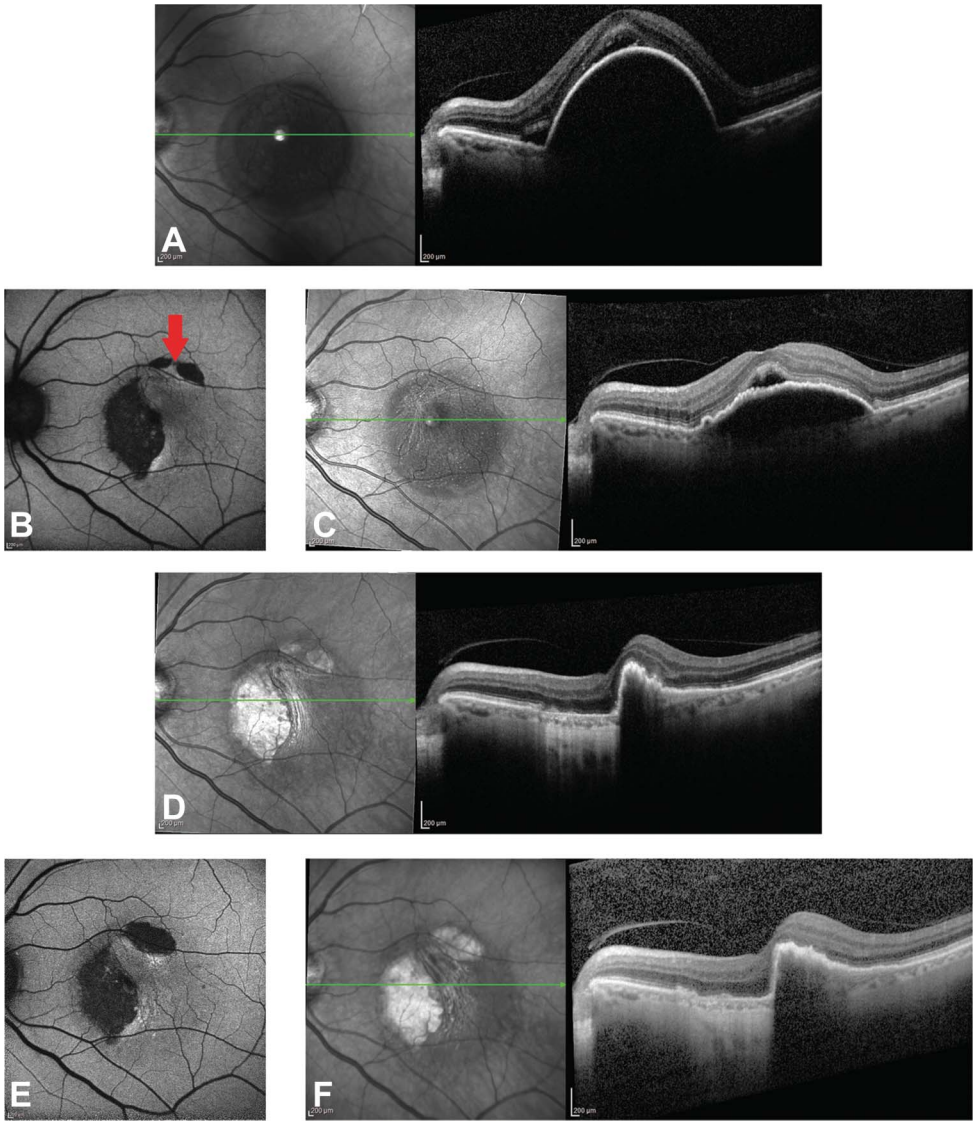

Fig. 2. Development of a multilobular RPE tear in a patient with large, elevated PED with associated subretinal fluid. **A.** Infrared & OCT: An 88-year-old male patient presented with large, elevated PED with associated subretinal fluid. Treatment with anti-VEGF was initiated. **B.** FAF/(**C**) infrared & OCT: 5 weeks later following one injection, development of a multilobular RPE tear was observed (nasal and superior) with radial lines visible in panel B (arrow). **D.** infrared & OCT: 4 weeks later, after one more injection, the RPE tear was observed to have progressed nasally. **E.** FAF/(**F**) infrared & OCT: The retinal bridge between the upper lobe has ruptured. FAF, fundus autofluorescence.

infrared reflectance imaging can be used to detect radial hyperreflective lines that may indicate changes in the RPE.[8] Finally, small tears may be detectable using fundus autofluorescence due to the high contrast of the hypoautofluorescent areas that lack RPE, compared with areas of intact retina.[10]

Various grading systems have been introduced to classify RPE tears according to their size following detection. In the classification system developed by Sarraf et al,[18] tears are graded according to both foveal involvement and linear diameter, measured using FA. Tears <200 μm in diameter are classed as Grade 1; 200 μm to 1-disc diameter tears as Grade 2; >1-disc diameter tears as Grade 3; and tears involving the foveal center as Grade 4. Other classification systems have included data on tear size (microrips, conventional RPE tears, and giant tears) or differentiated between multilobulate.[6,16] Grading of RPE tears is crucial to providing prognostic information, as lower-grade tears may be associated with an improved response to anti-VEGF therapy and better visual acuity outcomes.[18]

Incidence of Retinal Pigment Epithelium Tear Development During Anti–Vascular Endothelial Growth Factor Therapy

Currently, there are no clinical data demonstrating a difference in risk of RPE tear based on anti-VEGF agents used, or indeed that anti-VEGF causes RPE tears. The overall mean incidence of RPE tear during treatment with anti-VEGF agents from key Phase III clinical trials was $<1\%$ across all patients (Table 2), although several trials had excluded patients at high risk of RPE tear (i.e., those with large PED). However, in a recent real-world study of

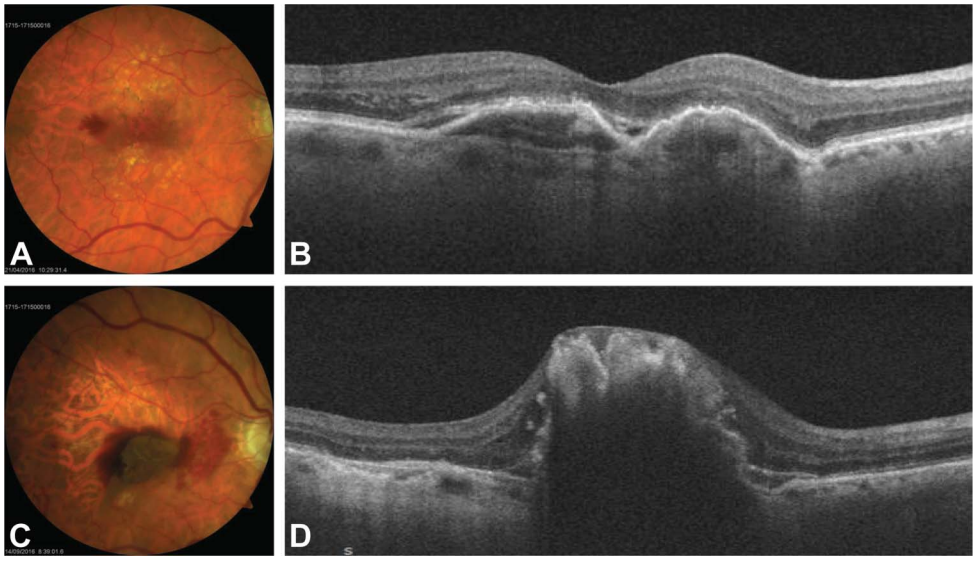

Fig. 3. Multilobular RPE tear in a patient with subretinal hemorrhage. **A.** Color fundus photograph/(**B**) OCT: A 78-year-old male patient with baseline visual acuity of 20/30 presented with multilobular PED with subretinal hemorrhage and both subretinal and intraretinal fluid. Treatment with anti-VEGF was initiated. **C.** Color fundus photograph/(**D**) OCT: 21 weeks later after four injections, the development of a large RPE tear with associated subretinal hemorrhage and a large "bare-area" were observed supero-temporally. A zone of retracted RPE tear was visible inferonasally, with severe vision loss (visual acuity of 20/200).

over 6,000 patients treated with ranibizumab, RPE tears were detected in 0.16% of patients, further supporting the rates reported from clinical trials.[29] There are several retrospective case series of the risk of RPE tear with anti-VEGF agents, with most reporting the incidence of RPE tear in patients receiving bevacizumab (Table 3). Several case reports are available for intravitreal aflibercept,[33–36] as well as a retrospective review of eight cases, all of which had PED.[37] Although RPE tears have been suggested as being associated with anti-VEGF therapy, they were frequently described before the introduction of anti-VEGF treatment in high-risk patients with PED,[5] with an incidence of 10% to 12% of eyes.[38,39] This is slightly lower than the 12% to 17% incidence reported following anti-VEGF treatment among very high-risk eyes (eyes with serous vascularized PED), and no association has been documented between the number of anti-VEGF injections administered and the incidence of RPE tear.[8]

Recommendations for the Management of Patients at High Risk of Developing Retinal Pigment Epithelium Tear

In the longer term, RPE tears are often associated with poor visual outcomes, particularly for tears involving the fovea[7] and in cases where subretinal hemorrhage and scar formation occur. Therefore, the assessment of several prognostic markers is

Table 2. Incidence of RPE Tear Reported in Key Phase III Trials of Anti-VEGF Agents

Study	Treatment	Duration, Months	Study Population Treated with Anti-VEGF, n	Incidence of RPE Tear Across Treatment Groups, n (%)	Reference
ANCHOR	Ranibizumab	12	277	0 (0)	19
CATT	Ranibizumab	12	599	1 (0.2)*	20
	Bevacizumab†		586	2 (0.3)*	
EXCITE‡	Ranibizumab	12	353	2 (0.6)	21
HARBOR	Ranibizumab	24	1,095	1 (0.1)	22
IVAN	Ranibizumab	24	314	3 (1.0)	23
	Bevacizumab†		296	1 (0.3)	
MARINA	Ranibizumab	24	716	2 (0.3)	24
PIER§	Ranibizumab	12	184	0 (0)	25
PrONTO	Ranibizumab	24	40	2 (5.0)	26
SUSTAIN¶	Ranibizumab	12	513	1 (0.2)	27
VIEW	Aflibercept	24	2,419	5 (0.2)	28

*Three cases were also reported in the fellow eye.

†Bevacizumab is not licensed for the treatment of retinal diseases.

‡Patients were excluded if they had angioid streaks or precursors of CNV in either eye due to other causes, clinically significant subretinal hemorrhage involving the foveal center in the study eye, or any other significant clinical condition detrimental to the study outcome.

§Patients were excluded if a subretinal hemorrhage of 1-disc area or 50% of the total lesion area and involving the fovea was present.

¶Patients were excluded if they had precursors of CNV in either eye due to other causes or subretinal hemorrhage involving the center of the fovea (hemorrhage 50% of the total lesion area or 1-disc area in size).

Table 3. Incidence of RPE Tear Across Retrospective Case Series With Anti-VEGF Treatment

Study	Treatment	Duration, Months	Eyes, n	Incidence of RPE Tear Across Treatment Groups, n (%)	Incidence of PED Across Treatment Groups, n (%)	Incidence of RPE Tear in Patients With PED, n (%)
Chan et al[11]	Bevacizumab*	12	1,064	22 (2.2)	123 (11.6)	21 (17.1)
Gelisken et al[30]	Bevacizumab*	12	409	15 (3.7)	NS	NS†
Leitritz et al[31]	Bevacizumab*	NA	393	15 (3.8)	NS	14.8
Empeslidis et al[12]	Ranibizumab or bevacizumab*	18	628‡	17 (2.7)	NS	NS
Konstantinidis et al[32]	Ranibizumab	24	74	4 (5.4)	NA	7 (12.3)

*Bevacizumab is not licensed for the treatment of retinal diseases.
†Patients with serious PED were excluded.
‡Number of patients.
NA, not applicable; NS, not stated.

recommended in patients with PED considered at high risk of developing RPE tear during anti-VEGF treatment (Table 1), although validation by prospective studies is necessary. We propose that "high risk" be defined as the presence of one or more of these risk factors at the onset or during the course of anti-VEGF treatment. Patients with these risk factors should have a detailed examination after each anti-VEGF injection. A recent recommendation suggested the need to consider treatment cessation if risk factors worsen and/or accumulate during anti-VEGF treatment, with re-evaluation of the PED lesion after 1 to 2 weeks.[15] However, the evidence to support suspension of anti-VEGF therapy in these cases remains limited.

A stronger argument could be made to suspend anti-VEGF therapy if certain features arise that suggest the imminent development of RPE tear, such as "RPE wrinkling" on OCT or "radial lines" seen on near-infrared reflectance, particularly in the presence of high-risk features such as multilobular PED.[15]

Therapy Recommendations Following Retinal Pigment Epithelium Tear Diagnosis

We recommend that anti-VEGF treatment not be stopped in most patients with RPE tear and active disease (as indicated by the presence of intraretinal or subretinal fluid); although this is advised for unilobar tears, cessation of injections should be considered in patients with multilobular tears.[15] After RPE tear, some eyes may have marked progression of CNV lesion fibrosis and subsequently have greatly reduced exudative activity. The presence of continued lesion activity will determine how long to continue treatment.[40] It should also be considered that fluid leakage may occur secondary to the absence of RPE.[12] In patients with active CNV, a number of reports have demonstrated functional and anatomical improvements with continued anti-VEGF therapy after RPE tears, particularly in patients with smaller tears. In a retrospective study, 5 of 7 patients with RPE tear of Grade 1 to 3 had improvements in their visual acuity after 12 months of continued anti-VEGF treatment and one

Table 4. Visual Acuity at the Time of RPE Tear and after 12 Months of Continued Anti-VEGF Treatment

Patient	VA at RPE Tear logMAR (Snellen)*	VA after 12 Months of Anti-VEGF logMAR (Snellen)*	Outcome
1	0.6 (20/80)	0.6 (20/80)	Stable
2	1.0 (20/200)	0.84 (20/138)	Improved
3	NA	0.82 (20/132)	Improved
4	0.6 (20/80)	1.0 (20/200)	Worsened
5	1.12 (20/264)	0.96 (20/182)	Improved
6	1.2 (20/320)	0.92 (20/166)	Improved
7	0.8 (20/125)	0.64 (20/87)	Improved

Table reproduced from Empeslidis et al[12]©; Licensee Bentham Open.
*Conversions of logMAR values to Snellen ratios completed as described in Holladay.[41]
logMAR, logarithm of the minimum angle of resolution; NA, not available; VA, visual acuity.

patient was stabilized (Table 4).[12] Sustained treatment may also help to stabilize and prevent further visual deterioration in patients with larger (Grade 4) tears, although the visual prognosis in these patients is generally poor.[4] Ultimately, anti-VEGF treatment cannot restore the disrupted interface between the photoreceptors and the RPE following a tear.

Given the possible etiology of RPE tears with the augmentation of choroidal neovascular membrane contraction, it is unclear whether changing the dosing schedule to include more frequent administration of half-dose anti-VEGF reduces the incidence.

In summary, we recommend that anti-VEGF treatment is continued in patients with RPE tear and active disease using an individualized approach, with careful and regular re-evaluation of retinal status and location of both tear and fluid.[15] There may be circumstances, such as increasing risk signs for RPE tear, in which suspension of anti-VEGF treatment could be considered, but this is based on relatively limited data at present.

Summary of Recommendations for Patients at Risk of Retinal Pigment Epithelium Tear

After reviewing the published evidence, we developed several recommendations around the topic of RPE tear in patients with nAMD.

Several risk factors for RPE tear have been described to date, including microrips in the RPE, recent PED, PED size, and type and presence of radial hyperreflective lines. Further research is required to elucidate the mechanisms and pathophysiology of RPE tear development. Multimodal imaging is recommended, particularly OCT and FA techniques, with OCT-A used to identify risk factors such as CNV/PED ratio. Retinal pigment epithelium tears should be graded according to their size and involvement of the fovea, with the latter indicating a poorer prognosis.

Overall, the incidence of RPE tear during anti-VEGF therapy in patients with PED is similar to that reported for untreated PED, with no clear evidence of differing risk according to use or type of anti-VEGF agent. We currently recommend continuing anti-VEGF treatment in cases of RPE tear in patients with active disease, because patients continue to show benefit with anti-VEGF therapy after a tear has occurred. This recommendation is in line with previously published guidance.[42] Data on the incidence of RPE tear from randomized controlled trials of anti-VEGF are limited because of the exclusion of high-risk patients from some studies (i.e., patients with large PED), and large randomized trials are required to further define the risk factors for RPE tear, and the optimal management strategy for these patients. Patients at high risk of developing RPE tear should be monitored following each injection and, if risk factors worsen or accumulate, therapy may be suspended for a period.

Key words: anti-VEGF, neovascular age-related macular degeneration, pigment epithelial detachment, RPE tear.

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