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.
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 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; 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. 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. 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, 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 | 4,8–10 |
| In particular, a large PED basal diameter and PED height ≥400 μm | 11 |
| 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 | 8,12 |
| Serous vascularized PED compared with fibrovascular PED | |
| As identified by areas of stippled hyperfluorescence and signs of leakage in the later phases | 8 |
| Presence of radial hyperreflective lines in patients with PED lesions | 13 |
| Recent PED | |
| PED duration of ≤4.5 months was a significant risk factor for RPE tear formation (odds ratio = 166.7; 95% CI 15.2–1,000) | 14 |
| Microrips in the RPE | |

*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 auto-fluorescence. 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. Fluorescein angiography is commonly used and can provide information on PED diameter and fluid leakage due to CNV. 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, although there may be difficulties with the interpretation of OCT-A in the presence of PED because of segmentation errors. In addition, near-
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 $<200$ $\mu$m in diameter are classed as Grade 1; $200$ $\mu$m 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
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 fovea7 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).
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

| 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 al11     | Bevacizumab*                       | 12               | 1,064   | 22 (2.2)                                             | 123 (11.6)                                       | 21 (17.1)                                       |
| Gelisken et al30 | Bevacizumab*                       | 12               | 409     | 15 (3.7)                                             | NS                                               | NS†                                             |
| Leitritz et al31 | Bevacizumab*                       | NA               | 393     | 15 (3.8)                                             | NS                                               | 14.8                                            |
| Empeslidis et al12 | Ranibizumab or bevacizumab*       | 18               | 628‡    | 17 (2.7)                                             | NS                                               | NS                                              |
| Konstantinidis et al32 | 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.

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

| 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 al12©; 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 hyperechoic 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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References

1. Al-Zamil WM, Yassin SA. Recent developments in age-related macular degeneration: a review. Clin Interv Aging 2017;12:1313–1330.
2. Wong T, Chakravarthy U, Klein R, et al. The natural history and prognosis of neovascular age-related macular degeneration: a systematic review of the literature and meta-analysis. Ophthalmology 2008;115:116–126.e1.
3. 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 Ophthalmol Soc 2014;112:142–159.
4. 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.
5. Hoskin A, Bird AC, Sehmi K. Tears of detached retinal pigment epithelium. Br J Ophthalmol 1981;65:417–422.
6. Ersoz MG, Karacorlu M, Arf S, et al. Retinal pigment epithelium tears: classification, pathogenesis, predictors, and management. Surv Ophthalmol 2017;62:493–505.
7. Guttleisch 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 (Lond) 2011;25:1181–1186.
8. Clemens CR, Bastian N, Alten F, et al. Prediction of retinal pigment epithelial tear in serous vascularized pigment epithelium detachment. Acta Ophthalmol 2014;92:e50–56.
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, Yu F, Sarraf D. Predictors of anti-VEGF-associated retinal pigment epithelial tear using FA and OCT analysis. Retina 2008;28:1265–1269.
11. 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.
12. Empesidis T, Vardarinos A, Konidaris V, et al. Incidence of retinal pigment epithelial tears and associated risk factors after treatment of age-related macular degeneration with intravitreal anti-VEGF injections. Open Ophthalmol J 2014;8:101–104.

13. 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.

14. Clemens CR, Alten F, Eter N. Reading the signs: Microrips as a prognostic sign for impending RPE tear development. Acta Ophthalmol 2015;93:e600–602.

15. Clemens CR, Eter N. Retinal pigment epithelium tears: risk factors, mechanism and therapeutic monitoring. Ophthalmologica 2016;235:1–9.

16. 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.

17. Clemens CR, Alten F, Heiduschka P, Eter N. OCT-angiography for assessing risk of retinal pigment epithelium tear in patients with vascular retinal pigment epithelium detachment due to AMD. Acta Ophthalmol 2016;94:e816–e817.

18. Sarraf D, Reddy S, Chiang A, et al. A new grading system for retinal pigment epithelial tears. Retina 2010;30:1039–1045.

19. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med 2006;355:1432–1444.

20. CATT Research Group, Martin DF, Maguire MG, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med 2011;364:1897–1908.

21. Schmidt-Erfurth U, Eldem B, Guymer R, et al. Efficacy and safety of monthly versus quarterly ranibizumab treatment in neovascular age-related macular degeneration: the EXCITE study. Ophthalmology 2011;118:831–839.

22. Busbee BG, Ho AC, Brown DM, et al. Twelve-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. Ophthalmology 2013;120:1046–1056.

23. Chakravarthy U, Harding SP, Rogers CA, et al. Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial. Lancet 2013;382:1258–1267.

24. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355:1419–1431.

25. Regillo CD, Brown DM, Abraham P, et al. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. Am J Ophthalmol 2008;145:239–248.e5.

26. Lalwani GA, Rosenfeld PJ, Fung AE, et al. A variable-dosing regimen with intravitreal ranibizumab for neovascular age-related macular degeneration: year 2 of the PrONTO Study. Am J Ophthalmol 2009;148:43–58.e1.

27. Holz FG, Amoako W, Donate J, et al. Safety and efficacy of a flexible dosing regimen of ranibizumab in neovascular age-related macular degeneration: the SUSTAIN study. Ophthalmology 2011;118:663–671.

28. Schmidt-Erfurth U, Kaiser PK, Korobelnik JF, et al. Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six-week results of the VIEW studies. Ophthalmology 2014;121:193–201.

29. Holz FG, Figueroa MS, Bandello F, et al. Ranibizumab treatment in treatment-naïve neovascular age-related macular degeneration: results from LUMINOUS, a global real-world study. Retina 2020;40:1673–1685.

30. Gelisken F, Ziemssen F, Voelker M, et al. Retinal pigment epithelial tears after single administration of intravitreal bevacizumab for neovascular age-related macular degeneration. Eye (Lond) 2009;23:694–702.

31. Leitritz M, Gelisken F, Inhoffen W, et al. Can the risk of retinal pigment epithelium tears after bevacizumab treatment be predicted? An optical coherence tomography study. Eye (Lond) 2008;22:1504–1507.

32. Konstantinidis L, Ambresin A, Zografos L, Mantel I. Retinal pigment epithelium tears after intravitreal injection of ranibizumab for predominantly classic neovascular membranes secondary to age-related macular degeneration. Acta Ophthalmol 2010;88:736–741.

33. Campos Polo R, Rubio Sánchez C. Anti-VEGF and its impact on the outer retina: retinal pigment epithelium tear after an injection of aflibercept in contralateral eye. Arch Soc Esp Oftalmol 2016;91:245–249.

34. Fujii A, Imai H, Kanai M, Azumi A. Effect of intravitreal aflibercept injection for age-related macular degeneration with a retinal pigment epithelial tear refractory to intravitreal ranibizumab injection. Clin Ophthalmol 2014;8:1199–1202.

35. Saito M, Kano M, Itagaki K, et al. Retinal pigment epithelium tear after intravitreal aflibercept injection. Clin Ophthalmol 2013;7:1287–1289.

36. Bertelmann T, Sekundo W, Werne Y. Tear in the retinal pigment epithelium by intravitreal injection of aflibercept [in German]. Ophthalmologe 2014;111:775–777.

37. Carle MV, Chu TG, Dayani P, et al. Tears of the retinal pigment epithelium during aflibercept therapy: PED and treatment characteristics. J Clin Exp Ophthalmol 2014;5:373.

38. Chuang EL, Bird AC. Repair after tears of the retinal pigment epithelium. Eye (Lond) 1988;2:106–113.

39. Pauliekhoff 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.

40. Wong DT, Lambrou GN, Loewenstein A, et al. Suspending anti-VEGF injections. Open Ophthalm J 2014;8:101.

41. Holladay JT. Proper method for calculating average visual acuity. J Refract Surg 1997;13:388–391.

42. Sasat-Ibáñez M, Martínez-Rubio C, Molina-Pallete R, et al. Retinal pigment epithelial tears. J Fr Ophthalm 2019;42:63–72.