Management of RPE tear during anti-VEGF therapy
Objectives

To provide an overview of the current evidence for the development and diagnosis of RPE tear

To provide guidance on the optimal treatment of RPE tear

To provide guidance on the management of patients at high risk of RPE tear

The Vision Academy provides ophthalmic specialists with a forum to share existing skills and knowledge, build best practice, and lead the wider community in the drive towards optimized, compassionate patient care.

Through their collective expertise, the Vision Academy seeks to provide guidance for best clinical practice in the management of retinal disease, particularly in areas with insufficient conclusive evidence.

QUESTION
What are the risk factors for the development of RPE tear?
Management of RPE tear during anti-VEGF therapy: Background

RPE, retinal pigment epithelium; VEGF, vascular endothelial growth factor.
RPE tear pathogenesis

- Tears in the RPE are associated with pigment epithelial detachment in patients with exudative AMD\(^1\)
  - Reported in 10–12.5% of eyes with nAMD and associated PED\(^1\)
- RPE tears occur as part of the natural history of PED and are recognized as a cause of severe central vision loss in AMD\(^2\)

- One hypothesis suggests that subretinal fluid (black arrows) creates hydrostatic pressure, causing the RPE to stretch, and contraction of the CNVM adds tractional force (yellow arrow)
  - Anti-VEGF therapy could augment this contraction, causing a tear at the junction of the attached-detached RPE (green arrow)\(^1\)

AMD, age-related macular degeneration; CNVM, choroidal neovascular membrane; nAMD, neovascular AMD; PED, pigment epithelial detachment; RPE, retinal pigment epithelium; VEGF, vascular endothelial growth factor.


As adapted from American Journal of Ophthalmology, 156 (5), Nagiel A et al., Mechanism of retinal pigment epithelium tear formation following intravitreal anti–vascular endothelial growth factor therapy revealed by spectral-domain optical coherence tomography, 981–988.e2, 2013, with permission from Elsevier.
Classification of RPE tears

• RPE tears are graded according to foveal involvement and linear diameter, as measured by FA

<table>
<thead>
<tr>
<th>Grade</th>
<th>Size / involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>&lt;200 µm in diameter</td>
</tr>
<tr>
<td>Grade 2</td>
<td>200 µm to 1-disc diameter</td>
</tr>
<tr>
<td>Grade 3</td>
<td>&gt;1-disc diameter</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Tears involving the foveal center</td>
</tr>
</tbody>
</table>

• Additional classification systems include data on microrips and differentiation of multilobular tears

CHALLENGE REQUIRING VISION ACADEMY GUIDANCE
What are the optimal imaging techniques to diagnose and monitor the development of RPE tear?

FA, fluorescein angiography; RPE, retinal pigment epithelium.
Predictors and risk factors for RPE tear

Several predictors and risk factors for RPE tear have been identified:

• Increased surface area and large linear diameter of subfoveal PED
  – PED height ≥400 µm²

• Small ratio of CNV size to PED size
  – CNV / PED ratio <50%³

• Serous vascularized PED
  – Stress on the RPE is focused on a defined compartment of lesions⁴

• Presence of hyperreflective lines in PED lesions⁴

• Microrips in RPE
  – Microrips or leakage at the edge of RPE detachment are thought to lower the threshold of RPE resistance⁵

CNV, choroidal neovascularization; PED, pigment epithelial detachment; RPE, retinal pigment epithelium.

Management of RPE tear during anti-VEGF therapy

- A multimodal imaging approach is important for the diagnosis and monitoring of RPE tear
  - Color fundus photography, OCT, fluorescein angiography, OCT-A, near-infrared reflectance imaging, and fundus autofluorescence should all be used
  - OCT can help differentiate between sub-RPE and subretinal hemorrhage

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In the images below, a large subretinal hemorrhage associated with an RPE tear is hard to interpret from the fundus image (A), but in combination with angiogram (B), autofluorescence (C), and OCT (D), it is possible to see complete RPE tear and crumbling of the RPE membrane
RPE tear development during anti-VEGF therapy

RPE, retinal pigment epithelium; VEGF, vascular endothelial growth factor.
Vascularized serous PEDs may progress while receiving anti-VEGF therapy

Baseline
20/20

Initiation of anti-VEGF

Baseline

Over time, PED might progress even after anti-VEGF treatment is initiated

1 year
20/40

3 months
20/40

3× anti-VEGF

After 3 months, large subretinal and subfoveal hemorrhages are associated with RPE tear

Images courtesy of Professor Antonia M. Joussen.
PED, pigment epithelial detachment; RPE, retinal pigment epithelium; VEGF, vascular endothelial growth factor.
Reported incidence of RPE tear occurring during anti-VEGF therapy is variable

- Most of the available data on RPE tear development during anti-VEGF therapy concern bevacizumab and ranibizumab; only single-case reports are available on aflibercept
- Larger studies have reported varying rates of RPE tear incidence

<table>
<thead>
<tr>
<th>Study</th>
<th>Anti-VEGF therapy</th>
<th>Duration, months</th>
<th>Eyes, N</th>
<th>Incidence of RPE tear across all treatment groups, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan et al.¹</td>
<td>Bevacizumab</td>
<td>12</td>
<td>1064</td>
<td>22 (2.2)</td>
</tr>
<tr>
<td>Gelisken et al.²</td>
<td>Bevacizumab</td>
<td>15</td>
<td>409</td>
<td>15 (3.7)</td>
</tr>
<tr>
<td>Empeslidis et al.³</td>
<td>Ranibizumab or bevacizumab</td>
<td>18</td>
<td>628*</td>
<td>17* (2.7)</td>
</tr>
<tr>
<td>Konstantinidis et al.⁴</td>
<td>Ranibizumab</td>
<td>24</td>
<td>74</td>
<td>4 (5.4)</td>
</tr>
</tbody>
</table>

*Number of patients.
N/A, not available; RPE, retinal pigment epithelium; VEGF, vascular endothelial growth factor.

Overall incidence of RPE tear in anti-VEGF trials in nAMD was <1%

- The overall incidence of RPE tear in clinical trials of anti-VEGF was low, although several trials excluded patients at high risk of RPE tear

<table>
<thead>
<tr>
<th>Study</th>
<th>Anti-VEGF therapy</th>
<th>Duration, months</th>
<th>Study population treated with anti-VEGF, N</th>
<th>Incidence of RPE tear across all treatment groups, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANCHOR³</td>
<td>Ranibizumab</td>
<td>12</td>
<td>277</td>
<td>0 (0)</td>
</tr>
<tr>
<td>CATT²</td>
<td>Ranibizumab or bevacizumab</td>
<td>12</td>
<td>1185</td>
<td>3 [study eye]; 2 [fellow eye] (0.4)</td>
</tr>
<tr>
<td>EXCITE³</td>
<td>Ranibizumab</td>
<td>12</td>
<td>353</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>HARBOR⁴</td>
<td>Ranibizumab</td>
<td>12</td>
<td>1095</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>IVAN⁵</td>
<td>Ranibizumab or bevacizumab</td>
<td>24</td>
<td>610</td>
<td>4 (0.7)</td>
</tr>
<tr>
<td>MARINA⁶</td>
<td>Ranibizumab</td>
<td>24</td>
<td>477</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>PIER⁷</td>
<td>Ranibizumab</td>
<td>12</td>
<td>121</td>
<td>0 (0)</td>
</tr>
<tr>
<td>PrONTO⁸</td>
<td>Ranibizumab</td>
<td>24</td>
<td>40</td>
<td>2 (5.0)</td>
</tr>
<tr>
<td>SUSTAIN⁹</td>
<td>Ranibizumab</td>
<td>12</td>
<td>513</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>VIEW¹⁰</td>
<td>Aflibercept or ranibizumab</td>
<td>24</td>
<td>2419</td>
<td>5 (0.2)</td>
</tr>
</tbody>
</table>

nAMD, neovascular age-related macular degeneration; RPE, retinal pigment epithelium; VEGF, vascular endothelial growth factor.

Anti-VEGF therapy for RPE tear

• A number of reports have demonstrated functional and anatomical improvements with continued anti-VEGF therapy after RPE tear
  - Improvements in VA were reported in patients with spontaneous RPE tear development subsequently treated with anti-VEGF therapy\(^1\)
  - A number of studies reported improvements in or stability of VA with continued anti-VEGF therapy after RPE tear development\(^2-6\)
    - One study suggested that continued anti-VEGF treatment may help to prevent further visual deterioration in larger (grade 4) tears, although prognosis in these patients is typically poor\(^7\)

<table>
<thead>
<tr>
<th>Patient</th>
<th>VA (logMAR) at RPE tear</th>
<th>VA (logMAR) after 12 months</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.6</td>
<td>0.6</td>
<td>Stable</td>
</tr>
<tr>
<td>2</td>
<td>1.0</td>
<td>0.84</td>
<td>Improved</td>
</tr>
<tr>
<td>3</td>
<td>CF</td>
<td>0.82</td>
<td>Improved</td>
</tr>
<tr>
<td>4</td>
<td>0.6</td>
<td>1.0</td>
<td>Worsened</td>
</tr>
<tr>
<td>5</td>
<td>1.12</td>
<td>0.96</td>
<td>Improved</td>
</tr>
<tr>
<td>6</td>
<td>1.2</td>
<td>0.92</td>
<td>Improved</td>
</tr>
<tr>
<td>7</td>
<td>0.8</td>
<td>0.64</td>
<td>Improved</td>
</tr>
</tbody>
</table>

Visual acuity improved in 5 patients with grade 1–3 RPE tear receiving anti-VEGF for CNV associated with nAMD after 12 months\(^8\)

CF, counting fingers; CNV, choroidal neovascularization; logMAR, logarithm of the minimum angle of resolution; nAMD, neovascular age-related macular degeneration; RPE, retinal pigment epithelium; VA, visual acuity; VEGF, vascular endothelial growth factor.

Anti-VEGF therapy for RPE tear: functional improvement

A retrospective analysis of patients who developed RPE tear during anti-VEGF treatment for PED found that patients receiving an increased number of anti-VEGF injections demonstrated stabilized or improved BCVA after 2 years. Visual stabilization was observed in 87.5% of patients with RPE tears in a study of patients with AMD receiving anti-VEGF treatment.

CHALLENGE REQUIRING VISION ACADEMY GUIDANCE

Should anti-VEGF therapy be continued in patients who develop an RPE tear?

Figure shows changes in mean VA (in number of ETDRS letters); without RPE tears, n=22; RPE tears, n=8. ETDRS 0 = baseline VA; ETDRS 1 = VA after the first ranibizumab injection; ETDRS 2 = VA after the second ranibizumab injection; ETDRS 3 = VA after the third ranibizumab injection; ETDRS 12 = VA after 12 months.

AMD, age-related macular degeneration; BCVA, best-corrected visual acuity; ETDRS, Early Treatment of Diabetic Retinopathy Study; PED, pigment epithelial detachment; RPE, retinal pigment epithelium; VA, visual acuity; VEGF, vascular endothelial growth factor.


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https://www.medscimonit.com/download/index/idArt/882198
Case study: Management of RPE tear during anti-VEGF therapy

- At baseline, SRF and fibrosis in the PED were observed in the left eye
  - Treatment was initiated in the left eye
  - Subsequently, treatment was also initiated in the second (right) eye once PED occurred and SRF presented

- The patient was followed every 8 weeks and injected accordingly
  - During treatment, the left eye deteriorated and the right eye changed in the formation of the PED, which remained stable over the course of treatment
  - PED was treated even when there was no SRF

- During subsequent years, the left eye developed RPE tear and crumbling of the RPE membrane, whereas the PED remained stable in the right eye when treatment was continued
  - Treatment of the left eye was stopped when the retina had flattened and stable subretinal fibrosis was seen

Infrared and OCT showing visits in (A) March 2011 at baseline (VA 0.9 OD / 0.4 OS), (B) February 2012 (VA 0.9 OD / 0.4 OS), and (C) February 2021 (VA 0.7 OD / 0.1 OS)
Clinical challenges
Clinical challenges requiring guidance

Click on a section

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Monitoring</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>• What criteria are used to define patients at high risk of RPE tear?</td>
<td>• What are the best investigations to perform for the diagnosis and monitoring of RPE tear?</td>
<td>• Should anti-VEGF treatment be continued in patients with RPE tear or in those at high risk of developing RPE tear?</td>
</tr>
</tbody>
</table>

RPE, retinal pigment epithelium; VEGF, vascular endothelial growth factor.
Vision Academy recommendations
Patients at high risk of developing RPE tear should continue treatment under close monitoring

The presence of one or more of the following risk factors, at baseline or during treatment with anti-VEGF agents, indicates that the patient is at high risk of developing RPE tear:

- Increased surface area and a large linear diameter of the subfoveal PED\(^1\)-\(^3\)
- A small ratio of CNV size to PED size\(^5\)
- Serous vascularized PED (as compared to fibrovascular PED)\(^4\)
- Presence of radial hyperreflective lines in patients with PED lesions\(^4\)
- Recent PED (duration ≤4.5 months)\(^6\)
- Microrips in the RPE\(^7\)

There is currently limited evidence to support the suspension of anti-VEGF therapy in high-risk patients.

Patients at high risk of developing RPE tear should continue treatment but undergo a detailed examination after each injection.

Suspension of anti-VEGF should be considered if signs of an imminent RPE tear occur, e.g., “wrinkling” on OCT or “radial lines” seen on near-infrared reflectance (particularly in the presence of other high-risk features such as multilobular PED).

General consensus
A multimodal approach to retinal imaging is recommended for diagnosis and monitoring.

A range of retinal imaging techniques are available for the diagnosis and assessment of risk factors for RPE tear, including:

- Color fundus photography
- OCT
- Fluorescein angiography
- OCT-A
- Near-infrared reflectance imaging
- Fundus autofluorescence

RPE tears can be graded by size and foveal involvement.

No officially recognized guidelines exist for the management of RPE tear.

A multimodal approach should be used to diagnose and monitor RPE tear.

General consensus.
Anti-VEGF treatment should be continued in most patients with RPE tear who have active disease.

Patients with active disease (as indicated by the presence of intra- or subretinal fluid) who develop RPE tear should be treated using an individualized approach, with comprehensive re-evaluation carried out at regular intervals to determine:

- Retinal status
- Location of both the tear and fluid

Patients with active disease continue to respond to anti-VEGF therapy after an RPE tear has occurred.

Cessation of injections should be considered in patients with multilobular tears.

RPE, retinal pigment epithelium; VEGF, vascular endothelial growth factor.
Vision Academy recommendations for the management of RPE tear

A multimodal approach utilizing several different imaging technologies will provide the most complete information for the diagnosis and monitoring of RPE tear.

For patients at high risk of developing RPE tear, anti-VEGF treatment should be continued under close supervision, with a detailed examination taking place after each injection.

Suspension of anti-VEGF therapy may be warranted if features such as “wrinkling” on OCT or “radial lines” seen on near-infrared reflectance arise, particularly in the presence of high-risk features such as multilobular PED.

An individualized approach should be used to treat patients with active disease who develop RPE tear, with careful and regular re-evaluation of retinal status and location of both tear and fluid.

The Viewpoint ‘Management of retinal pigment epithelium tear during anti-VEGF therapy’ can be downloaded from: https://www.visionacademy.org/resources

OCT, optical coherence tomography; PED, pigment epithelial detachment; RPE, retinal pigment epithelium; VEGF, vascular endothelial growth factor.
Further considerations

• Progression of CNV lesion fibrosis can occur after RPE tear in some patients, leading to greatly reduced exudative activity of the eye:¹
  − These patients should be carefully monitored and anti-VEGF treatment restarted if exudation recurs
  − Secondary fluid leakage can also occur in the absence of RPE²

• In patients with larger (grade 4) tears, sustained treatment may help to stabilize and prevent further visual deterioration, although the prognosis in these patients is typically poor³

• 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 CNV contraction, it is unclear whether changing the dosing schedule of anti-VEGF therapy reduces the incidence of RPE tear

CNV, choroidal neovascularization; RPE, retinal pigment epithelium; VEGF, vascular endothelial growth factor.