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Management of RPE tear during anti-VEGF therapy

The Vision Academy is supported by Bayer. This presentation has been developed by Vision Academy members and does not necessarily reflect the views of Bayer.
RPE, retinal pigment epithelium; VEGF, vascular endothelial growth factor.
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RPE, retinal pigment epithelium; VEGF, vascular endothelial growth factor.

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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.

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QUESTION

What are the risk factors for the development of RPE tear?

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

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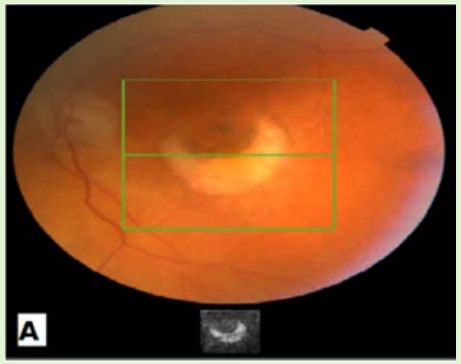
Management of RPE tear during anti-VEGF therapy: Background

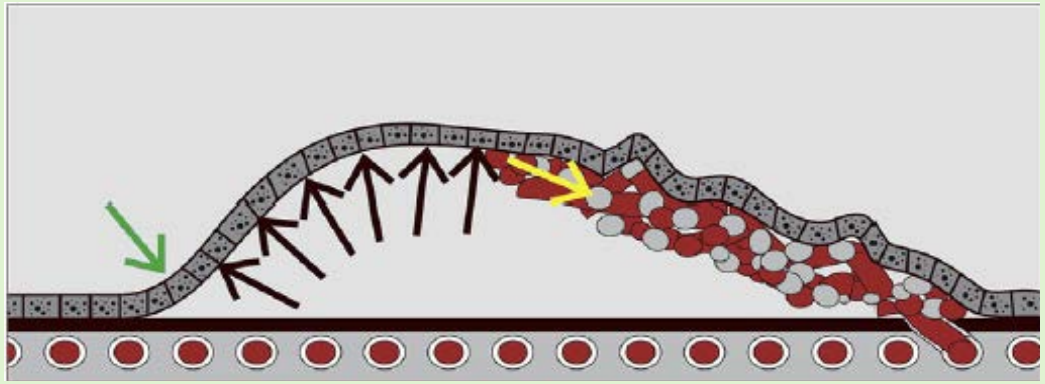
RPE, retinal pigment epithelium; VEGF, vascular endothelial growth factor.

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]



Reprinted from Ersoz *et al*. (2017), adapted from Nagiel *et al.* (2013)

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.

1. Ersoz MG *et al. Surv Ophthalmol* 2017; 62 (4): 493–505; 2. Empeslidis T *et al. Open Ophthalmol J* 2014; 8: 101–104.

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Classification of RPE tears

- RPE tears are graded according to foveal involvement and linear diameter, as measured by FA[1]

Grade	Size / involvement
Grade 1	<200 µm in diameter
Grade 2	200 µm to 1-disc diameter
Grade 3	>1-disc diameter
Grade 4	Tears involving the foveal center

- Additional classification systems include data on microrips and differentiation of multilobular tears[2,3]

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CHALLENGE REQUIRING VISION ACADEMY GUIDANCE

What are the optimal imaging techniques to diagnose and monitor the development of RPE tear?

RECOMMENDATION

FA, fluorescein angiography; RPE, retinal pigment epithelium.

1. Sarraf D *et al. Retina* 2010; 30 (7): 1039–1045; 2. Ersoz MG *et al. Surv Ophthalmol* 2017; 62 (4): 493–505; 3. Clemens CR *et al. Retina* 2014; 34: 24–31.

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Predictors and risk factors for RPE tear

Several predictors and risk factors for RPE tear have been identified[1]

- Increased surface area and large linear diameter of subfoveal PED
  - PED height ≥400 µm[2]
- 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 lesions[4]
- Presence of hyperreflective lines in PED lesions[4]
- Microrips in RPE
  - Microrips or leakage at the edge of RPE detachment are thought to lower the threshold of RPE resistance[5]

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CHALLENGE REQUIRING VISION ACADEMY GUIDANCE

How should treatment be managed in patients with risk factors that suggest they are at "high risk" of developing RPE tear?

RECOMMENDATION

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

1. Clemens CR and Eter N. *Ophthalmologica* 2016; 235 (1): 1–9; 2. Chan CK *et al. Retina* 2010; 30 (2): 203–211; 3. Chan CK *et al. Retina* 2007; 27 (5): 541–551;
4. Clemens CR *et al. Acta Ophthalmol* 2014; 92 (1): e50–e56; 5. Clemens CR *et al. Acta Ophthalmol* 2015; 93 (7): e600–e602.

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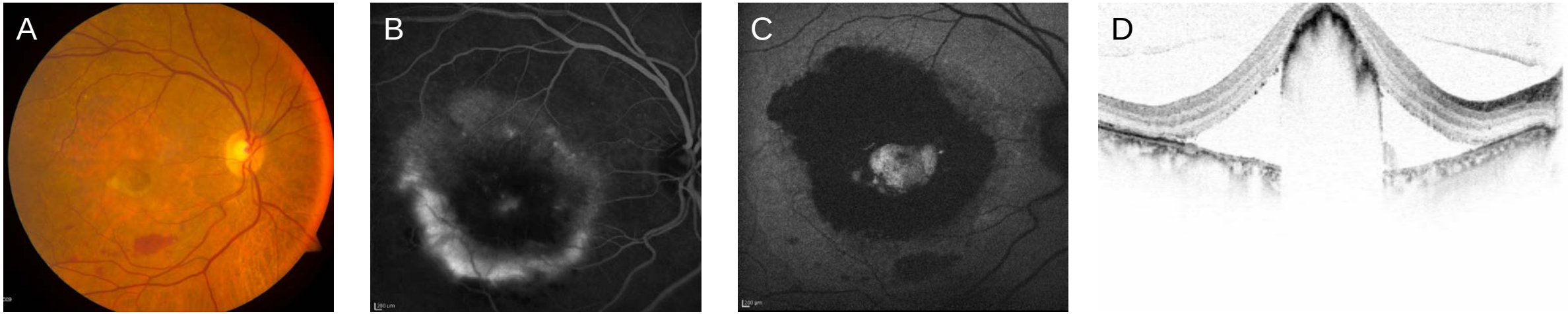
Management of RPE tear during anti-VEGF therapy

- 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[1]

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



Images courtesy of Professor Antonia M. Joussen.
OCT, optical coherence tomography; OCT-A, optical coherence tomography angiography; RPE, retinal pigment epithelium; VEGF, vascular endothelial growth factor.
1. Stanescu-Segall D *et al. Surv Ophthalmol* 2016; 61 (1): 18–32.

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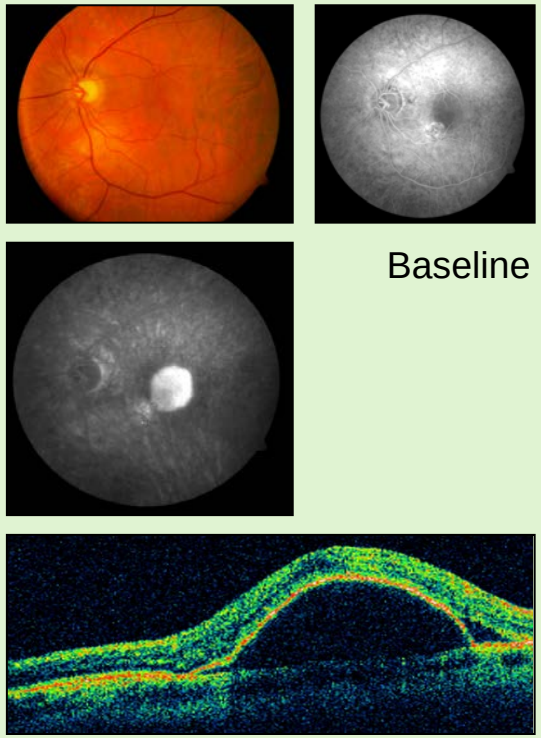
RPE tear development during anti-VEGF therapy

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

Vascularized serous PEDs may progress while receiving anti-VEGF therapy

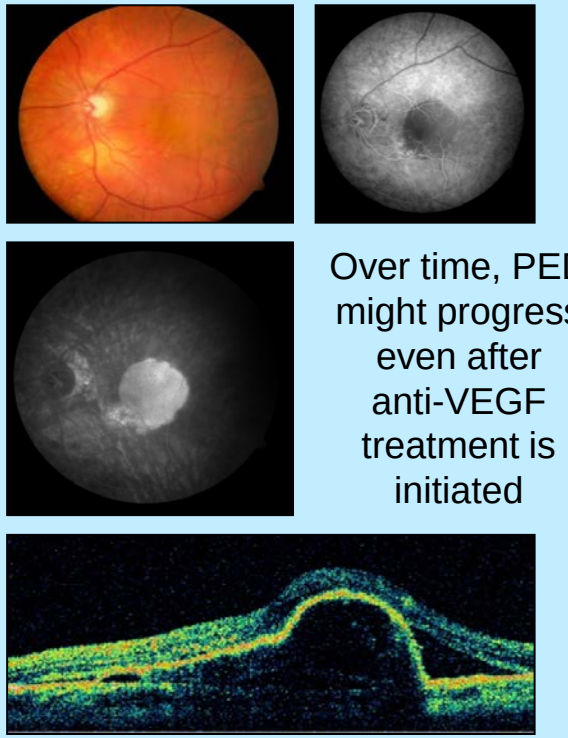
Baseline
20/20



Baseline

1 year
20/40

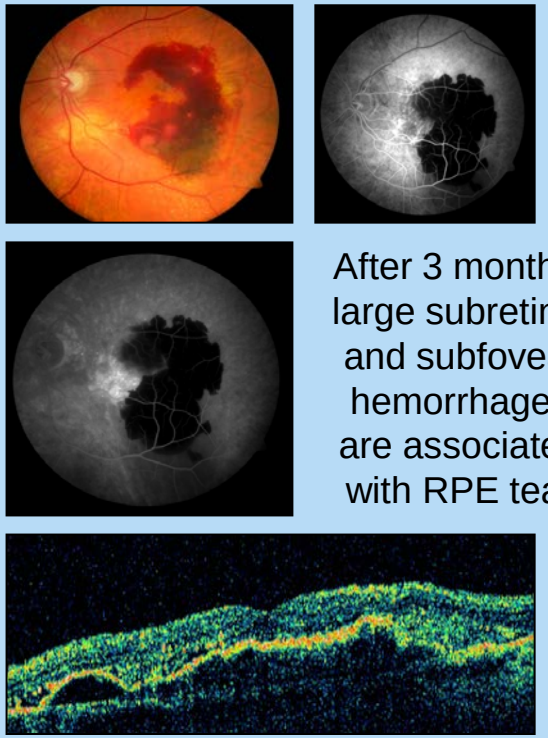
Initiation of anti-VEGF



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

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

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

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Should anti-VEGF therapy be continued in patients who are at risk of developing RPE tear?

RECOMMENDATION

*Number of patients.
N/A, not available; RPE, retinal pigment epithelium; VEGF, vascular endothelial growth factor.
1. Chan CK *et al. Retina* 2007; 27 (5): 541–551; 2. Gelisken F *et al. Eye (Lond)* 2009; 23 (3): 694–702; 3. Empeslidis T *et al. Open Ophthalmol J* 2014; 8: 101–104;
4. Konstantinidis L *et al. Acta Ophthalmol* 2010; 88 (7): 736–741.

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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

Study	Anti-VEGF therapy	Duration, months	Study population treated with anti-VEGF, N	Incidence of RPE tear across all treatment groups, n (%)
ANCHOR[1]	Ranibizumab	12	277	0 (0)
CATT[2]	Ranibizumab or bevacizumab	12	1185	3 [study eye]; 2 [fellow eye] (0.4)
EXCITE[3]	Ranibizumab	12	353	2 (0.6)
HARBOR[4]	Ranibizumab	12	1095	1 (0.1)
IVAN[5]	Ranibizumab or bevacizumab	24	610	4 (0.7)
MARINA[6]	Ranibizumab	24	477	2 (0.4)
PIER[7]	Ranibizumab	12	121	0 (0)
PrONTO[8]	Ranibizumab	24	40	2 (5.0)
SUSTAIN[9]	Ranibizumab	12	513	1 (0.2)
VIEW[10]	Aflibercept or ranibizumab	24	2419	5 (0.2)

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

1. Brown DM *et al. N Engl J Med* 2006; 355 (14): 1432–1444; 2. CATT Research Group. *N Engl J Med* 2011; 364 (20): 1897–1908 – supplementary appendix; 3. Schmidt-Erfurth U *et al. Ophthalmology* 2011; 118 (5): 831–839 – supplementary appendix; 4. Busbee BG *et al. Ophthalmology* 2013; 120 (5): 1046–1056; 5. Chakravarthy U *et al. Lancet* 2013; 382 (9900): 1258–1267; 6. Rosenfeld PJ *et al. N Engl J Med* 2006; 355 (14): 1419–1431; 7. Regillo CD *et al. Am J Ophthalmol* 2008; 145 (2): 239–248; 8. Lalwani GA *et al. Am J Ophthalmol* 2009; 148 (1): 43–58.e1; 9. Holz FG *et al. Ophthalmology* 2011; 118 (4): 663–671; 10. Schmidt-Erfurth U *et al. Ophthalmology* 2014; 121 (1): 193–201.

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]

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

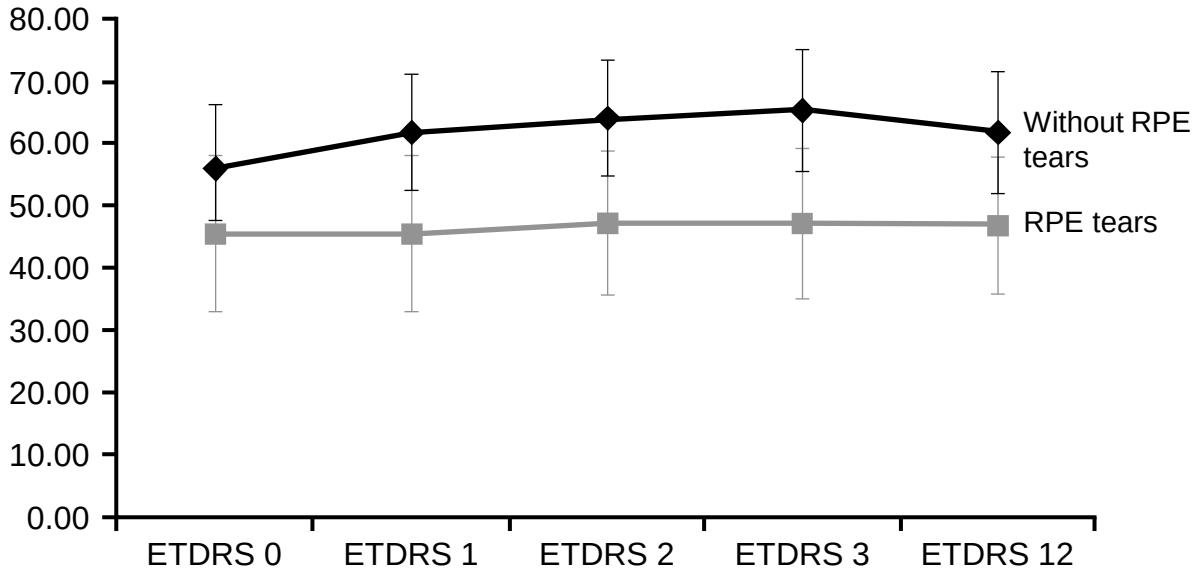
Patient	VA (logMAR) at RPE tear	VA (logMAR) after 12 months	Outcome
1	0.6	0.6	Stable
2	1.0	0.84	Improved
3	CF	0.82	Improved
4	0.6	1.0	Worsened
5	1.12	0.96	Improved
6	1.2	0.92	Improved
7	0.8	0.64	Improved

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.

1. Lesniak SP *et al. Eur J Ophthalmol* 2011; 21 (1): 73–76; 2. Doguizi S and Ozdek S. *Retina* 2014; 34 (6): 1156–1162;
3. Coco RM *et al. Ophthalmologica* 2012; 228 (2): 78–83; 4. Heimes B *et al. Retina* 2016; 36 (5): 868–874; 5. Erol MK *et al. Arq Bras Oftalmol* 2015; 78 (3): 168–172;
6. Bartels S *et al. Ophthalmologe* 2014; 111 (5): 460–464; 7. Sarraf D *et al. Retina* 2013; 33 (8): 1551–1557; 8. Empeslidis T *et al. Open Ophthalmol J* 2014; 8: 101–104.

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[1]



Visual stabilization was observed in 87.5% of patients with RPE tears in a study of patients with AMD receiving anti-VEGF treatment[2]

CHALLENGE REQUIRING VISION ACADEMY GUIDANCE

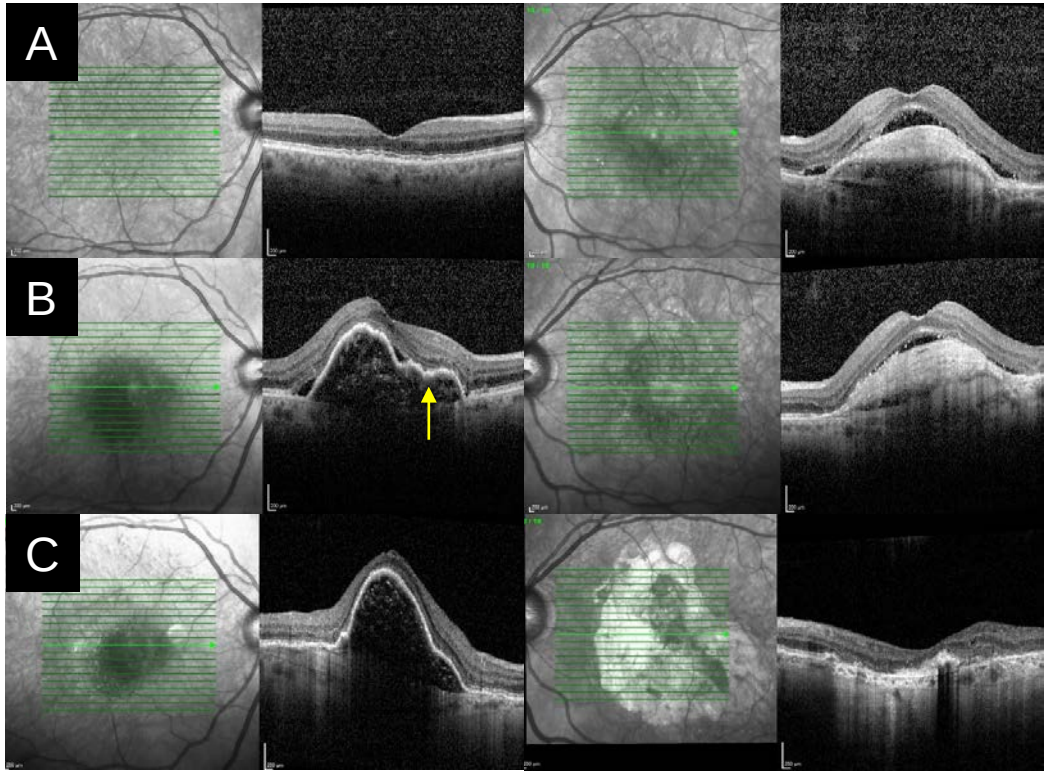
Should anti-VEGF therapy be continued in patients who develop an RPE tear?

RECOMMENDATION

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.

1. Heimes B *et al. Retina* 2016; 36 (5): 868–874; 2. Figurska M. *Med Sci Monit* 2012; 18 (1): CR32–38.

Case study: Management of RPE tear during anti-VEGF therapy



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)

- 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

Images courtesy of Professor Antonia M. Joussen.
OCT, optical coherence tomography; OD, oculus dexter (right eye); OS, oculus sinister (left eye); PED, pigment epithelial detachment; RPE, retinal pigment epithelium; SRF, subretinal fluid; VA, visual acuity; VEGF, vascular endothelial growth factor.

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Clinical challenges

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Clinical challenges requiring guidance

Click on a section

Risk factors

- What criteria are used to define patients at high risk of RPE tear?

Monitoring

- What are the best investigations to perform for the diagnosis and monitoring of RPE tear?

Treatment

- Should anti-VEGF treatment be continued in patients with RPE tear or in those at high risk of developing RPE tear?

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

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Vision Academy recommendations

BACK TO CHALLENGES

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,[8] 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

CNV, choroidal neovascularization; OCT, optical coherence tomography; PED, pigment epithelial detachment; RPE, retinal pigment epithelium; VEGF, vascular endothelial growth factor.

1. Sarraf D *et al. Retina* 2013; 33 (8): 1551–1557; 2. Chan CK *et al. Retina* 2010; 30 (2): 203–211; 3. Chiang A *et al. Retina* 2008; 28 (9): 1265–1269; 4. Clemens CR *et al. Acta Ophthalmol* 2014; 92 (1): e50–56; 5. Chan CK *et al. Retina* 2007; 27 (5): 541–551; 6. Doguizi S and Ozdek S. *Retina* 2014; 34 (6): 1156–1162; 7. Clemens CR *et al. Acta Ophthalmol* 2015; 93 (7): e600–602; 8. Clemens CR and Eter N. *Ophthalmologica* 2016; 235 (1): 1–9.

BACK TO CHALLENGES

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

OCT, optical coherence tomography; OCT-A, optical coherence tomography angiography; RPE, retinal pigment epithelium.

BACK TO CHALLENGES

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

Anti-VEGF treatment should be continued in most patients with unilobular tears and active disease using an individualized approach

Cessation of injections should be considered in patients with multilobular tears

General consensus

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

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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.

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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 RPE[2]

- 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 poor[3]
- 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.

1. Mitchell P *et al. Retina* 2021; 41 (4): 671–678; 2. Empeslidis T *et al. Open Ophthalmol J* 2014; 8: 101–104; 3. Sarraf D *et al. Retina* 2013; 33 (8): 1551–1557.