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Suspending treatment of neovascular age-related macular degeneration in cases of futility

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VEGF, vascular endothelial growth factor.

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Objectives

To provide an overview of current recommendations for treatment suspension in cases of futility

To provide criteria for determining benefits from anti-VEGF therapy

To provide guidance on the management of patients who do not see benefits from anti-VEGF treatment

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

Should anti-VEGF therapy be continued in patients without a perceived treatment benefit?

VEGF, vascular endothelial growth factor.

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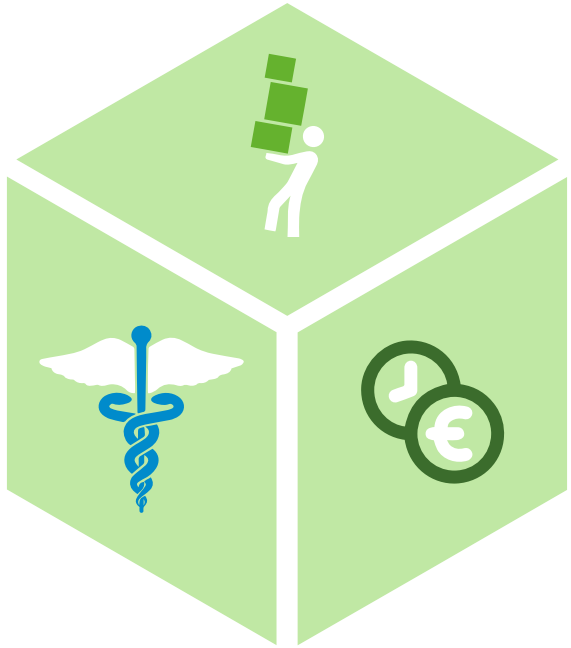
Suspending treatment of neovascular age-related macular degeneration in cases of futility: Background

What is medical futility?

Medical futility is the moment when a treatment has no realistic chance of providing an effect that the patient would have the capacity to appreciate as a benefit[1]

Overburden[2]



Hippocratic oath

- *Primum non nocere*, first, do no harm

Cost

- Cost, irrespective of the drug
- Time
  - Patient's
  - Physician's
  - Carer's
- Complications / risk

1. Schneiderman LJ. *J Bioeth Inq* 2011; 8 (2): 123–131; 2. Schneiderman LJ *et al. Ann Intern Med* 1990; 112 (12): 949–954.

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Anti-VEGF treatment in nAMD should aim to produce optimal responses

Despite regular anti-VEGF therapy, **~25–35% of patients with nAMD still have evidence of active exudation** on either angiography or OCT after 1 year of therapy[1,2]

While there is currently a **lack of consensus on what constitutes non-response**, several guidelines have attempted to address the issue

A poor or lack of response may be due to **misdiagnosis of nAMD** that is unresponsive to treatment.[3] The following can be misdiagnosed as nAMD:

1. Chronic central serous chorioretinopathy (persistent exudation can mimic treatment-resistant nAMD)[3,4]
2. Vitelliform lesion[4]

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CHALLENGE REQUIRING VISION ACADEMY GUIDANCE

What are the criteria for determining benefits from anti-VEGF therapy?

RECOMMENDATION

nAMD, neovascular age-related macular degeneration; OCT, optical coherence tomography; VEGF, vascular endothelial growth factor.

1. CATT Research Group; Martin DF *et al. N Engl J Med* 2011; 364 (20): 1897–1908; 2. Heier JS *et al. Ophthalmology* 2012; 119 (12): 2537–2548; 3. Broadhead GK *et al. Acta Ophthalmol* 2014; 92 (8): 713–723; 4. Ozkaya A *et al. Eye (Lond)* 2016; 30 (7): 958–965.

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The criteria for defining responses to treatment should be carefully assessed

- There are currently no standardized guidelines for defining a poor or non-response to therapy
  - Responses to anti-VEGF therapy may be classified into functional and morphological responses; however, function and morphology do not always correlate
- Morphological failures may or may not be associated with a loss of visual acuity

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CHALLENGE REQUIRING VISION ACADEMY GUIDANCE

How do we guide and manage patients with nAMD who do not perceive any benefits from anti-VEGF treatment?

RECOMMENDATION

nAMD, neovascular age-related macular degeneration; VEGF, vascular endothelial growth factor.

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Futility of treatment with anti-VEGF agents

VEGF, vascular endothelial growth factor.

The Royal College of Ophthalmologists recommends treatment suspension in cases of futility

The Royal College of Ophthalmologists has differing criteria for poor or non-response, and recommends permanent discontinuation of anti-VEGF treatment in cases where:

- BCVA in the treated eye has decreased to fewer than 15 ETDRS letters (absolute) on 2 consecutive visits, attributable to AMD (in the absence of other pathology)
- BCVA in the treated eye has decreased by ≥30 letters vs. baseline and/or there is a reduction in best recorded level since baseline
- There is evidence of deterioration in lesion morphology despite optimal anti-VEGF treatment

AMD, age-related macular degeneration; BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; VEGF, vascular endothelial growth factor.

The Royal College of Ophthalmologists. Age-related macular degeneration: guidelines for management. September 2013. Available at: https://www.rcophth.ac.uk/wp-content/uploads/2014/12/2013-SCI-318-RCOphth-AMD-Guidelines-Sept-2013-FINAL-2.pdf. Accessed October 2021.

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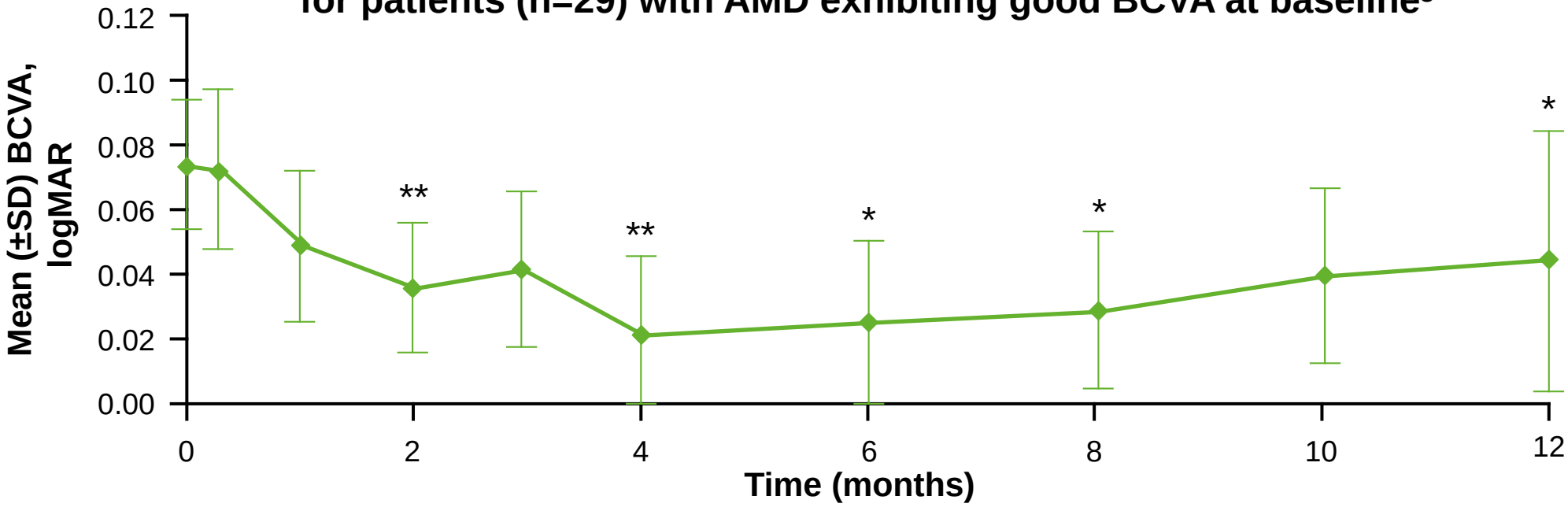
In some patients, response to treatment may occur later in the treatment regimen

- Response at Month 4 is not always predictive of long-term visual acuity gains
  - Responses in some patients were observed after 4 months of treatment in the MARINA and ANCHOR trials[1,2]

Clinical outcomes after initial intravitreal aflibercept injections for patients (n=29) with AMD exhibiting good BCVA at baseline[3]



*p<0.05; **p<0.01.
AMD, age-related macular degeneration; BCVA, best-corrected visual acuity; logMAR, logarithm of the minimum angle of resolution; SD, standard deviation.
1. Brown DM *et al. N Engl J Med* 2006; 355 (14): 1432–1444; 2. Rosenfeld PJ *et al. N Engl J Med* 2006; 355 (14): 1419–1431;
3. Minami S *et al. Sci Rep* 2018; 8 (1): 58.

Even in eyes with VA loss ≥1 line at 3 months, gains of ≥1 line are seen in ~30% of patients at Year 2 (CATT)

		VA change in patients from baseline to Month 3		
		≥1 line gain (n=586)	<1 line change (n=312)	≥1 line loss (n=127)
VA change in patients at Year 1	≥1 line gain	85%	45%	17%
	<1 line change	12%	41%	25%
	≥1 line loss	3%	14%	58%

Year 1

		VA change in patients from baseline to Month 3		
		≥1 line gain (n=586)	<1 line change (n=312)	≥1 line loss (n=127)
VA change in patients at Year 2	≥1 line gain	79%	42%	27%
	<1 line change	13%	35%	21%
	≥1 line loss	8%	23%	52%

Year 2

CATT, Comparison of Age-Related Macular Degeneration Treatments Trials; VA, visual acuity.
Ying G-S *et al. Ophthalmology* 2015; 122 (12): 2523–2531.e1.

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Treatment intervals should be investigated before treatment is suspended

- Poor response to treatment may be due to less frequent treatment than is required for a particular patient
- This may be due to pathophysiologic factors such as:[1,2]
  - Chronic disease with a change in cytokine profile
  - Chronic inflammation or high levels of VEGF
- Or external factors (e.g., logistical or other factors) such as:[1]
  - Patient difficulty in traveling to the retina center
  - Capacity of retina center

Before treatment can be discontinued, several key assumptions must be confirmed

Loss of response to currently used drug, **AND**:

- The patient has nAMD
- The patient has unilateral disease (good vision in the fellow eye)
- Anti-VEGF treatment was administered in a correct and timely fashion

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CHALLENGE REQUIRING VISION ACADEMY GUIDANCE

What criteria should be used for determining when treatment suspension should be considered?

RECOMMENDATION

nAMD, neovascular age-related macular degeneration; VEGF, vascular endothelial growth factor.

1. Amoaku WM *et al. Eye (Lond)* 2015; 29 (6): 721–731; 2. Stewart MW *et al. Retina* 2012; 32 (3): 434–457.

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Clinical challenges

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Clinical challenges requiring guidance

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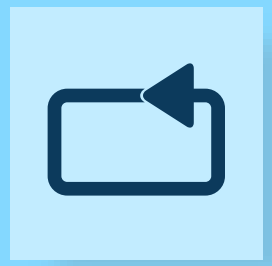

Treatment continuation

How do we determine whether anti-VEGF therapy should be continued in patients without perceived benefits?

Monitoring

How do we guide the management of patients with nAMD who do not perceive any benefits from anti-VEGF treatment?

Treatment suspension

What criteria are used to determine when treatment suspension should be considered?

nAMD, neovascular age-related macular degeneration; VEGF, vascular endothelial growth factor.

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Vision Academy recommendations

A treatment futility algorithm has been developed to determine whether anti-VEGF treatment should continue when response is poor

The algorithm consists of 5 key stages

1. **Patient decision**
2. **Treatment per protocol**
3. **Treatment protocol adjustment**
4. **Investigation of inadequate response**
5. **Establishment of anti-VEGF treatment futility**

The algorithm is appropriate for patients meeting the following criteria:

- The patient has unilateral or bilateral nAMD (applicability of the algorithm flow chart is limited to the worse-seeing eye in bilateral disease; in cases of approximately equivalent VA in both eyes, the flow chart should be limited to only 1 eye)
- No previous under- or overtreatment with an anti-VEGF
- No permanent damage to the macular center that is incompatible with visual improvement by anti-VEGF treatment
- Lesion size ≤12 disc areas in greatest linear dimension
- Evidence of disease progression from worsening retinal morphology (>100 µm of increased retinal fluid, and/or leakage), as seen using OCT or fluorescein angiography, or from recent changes in VA (worsened by ≥5 letters)

There is a lack of guidance on the criteria for determining when treatment suspension should be considered

The flow chart should be used to help determine anti-VEGF treatment futility in patients with nAMD

nAMD, neovascular age-related macular degeneration; OCT, optical coherence tomography; VA, visual acuity; VEGF, vascular endothelial growth factor.

Wong DT *et al. Retina* 2020; 40 (6): 1010–1020.

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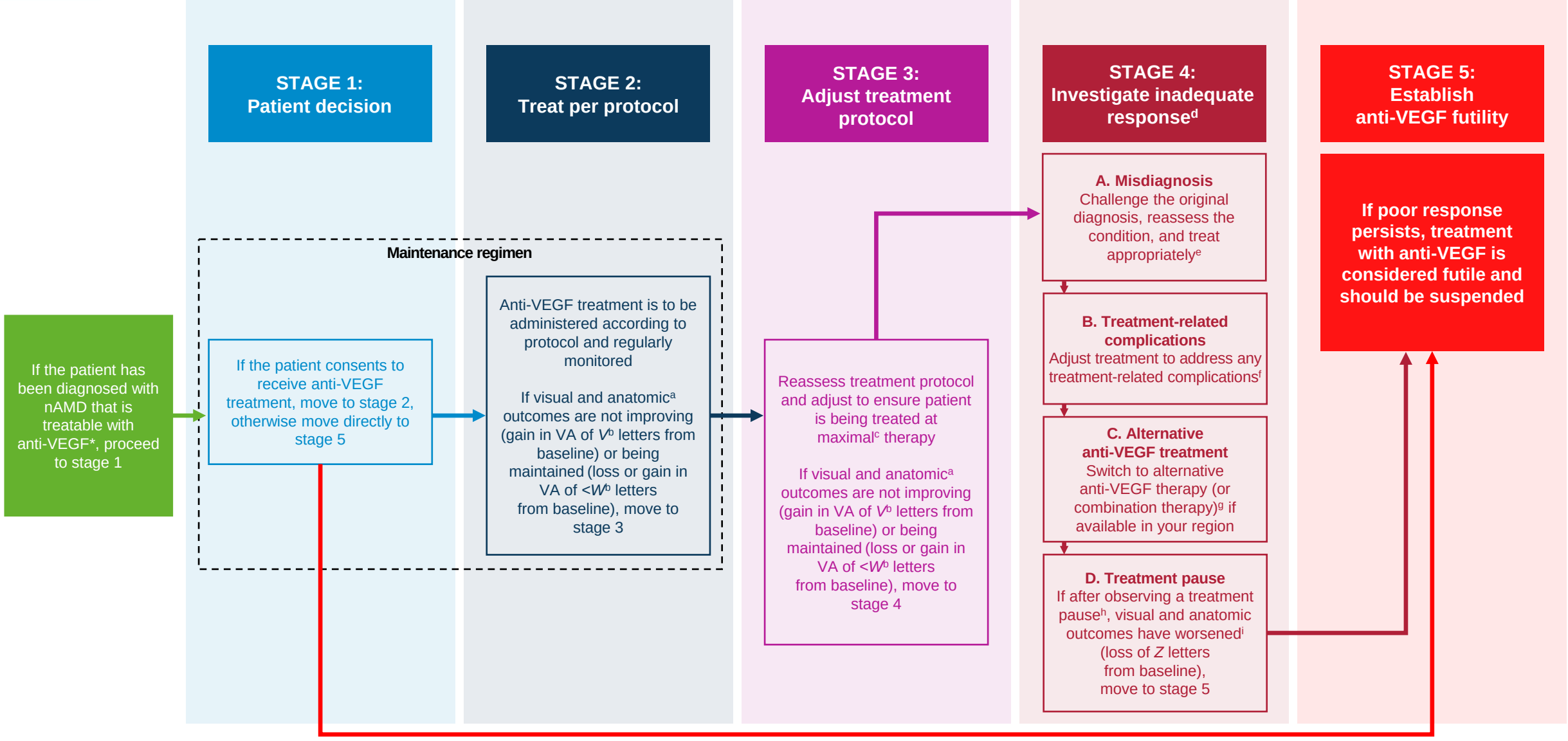

*All of the following apply to the eye in question: the patient has unilateral or bilateral nAMD (algorithm limited to the worse-seeing eye); anti-VEGF was administered in a correct and timely manner in previously treated patients; there is no permanent damage to the macular center that is incompatible with visual improvement by anti-VEGF treatment; lesion size is ≤12 disc areas in greatest linear dimension; and there is evidence of disease progression as seen using fluorescein angiography or recent VA changes. Within the algorithm, futility is defined as a state in which the recommendation is to suspend treatment, which is not limited to medical futility. [a]Optical coherence tomography changes also to be considered here, in accordance with region- and physician-specific criteria. [b]As defined by region-specific criteria. [c]"Maximal therapy" is defined as the shortest dosing interval of 2–4 weeks (as defined by region- and physician-specific criteria). [d]"Inadequate response" is defined as progressive deterioration in visual acuity of ≥*X* letters from baseline in treated eye in primary phase (*X* defined by region-specific criteria). [e]Alternative treatment options are available for subtypes of nAMD, such as PCV and retinal angiomatous proliferation. [f]Complications may include thromboembolic events; anti-VEGF treatment should be suspended temporarily and then recommenced (period defined by region-specific criteria). [g]When alternative anti-VEGF monotherapy is unavailable, the physician may consider combining with photodynamic therapy. [h]"Treatment pause," or "treatment-free interval," is defined as *Y* weeks of no anti-VEGF treatment (period of time defined by region-specific criteria). i"Worsening" is defined as loss of *Z* letters from baseline (*Z* defined by region-specific criteria).
nAMD, neovascular age-related macular degeneration; PCV, polypoidal choroidal vasculopathy; VA, visual acuity; VEGF, vascular endothelial growth factor.

Stage 1: Patient decision

Patients consenting to intravitreal injections of anti-VEGF should receive treatment in accordance with the licensed protocol, with regular follow-up visits to:

- Assess nAMD disease activity
- Assess response to treatment
- Guide re-treatment or treatment protocol adjustment

The patient's decision on the use of anti-VEGF treatment is important

Treatment can proceed in patients who provide their consent

Anti-VEGF treatment is suspended in those patients who do not give consent

Patient willingness to receive anti-VEGF treatment should be reassessed periodically for those who do not wish to proceed

General consensus

nAMD, neovascular age-related macular degeneration; VEGF, vascular endothelial growth factor.
Wong DT *et al. Retina* 2020; 40 (6): 1010–1020.

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Stage 2: Treatment per protocol

When evaluating response to anti-VEGF treatment in patients with nAMD, both functional (determined using VA) and morphological changes (determined using a combination of imaging modalities, including OCT) should be considered, rather than VA alone, in accordance with country-specific criteria for classifying response[1,2]

Anti-VEGF treatment should be continued:[3]

- In cases where there is an improvement in lesion morphology despite a lack of functional response
- In cases where there is an improvement in VA without morphological response

When assessing response to anti-VEGF treatment in patients with nAMD

Consideration of non-response should be based on both functional and morphological changes[3]

General consensus

nAMD, neovascular age-related macular degeneration; OCT, optical coherence tomography; VA, visual acuity; VEGF, vascular endothelial growth factor.

1. Amoaku WM *et al. Eye (Lond)* 2015; 29 (6): 721–731; 2. The Royal College of Ophthalmologists. Age-related macular degeneration: guidelines for management. September 2013. Available at: https://www.rcophth.ac.uk/wp-content/uploads/2014/12/2013-SCI-318-RCOphth-AMD-Guidelines-Sept-2013-FINAL-2.pdf Accessed October 2021; 3. Wong DT *et al. Retina* 2020; 40 (6): 1010–1020.

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Stage 3: Treatment protocol adjustment

In patients with poor response to anti-VEGF treatment after the initial loading phase of 3 monthly injections (as defined by country- and physician-specific criteria):

- The treatment protocol should be reassessed
- The treatment protocol should be adjusted to ensure maximal therapy, if necessary

After initial loading phase of 3 monthly injections

Maximal therapy should be provided in cases of poor response to anti-VEGF treatment

If a poor response to anti-VEGF is still observed with maximal therapy, the reason for the inadequate response should be investigated (see key statements listed in stage 4 of the flow chart)

General consensus

VEGF, vascular endothelial growth factor.

Wong DT *et al. Retina* 2020; 40 (6): 1010–1020.

Stage 4: Investigation of inadequate response

Misdiagnosis

- Where there is a lack of response after the initial 3-month loading phase, misdiagnosis should be considered and a reassessment of the condition and intervention should be carried out
- Reassessment should use multimodal imaging, including fluorescein angiography, ICGA, and OCT

Treatment-related complications

- Treatment should be suspended temporarily if complications occur, until adequately resolved
- In less severe cases of subfoveal hemorrhage secondary to nAMD, anti-VEGF treatment should be continued before referring the patient for alternative treatment

Investigation of inadequate response to anti-VEGF treatment

- Misdiagnosis should be considered and a reassessment should be carried out
- Suspend treatment if complications occur and resume when resolved

General consensus

ICGA, indocyanine green angiography; nAMD, neovascular age-related macular degeneration; OCT, optical coherence tomography; VEGF, vascular endothelial growth factor.

Wong DT *et al. Retina* 2020; 40 (6): 1010–1020.

Stage 4: Investigation of inadequate response

Alternative anti-VEGF treatment

- Patients with nAMD who have insufficient functional and morphological responses to anti-VEGF should, where possible, receive an alternative agent in cases where potential confounding factors to treatment have been investigated and managed, and the diagnosis has been confirmed
- If an alternative anti-VEGF monotherapy is not available, combination treatment with photodynamic therapy should be considered

Treatment pause

- In cases of insufficient or no response to anti-VEGF treatment, a 1-month treatment pause followed by monthly monitoring visits (up to 6 months) should occur to assess for treatment futility
- Re-initiation of optimal anti-VEGF therapy is recommended if there is a noticeable deterioration in visual or anatomical outcomes during the treatment pause

Investigation of inadequate response to anti-VEGF treatment

- Alternative anti-VEGF treatments should be given to patients with an inadequate response
- To assess for treatment futility, a 1-month treatment pause should be carried out

General consensus

nAMD, neovascular age-related macular degeneration; VEGF, vascular endothelial growth factor.

Wong DT *et al. Retina* 2020; 40 (6): 1010–1020.

Stage 5: Establishment of anti-VEGF treatment futility

Anti-VEGF therapy should be suspended in patients with nAMD who are classified as non-responders, including:

- Patients with an insufficient response to treatment that persists despite protocol adjustment
- Patients for whom complications / confounding factors have been addressed
- Patients who have been switched to an alternative anti-VEGF agent(s)
- Patients who have had a treatment pause (where appropriate)

Continued monitoring at follow-up visits is recommended at the discretion of the physician

Establishment of anti-VEGF futility

Patients may be considered non-responders and futility may be established if stages 1–4 of the futility algorithm flow chart have been followed but a poor response persists

General consensus

nAMD, neovascular age-related macular degeneration; VEGF, vascular endothelial growth factor.
Wong DT *et al. Retina* 2020; 40 (6): 1010–1020.

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Vision Academy recommendations for the treatment of poor anti-VEGF responders

- A treatment futility algorithm was developed to help clinicians identify the causes of non-response to anti-VEGF treatment in patients with nAMD and guide treatment protocol adjustment
- The 5 stages of the algorithm are: Patient Decision, Treatment per Protocol, Treatment Protocol Adjustment, Investigation of Inadequate Response, and Establishment of Anti-VEGF Futility
- In cases of inadequate response, factors such as misdiagnosis, treatment-related complications, and alternative anti-VEGF treatments must be considered, and treatment pauses may be required to confirm futility

The Viewpoint “Suspending Treatment of Neovascular Age-Related Macular Degeneration in Cases of Futility” can be downloaded from:
https://www.visionacademy.org/resources

nAMD, neovascular age-related macular degeneration; VEGF, vascular endothelial growth factor.

Wong DT *et al. Retina* 2020; 40 (6): 1010–1020.

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Further considerations

Further consideration of what constitutes treatment “success” with anti-VEGF therapy and the circumstances in which treatment suspension is appropriate may be warranted

Investigating the potential to reintroduce anti-VEGF and developing a re-treatment protocol for patients for whom treatment was previously considered futile may be beneficial

VEGF, vascular endothelial growth factor.

Wong DT *et al. Retina* 2020; 40 (6): 1010–1020.