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Discussion and debate:

Treatment with anti-VEGF agents in AMD should be stopped when benefits to the patient can no longer be expected

For: Professor Anat Loewenstein

Against: Professor Paolo Lanzetta

Presentation of viewpoint: Professor Anat Loewenstein

The Vision Academy is sponsored by Bayer. This presentation has been developed independently by Vision Academy members and does not necessarily reflect the views of Bayer. This presentation reflects the views of a majority of Vision Academy members; individual views may vary. The Vision Academy Steering Committee comprises Bora Eldem, Alex Hunyor, Antonia M. Joussen, Adrian Koh, Jean-François Korobelnik, Paolo Lanzetta, Anat Loewenstein, Monica Lövestam-Adrian, Rafael Navarro, Lihteh Wu, Annabelle A. Okada, Ian Pearce, Francisco J. Rodríguez, Sebastian Wolf, and David Wong.

Session aims

- To debate and discuss evidence for and against the argument that treatment with anti-VEGF agents in AMD should be stopped when benefits to the patient can no longer be expected
- To provide a summary of the Vision Academy's position on the topic

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

Debate:
Is there a case FOR stopping treatment?

Professor Anat Loewenstein

Tel Aviv Sourasky Medical Center, Israel

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Financial and other disclosures

I have the following financial interests or relationships to disclose	Disclosure code
Allergan, Bayer, ForSight Labs, Notal Vision, Novartis	C

C, consultant.

What is medical futility?

"The moment when a treatment has no realistic chance of providing an effect that the patient would have the capacity to appreciate as benefit…"

Quantitative medical futility is related to the **success of a treatment** in achieving its intended goals

Qualitative medical futility is related to the **value of a treatment** to a patient's quality of life

Schneiderman LJ. *J Bioeth Inq* 2011; 8: 123–131.

Why is medical futility important?

Overburden

Hippocratic oath

- *Primum non nocere*, do no harm

Cost

- Cost of drug and procedure
- Time
  - Patient's
  - Physician's
- Complications

Schneiderman LJ *et al. Ann Intern Med* 1990; 112: 949–954.

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

- Despite regular anti-VEGF therapy, **~25–35% of patients 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 over what constitutes non-response, several guidelines have attempted to address the issue
- A poor or lack of response may be due to misdiagnosis with entities such as:[3]
  - Polypoidal choroidal vasculopathy
  - Chronic central serous chorioretinopathy (persistent exudation can mimic treatment-resistant nAMD)

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

1. Martin DF *et al. N Engl J Med* 2011; 364: 1897–1908; 2. Heier JS *et al. Ophthalmology* 2012; 119: 2537–2548;
3. Broadhead GK *et al. Acta Ophthalmol* 2014; 92: 713–723.

Guidelines are in agreement that in cases of poor or suboptimal response, treatment with anti-VEGF should be discontinued

VA \ Morphology	No response	Poor response	Partial response	Good response
Good response	Continue current therapy or undertake more imaging and consider switch / combination	Continue current therapy or undertake more imaging and consider switch / combination	Continue current therapy	Continue current therapy
Partial response	More imaging and consider switch / combination	More imaging and consider switch / combination	Continue current therapy or undertake more imaging and consider other treatment	Continue current therapy
Poor response	Discontinue. Consider review with further imaging or change therapy	More imaging and consider switch / combination unless poor visual potential	More imaging and consider switch / combination unless poor visual potential	Continue current therapy unless poor visual potential
No response	Discontinue. Consider review with further imaging or change therapy	Discontinue. Consider review with further imaging or change therapy	More imaging and consider switch / combination unless poor visual potential	Continue current therapy unless poor visual potential

VA, visual acuity; VEGF, vascular endothelial growth factor.

Amoaku WM *et al. Eye (Lond)* 2015; 29 (6): 721–731.

The Royal College of Ophthalmologists also recommend suspension of treatment in cases of futility

- **The Royal College of Ophthalmologists 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 two consecutive visits, attributable to nAMD (in the absence of other pathology)**
  - **BCVA in the treated eye has decreased by ≥30 letters vs. baseline and/or best recorded level since baseline**
  - **There is evidence of deterioration in lesion morphology despite optimal anti-VEGF therapy**

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

Royal College of Ophthalmologists. Age-related macular degeneration: guidelines for management. September 2013.

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

- The patient has nAMD
- Anti-VEGF treatment was administered in a correct and timely fashion

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

When to stop therapy?

- **Stopping anti-VEGF therapy should be considered:**
  - **No anatomical and no functional response**
  - **Misdiagnosis**
  - **Foveal scarring**
  - **Other major ocular pathology (e.g. retinal detachment)**
- **All of this should only be considered after verifying appropriate anti-VEGF treatment has been administered**

VEGF, vascular endothelial growth factor.
Amoaku WM *et al. Eye (Lond)* 2015; 29 (6): 721–731.

Debate:
Is there a case AGAINST stopping treatment?

Professor Paolo Lanzetta

University of Udine, Italy

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Financial and other disclosures

I have the following financial interests or relationships to disclose	Disclosure code
Bayer	C, L, S
Genentech	C
Novartis, Alcon	C, L, S
Centervue	C
Topcon	C, L

C, consultant; L, lecture fees; S, grant support

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

VEGF, vascular endothelial growth factor.

Amoaku WM *et al. Eye (Lond)* 2015; 29 (6): 721–731.

Treatment intervals and number of injections should be reassessed before stopping treatment

- 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 change in cytokine profile
  - Chronic inflammation or high levels of VEGF
  - Tachyphylaxis
- Or external factors (e.g., logistical or other factors) such as:[1]
  - Physicians misinterpretation of retreatment criteria
  - Capacity of retinal center
  - Patient difficulty in traveling to the retina center

VEGF, vascular endothelial growth factor.

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

Lack of visual acuity gain does not always mean a treatment is not beneficial

- Even if treatment does not lead to visual acuity gains, treatment cessation may lead to a deterioration in visual acuity and / or morphology
  - Treatment should be continued to ensure a stable condition is maintained

Summary

- If the patient's condition is stabilized under treatment (i.e., no gains or losses in visual acuity), the treatment regimen should be maintained to avoid disturbing this established balance
- If the patient's condition is deteriorating under treatment, stopping the treatment may actually accelerate deterioration
- Conclusion: do not give up hope and do not leave the patient alone without monitoring and treatment

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What is the Vision Academy's position?

Professor Anat Loewenstein

Tel Aviv Sourasky Medical Center, Israel

Stopping anti-VEGF treatment of nAMD in cases of futility

Vision Academy objective:

To provide a practical, expert opinion on when to stop anti-VEGF treatment in cases of futility, and how this may differ from the decision to switch therapies

Algorithm has been developed following a thorough review of the literature and employing the combined knowledge and expertise of the Vision Academy

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

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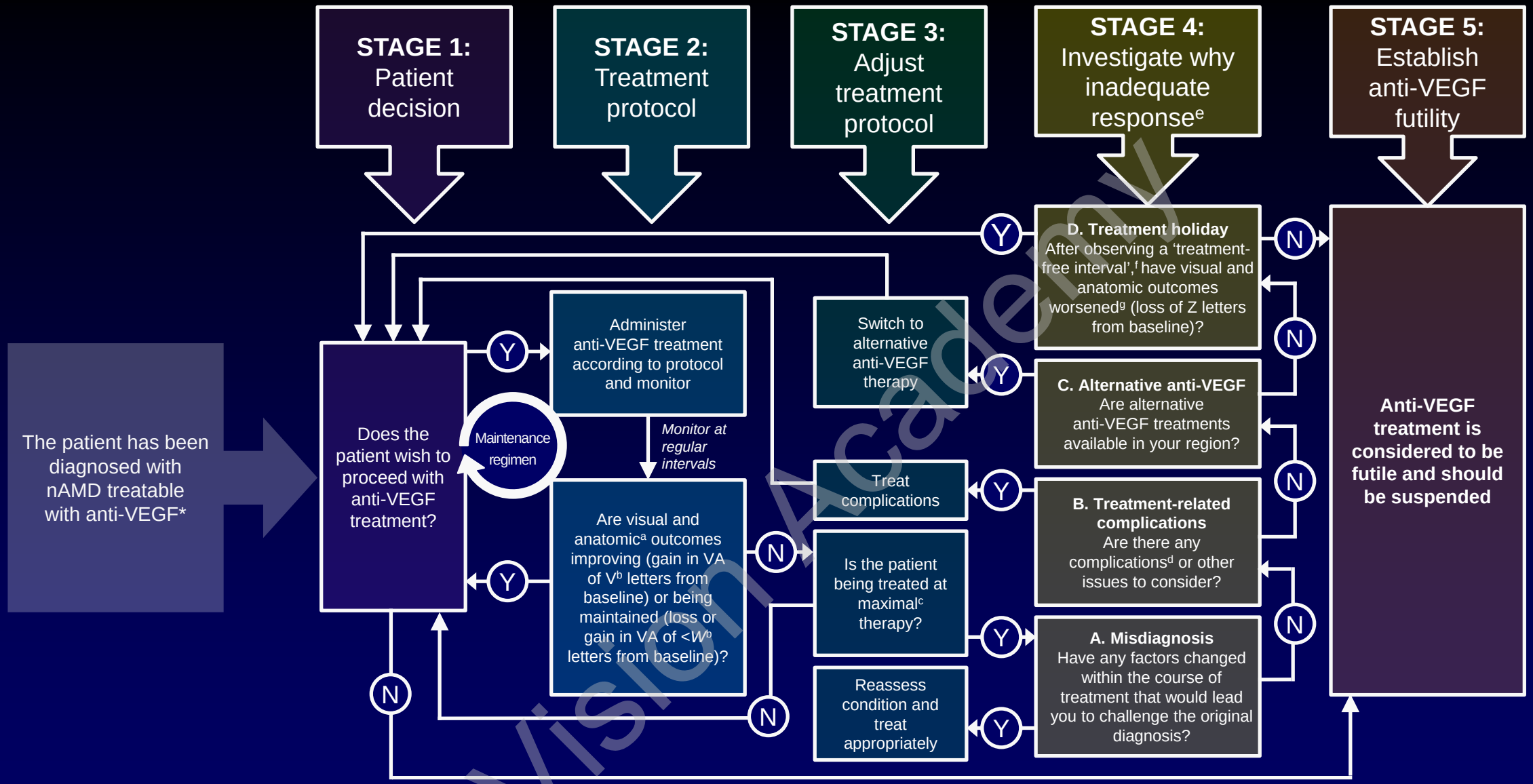
Stopping anti-VEGF treatment of nAMD in cases of futility

- The decision tree on the next slide sets out the key decisions that need to be made before stopping anti-VEGF treatment
- This decision tree was drafted based on the following assumptions:
  - The patient has nAMD
  - The patient has unilateral disease
  - Anti-VEGF treatment is administered in a correct and timely fashion (i.e., the patient is neither under- nor over-treated)

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



*All of the following apply to the eye in question: the patient has unilateral nAMD; there is no permanent damage to the central fovea; lesion size is ≤12-disc areas in greatest linear dimension; and there is evidence of disease progression from fluorescein angiography, or recent VA changes. [a]OCT 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]Complications may also include thromboembolic events; anti-VEGF treatment should be suspended temporarily and then recommenced (period of time defined by region-specific criteria). [e]'Inadequate response' is defined as progressive deterioration in VA of ≥X letters from baseline in treated eye in primary phase (X defined by region-specific criteria). [f]'Treatment-free interval' is defined as Y weeks of no anti-VEGF treatment (period of time defined by region-specific criteria). [g]'Worsening' defined as loss of Z letters from baseline (Z defined by region-specific criteria).

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

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Summary

- **This decision tree has been drafted to prompt discussion and debate within the ophthalmic community**
- **The key decision points can be categorized into four stages:**
  - Diagnosis, recommendation and patient decision
  - Treatment protocol
  - Adjusting the treatment protocol
  - Investigating inadequate responses to treatment