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Review

SUSPENDING TREATMENT OF NEOVASCULAR AGE-RELATED MACULAR DEGENERATION IN CASES OF FUTILITY

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Purpose: To provide guidance on the management of patients with neovascular age-related macular degeneration and its subtypes who respond poorly to anti–vascular endothelial growth factor (anti-VEGF) therapy, and to identify cases where suspending anti-VEGF treatment may be warranted.

Methods: Through a literature review and the combined knowledge and clinical experience of retinal experts, the Steering Committee of the Bayer-sponsored Vision Academy developed an algorithm for determining when to suspend anti-VEGF treatment of neovascular age-related macular degeneration in cases of futility.

Results: Consideration of factors that may cause suboptimal response to anti-VEGF therapy, such as undertreatment or misdiagnosis of the underlying condition, and factors that may preclude continued treatment, such as injection- or drug-induced complications, is necessary for adjusting treatment protocols in patients who respond poorly to anti-VEGF. If poor response to treatment persists after switching to an alternative anti-VEGF agent and no change in response is observed after withholding treatment for a predetermined period of time ("treatment pause"), anti-VEGF treatment may be considered futile and should be suspended.

Conclusion: This publication introduces an algorithm to guide the management of neovascular age-related macular degeneration in patients showing poor response to anti-VEGF treatment and provides expert guidance for suspending anti-VEGF treatment in cases of futility.

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Medical futility is defined as the point at which a treatment has no realistic chance of providing an effect that the patient would have the capacity to appreciate as a benefit.[1] Medical futility has two components: quantitative medical futility, which is related to the success of a treatment in achieving the intended goals, and qualitative medical futility, which is related to the value of a treatment to quality of life of the patient.[1,2] Currently, there is variation in opinion and a lack of guidance within the ophthalmic community on when it may be appropriate to suspend anti–vascular endothelial growth factor (anti-VEGF) treatment of neovascular age-related macular degeneration (nAMD) in cases of medical futility.

The Vision Academy is an initiative that brings together global leaders in ophthalmology, providing a forum to share skills and knowledge. Together, Vision Academy members seek to address key clinical challenges in the field of retinal disease, providing outputs to build best practice and lead the wider ophthalmic community in the drive toward optimized, compassionate patient care. As a key area of uncertainty that may have a significant impact on the clinical management of patients with nAMD, determining futility of anti-VEGF treatment falls within the scope of the Vision Academy.

Members of the Vision Academy Steering Committee (Appendix 1) met in 2017 to discuss the concept of treatment futility in nAMD, with particular focus on

the criteria for determining response to anti-VEGF treatment in clinical practice and the key factors that should be explored before deciding to suspend anti-VEGF treatment. This publication introduces an algorithm to guide the management of patients with nAMD who respond poorly to anti-VEGF treatment. It provides expert recommendations for investigation of factors that may confound response to anti-VEGF treatment, appropriate adjustment of the treatment protocol, and suspension of treatment in cases of futility.

Methods: Development of a Treatment Futility Algorithm

This article was based on a review of the literature and a consensus among retinal specialists who are members of the Vision Academy, an international group of over 90 retinal experts who work together to share existing skills and knowledge and provide collective recommendations on clinical challenges in areas where there is a lack of conclusive evidence in the literature (www.visionacademy.org). For this review, the initial concept of suspending anti-VEGF therapy for nAMD in patients who respond poorly to treatment was first proposed to the Vision Academy membership in 2017 as an important topic for further development. Subsequently, a review of the available literature published on the online PubMed database was performed to drive discussions at a meeting of the Vision Academy Steering Committee in 2017, to establish consensus on the key factors that make up the treatment futility algorithm.

The Vision Academy Steering Committee developed an algorithm for determining when to consider suspending anti-VEGF therapy for nAMD in patients who respond poorly to treatment (Figure 1). The treatment futility algorithm was created for use in the clinic to: guide investigation of the factors that may confound administration of, or response to, anti-VEGF therapy; drive adjustment of the treatment protocol as necessary; and determine when suspension of anti-VEGF treatment may be suitable in cases of futility. For the purposes of algorithm development, a state of futility is also considered to be reached when the recommendation is to suspend treatment for patient-specific reasons (i.e., patient no longer consents to treatment) or physician-specific reasons (no observed worsening after treatment pause). Although treatment may not be medically futile in these cases, it is considered futile per the algorithm, and the guidance provided is to suspend treatment. In developing the treatment futility algorithm, the Vision Academy Steering Committee agreed on the following key assumptions in terms of the suitability of patients for management using the algorithm.

Patients being considered for inclusion in the algorithm should meet all of the following assumptions:

1. The patient has nAMD.
2. The patient has unilateral or bilateral disease (in bilateral disease, the applicability of the algorithm is limited to the worse-seeing eye; in cases of approximately equivalent visual acuity in both eyes, the algorithm should be limited to only one eye).
3. In previously treated patients, anti-VEGF treatment was administered in a correct and timely fashion (i.e., the patient was neither under- nor overtreated).
4. There is no permanent damage to the macular center that is incompatible with visual improvement by anti-VEGF treatment (i.e., treatment of patients with permanent damage should be considered futile per the algorithm, as determined at the discretion of the physician).

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Members of the Vision Academy Steering Committee and their affiliations are listed in the Appendix 1.

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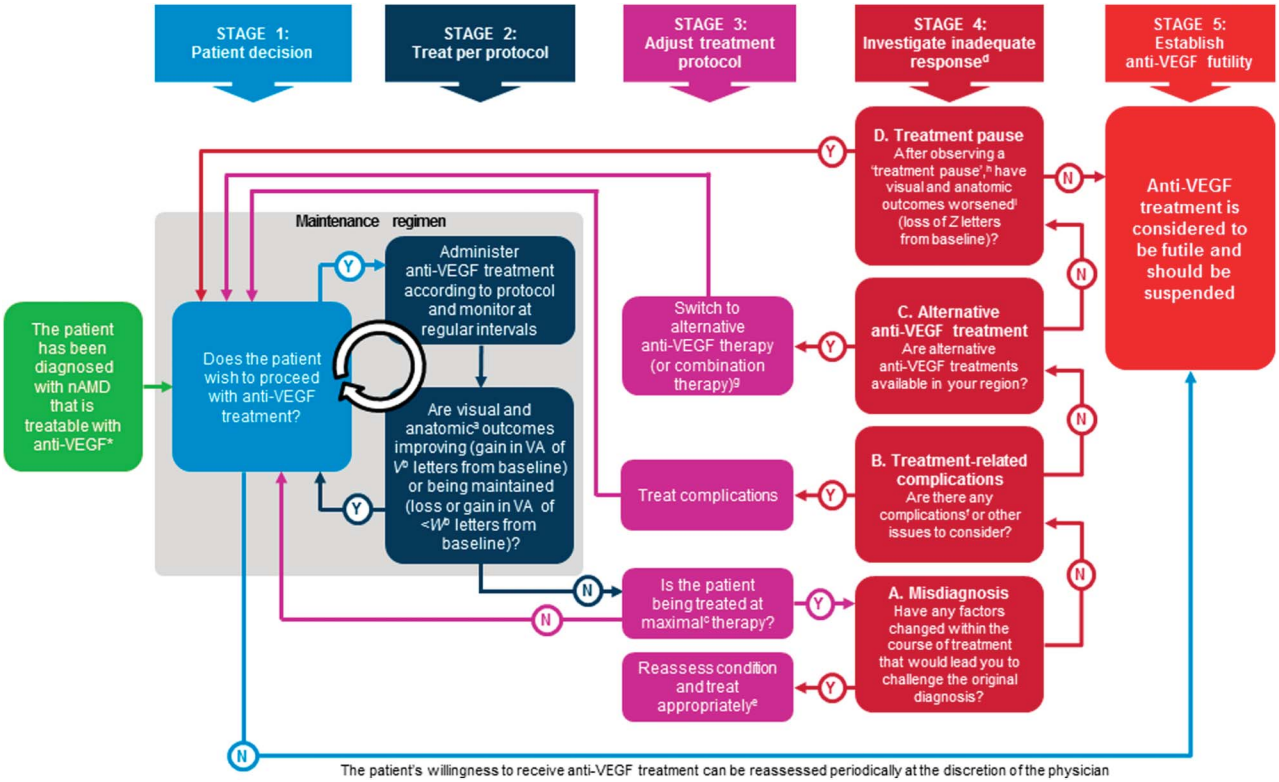

Fig. 1. The algorithm for determining anti-VEGF treatment futility in patients with nAMD. *All of the following apply to the eye in question: the patient has unilateral or bilateral nAMD (algorithm limited to the worse-seeing eye); anti-VEGF was administered in a correct and timely manner in previously 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 disk areas in greatest linear dimension; and there is evidence of disease progression as seen using fluorescein angiography or recent visual acuity 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 to 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).

5. The lesion size is ≤12 disk areas in greatest linear dimension (i.e., treatment of patients with lesion size ≥12 disk areas in greatest linear dimension should be considered futile per the algorithm, as determined at the discretion of the physician).
6. There is evidence of disease progression from worsening retinal morphology (>100 μm of increased retinal fluid, and/or leakage), as seen using optical coherence tomography (OCT) or fluorescein angiography, or from recent changes in visual acuity (worsened by ≥5 letters).

Results

Taking into consideration the assumptions previously defined, a patient diagnosed with nAMD that is treatable with anti-VEGF can be evaluated using a treatment futility algorithm to determine whether treatment with anti-VEGF therapy should continue when response is poor (Figure 1). The algorithm comprised five steps: patient decision, treatment per protocol, adjustment of treatment protocol, 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.

Discussion

Each step of the anti-VEGF treatment futility algorithm is discussed in detail in the following section, accompanied by Vision Academy recommendations.

Stage 1: Patient Decision

Provided all the aforementioned assumptions are correct and the patient has consented to receiving

intravitreal injections of anti-VEGF, treatment can proceed in accordance with the licensed protocol after the treatment "maintenance regimen" (as shown in Stages 1 and 2 of the treatment futility algorithm). After initiation of anti-VEGF therapy, patients are typically monitored at regular follow-up visits to assess nAMD disease activity and response to treatment, and to guide retreatment or appropriate adjustment of the treatment protocol. If the patient does not consent to receiving intravitreal injections of anti-VEGF, a lack of perceived benefit is assumed, and anti-VEGF treatment is suspended (i.e., considered futile per the algorithm [see Stage 5]). In cases where the patient does not wish to proceed with anti-VEGF therapy, their willingness to receive anti-VEGF treatment can be reassessed periodically at the discretion of the physician (i.e., management of the patient recommences at Stage 1).

Stage 2: Treat per Protocol

In 2013, the Royal College of Ophthalmologists[3] published a set of guidelines which intended to set the standard for best clinical practice for the treatment of nAMD in the United Kingdom. These guidelines provide recommendations by using both visual function and anatomical parameters to guide the diagnosis and management of nAMD with anti-VEGF therapy.[3] Included in the guidelines are recommendations for the permanent suspension of anti-VEGF treatment, in cases where best-corrected visual acuity (BCVA) in the treated eye has decreased to fewer than 15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (absolute) on two consecutive visits, attributable to nAMD in the absence of other pathologies; BCVA in the treated eye has decreased by $\geq$30 ETDRS letters compared with baseline and/or best-recorded level since baseline, or there is evidence of deterioration in lesion morphology despite optimal anti-VEGF therapy.[3] Subsequently, Amoaku et al[4] characterized response to anti-VEGF treatment based on changes in visual function and anatomical features after the initial loading (primary) and maintenance (secondary) phases. Functional and morphological responses were defined as optimal (good), suboptimal (partial), poor, or failure (no response).[4] In addition, Amoaku et al[4] made recommendations for suspending anti-VEGF therapy based on the assumptions that optimal therapy was being provided, misdiagnosis had not occurred, and use of alternative anti-VEGF agents would be of no additional benefit; all of these were deemed to be key steps to consider in the Vision Academy's treatment futility algorithm for nAMD.

In terms of determining whether anti-VEGF treatment is having the desired effect of restoring vision or preventing further vision loss due to nAMD, visual acuity is an essential measurement of functional response to treatment. The recommendations provided by Amoaku et al[4] classified a change in visual acuity of 0 to 4 ETDRS letters from baseline after the primary phase as a poor functional response to anti-VEGF therapy, while a loss of more than 5 letters from baseline 1 month after the third initial loading dose (i.e., at Month 4) was defined as a "non-response." Lesion morphology, taking into account characteristics such as changes in central retinal thickness and fluid accumulation, is routinely assessed when determining response to anti-VEGF treatment in patients with retinal disease.[4] Amoaku et al[4] defined a poor morphological response to anti-VEGF therapy as one with minimal or no change in central retinal thickness, subretinal fluid, intraretinal fluid, and intraretinal cysts from baseline, or where new fluid or lesions were detected using OCT. Where there was evidence of deterioration in lesion morphology from baseline during the primary phase, patients were defined as primary failures and "non-responders" to anti-VEGF therapy.[4] Where there was evidence of improvements in lesion morphology from baseline during the primary phase but subsequent deterioration during the maintenance phase (from Month 4 onwards), patients were defined as secondary failures. In patients with poor or no response in terms of both functional and morphological changes, further exploration of a precise cause through further imaging and appropriate adjustment of the treatment protocol was recommended, and permanent discontinuation of anti-VEGF therapy was recommended in cases where further treatment would be of no additional benefit.[4]

Current guidelines for determining response to anti-VEGF therapy have limitations and should be used at the discretion of the physician in the context of the patient's circumstances, and taking into account the regional factors that affect treatment decisions. For example, secondary failure during the maintenance phase may be due to less frequent treatment than is required for a particular patient.[4] Furthermore, it is important to note that a deterioration in morphological response may not always correlate with a loss of functional response.

Therefore, consideration of nonresponse should be based on both functional and anatomical criteria. Numerous studies in patients with AMD, diabetic macular edema, and retinal vein occlusion have demonstrated only modest correlations between anatomical outcomes, such as subretinal fluid heights or OCT center point thickness, and visual acuity improvements.[5–7] Furthermore, morphological failures may not be associated with a loss of visual acuity.[4]

Finally, practical considerations of visual acuity measurements in a clinic setting should be considered, as the precision and reliability can vary dramatically.

In cases where visual acuity is stable but there is underlying deterioration of lesion morphology, patients will not fall into one of the distinct response categories as defined by Amoaku et al[4]; therefore, both functional and morphological responses must be categorized separately. The criteria for determining response to anti-VEGF treatment may depend heavily on the baseline vision; a ceiling effect on improvement of visual acuity gains exists in patients with good baseline visual acuity (defined as ≥70 ETDRS letters), and this can negate the currently used criteria for determining functional response.[4,8] Similarly, even small increases in visual acuity (gains of ≥5 ETDRS letters) have been shown to provide meaningful improvements in vision-related quality of life in patients with nAMD[9]; therefore, retreatment decisions based on functional response to anti-VEGF therapy should be determined relative to baseline pretreatment vision.

In patients with nAMD for whom anti-VEGF treatment is failing to restore or prevent further loss of vision, Stages 3 and 4 of the Vision Academy treatment algorithm offers a series of key questions that should be systematically addressed to determine the most appropriate course of action. Expert recommendations, such as those provided by Amoaku et al,[4] for defining response to anti-VEGF treatment are essential for use in conjunction with the treatment futility algorithm, particularly when determining treatment response during the maintenance regimen (Stages 1 and 2), to determine when review of the patient's condition and adjustment of the treatment protocol may be required (Stages 3 and 4).

The Vision Academy Steering Committee recommends that, when assessing response to anti-VEGF treatment in patients with nAMD, both functional changes (determined using visual acuity) and morphological changes (determined using OCT in combination with other imaging modalities) should be considered, rather than visual acuity alone, in accordance with region-specific criteria for classifying response. In cases where lesion morphology is improved by anti-VEGF treatment, but there is a lack of functional response, the Vision Academy Steering Committee recommends continuing anti-VEGF treatment. Similarly, in cases where visual acuity has improved, but there is a lack of morphological response, continuation of treatment in accordance with the licensed posology is recommended.

Stage 3: Adjust Treatment Protocol

Maximal therapy. In patients where visual and anatomical outcomes are deteriorating, adjustment of the treatment protocol may restore some of this decline. Poor visual outcomes in clinical practice may be attributed to undertreatment and poor resource utilization; therefore, consideration should be given to whether the patient is receiving "optimal" or "maximal" therapy.

A review by Chong[10] reported that real-world outcomes at Year 1 with ranibizumab did not match those seen in randomized controlled trials of both fixed and pro re nata (as needed) treatment regimens in nAMD. Across the 20 real-world studies included in the review, the mean (±SD) change in visual acuity from baseline was 2.9 ± 3.2 ETDRS letters compared with 7.2 and 11.3 ETDRS letters with fixed monthly dosing in the MARINA and ANCHOR trials, respectively, and 6.8 and 8.2 ETDRS letters with pro re nata dosing in the CATT and HARBOR study arms, respectively.[10–14] The mean (±SD) number of ranibizumab injections over 12 months was 5.5 ± 0.8 across the real-world studies, compared with 12 monthly injections in the MARINA and ANCHOR trials, and 6.9 and 7.7 injections in the CATT and HARBOR studies, respectively.[10–14] These findings suggest that suboptimal visual outcomes seen with ranibizumab in clinical practice may be explained by patients receiving an insufficient number of anti-VEGF injections in the first year of treatment. Similarly, 5-year outcomes from the CATT study showed that reductions in visual acuity to below baseline in patients treated with bevacizumab (not licensed for intravitreal use) or ranibizumab may have been due to an insufficient number of injections after release from the stringent clinical trial treatment protocol.[15] In the AURA study, good visual outcomes with ranibizumab were achieved in clinical practice in countries where strict monitoring and retreatment criteria were followed; however, in many countries, outcomes similar to those seen in clinical trials were not replicated, particularly in countries where pro re nata regimens are routinely used in clinical practice.[16] Furthermore, evaluations of anti-VEGF treatment at shorter intervals, such as 2 weeks, could be useful in determining if any short-term response to anti-VEGF therapy is present, and could further inform the identification of maximal therapy.

A number of clinical and nonclinical factors may limit the ability to administer "maximal therapy" in clinical practice. Clinical limiting factors that may lead to suboptimal response to anti-VEGF treatment include uncommon or rare ocular or systemic comorbidities that restrict injection of anti-VEGF; immunogenic response to treatment that may cause an incomplete initial effect or resistance to an anti-VEGF agent; or the genetic profile of the individual.[4,17] Several studies have suggested that some

patients may require more frequent injections than the three initial monthly loading doses used.[18–20] In addition, a post hoc analysis of data from the PIER study showed that some patients with suboptimal responses to anti-VEGF treatment may require longer than the conventional loading phase of three monthly injections to show a clinically meaningful response.[21] Qualitative assessments of OCT images at Months 5 and 8 may help to identify eyes that require more frequent follow-up treatment than the three initial anti-VEGF loading doses recommended to achieve the primary response.[4,21]

Nonclinical factors for suboptimal treatment may include both service- and patient-related issues. Poor access to ophthalmology services or delays to appointments have been shown to contribute to less-frequent anti-VEGF treatment and suboptimal visual outcomes in several countries across the globe.[4,22,23] Poor treatment outcomes may also be caused by a lack of patient compliance to the optimal regimen of anti-VEGF injections. Polat et al[24] reported that the following factors are most likely to improve patient compliance to a preplanned anti-VEGF treatment regimen: BCVA in the affected eye of 70 ETDRS letters or more (>20/40) at the time of diagnosis; increases or decreases in BCVA seen with anti-VEGF treatment; and a short traveling distance to the treatment center.

The Vision Academy recommends that maximal therapy should be provided in cases with poor response to anti-VEGF treatment after the initial loading phase of three monthly injections (as defined by region- and physician-specific criteria). If a poor response to anti-VEGF treatment is still observed with maximal therapy, a series of key questions (as listed in Stage 4 of the treatment algorithm) should be considered to further investigate the reason for inadequate response and to determine the most appropriate course of action (Figure 1).

Stage 4: Investigate Inadequate Response

Misdiagnosis. When managing a patient with nAMD who is showing little or no response to maximal anti-VEGF therapy, it is important to consider whether any factors have changed within the course of treatment that indicate reassessment of the original diagnosis may be required (Stage 4A). Incorrectly identifying the subtype features of nAMD, such as polypoidal choroidal vasculopathy (PCV) or typical choroidal neovascularization, is a common clinical factor that results in poor response to anti-VEGF treatment.[17,25] Yang et al[17] suggested that 46% of poor responders to anti-VEGF treatment require revision of the primary diagnosis. For example, PCV may account for 22% to 62% of nAMD cases in Asian patients compared with 8% to 13% in Caucasian patients, and PCV has been shown to be present in some cases of nAMD that are refractory to anti-VEGF upon further examination using indocyanine green angiography.[17,25] Identification of focal hyperfluorescent polyps on indocyanine green angiography remains the gold standard imaging technique for the diagnosis of PCV, but it is not universally used; therefore, PCV may be misdiagnosed as choroidal neovascularization in many countries where indocyanine green angiography is not routinely used in clinical practice.[17] Several other clinical features may lead to misdiagnosis in nAMD, including retinal angiomatous proliferation, ocular hemorrhage, central serous chorioretinopathy, cystic spaces, and branch retinal vein occlusion.[26] Alternative treatment options may be available, which might improve visual and anatomical outcomes in patients with these conditions. However, there is currently a lack of published evidence on the management of patients who respond poorly to anti-VEGF treatment due to misdiagnosis of nAMD.

The Vision Academy Steering Committee recommends that the original diagnosis should be challenged in cases where there is a lack of response after the initial 3-month anti-VEGF loading phase. In such cases, thorough reassessment of the condition and appropriate intervention, as shown in Stage 3 of the treatment futility algorithm, should be made at the discretion of the physician and in line with region-specific factors. Multimodal imaging, including fluorescein angiography, indocyanine green angiography, and OCT, is key to reassessing the full extent of the condition after poor initial response to anti-VEGF treatment and/or deterioration after the loading phase.

Treatment-related complications. Complications potentially linked to treatment, such as sustained elevation of intraocular pressure, retinal detachment, tear of the retinal pigment epithelium (RPE), or large subretinal hemorrhage involving the macular center, may confound response to anti-VEGF treatment, and their presence should be considered after ascertaining an accurate diagnosis (Stage 4B).[27,28]

Intraocular pressure typically increases immediately after intravitreal anti-VEGF injection, returning to baseline levels within 30 to 60 minutes.[27,29–31] Studies have shown that sustained elevation of intraocular pressure after anti-VEGF injection occurs in around 3.5% to 12% in clinical practice, suggesting the need for close monitoring of intraocular pressure, especially in patients with nAMD and pre-existing glaucoma.[27,29,32,33] Although the precise mechanisms for sustained elevation of intraocular pressure after anti-VEGF treatment are unknown, it may occur through mechanical blockage of the trabecular meshwork or as

a result of drug-induced trabeculitis or uveitis and may require medical intervention with ocular hypotensive treatment.[27,29,32] Patients who suffer loss of central vision due to glaucoma are unlikely to benefit from further anti-VEGF treatment, and alternative intervention may be required at the discretion of the physician.

Rhegmatogenous retinal detachment is the most common type of retinal detachment, whereby fluid accumulation leads to the separation of the neurosensory retina from the underlying RPE.[34] Although the overall incidence of rhegmatogenous retinal detachment after anti-VEGF therapy is low (0%–0.67%), it may confound the ability of anti-VEGF to have a beneficial effect on the treatment of nAMD in affected patients.[27,35]

In clinical practice, RPE tears typically occur in around 0% to 5% of nAMD cases during anti-VEGF treatment,[36–40] and the risk may increase in the presence of pigment epithelial detachment (PED).[36,41,42] Similarly, in major clinical trials of aflibercept and ranibizumab, RPE tear was reported in <1% of patients with nAMD after anti-VEGF treatment; however, this lower incidence could be due to the exclusion of patients with large PEDs from entering the trials.[12,13,43] Clemens and Eter[44] provided evidence-based recommendations for the management of patients at high risk of developing RPE tear. Patients with PED at high risk of developing RPE tear were defined as showing one or more RPE tear risk factors at the beginning or during the course of anti-VEGF treatment. In such high-risk patients, it was recommended that a thorough examination should be performed after each anti-VEGF injection. If risk factors worsened or accumulated during anti-VEGF treatment, discontinuation of therapy was recommended pending re-evaluation of the PED lesion 1 to 2 weeks later; however, postponing therapy further carries the risk of progression of choroidal neovascularization.[44]

Subretinal hemorrhage is an uncommon manifestation of nAMD whereby blood from the retinal or choroidal circulation accumulates between the RPE and the neurosensory retina.[45] Large subretinal hemorrhage may result from anti-VEGF injection and cause severe visual impairment when the fovea is involved, requiring immediate intervention to reduce the risk of severe or permanent damage to vision.[45–47] Although anti-VEGF monotherapy is often advocated for the treatment of small subfoveal hemorrhages secondary to nAMD,[48] vitrectomy in combination with tissue plasminogen activator and pneumatic displacement may be necessary for the treatment of extensive subretinal lesions of short duration, based on lesion thickness, diameter, and location.[28,49] To address the lack of rigorous guidelines for the management of nAMD, the Vision Academy has issued a consensus Viewpoint article offering recommendations on defining, imaging, and treating subfoveal hemorrhage in nAMD.[50]

The Vision Academy Steering Committee recommends temporarily suspending anti-VEGF therapy when complications of such treatment arise, determined at the discretion of the physician, until those complications are adequately managed. However, in less severe cases of subfoveal hemorrhage secondary to nAMD, continuation of anti-VEGF treatment is recommended before referring the patient for alternative treatments, such as tissue plasminogen activator, pneumatic displacement, and vitrectomy.[50]

Alternative anti–vascular endothelial growth factor treatment. In cases where treatment-related complications have been considered and managed appropriately, and anti-VEGF treatment has been resumed, but a lack of functional and morphological response remains, the treatment futility algorithm states that, where possible, switching to an alternative anti-VEGF agent should be considered next (Stage 4C). When alternative anti-VEGF monotherapy is unavailable, the physician may consider combination treatment with photodynamic therapy.

Several small-scale studies have reported the potential benefits of switching anti-VEGF agents after poor response to first-line therapy.[51–54] In one study, Waizel et al[51] reported that switching from bevacizumab to either aflibercept or ranibizumab led to a significant decrease in mean central macular thickness at the final follow-up. However, mean BCVA only improved slightly at the final follow-up in both the aflibercept and ranibizumab groups, and there was no significant difference between switch treatment groups in both outcomes.[51] In a retrospective case series of 94 patients with nAMD, 68 of whom were refractory to previous bevacizumab or ranibizumab treatment (categorized by the presence of persistent intraretinal and/or subretinal fluid despite monthly injections), Yonekawa et al[52] reported visual and anatomical outcomes with switching to aflibercept treatment. In refractory patients, stabilization of visual acuity was reported after one aflibercept injection and at the final follow-up compared with visual acuity before switching to aflibercept ($P = 0.897$ and $P = 0.215$, respectively); however, significant improvements in mean central macular thickness compared with before switching were reported at these endpoints ($P < 0.001$ for both time points).[52] The lack of correlation between visual and anatomical outcomes was attributed to the fact that these patients had received a mean of 20 previous monthly injections of bevacizumab or ranibizumab and yet had continuous exudation.[52] More recently,

Spooner et al[53] systematically reviewed outcomes after switching from bevacizumab or ranibizumab to aflibercept in patients with treatment-resistant nAMD; a total of 28 publications, predominantly made up of small-scale retrospective studies, were included in the review. Although the pooled results did not reveal a significant change in BCVA from baseline to Month 6 (mean increase of 1.11 ETDRS letters; 95% confidence interval, −0.25 to 2.46; $P = 0.11$) and Month 12 (mean increase of 0.63 ETDRS letters; 95% confidence interval, −0.26 to 1.52; $P = 0.17$), significant reductions were observed in central retinal thickness height from baseline at Month 12 (mean reduction of 50.00 μm; 95% confidence interval, −63.20 to −36.80; $P < 0.001$) and PED height at Month 6 (mean reduction of 51.20 μm; 95% confidence interval, −55.10 to −47.40; $P < 0.001$) after switching to aflibercept.[53] The findings from these studies suggest that switching to aflibercept monotherapy may maintain or improve visual and anatomical outcomes, with the potential to reduce the treatment burden through a need for fewer intravitreal injections or by extending injection intervals in patients with nAMD who had poor previous response to other anti-VEGF agents.[52,53] However, because of generally small sample sizes, variability in design, and the retrospective nature of the studies included in the Spooner et al[53] meta-analysis, the ability to draw robust conclusions from these data is somewhat limited. When interpreting data from studies of patients switching anti-VEGF agents, it is important to note that without a randomized control group, it is not possible to accurately compare the effects of switching treatments with the effects of continuing the original treatment.[55] In small-scale studies, without a comparison group, it is not clear whether any improvements observed after switching anti-VEGF agents are related to the new treatment, or if, in fact, they represent regression to the mean or to time effects.[55] There remains a lack of evidence from large-scale clinical trials to support switching to alternative anti-VEGF agents.

In some patients who respond poorly to anti-VEGF treatment (e.g., patients with PCV), combination therapy may be beneficial.[17,25] In patients with treatment-naïve PCV, combination treatment with bevacizumab and photodynamic therapy resulted in improved BCVA for up to 12 months, as compared to photodynamic therapy alone,[56] and combination therapy also demonstrated increased benefit over anti-VEGF monotherapy in patients with macular PCV.[57]

Where possible, the Vision Academy Steering Committee recommends switching to an alternative anti-VEGF agent in patients with nAMD who are showing poor functional and morphological responses to treatment with one anti-VEGF agent, where diagnosis has been confirmed and all possible confounding factors to anti-VEGF treatment have been considered and appropriately managed. When switching to an alternative anti-VEGF agent, the treatment should be proceeded through Stages 1 and 2 of the treatment futility algorithm at the discretion of the physician and in line with region-specific factors. When alternative anti-VEGF monotherapy is unavailable, the physician may consider combination treatment with photodynamic therapy.

Treatment pause. If use of an alternative anti-VEGF agent does not improve response to treatment, or if it is not possible to switch to an alternative anti-VEGF agent because of reimbursement or other region-specific issues, implementation of a "treatment pause" (or "treatment-free interval") should be considered (Stage 4D). During a treatment pause, anti-VEGF therapy is temporarily suspended for a predetermined period of time, at the discretion of the physician, to assess whether pharmacologic treatment is having any effect on visual and anatomical outcomes. If there is noticeable worsening of visual or anatomical outcomes after an extended period of treatment being withheld, it can be presumed that the drug was having an effect and should therefore no longer be suspended. Careful observation during a treatment pause could also determine whether there was short-term benefit to anti-VEGF treatment, as previously discussed when identifying maximal therapy.

The Vision Academy Steering Committee recommends that a 1-month treatment pause followed by monthly monitoring visits for up to 6 months is an appropriate protocol for temporarily suspending anti-VEGF therapy in a patient with nAMD showing poor or no response to previous treatment. If the patient shows noticeable deterioration of visual or anatomical outcomes when observing a treatment pause, reinitiation of optimal anti-VEGF therapy is recommended at the discretion of the physician and in line with region-specific factors.

Stage 5: Establish Anti–Vascular Endothelial Growth Factor Futility

If Stages 1 to 4 of the treatment futility algorithm have been followed but there is still a poor response to treatment when it is administered in a correct and timely fashion, the patient may be considered to be a nonresponder to anti-VEGF therapy and treatment futility may be established (Stage 5).

The Vision Academy Steering Committee recommends that anti-VEGF therapy should be suspended in patients with nAMD who are classed as

nonresponders based on use of the treatment futility algorithm. Continued monitoring at follow-up visits is recommended at the discretion of the physician. Investigation of the potential for reintroduction of anti-VEGF therapy in patients for whom previous treatment was considered to be futile may be of benefit to the ophthalmic community. Similarly, there may be an interest in exploring the concept of anti-VEGF treatment "success" and determining the circumstances of those cases where suspension of treatment may be appropriate.

Conclusion

On behalf of the Vision Academy Steering Committee, this publication summarizes recommendations on the treatment of patients with nAMD who respond poorly to anti-VEGF therapy. A treatment futility algorithm was developed to help clinicians explore the causes of poor response to anti-VEGF treatment in patients with nAMD, and to guide adjustment of the retreatment protocol where appropriate. Consideration of factors that may cause suboptimal response to anti-VEGF therapy, such as insufficient administration of injections or misdiagnosis of the underlying condition, and factors that may restrict continued treatment, such as injection- or drug-induced complications that require immediate attention, is a necessary step in adjusting the treatment protocol. If poor response to treatment persists after switching to alternative anti-VEGF agents and implementing a "treatment pause" (where appropriate), anti-VEGF treatment may be considered futile, at which point the Vision Academy Steering Committee recommends that treatment should be suspended. This treatment futility algorithm is based on currently available evidence; however, there remains a lack of high-level evidence on the management of patients with nAMD who are unresponsive to anti-VEGF therapy. Further investigation is warranted to determine the most appropriate retreatment protocol in patients with nAMD who respond poorly to anti-VEGF therapy, and for the continued management of patients for whom anti-VEGF therapy is considered to be futile.

Key words: AMD, anti-VEGF, neovascular age-related macular degeneration, treatment futility, Vision Academy.

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Appendix 1. Vision Academy Steering Committee

Members of the Vision Academy Steering Committee advised on the initial publication concept, and this manuscript is based on their discussions around the subject area. The Vision Academy Steering Committee is a global group of ophthalmologists, convened by Bayer to share best practice and knowledge and to lead the wider community in the drive toward optimized patient care. The Vision Academy Steering Committee comprises the following members: Bora M. Eldem, Hacettepe University, Ankara, Turkey; Alex P. Hunyor, University of Sydney, Australia; Antonia Joussen, Charité—Universitätsmedizin Berlin, Germany; Adrian Koh, Eye & Retina Surgeons, Camden Medical Centre, Singapore; Jean-François Korobelnik, University Hospital of Bordeaux, France; Paolo Lanzetta, University of Udine, Italy; Anat Loewenstein, Tel Aviv Sourasky Medical Center, Israel; Monica Lövestam-Adrian, Lund University Hospital, Sweden; Rafael Navarro, Instituto de Microcirugía Ocular, Barcelona, Spain; Annabelle A. Okada, Kyorin University, Japan; Ian Pearce, Royal Liverpool University Hospital, UK; Francisco J. Rodríguez, Fundación Oftalmológica Nacional, Bogotá, Colombia; Sebastian Wolf, Inselspital, Bern, Switzerland; David T. Wong, University of Toronto, ON, Canada.