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REVIEW

Discontinuing Anti-VEGF Therapy in Patients with Neovascular Age-Related Macular Degeneration That Remains Inactive with Treatment at the Maximum Injection Interval

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Abstract: This review aims to provide guidance on the management of patients with neovascular age-related macular degeneration (nAMD) whose disease becomes inactive on anti-vascular endothelial growth factor (VEGF) treatment. The Vision Academy's membership of international retinal disease experts reviewed the literature and developed consensus recommendations and an algorithm to determine the appropriate timing of treatment suspension and a post-treatment follow-up strategy for appropriate patients with nAMD who achieve a good response to anti-VEGF therapy. Patients with inactive disease (defined as absence of both intraretinal and subretinal fluid, absence of deterioration in vision, and absence of new retinal hemorrhage) for at least three consecutive maximum treatment intervals as outlined in the clinic's protocol may be considered for treatment exit. However, in patients with stable disease that remains active and those with only one good seeing eye and a history of disease recurrence, treatment continuation may be preferred. An appropriate interval for continued monitoring with optical coherence tomography and visual acuity testing should be decided following discussion with the patient and consideration of patient-specific factors. This article presents consensus guidelines for nAMD management in patients who respond well to anti-VEGF therapy, and for the discontinuation of treatment in cases of success.

Keywords: intravitreal injections, inactive disease, treatment discontinuation, treatment success

Introduction

Neovascular age-related macular degeneration (nAMD) is a condition that causes significant and progressive vision loss.[1,2] Monthly or bi-monthly anti-vascular endothelial growth factor (VEGF) injections have been proven to improve functional and anatomical results in patients with nAMD in pivotal studies.[3–5] However, there are large, inter-individual variations in anti-VEGF drug response, in terms of both functional and morphological characteristics.[6] Anti-VEGF therapeutic response has been shown to be influenced by a number of parameters, including patient age, lesion features, lesion duration, baseline visual acuity, and the existence of certain genetic risk alleles.[6] To alleviate the treatment burden, customized treatment regimens were designed to minimize the number of required clinic visits and injections.[5,7] In personalized approaches where treatment is largely of a dry retina, there may be uncertainty over whether disease is

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considered stable or inactive and hence whether anti-VEGF medication should be discontinued in cases of functional and morphological stability.

The Vision Academy previously established guidelines for the suspension of anti-VEGF medication in cases of futility, where patients with nAMD do not respond well to anti-VEGF treatment.[8] The purpose of the present article is to examine the rationale for discontinuing anti-VEGF medication in patients who have responded favorably to treatment, and to provide guidelines for case selection and strategies for monitoring after discontinuation of therapy.

Methods

This article is based on a review of the literature and consensus among retinal experts from the Vision Academy. The Vision Academy comprises an international group of over 80 retinal physicians who work together to share skills and knowledge and to provide recommendations, based on their collective clinical expertise, on clinical challenges in areas where there is a lack of conclusive evidence in the literature (www.visionacademy.org).

Two comprehensive literature searches were performed using the PubMed database (from December 22, 2008, to March 17, 2026) to identify articles published in English that investigated exit from intravitreal anti-VEGF treatment regimens in patients with nAMD who had responded well to therapy. The search strategy is summarized in Table 1. A single reviewer (GS) screened titles and abstracts for eligibility. Articles discussing studies with treatment discontinuation were selected for review. An algorithm including criteria for the suspension of anti-VEGF treatment in patients with nAMD with successful outcomes (Figure 1) was developed based on the findings of the literature search and the collective expertise of the authors. The recommendations contained within the algorithm were subsequently reviewed, commented upon, and endorsed by a majority of the Vision Academy membership before finalization. Vision Academy members were asked to rate their agreement with the proposed recommendations using the options "strongly agree", "agree", "neither agree nor disagree", "disagree", and "strongly disagree". Responses from more than 50% of members were required for the survey to be valid. Respondents were also asked for the reimbursement status of treatment in their country of practice (ie, mostly reimbursed or mostly out of pocket) to determine whether this may have influenced their responses. Biases were assessed using χ^2. Endorsement was considered "strong" if 75% or more of respondents indicated that they agreed or strongly agreed with a recommendation. The list of Vision Academy members who contributed to the recommendations is provided at the end of the article.

Results

The optimal exit strategy for suspending treatment in patients with inactive nAMD is unclear. In this article, the Vision Academy aims to provide guidance for treatment exit with a preplanned follow-up strategy in patients with successful treatment responses in order to prevent potentially unnecessary lifelong treatment. Response to treatment is generally considered good if the disease is inactive, as defined in the "Disease activity, stability, and inactivity criteria" section below.

Table 1 Search Terms and Search Strategy

	Search Terms
Health condition	(age-related macular degeneration OR AMD OR neovascular age-related macular degeneration OR nAMD OR macular degeneration AND wet) OR polypoidal choroidal vasculopathy OR PCV OR choroidal neovascularization* *Major MeSH terms to be included
	AND
Intervention	Anti-VEGF OR anti-vascular endothelial growth factor OR bevacizumab or ranibizumab OR aflibercept OR brolucizumab OR angiogenesis inhibitors
	AND
Treatment protocol/outcome	Treat-and-extend OR TAE OR T&E OR treat–extend–stop OR TES OR pro re nata OR PRN OR exit strategy OR choroidal neovascularization inactivity OR CNV inactivity OR inactive choroidal neovascularization OR inactive CNV OR treatment success OR treatment cessation OR quarterly OR every 3 months

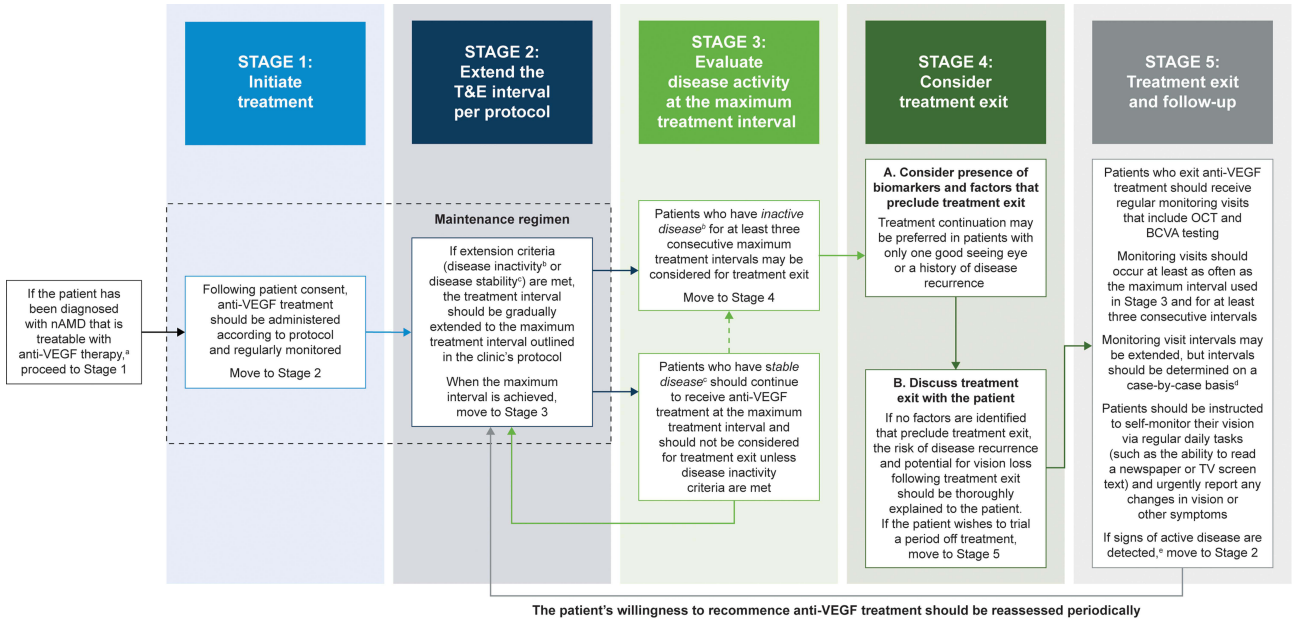

Figure 1 Algorithm for considering treatment exit in patients with nAMD who respond well to anti-VEGF therapy.
Note: [a]The patient must have unilateral or bilateral nAMD in the eye in question; [b]Disease inactivity is defined as the absence of IRF and SRF attributable to VEGF activity, absence of deterioration in vision attributable to MNV activity, and absence of new retinal hemorrhage attributable to MNV activity; [c]Disease stability is defined as no fluid or a small amount of persistent residual SRF without a further decrease, despite adequate regular injections, until maximal anatomic effect (with at least an initial three monthly injections during the induction phase). In this case, and only in the absence of any other signs of disease activity, the disease can be considered stable and the treatment interval maintained or cautiously increased; [d]An appropriate interval for continued monitoring should be decided after careful discussion of risk profile and visual potential of the affected eye and the fellow eye, at the physician's discretion; [e]Disease activity is defined as the presence of IRF and/or SRF attributable to VEGF activity, deterioration in vision attributable to MNV activity, presence of new retinal hemorrhage attributable to MNV activity, and/or an increasing amount of SRF/IRF despite regular injections.
Abbreviations: BCVA, best corrected visual acuity; IRF, intraretinal fluid; MNV, macular neovascularization; nAMD, neovascular age-related macular degeneration; OCT, optical coherence tomography; SRF, subretinal fluid; T&E, treat-and-extend; VEGF, vascular endothelial growth factor.

Disease Activity, Stability, and Inactivity Criteria

Anti-VEGF treatments are beneficial in nAMD; however, not all patients benefit in the same way in terms of functional and morphological results. Measurement of treatment response using both visual function and morphological indicators assessed with optical coherence tomography has been used in pivotal studies.[6,7,9,10]

The Vision Academy has recently published recommendations on how to define disease activity, stability, and inactivity that take account of evidence from large clinical trials regarding the impact of different types of residual retinal fluid on treatment outcomes (Table 2). According to these recommendations, inactive disease is defined as the absence of all of the following: intraretinal fluid and subretinal fluid attributable to VEGF activity; deterioration in vision attributable to macular neovascularization activity; and new retinal hemorrhage attributable to macular neovascularization activity.[11] Treatment exit should be considered only in cases of inactive age-related macular degeneration, with treatment continuation being advised in cases of stable disease.[12–14]

Treatment Regimens, Maximum Re-Treatment Intervals, and Exit Criteria

While the extension and reduction of treatment intervals are clearly characterized in published research, there is much controversy regarding the maximum treatment interval, and evidence of the effects of exit strategies when treating patients using a treat-and-extend (T&E) protocol is limited. In pro re nata (PRN; "as needed") trials, the number of injections required in a particular period of time varied significantly among patients.[5,9] Different maximum treatment intervals and treatment protocols have been used for stability requirements in investigations where a treatment exit was envisaged (Table 3). Several studies used disease stability at three consecutive 12- or 16-week treatment intervals as the criterion for discontinuing anti-VEGF treatment (Table 3).[12,15–17]

Menke et al[18] reported the outcome of patients with exudative age-related macular degeneration who met the exit criteria of the Bern treatment regime. Patients with no disease activity after the loading phase received fixed injections

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Table 2 Vision Academy Definitions of nAMD Disease States[11]

nAMD Disease State	Criteria
Inactive disease	• Absence of IRF and SRF attributable to VEGF activity • Absence of deterioration in vision attributable to MNV activity • Absence of new retinal hemorrhage attributable to MNV activity
Stable disease	• No fluid or a small amount of persistent residual SRF without a further decrease following adequate regular injections until maximal anatomic effect (with at least three monthly injections during the induction phase) ○ In this case, and only in the absence of any other signs of disease activity, the disease might be considered stable and the treatment interval maintained or cautiously increased
Active disease	The above states not being met, ie: • Presence of IRF and/or SRF attributable to VEGF activity • Deterioration in vision attributable to MNV activity • Presence of new retinal hemorrhage attributable to MNV activity • Increasing amount of SRF and/or IRF despite regular injections

Abbreviations: IRF, intraretinal fluid; MNV, macular neovascularization; nAMD, neovascular age-related macular degeneration; SRF, subretinal fluid; VEGF, vascular endothelial growth factor.

every 3 months for the first year of follow-up, then fixed injections at 6 and 12 months in the second year of follow-up, before therapy was stopped (Table 3).

Several studies have investigated anti-VEGF treatment exit following T&E regimens in patients with nAMD (Table 3). Adrean et al[15] found that 37.3% of eyes met the criteria for discontinuing therapy (a dry macula at three consecutive 12-week visits) after an average of 27 months of follow-up, while disease recurrence was reported in 29.4% of eyes after an average of 14 months (range: 4–42 months). Similarly, Garay-Aramburu et al[19] discontinued therapy in 31.9% of their patients after inactivity following three consecutive 12-week injections. They have observed relapse of the membrane in 42% of these patients in a 4-year follow-up. Arendt et al[16] and Jaggi et al[17] gradually extended the treatment interval in patients who were stable after a loading dose, and reported that patients met the exit requirements at three consecutive 16-week intervals, with disease recurrences observed in 13% and 28%, respectively. Amarakoon et al[20] evaluated recurrence rates at 1 year after treatment cessation in patients who had been treated with fixed-interval dosing (4, 6, or 8 weeks), finding an overall reactivation rate of 67% with a mean time to recurrence of 4.28 ± 0.29 months, regardless of the previous injection frequency. The patients included in these studies were treated with bevacizumab, ranibizumab, or aflibercept, and the maximum treatment interval or treatment cycle was not determined by the specific agent used.[15–17] In the era of second-generation anti-VEGF agents, a 2-year prospective study by Yoshida et al[21] showed that 47% of eyes discontinued treatment after reaching a 16-week interval twice and a recurrence rate of 5.6% was observed during the 1-year follow-up period. Thus, between-study variations in the rates of disease recurrence may not be attributable solely to differences in maximal treatment intervals, with other factors potentially also playing a role.

Exit criteria and outcomes in studies where anti-VEGF treatment for nAMD was stopped are listed in Table 3. With most of the studies following a T&E protocol, only two have followed or incorporated a PRN regime. A retrospective study by Madhusudhana et al[22] followed a PRN protocol and reported that a high proportion of patients required re-treatment after treatment cessation, and a study by Menke et al[18] used a capped PRN protocol and reported a low proportion of patients meeting exit criteria. A study by Arendt et al,[16] employing a T&E regimen, observed a higher proportion of patients achieving the exit criteria (Table 3) compared to the findings from Menke et al.[18] Arendt et al suggested that this difference between the T&E and PRN studies may have been due to possible undertreatment in the PRN study with more disease recurrences; this, in turn, may have resulted in a lower likelihood of patients on a PRN regimen reaching the predefined exit criteria. However, Liu et al[23] reported no significant disparity in the rates of long-term remission or the incidence of recurrence between patients managed with PRN vs. T&E protocols.

Biomarkers to Guide Treatment Exit

Studies have been reported of several morphological and demographic prognostic indicators that can predict response to therapy in nAMD.[24] Patients with posterior vitreous detachment require significantly fewer injections than those with

Table 3 Exit Criteria and Outcomes in Studies Where Anti-VEGF Treatment for nAMD Was Discontinued

Study	Disease Activity Criteria	Exit Strategy	Findings	Reference
Retrospective study of 385 eyes (321 patients) with nAMD and CNV receiving anti-VEGF agents on a treat–extend–discontinue protocol between 2008 and 2016	• Treatment response defined as a decrease in fluid or an increase in visual acuity • Inadequate response defined as increasing fluid, decreasing vision, or both, related to CNV	• Maximum treatment interval: 12 weeks • Anti-VEGF injections every 4–5 weeks for ≥3 injections until the macula was dry • Treatment interval gradually increased by 1–2 weeks if the macula remained dry • Treatment discontinued if the macula was dry at the third 12-week visit	• 37.3% of eyes met the exit criteria • Average follow-up: 27 months • CNV recurred in 29.4% of eyes after a mean interval of 14 months (range: 4–42 months) • 54.8% of which recurred in the first year and 26.2% recurred in the second year after treatment cessation	Adrean et al[15]
Retrospective study of 191 treatment-naïve patients with nAMD treated with bevacizumab, ranibizumab, or aflibercept on a T&E regimen between 2014 and 2017	• Treatment intervals were extended in the absence of SRF or IRF	• Maximum treatment interval: 12 weeks • Anti-VEGF injections every 4–5 weeks for ≥3 injections until the macula was dry • Treatment interval was gradually increased by 1–2 weeks if stable • Treatment was discontinued if the macula was dry at the third 12-week visit	• Treatment discontinued in 69 (31.9%) eyes • Patients followed for 4 years • Relapse of membrane in 29 (42%) of discontinued eyes • The presence of membrane activity at 36 months and baseline BCVA >61 letters were independent predictors of recurrence	Garay-Aramburu et al[19]
Retrospective study of 598 eyes (488 patients) with nAMD receiving ranibizumab or aflibercept on a T&E regimen until 2016	• Stable disease defined as: ○ No evidence of intra-RPE, sub-RPE, or sub-RPE fluid on OCT ○ SRF below the fovea <50 μm and no change in sub-RPE and sub-RPE fluid ○ Stable visual acuity at the third consecutive examination (within five ETDRS letters on any of the last three visits)	• Maximum treatment interval: 16 weeks • Patients received a second anti-VEGF injection 4 weeks after the first injection, and treatment interval was extended by 2 weeks if stable disease was present • If disease remained stable at three consecutive 16-week intervals, treatment was discontinued	• 17% of eyes met the exit criteria • 13% of eyes recurred after a mean period of 37 ± 16 weeks (mean ± SD)	Arendt et al[16]
Study of 105 patients with nAMD receiving aflibercept on a T&E regimen between 2017 and 2019	• Disease activity was defined as hemorrhage, intraretinal macular edema, or SRF on OCT	• Maximum treatment interval: 12 weeks • Patients received three monthly aflibercept injections followed by a T&E regimen with extensions of 2 weeks if no signs of disease activity • Patients without any evidence of disease activity on three consecutive 12-week visits, BCVA between 35 and 88 letters, and near vision of ≥24 points were eligible for treatment exit	• 52.9% of patients had recurrence of nAMD after 12 months of follow-up • Mean time to recurrence after the last injection was 6.7 ± 2.2 months	Aslanis et al[12]
Retrospective study of 321 patients with wet AMD receiving bevacizumab on a T&E regimen between 2012 and 2014	• CNV activity defined as SRF, IRF, and intraretinal or subretinal hemorrhage related to exudative AMD	• Maximum treatment interval: 12 weeks • Patients were treated until no signs of CNV activity were present and visual acuity was stable before treatment was extended by 1- to 2-week intervals • Patients who were stable on 12-week treatment intervals were either maintained at this interval or discontinued anti-VEGF therapy	• Eight eyes discontinued bevacizumab treatment after a 12-week extension interval • 63% had recurrence at an average of 4 months after discontinuing therapy	Hwang et al[14]
Retrospective study of 82 patients with nAMD receiving aflibercept on a T&E regimen between 2014 and 2016	• Stable lesions defined as at least one of the following required: • No evidence of any IRF or SRF or sub-RPE fluid on OCT • SRF <50 μm and/or present sub-RPE fluid, no IRF, and no change in SRF and sub-RPE fluid, with stable BCVA at the third consecutive visit	• Maximum treatment interval: 16 weeks • Patients received a second anti-VEGF injection 4 weeks after the first injection, and treatment interval was extended by 2 weeks if disease was stable • If disease remained stable at three consecutive 16-week intervals, treatment was discontinued	• 35% of patients met the exit criteria • 28% of patients recurred and therapy was resumed at 52.24 ± 25.9 weeks (mean ± SD) • 62% of exit patients were followed up without recurrence until year 4	Jaggi et al[17]

(*Continued*)

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Table 3 (Continued).

Study	Disease Activity Criteria	Exit Strategy	Findings	Reference
Retrospective study of 12,951 eyes (11,135 patients) with nAMD assessing time to re-treatment in eyes that had been treatment-free for intervals of 3–12 months during the maintenance phase of ranibizumab therapy	• Disease activity defined as persistent retinal, SRF, or sub-RPE fluid or hemorrhage as determined clinically and/or on OCT, lesion growth on fundus autofluorescence, and/or deterioration of vision	• After a loading phase of three monthly intravitreal injections, patients received PRN treatment if disease activity was present	• After treatment-free intervals of 3, 6, 9, and 12 months, 68%, 44%, 31%, and 21% of eyes, respectively, required re-treatment after a further 6 months of follow-up • After 12 months of follow-up, 77%, 56%, 43%, and 34% of eyes from the above groups required re-treatment	Madhusudhana et al[22]
Retrospective study of 575 patients with nAMD receiving ranibizumab on a fixed treatment regimen between 2008 and 2013	• Active CNV was defined as loss of ≥5 letters on the ETDRS chart (not due to atrophy or scar formation), abnormal retinal thickness on OCT with signs of IRF or SRF, or new retinal hemorrhage	• Patients treated PRN after three monthly loading doses • In case of no disease activity, patients received fixed injections every 3 months for 1 year. In year 2 without disease activity, two further injections were given after 6 and 12 months before treatment was discontinued	• 2.6% of patients receiving ranibizumab met the exit criteria	Menke et al[18]
Study of 122 eyes with newly diagnosed or newly active nAMD who were followed after initiating treatment with anti-VEGF therapy for ≥1 year	• Treatment intervals were extended in the absence or near absence of fluid, hemorrhage, or a decline in vision	• Patients received three consecutive monthly injections followed by extension of intervals by 2 weeks at each visit in the absence of disease activity • Patients who achieved 12-week intervals had their treatment suspended and entered a PRN phase (treat–extend–suspend–monitor protocol) • Successful suspension of treatment was defined as no requirement for treatment on three consecutive visits following treatment cessation (≥30 weeks)	• Treatment was discontinued for ≥30 weeks in 32 patients (31%), 44 of the 102 eyes studied (43%) • At year 2, treatment was discontinued in 25 of 65 patients (38%) • 22 patients were followed up for a minimum of 2 years after treatment suspension. Of these patients, 16 (73%) remained off treatment at the end of year 2. 13/15 (87%) patients off treatment at the end of year 2 remained off treatment at the end of year 3	Cao et al[25]
Study of 49 treatment-naïve patients receiving aflibercept or ranibizumab on a T&E protocol	• Evidence of retinal exudative change on SD-OCT ○ New retinal hemorrhage ○ Presence of IRF and/or SRF ○ Enlargement in pigment epithelial detachment	• Three monthly anti-VEGF injections • Treatment interval gradually increased by 1–2 weeks when there was no evidence of retinal exudative change • Treatment discontinued if the macula was dry at the 12-week visit	• Recurrence rates were 33% at the first year and 48% at the second year of treatment cessation • Out of the recurrences, two patients lost two lines of vision despite restarting treatment	Hirata et al[13]
Prospective study of 191 patients with nAMD randomly assigned to intravitreal bevacizumab injections every 4, 6, or 8 weeks for 1 year	• CNV activity defined as SRF, IRF, and sub-RPE fluid related to exudative AMD	• A patient with no active CNV after 1 year was instructed about self-monitoring and routinely scheduled for a review every 3 months	• 91 (58%) patients met the exit criteria • 61 (67%) patients needed re-treatment for active CNV within the first year after discontinuation of treatment (mean 4.28 ± 0.29 months)	Amarakoon et al[20]
Prospective study of 53 patients treated with brolucizumab using a modified T&E regimen that included a loading phase	• Stable lesions defined as complete resolution of IRF or SRF, absence of new hemorrhage, and no difference in PED	• Three monthly injections • Fourth injection 2 months after if disease was active, 3 months after if macula was dry • Injection intervals increased 4 weeks at a time • If patients achieved an interval of 16 weeks twice, the treatment was discontinued	• 38 (71%) patients completed the 2-year observation period • 18 (47%) could discontinue the T&E regimen at a median of 13.1 (12.9–16.8) months	Yoshida et al[21]
Retrospective study of 68 treatment-naïve patients with nAMD who received intravitreal injections of ranibizumab or aflibercept under a modified T&E regimen	• Recurrence was defined as the presence of a new retinal hemorrhage, IRF, or SRF, or enlargement of PED	• Loading dose of three-monthly injections • Initial treatment interval was determined based on the interval at which the first signs of recurrence occurred • Patients were treated until no signs of CNV activity were present, and visual acuity was stable before treatment was extended by 1- to 2-week intervals • Treatment was suspended after a 24-week disease-free interval	• Recurrence rates were 22.2%, 42.2%, and 54.4% at 1-, 2-, and 3-year follow-ups, respectively, with a median time to recurrence of 16 months	Lee et al[26]

Abbreviations: AMD, age-related macular degeneration; BCVA, best corrected visual acuity; CNV, choroidal neovascularization; ETDRS, Early Treatment Diabetic Retinopathy Study; IRF, intraretinal fluid; nAMD, neovascular age-related macular degeneration; OCT, optical coherence tomography; PED, pigment epithelial detachment; PRN, pro re nata ("as needed"); RPE, retinal pigment epithelial; SD, standard deviation; SD-OCT, spectral domain optical coherence tomography; SRF, subretinal fluid; T&E, treat-and-extend; VEGF, vascular endothelial growth factor.

vitreomacular adhesion, and also meet the treatment exit criteria more frequently. Also, patients with an epiretinal membrane have a lower likelihood of achieving treatment-free disease stability than patients without an epiretinal membrane[27] (Table 4).

In a post hoc analysis of the results of the VIEW 1 and VIEW 2 studies, patients with baseline pigment epithelial detachment were less likely to achieve improvement in visual acuity from baseline, and were more likely to experience disease reactivation when switched from a fixed-dose regimen to a flexible-dose regimen.[28,29] Several studies have also implicated the presence of serous pigment epithelial detachment in increased risk of disease recurrence in patients exiting anti-VEGF treatment (Table 4), suggesting that serous pigment epithelial detachment may be a helpful imaging marker for risk stratification when considering discontinuation of anti-VEGF treatment.[12,16]

Post-Exit Follow-Up and Recurrence

In cases of planned suspension of a treatment regimen, the follow-up approach should be properly managed, with the goal of detecting any prospective recurrences in a timely manner while limiting unnecessary visits. Numerous studies have examined the rates of recurrence of disease in patients with nAMD following stabilization across maximum treatment intervals (Table 3).

In a study by Hwang et al,[14] patients were offered the option of continuing bevacizumab maintenance treatment at 12-week intervals or undergoing a trial off treatment. Recurrence was evident in 63% of eyes after an average of 4 months (16 weeks) since discontinuing maintenance therapy (Table 3).

Aslanis et al[12] reported evidence of nAMD recurrence in 52.9% of patients who discontinued T&E aflibercept injections on achieving disease stability (Table 3), with a mean time to recurrence of 6.7 ± 2.2 months. In 85.2% of these patients, the recurrence occurred during the first 8 months of follow-up.[12] Hirata et al[13] reported nAMD recurrence rates of 33% in the first year and 48% in the second year after cessation of treatment with aflibercept or ranibizumab in patients receiving treatment under a T&E protocol where treatment intervals were extended to over 12 weeks (Table 3).

A study using a national UK database assessed time to re-treatment in eyes with nAMD treated with ranibizumab.[22] Following the treatment-free intervals of 3, 6, 9, or 12 months and a further 6 months of follow-up, 68%, 44%, 31%, and 21% of eyes, respectively, needed re-treatment.[22]

Adrean et al[15] investigated the disease recurrence rates in a treat–extend–discontinue paradigm where therapy was discontinued at the third 12-week visit until recurrence, which was reported in 29.4% of eyes after a mean interval of 14 months (range: 4–42 months; Table 3). Arendt et al[16] and Jaggi et al[17] established a 16-week maximum treatment interval following a T&E regimen and permitted patients to discontinue therapy after three consecutive injections at the maximum interval. Disease recurrence was reported in 13% of eyes after 37 ± 16 weeks (mean ± standard deviation) in the study by Arendt et al, and in 28% of patients after 52.24 ± 25.9 weeks in the study by Jaggi et al, respectively (Table 3). In a long-term real-world analysis with a mean follow-up of 8.1 ± 3.4 years, Cho et al[30] reported that while 66% of eyes eventually met the criteria for treatment discontinuation, 66.8% of those eyes with initial stable responses subsequently experienced disease recurrence. Although the median time to reactivation was 3.3 years, late-onset recurrences were observed up to 10 years after treatment cessation. In a study by Lee et al[26] recurrence rates at 1, 2, and 3 years of follow-up were 22.2%, 42.2%, and 54.4%, respectively, after a T&E protocol with a maximum treatment interval of 24 weeks. While disparities in recurrence rates cannot be directly linked to differences in maximum treatment intervals, they should be taken into account.

In two of the trials with a defined exit strategy, a follow-up time of 3–4 months was designated following the cessation of medication.[16,27] Adrean et al[15] used a more stepwise follow-up technique with patients followed up for 4 weeks after discontinuation and examined again in a progressive method, extending the follow-up duration by 2 weeks at a time until it reached 12 weeks. Patients were then followed up at 3-monthly intervals.[15] In a study by Garweg et al,[31] patients with stable disease opted to either continue treatment at intervals of 12–14 weeks or discontinue treatment and attend follow-up visits every 8–12 weeks. Recurrent disease was observed in both groups, with the time from the achievement of stable disease to recurrence being comparable between the two strategies.[31]

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Table 4 Biomarkers for Anti-VEGF Treatment Exit and Disease Recurrence

Study	Biomarker	Findings	Reference
Retrospective study of 593 eyes (498 patients) with nAMD receiving a T&E regimen between 2014 and 2015	Vitreomacular interface configuration and presence of an ERM	• Patients with PVD required significantly fewer injections (mean: 10.6 ± 5.9) than those with VMA (mean: 12.6 ± 6.7; p=0.0008) • Eyes with PVD at baseline were 9.2 times more likely to meet the exit criteria than eyes with VMA • Eyes without an ERM were 11.4 times more likely to meet the exit criteria than eyes with an ERM	Munk et al[27]
Retrospective study of 598 eyes (488 patients) with nAMD receiving ranibizumab or aflibercept on a T&E regimen until 2016	PED	• Patients with PED and serous PED at treatment termination comprised a significantly higher proportion of recurrent cases than those without: 77% vs. 30% (p=0.0018) and 31% vs. 7% (p=0.0247), respectively	Arendt et al[16]
Study of 105 patients with nAMD receiving aflibercept on a T&E regimen between 2017 and 2019	PED	• Recurrence within 12 months was 74% in patients with PED at baseline versus 48% in patients without PED (p<0.05)	Aslanis et al[12]
Retrospective study of 392 patients with nAMD receiving ranibizumab or aflibercept with three loading doses and a PRN regimen between 2016 and 2019	PED	○ 58 (14.8%) eyes showed no exudative recurrence and did not require additional anti-VEGF injections at 2-year follow-up ○ Absence of fibrovascular PED (odds ratio 1.349; p=0.028) was associated with higher odds of no recurrence	Cho et al[32]

Abbreviations: ERM, epiretinal membrane; nAMD, neovascular age-related macular degeneration; PED, pigment epithelial detachment; PVD, posterior vitreous detachment; T&E, treat-and-extend; VEGF, vascular endothelial growth factor; VMA, vitreomacular adhesion.

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Other Considerations for Treatment Exit

Numerous papers demonstrate an increased risk of intraocular hemorrhagic consequences in individuals with nAMD who are using antiplatelet or anticoagulant medicines. Kiernan et al[33] reported an annual incidence of combined subretinal and vitreous hemorrhage of 0.009% in patients receiving daily antiplatelet or anticoagulant drugs and 0.001% in patients not receiving them. Additionally, Kuhli-Hattenbach et al[34] reported that patients receiving antithrombotic medication had considerably greater subretinal hemorrhages (mean: 9.71-disc areas) than those who did not. While the evidence is limited concerning possible complications of antiplatelet or anticoagulant medications in patients with nAMD, their risks should be considered before treatment exit.

Treatment continuation may be preferred in patients with the only eye that is being treated, especially if the vision loss of the contralateral eye has been secondary to undertreatment or subretinal fibrosis.

Discussion and Vision Academy Recommendations

There is a lack of guidance on the criteria for determining when discontinuation of anti-VEGF treatment should be considered for patients with nAMD who have responded favorably to therapy. Based on a review of the published literature and our collective experience, we propose a five-stage algorithm to assist ophthalmologists in identifying patients who may be candidates for treatment discontinuation (Figure 1).

The recommendations listed below were formulated by the authors and submitted to the entire Vision Academy membership for endorsement; 72 responses (including from the authors) were received. Overall, the recommendations were endorsed by 92.4% of the respondents (a response of "agree" or "strongly agree"), with the level of endorsement for each individual recommendation ranging from 84.7% to 98.6%. The mean rate of non-endorsement was 7.72% (1.4–31.9%) for a response of either "disagree" or "strongly disagree" and 3.24% (0–5.6%) for a response of "neither agree nor disagree". One recommendation was not endorsed (<75% of respondents selected "agree" or "strongly agree") and was subsequently revised based on the feedback and submitted to the authors and the Vision Academy Steering Committee for re-endorsement. It should be noted that these recommendations represent the ideal scenario, and full implementation may not be possible in all clinics.

Stage 1: Initiate treatment after obtaining the patient's consent to intravitreal injections of anti-VEGF therapy in accordance with the protocol, and regularly monitor to assess nAMD activity as defined in Table 2 and reassess periodically the patient's willingness to receive anti-VEGF treatment.

Stage 2: Extend the T&E interval per protocol. If disease inactivity or disease stability is achieved based on both functional and morphological changes, extend the T&E interval per protocol (Table 2). The T&E interval should be gradually extended, per protocol, to the maximum treatment interval outlined in the clinic's protocol.

Stage 3: Evaluate disease activity at the maximum treatment interval. Patients who have inactive disease (Table 2) for at least three consecutive maximum intervals or for a predefined period of time may be considered for treatment exit. Patients who have stable disease (Table 2) should continue receiving anti-VEGF treatment at the maximum treatment interval and should not be considered for treatment exit unless the disease inactivity criteria are met. If the disease inactivity criteria are not met, patients should continue to receive anti-VEGF treatment.

Stage 4: Consider treatment exit. Consider the presence of factors that may preclude treatment exit. Treatment continuation may be preferred in patients with only one good seeing eye or in those with a history of disease recurrence. Discuss treatment exit with the patient and thoroughly explain the risk of disease recurrence and potential for vision loss following treatment exit. If no factors are identified that preclude treatment exit, discuss with the patient whether they wish to trial a period off treatment.

Stage 5: Treatment exit and follow-up. Patients who wish to trial a period off anti-VEGF treatment should attend regular monitoring visits that include optical coherence tomography and best corrected visual acuity testing. Monitoring visits should occur at least as often as the maximum treatment interval used in Stage 3, and for at least three consecutive intervals. Monitoring visits may be extended, but intervals should be determined on a case-by-case basis after careful discussion of risk profile and visual potential of the affected and the fellow eye, at the physician's discretion. Patients should be instructed to self-monitor their vision via regular daily tasks (such as the ability to read a newspaper or TV

screen text) and urgently report any changes in vision or other symptoms, without waiting for the next appointment. Patients should be made aware of the significance of monitoring both eyes separately and adhering to follow-up appointments in order to prevent potential recurrences in the treated eyes and potential activation of nAMD in the untreated eyes. If signs of active disease are detected (Table 2), treatment should be reinitiated. While earlier reports raised concerns about VEGF suppression and macular atrophy, more recent data from the RIVAL and TREX-AMD studies[35,36] indicate that macular atrophy reflects the natural history of the underlying disease rather than a treatment side effect. Nevertheless, Stage 5 facilitates a transition to monitoring in inactive cases, ensuring anatomical stability while avoiding unnecessary treatment.

Beyond clinical outcomes, the sustainability of lifelong anti-VEGF therapy is a growing concern. In practice, "indefinite" treatment often leads to clinic overcrowding, which can delay care for new patients or cases with active lesions. Our algorithm provides a clear exit strategy that helps reclaim outpatient capacity, ensuring limited medical resources are focused where they are most needed and making nAMD management more sustainable for both the clinic and the healthcare system.

Future Perspectives

The management of nAMD is transitioning towards higher-durability therapies that allow for more rapid extension of treatment intervals. In the PULSAR trial, aflibercept 8 mg demonstrated substantial durability; by Week 96, 53% of patients maintained dosing intervals of 20 weeks or longer, and 31% reached a 24-week interval.[37] Similarly, 2-year data from the TENAYA and LUCERNE trials showed that 59–67% of patients treated with faricimab remained on a 16-week schedule, with post hoc analyses suggesting that a specific subset could extend to 20-week intervals.[38,39] These clinical trial findings are supported by real-world evidence, such as the "treat, extend, and stop" protocol used with brolucizumab, where patients successfully discontinued therapy after remaining stable through two consecutive 16-week intervals.[21]

Future strategies are expected to incorporate sustained-release platforms, such as tyrosine kinase inhibitor implants (eg, OTX-TKI, EYP-1901) and port delivery systems, to maintain continuous VEGF inhibition over extended periods.[40] Furthermore, the development of gene therapy (eg, RGX-314) represents a significant frontier, aiming to provide a single-administration approach by enabling the retina to continuously produce therapeutic proteins, potentially eliminating the need for regular injections.[41] Combining these long-acting delivery systems with routine genomic profiling – specifically identifying patients at lower risk of recurrence, such as those lacking the *ARMS2 A69S* risk allele – may establish a structured and safer strategy for discontinuation of therapy.[42,43] Overall, the enhanced durability of these next-generation agents is expected to better support successful treatment discontinuation by maintaining longer periods of disease inactivity.

Conclusion

This article provides guidelines for the management of patients with nAMD who respond well to anti-VEGF medication. We present a treatment success algorithm using predetermined treatment protocols, a variety of biomarkers, and clinical indications, to help practitioners distinguish patients with nAMD with a good response to anti-VEGF treatment, who may be candidates for treatment exit. Additionally, the algorithm includes a post-treatment follow-up strategy to aid detection of prospective disease recurrences and avoid the need for late intervention.

Abbreviations

AMD, age-related macular degeneration; BCVA, best corrected visual acuity; CNV, choroidal neovascularization; ERM, epiretinal membrane; ETDRS, Early Treatment Diabetic Retinopathy Study; IRF, intraretinal fluid; MNV, macular neovascularization; nAMD, neovascular age-related macular degeneration; OCT, optical coherence tomography; PED, pigment epithelial detachment; PRN, pro re nata ("as needed"); PVD, posterior vitreous detachment; RPE, retinal pigment epithelial; SD, standard deviation; SD-OCT, spectral domain optical coherence tomography; SRF, subretinal fluid; T&E, treat-and-extend; VEGF, vascular endothelial growth factor; VMA, vitreomacular adhesion.

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Author Contributions

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