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REVIEW

Defining response to anti-VEGF therapies in neovascular AMD

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Abstract

The introduction of anti-vascular endothelial growth factor (anti-VEGF) has made significant impact on the reduction of the visual loss due to neovascular age-related macular degeneration (n-AMD). There are significant inter-individual differences in response to an anti-VEGF agent, made more complex by the availability of multiple anti-VEGF agents with different molecular configurations. The response to anti-VEGF therapy have been found to be dependent on a variety of factors including patient's age, lesion characteristics, lesion duration, baseline visual acuity (VA) and the presence of particular genotype risk alleles. Furthermore, a proportion of eyes with n-AMD show a decline in acuity or morphology, despite therapy or require very frequent re-treatment. There is currently no consensus as to how to classify optimal response, or lack of it, with these therapies. There is, in particular, confusion over terms such as 'responder status' after treatment for n-AMD, 'tachyphylaxis' and 'recalcitrant' n-AMD. This document aims to provide a consensus on definition/categorisation of the response of n-AMD to anti-VEGF therapies and on the time points at which response to treatment should be determined. Primary response is best determined at 1 month following the last initiation dose, while maintained treatment (secondary) response is determined any time after the 4th visit. In a particular eye, secondary responses do not mirror and cannot be predicted from that in the primary phase. Morphological and functional responses to anti-VEGF treatments, do not necessarily correlate, and may be dissociated in an individual eye. Furthermore, there is a ceiling effect that can negate the currently used functional metrics such as >5 letters improvement when the baseline VA is good (ETDRS >70 letters). It is therefore important to use a combination of both the parameters in determining the response.The following are proposed definitions: optimal (good) response is defined as when there is resolution of fluid (intraretinal fluid; IRF, subretinal fluid; SRF and retinal thickening), and/or improvement of >5 letters, subject to the ceiling effect of good starting VA. Poor response is defined as $<25\%$ reduction from the baseline in the central retinal thickness (CRT), with persistent or new IRF, SRF or minimal or change in VA (that is, change in VA of 0+4 letters). Non-response is defined as an increase in fluid (IRF, SRF and CRT), or increasing haemorrhage compared with the baseline and/or loss of >5 letters compared with the baseline or best corrected vision subsequently. Poor or non-response to anti-VEGF may be due to clinical factors including suboptimal dosing than that required by a particular patient, increased dosing intervals, treatment initiation when disease is already at an advanced or chronic stage), cellular mechanisms, lesion type, genetic variation and potential tachyphylaxis); non-clinical factors including poor access to clinics or delayed appointments may also result in poor treatment outcomes. In eyes classified as good responders, treatment should be continued with the same agent when disease activity is present or reactivation occurs following temporary dose holding. In eyes that show partial response, treatment may be continued, although re-evaluation with further imaging may be required to exclude confounding factors. Where there is persistent, unchanging accumulated fluid following three consecutive injections at monthly intervals, treatment may be withheld temporarily, but recommenced with the same or alternative anti-VEGF if the fluid subsequently increases (lesion considered active). Poor or non-response to anti-VEGF treatments requires re-evaluation of diagnosis and if necessary switch to alternative therapies including other anti-VEGF agents and/or with photodynamic therapy (PDT). Idiopathic polypoidal

choroidopathy may require treatment with PDT monotherapy or combination with anti-VEGF. A committee comprised of retinal specialists with experience of managing patients with n-AMD similar to that which developed the Royal College of Ophthalmologists Guidelines to Ranibizumab was assembled. Individual aspects of the guidelines were proposed by the committee lead (WMA) based on relevant reference to published evidence base following a search of Medline and circulated to all committee members for discussion before approval or modification. Each draft was modified according to feedback from committee members until unanimous approval was obtained in the final draft. A system for categorising the range of responsiveness of n-AMD lesions to anti-VEGF therapy is proposed. The proposal is based primarily on morphological criteria but functional criteria have been included. Recommendations have been made on when to consider discontinuation of therapy either because of success or futility. These guidelines should help clinical decision-making and may prevent over and/or undertreatment with anti-VEGF therapy.
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Introduction

The introduction of anti-vascular endothelial growth factor (anti-VEGF) therapies is leading to meaningful reductions in the severe visual impairment for patients with neovascular age-related macular degeneration (n-AMD). Importantly reductions in the rates of disability from n-AMD are now being observed at a population level in various developed economies such as Denmark,[1] Israel[2] and in regions of the United Kingdom where such data has been tracked or audited.[3,4] The overall effectiveness of anti-VEGF therapies in n-AMD is unquestionable. However, not all patients benefit in an identical manner and, as such, there have been multiple attempts to group and characterise patients' responses based on both functional and morphological outcomes. At present there is no consensus on what constitutes responsiveness to treatment, and whether pre-existing characteristics such as ocular and or genetic make up and, or bio-therapeutic interactions such as tachyphylaxis have any role in determining outcome.

The expectations of patients, carers and clinicians on what constitutes successful treatment are different. Patient expectations are influenced by fellow-eye status, the longevity of the course of treatment and the consequential burden of multiple attendances, investigations and invasive treatment delivery.[5,6] Furthermore, there is also the emerging issue of when to continue, discontinue or change treatment from one n-AMD therapy to another.

In the context of the above, a group of retinal specialists was convened to arrive at a consensus on responsiveness to treatment and to suggest an improved, user-friendly lexicon for use with anti-VEGF therapies, including recommended strategies in the management of patients showing suboptimal response to particular treatments. The membership of the group is similar to that which developed the Royal College of Ophthalmologists (RCOphths) guidelines to ranibizumab.[7]

The aims of this paper are to address the following.

(i) Define the parameters that determine the response to anti-VEGF therapy in n-AMD.
(ii) Categorise the types of response of n-AMD to anti-VEGF therapy.
(iii) Define at what point in the course of treatment response should be determined.
(iv) Help link individual responses to that in clinical cohorts and the interpretation of clinical trials and their translation.
(v) Recommend how patients with n-AMD showing suboptimal response to anti-VEGF therapy should be managed.

Individual aspects of the guidelines were proposed by the committee lead (WMA) based on relevant reference to published evidence base and circulated to all committee members for discussion before approval or modification. Each draft was modified according to the feedback from committee members until unanimous approval was obtained in the final draft.

It is suggested that the definitions and recommendations included in this document would apply generically to all anti-VEGFs used in the treatment of n-AMD.

General recommendations on optimal management of patients with n-AMD

The RCOphth guidelines for the management of n-AMD with anti-VEGF therapy recommend the use of both visual function and morphological parameters to guide the diagnosis and management of this disease.[7,8] Other guidelines or consensus documents have been published by Mitchell *et al*[9] and Pauliekhoff *et al*.[10] The change in visual function is assessed by visual acuity (VA) measurement at the baseline and all follow-up visits while the macular morphology is accurately assessed by optical coherence tomography (OCT; spectral domain (SD) or higher specification). OCT is a non-invasive imaging modality of the posterior pole that yields important information on the health of the neurosensory retina,

retinal pigment epithelium–Bruch's membrane complex and choroidal vasculature and the modulation of these layers with anti-VEGF therapy. In addition, it aids in the diagnosis and classification of the lesion morphology and activity as depicted by the presence or absence of fluid in the various compartments of the retina–choroidal interface including intraretinal, subretinal and sub-RPE fluid. The tomogram also provides an objective quantification of the amount of fluid.

It is, however, recommended that the clinical diagnosis of n-AMD (CNV) is confirmed by fundus fluorescein angiography (FFA). There are considerable regional variations in the use of indocyanine green angiography (ICGA) as a diagnostic tool for n-AMD. In the United Kingdom, ICGA is not available in all units and is usually reserved for cases presenting with clinical features suspicious of polypoidal choroidopathy (IPCV) or retinal angiomatous proliferation (RAP) or when response to anti-VEGF therapy is suboptimal.[11,12] On the contrary, ICGA is more important and routinely performed in far eastern countries where IPCV is thought to be more prevalent. Where IPCV is suspected, confirmation with ICGA is required as soon as possible, and ideally within 4 weeks, which could avoid unnecessary dependence on anti-VEGF monotherapy.

Despite the evolution of several regimens for the monitoring of disease activity while on anti-VEGF therapy, the visual outcomes vary significantly from individual to individual, and may be dependent on the lesion type, genetic profile and the starting visual acuity.[13–18] Similarly, the morphological outcomes may also vary from complete resolution of the lesion to a fibrovascular scar despite presumed adequate monitoring of the disease.[14] Therefore, it is very important to classify the response to therapy in defined categories to better understand the visual potential with a particular treatment option and explore time points when one may decide to switch to another agent.

Parameters used to assess response to anti-VEGF therapies

Following initiation of anti-VEGF therapy in n-AMD, patients are followed up at regular intervals to monitor the disease activity. The two parameters that are used to assess response to anti-VEGF therapy at pre-determined intervals include VA and macular morphology on SD-OCT. Repeat FFA and/or ICG are usually reserved for 'non-responders' with the aim to re-visit the diagnosis. Visual acuity measurement is done using the logMAR chart. The degree of change in VA is contingent on the baseline acuity, that is, at the time-point at which treatment is initiated.[16,19–21] It is intuitive to suppose that treatment given when the disease has not caused permanent destruction of the neural and supporting cells will result in best outcomes. Morphological changes precede the loss of visual function. Therefore, an ideal situation would be the detection of the onset of neovascular disease before any impact on visual acuity. However, this is generally not achieved in clinical practice. Monitoring of the second eye at the regular follow-up visits for the first eye undertreatment leads to earlier diagnosis.[16,17] Clinical trial reports often do not include data on fellow or second eyes and are not designed to emphasise the importance of potential visual loss in this group. As good starting VA results in better final VA outcome, it is particularly important to diagnose the disease early in the second eye in individuals undergoing treatment for n-AMD in the first eye.[16,17]

It is now accepted that the best outcomes with anti-VEGF therapies in n-AMD are achieved with regular dosing at specific intervals, usually monthly, as demonstrated in the pivotal trials of ranibizumab, and sometimes two monthly in the first year with aflibercept after the ' three monthly initiation doses'.[22–25] Where this is not possible, treatment initiation with three initiation (or so called 'loading') doses at monthly intervals followed by flexible dosing (PRN) based on monthly monitoring and VA/OCT guided re-treatment criteria achieve functional and morphological changes close to those achieved after the three initiation doses.[26,27] However, regular monthly monitoring is required to achieve optimal outcomes. As the risk of undertreatment is high in this treatment option, further refinement of monitoring has enabled a treat-to-target regimen where patients are monitored and injected monthly until a pre-defined target is achieved. The most commonly used target is the attainment of stability of visual and anatomic outcomes for three consecutive months. Another option is to 'treat and extend' to aim for a persistent dry retina.[28,29] However, the treatment schedule may vary depending on the course of the disease. Whatever the treatment regimen, the response to anti-VEGF therapy may be classified largely into functional and morphological responses. As function and morphology do not correlate, these responses may sometimes be mutually exclusive. It is therefore important not to dissociate these responses in an individual patient.

As a result of this 'disconnect' between morphological and functional measures of response, it is necessary to use a combination of morphological and functional evaluations to guide clinical decisions.

Response based on change in VA in terms of ETDRS letters

The response to treatment may be categorised based on acuity changes immediately after the primary (loading or

Table 1 Response to anti-VEGF therapy in n-AMD

Response	*Morphology*	*Functional*
Good	Absence of SRF, IRF, IRC or a reduction of CRT >75% of the baseline values	Improvement in VA >5 letters from the baseline (ceiling effect in eyes with good starting VA defined as ETDRS 70 letters or above). Pay more attention to morphological features if VA is good esp >70)
Partial	Reduction of CRT of between 25 and 75% of the baseline values, and/or persistence of SRF, IRF, IRC and or appearance of new IRC, IRF and SRF	Change in VA of 1–5 letters from the baseline
Poor	Between 0 and <25% reduction in CRT and/or persistence of SRF, IRF, IRC and or appearance of new IRC, IRF and SRF	Change in VA of 0 – 4 letters
Non-response	Unchanging or increasing CRT, SRF, IRF and/or PED compared with the baseline	Change > – 5 letters ie decline in VA from the baseline from 1 month after third initiation injection

Abbreviations: CRT, central retinal thickness in the central 1000-μm subfield; IRC, intraretinal cysts; IRF, intraretinal fluid; SRF, subretinal fluid.
Notes: 1. Retinal atrophy/thinning and/or subretinal fibrosis do not imply poor response, but confound VA.Similarly, minimal change of fluid over scar tissue etc may not imply poor response. These may resultfrom longstanding disease, rather than treatment outcomes.
2. Outer retinal tubulations (ORT) do not represent active fluid leakage.
3. PED presence - evidence to date does not indicate that flattening of PED determines outcomes;however, PED progression indicates active disease and requires ICGA to exclude IPCV, and/orconsideration of treatment change.
4. Morphological and functional features (responses) may not correlate.
5. Primary response determined after initiation phase ie at first visit after the 3rd initiation injection.
6. Secondary response determined any time from 1 month after the 3rd initiation injection (months 4–11).
7. Late response determined at month 12 or after.

initiation) phase or during the secondary (maintenance) phase of treatment. However, irrespective of what phase in the treatment, or particular anti-VEGF agent, responses are based on the same parameters as described in Table 1. VA measurements may be described as 'stable VA' if within ± 5 letters from the baseline values.

The response after the primary phase may be:

(a) An optimal (good) response is one where the treated eye gains >5 ETDRS letters from the baseline. The eye of this patient is described as a 'good (optimal) responder'. Some clinicians prefer to use the term 'supernormal response or hyper-normal response' to describe eyes that gain 15 or more letters after the primary phase of therapy. A ceiling effect on improvement—in terms of letters of VA gained—will exist in eyes with good pre-treatment visual acuity.

(b) Primary suboptimal ('partial') response (that is, VA gain of 0–5 letters from the baseline) may be described at the end of the primary phase despite optimal (monthly) delivery of treatment ('partial responder'). Approximately 20–26% of eyes belong to the 'no initial VA gain' group.[27] Some may describe this as a partial response, where there is reduction of sub-retinal fluid (SRF) and intraretinal fluid (IRF) to 25 and 75% of the baseline but persistence of fluid.

(c) Poor response is defined as no change in VA, that is, VA change of 0 or less letters (but not >4 letter loss) when associated with morphological features of poor response.

(d) Non-response is defined as progressive deterioration of acuity of >5 letters in the treated eye in the primary phase. Such an eye is described as a 'non-responder' to the particular treatment. Primary failures may represent true non-response or may be due to a number of other factors including missing the ideal time window for treatment (that is, treating too late in the disease), treating patients with foveal scarring, which is unlikely to be responsive to anti-VEGF treatment, or other co-existent disease/misdiagnosis (for example, other retinal disease such as IPCV (which forms part of the AMD spectrum), chronic central serous choroidoretinopathy (CSCR), inflammatory or infective choroidoretinitis and so on).

This primary response is best determined at 1 month following the last initiation dose (that is, at month 4). However, this initial response at month 4 is not always predictive of long-term VA gains, as a proportion of such eyes continue to accrue gains in vision even after month 4 as in the ANCHOR and MARINA studies,[22,24] HARBOR study[30] and subsequent case series.[31] Furthermore, the PIER,[32] SUSTAIN[27] and EXCITE[33] studies suggested response to treatment may not always reflect the visual outcome after the initiation (loading) initiation phase.

The secondary response uses similar parameters, except that this refers to treatment response in the period following the initiation phase ie at least 4 months from treatment commencement. The response in the primary

phase does not necessarily mirror that in the secondary phase.

On the basis of these studies (above), the functional response over both the primary and secondary phases may be further refined to:

(a) Initial vision gain after primary phase and maintenance of the initial VA gain without further treatment.
(b) Initial vision gain after primary phase and maintenance of the initial VA gain with further treatment.
(c) Initial vision gain after primary phase and continuing improvement in VA with further treatment in the secondary phase. In the ANCHOR and MARINA studies, 8–14% of eyes gained >15 letters during months 4 to 12.[22–24] Hariprasad *et al*[34] have reported that although long-term visual gain may be predicted by VA at month 3 of treatment, some eyes especially those with better VA had a continuing or further gain in their vision when the continued dosing was maintained.
(d) Initial vision gain followed by a loss of VA in the secondary phase. This is often termed as secondary failure.
(e) No initial VA gain after primary phase and no further change in VA in secondary phase.
(f) No initial gain in VA after primary phase, but late gain in 4–12 months ('late response').

Morphological response

Morphological response takes into account the different lesion components including vascularised pigment epithelial detachment (PED), serous PED,IRF, SRF, central retinal thickness (CRT), retinal or subretinal blood and the presence of vitreomacular interface changes. The appearance of new retinal or subretinal haemorrhage indicates disease activity at any stage of the treatment. This may not be detectable on OCT, but on fundoscopy or colour fundus photographs. Similar to functional features, morphologic response may be classified as primary (determined at 1 month following the third initiation dose) or secondary (after the fourth visit).

Morphological response may be further categorised as:

(a) Optimal (good) response is defined as the absence of lesion activity (that is, disappearance of the features of fluid in any of the macular tissue compartments), or the reduction in fluid (IRF, SRF or CRT) by up to 75% at the end of the primary treatment phase.
(b) Suboptimal (partial) or poor morphological response to treatment of n-AMD may be defined as the deterioration of lesion morphology despite optimum treatment (increased FFA lesion size, worsening of OCT indicators of disease activity, other disease activity indicators, for example, new haemorrhage or exudate). OCT indicators are reduction of SRF, IRF and CRT to 25 and 75% of the baseline values but not total absence of these fluid parameters. This may or may not be associated with progressive VA reduction by >5 letters compared with the baseline and/or BCVA achieved on treatment since the baseline in the treated eye attributable to the reactivation of the n-AMD lesion.
(c) Primary failures are determined by the fourth visit (that is, 1 month following the third initiation dose). Secondary failures (poor or no response to treatment) are those eyes that show a morphological response during the initiation phase but later demonstrate a decreasing responsiveness to anti-VEGF treatment.

Morphological 'failures' may or not be associated with a loss of VA. Evidence of deterioration of the lesion morphology despite optimum treatment includes progressive increase in lesion size confirmed with FFA, worsening of OCT indicators of CNV disease activity or other evidence of disease activity in the form of significant new haemorrhage or exudates despite optimum therapy over three consecutive visits. Where there is minimal or no change in IRF, SRF and intraretinal cysts from baseline on OCT and no improvement in vision (that is, change in VA of ≤ 0 letters), response will be defined as poor. Where there are increasing intraretinal cysts/ IRF/SRF compared with the baseline, the lesion will be described as non-responding to treatment. This group is likely to represent the majority of patients over the very long-term; however, disease progression in the form of 'dry' AMD may also occur and contribute to deteriorating visual function. The mechanisms contributing to reduced efficacy are also likely to be multifactorial with drug specific factors (for example, the development of neutralising antibodies, increased clearance from the eye, tachyphylaxis, reflux of drug following injectionand so on) likely to be relevant in only a small proportion of cases. As with primary failures, the development of other retinal disease may also contribute to worsening VA/symptoms and requires specific investigation.

Suboptimal or poor response to intravitreal anti-VEGF agents may be due to less frequent treatment than is required for a particular patient. This may be due to clinical and/or non-clinical factors. Clinical factors include chronicity, with associated change of cytokine profile of the disease, chronic inflammation or high levels of VEGF requiring more frequent therapy. It is recognised that patients on a PRN regime of anti-VEGFs for n-AMD require two or more re-treatments to control the lesion

and regain lost vision following recurrences of CNV activity.[27] Similarly some eyes require more frequent injections of anti-VEGF agent than monthly dosing, such as 2–3 weekly in order to achieve primary response or following recurrences.[35] A *post hoc* analysis of the PIER study data shows that qualitative assessments of OCT at months 5 and 8 may determine those eyes that may require more treatment than the three monthly maintenance regime used in that study.[36] Thus far, the larger studies have not found pharmacogenetic associations with responsiveness to treatment.[37,38] There is, however, emerging evidence that responses to anti-VEGF therapy in n-AMD may be influenced by the genetic profile of the individual.[13,15,18] It is possible that other factors such as lifestyle may also affect the responsiveness to treatment and patients should be encouraged to quit smoking even if there is no evidence of reduced effectiveness of anti-VEGF agents in smokers[39,40] given the link between smoking and AMD and the risk to the fellow eye.

Metabolic causes of reduced response may be the result of alterations in drug absorption, distribution or metabolism, which decreases the effective concentration of the drug. That is unlikely to explain reduced response to intravitreal injections. Cellular mechanisms include the reduction in the number or concentration of, or binding to drug receptors. Alternatively, associated inflammation or upregulation of cytokines/molecules other than VEGF in the CNV lesions (for example, HGF, FGF, PDGF, E-Selectin and ICAM-1)[41–44] may alter the lesion response to anti-VEGFs. This would be explained by the reported response of some CNV lesions to the supplementary administration of triamcinolone.[45] Resistance to anti-VEGF therapies in cancer therapy is well recognised[46] and are thought to be due to compensatory angiogenic signalling, which may be specific to the particular tissue environment.[46–48]

Some lesion types are thought to be less responsive than others to anti-VEGF therapy, for example, IPCV. The EVEREST study suggested that combination therapy of IPCV with photodynamic therapy (PDT) and ranibizumab led to a better outcome than monotherapy with ranibizumab.[11,12] Similarly, it has been suggested (anecdotally) that some lesions, especially those complicating inflammatory lesions, may have suboptimal response unless the associated inflammation is treated. ICGA is necessary to make a definitive diagnosis of IPCV. Suboptimal response, haemorrhagic PEDs or large serous PEDs associated with a presumed CNV should raise suspicions of IPCV and serve as an indication for ICGA. Access to PDT or referral to a PDT centre is recommended for such cases.

'Recalcitrant' CNV has been defined as persistence of IRF or SRF on SD-OCT at <30 days after the last of six intravitreal injections of an anti-VEGF agent at monthly intervals,[49] while Brown *et al*[36] use such a term for AMD lesions previously treated in the CATT study that had received at least nine injections of anti-VEGF in 12 months but had evidence of chronic persistent IRF or SRF on OCT and FFA. Such 'recalcitrant' CNV suggests poor or suboptimal response to the anti-VEGF therapy administered. However, such lesions may be difficult to categorise as there are a group of 'delayed responders' who will not gain vision until well after 3 and sometimes not until after 12 months.[22,24]

'Tachyphylaxis' may be defined as a decreasing therapeutic response to a pharmacological agent following repeated administration over time.[50] It has been reported to occur with drugs such as salmeterol,[51] alpha agonists including apraclonidine and brimonidine,[52] and infliximab.[53] Keane *et al*[54] first suggested possible tachyphylaxis in the treatment of n-AMD after investigating retinal morphology by OCT following treatment with ranibizumab for CNV. It has been suggested that reduced response, presumed 'tachyphylaxis' may occur as early as after 2 anti-VEGF injections while others occurred after 10 injections.[45,55–59]

However, some cases of alleged tachyphylaxis may represent poor or suboptimal response to treatment, rather than true tachyphylaxis. This is depicted by the scans of the patient shown in Figure 1 in the report by Gasperini *et al*.[59] It is suggested that many such eyes may respond favourably to a change of in the anti-VEGF agent used.[59] Others have referred to a lack of response to anti-VEGF drugs at the time of reactivation of CNV that was previously responsive to that drug as 'tachyphylaxis'. Tachyphylaxis was thought to occur in 2% when treatment was given for recurrent CNV.[60] Thus such a designation as tachyphylaxis may be incorrect as it is unlikely that a single injection of anti-VEGF would provide an optimum response. This concept is well captured in the SUSTAIN study where more than one injection was required to restore VA when CNV leakage recurred after previous quiescence was achieved.[27] However, there is emerging evidence that switching from one anti-VEGF therapy to another may result in increased response.[61–65]

Non-clinical factors for less frequent treatment in NHS care in England include poor access to services, appointment delays and other systems failures.[66] Similar delay in access to services has been recorded in Canada,[67] Spain[68] and Germany.[69,70] Some of the presumed reduced response to anti-VEGFs may be due to non-clinical or patient safety incidents such as irregular dosing or suboptimal follow-up visits (as discussed above), as well as non-standardisation of treatment response quantification. A true clinical decreased response to therapy may be metabolic, cellular or genetic.

Table 2 Management algorithm in neovascular AMD

	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
VA	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
		No response	Poor response	Partial Response	Good Response
			MORPHOLOGY		

Combines functional (LogMAR visual acuity, VA) and morphological (OCT and fundoscopy) changes to determine management.
Notes: Recommended imaging includes fluorescein and ICG angiography.
Switch therapy between intravitreal anti-VEGF agents may be considered.
Combination with PDT may be considered if evidence of idiopathic polypoidal.

Management of suboptimal response to anti-VEGF therapy in AMD

The management paradigm of eyes that are not responding optimally to treatment with anti-VEGF therapy in AMD is summarised in Table 2. The presence of intraretinal cystoid oedema, subretinal fluid, diffuse thickening of the fovea, expanding serous PED, new sub- or intraretinal haemorrhage, BCVA loss attributable to other signs of lesion activity are all considered as indicators of disease activity, which therefore merit re-treatment.[7] It is recommended that as long as there is no morphological or functional deterioration, re-treatment may continu (Table 2). In order to accommodate 'late responders' it is recommended that treatment should not be discontinued before five consecutive injections have been administered at the optimum recommended interval for the specific anti-VEGF agent, unless there is an obvious deterioration of lesion morphology (poor response) within this period. However, where there is persistent SRF in the absence of FFA leak, or other evidence of disease activity (increase lesion size, new haemorrhage or exudate), or when there is no re-appearance or worsening of OCT signs of disease activity, no additional lesion growth or other signs of disease activity on follow-up, or no reduction in VA attributable to CNV, the disease may be considered as inactive.[7] Persistence of PED in the absence of other disease activity does not merit re-treatment. However, an expanding or increased elevation in PED indicates activity that merits evaluation and treatment.[11,12]

Hypersensitivity to an anti-VEGF or similar product should merit discontinuation of therapy and switch to another product.[7]

It has been reported that predictors for poor response at 12 months include: older age, better baseline acuity, larger CNV size, angiographic lesion type, the absence of RAP and the presence of GA, in addition to higher foveal thickness, PED or elevation on OCT.[21] This confirms the earlier reports from Kaiser *et al*[71] that baseline vision, CNV size and age were important predictors of treatment outcomes with ranibizumab. Higher gain in acuity is often a function of poor starting vision and reflects a ceiling effect of BCVA measurements in n-AMD.[16] It is

also suggested that early visual gains may predict visual outcomes in anti-VEGF therapy.[72] Delay in commencing treatment from symptom/disease onset has a detrimental effect on the outcomes of treatment of n-AMD with ranibizumab.[20] Each patient with n-AMD, however, needs to be managed with an individualised treatment plan. This requires follow-up at regular monthly intervals, and treatment as necessary. Some clinicians may prefer fixed dosing at extended intervals from 6 months onwards from treatment initiation, for example, 2–3 months intervals as shown by *post hoc* analysis of the EXCITE data[73] and VIEW studies.[74] Alternatively, a 'treat and extend' strategy (as described by Regillo's team) may be adopted.[28,75–77]

In eyes where, despite good VA response, there is persistent intraretinal fluid, which does not change after three monthly injections of anti-VEGF, treatment may be withheld. If the fluid subsequently increases after dose withholding, the lesion would be considered 'active' and treatment recommenced with the same or alternative anti-VEGF agent.[58,61–65]

Eyes that demonstrate no significant benefit during the first 4 months of optimal anti-VEGF therapy may be considered to have failed to meet treatment targets (primary failure). Such patients should therefore be re-assessed and, if necessary, alternative therapies including other anti-VEGFs and PDT recommended as necessary subject to lesion characteristics. In some case where it is considered that further treatment will be of no benefit, that is, futile because of the lesion morphology including mature scars, treatment may be discontinued permanently (Table 2). It is important to ensure that smoking is not continuing (during and after therapy) or inadequate/infrequent dosing of the anti-VEGF is not the cause of treatment failure, as well as misdiagnosis.

Where there is secondary failure of particular anti-VEGF therapies, a detailed assessment is necessary to exclude a potential (mis-) diagnosis and other lesion types, for example, IPCV. It is necessary to establish that therapy has been optimal before a firm decision is made about non-response. There is emerging evidence that responses to anti-VEGF therapy in n-AMD may also be influenced by the genetic profile of the individual.[18] If optimum treatment is confirmed with the previous treatment of choice, the clinician may consider changing therapy to a different anti-VEGF agent[58,61–65] or PDT.[11,12]

Conflict of interest

WA has provided consultancy services to Alcon, Allergan, Bayer, Novartis and Thrombogenics. He has received travel grants from Allergan, Bayer and Novartis, and honoraria for lectures from Allergan and Novartis. He has participated in clinical trials for which his institution has received funding from Allergan, Novartis and Pfizer. His institution has further received research grants from Allergan and Novartis for non-clinical studies, and CentreVue (Italy) for clinical studies. The remaining authors declare no conflict of interest.

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