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Neovascular age-related macular degeneration: decision making and optimal management

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Abstract

Aim **To review the decision-making processes and dilemmas in the delivery of services for neovascular age-related macular degeneration (nAMD) and describe its optimal management.**

Methods **Review of literature and presentation of illustrative cases.**

Results **Guidelines are available to aid commissioners and providers of services but with important gaps in advice. Increasing awareness of variants and diseases that mimic nAMD means that clinicians need to carefully assess lesions at presentation, using stereo imaging, fluorescein and indocyanine green angiography, and new generation optical coherence tomography. Current evidence supports the use of ranibizumab as first-line therapy. Evidence is unclear on the most appropriate treatment regime, especially in protocols relying on clinician-determined re-treatment. Current consensus recommends initiation with monthly injections for 3 months followed by maintenance comprising regular monthly visits with clinician-determined re-treatment. Further evidence on treatment protocols and the comparison with bevacizumab is awaited.**

Conclusions **Owing to incomplete evidence base health professionals face a large number of controversies and dilemmas in care pathways for patients with nAMD. Treatment should be delivered against protocols developed locally in a systematic manner with consensus and a cautious approach to change.**

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Keywords: neovascular age-related macular degeneration; decision making; management

Introduction

Until 1999 and the evidence of efficacy of verteporfin photodynamic therapy (VPDT),[1,2] the management of neovascular age-related macular degeneration (nAMD) comprised limited clinical assessment and follow-up with best supportive care. This typically comprised rehabilitation and, for patients with some preserved central visual function, the provision of visual aids and magnification. Confluent argon laser photocoagulation for extrafoveal and juxtafoveal choroidal neovascularisation (CNV) was an option applicable to approximately 5% of eyes.

The introduction of VPDT into clinical practise offered the chance of maintenance of visual function, at least at a moderate level, in a significant proportion of patients. It revolutionised the management of macular degeneration from a wide range of causes, driving the development of new imaging techniques, and subsequent therapeutic strategies. New models of service delivery have needed to be developed across the world with challenges to the previous relatively stable level of investment in ophthalmology services. Clinicians have needed to maintain a high level of knowledge and flexibility to respond to the introduction of new therapies.

In this article, I will review aspects of the current delivery of care and treatment options and address some of the difficulties and uncertainties in the decision making for health professionals in a rapidly changing field.

Pathways of care

Delivery of ophthalmology services varies widely across the world. Difficult decisions

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have had to be made by commissioners of health care in public and private sectors. Guidance has been produced in recent years on service delivery and access to care.[3–7] Although often observed as mandatory, variations in local priorities and clinical interpretation together with restrictions in guidance to selected groups of patients has meant that a close partnership has been needed between commissioners and providers. When this has not been the case, clinicians have frequently found themselves isolated and consequently facing difficult decisions.

In countries with a high prevalence of macular degeneration, the model adopted has depended on the relative proportions of ophthalmologists to the population and of public to private service provision. The first point of contact for the patient experiencing symptoms in countries with predominantly private service delivery will be to an ophthalmologist. In countries with fewer ophthalmologists or with a public sector service delivery, presentation will more typically be to a non-ophthalmological health professional in primary care, either an optometrist or a general practitioner–family physician. The level of education and technical skill among these health professionals outside eye care prevents diagnosis of neovascularisation and so guidance has tended to be based on education of patients to attend an optometrist for dilated fundal examination.

In delivery systems in which access to an ophthalmologist is through a primary care specialist, then the establishment of some sort of rapid access clinic is essential. Such a service requires training of the linked optometrists and a guidance document.[8] For the optometrist the diagnosis of nAMD is based on the detection of haemorrhage, exudates and/or retinal elevation typically with a direct ophthalmologist. Data from the Network of Reading Centres in the United Kingdom has indicated that the presence of blood on clinical examination can be taken as a reliable indicator of activity: only 12.8% of 296 cases with subretinal and only 8.8% of 26 cases with sub-RPE blood were found to be inactive on the fluorescein angiography (FA).[9] In the rapid access clinic model, visual acuity (VA), colour photography, and optical coherence tomography (OCT) are assessed by nurses, optometrists, orthoptists, photographers, or graders according to an established diagnostic and referral pathway with access to FA, if required.

Figure 1 sets out the options for pathways of care for patients with nAMD from onset of symptoms to treatment service. The central pathway shown in the figure from general–family practitioner with or without an additional step through an optometrist is the least efficient introducing considerable delay and reducing the prospects of maintenance of useful vision. Presentation through an optometrist to a rapid access clinic can speed

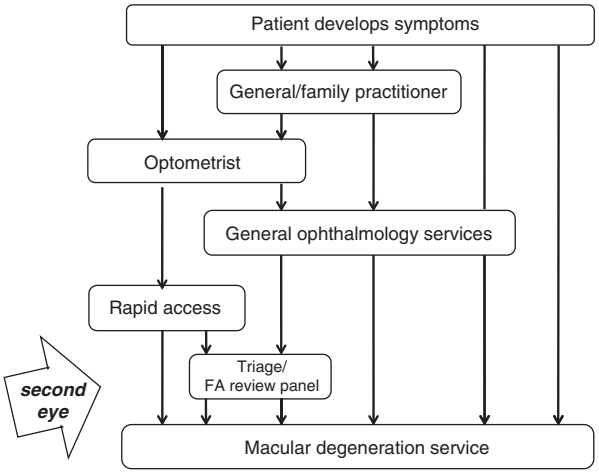

Figure 1 Pathways of referral from onset of patient symptoms to macular degeneration treatment services.

referral time. In health models with increased numbers of available ophthalmologists direct attendance at a macular clinic may be possible although frequently referral through a general ophthalmology service is required, again introducing delay. A triage step using a review of images can reduce unnecessary attendance. Patients who have already attended for management of the first affected eye should have direct access to the later stages of the pathway and know the importance of doing so. Guideline groups have set a target of 2 weeks between presentation to a primary health-care provider and the first treatment.[4]

As a minimum, providers of AMD services should ensure that the following are available: best-corrected visual acuity (BCVA) assessments by optometrist or certified examiners, stereoscopic fundus FA and OCT by trained technical staff, treatment initiated within a week of assessment, appropriate facilities for intravitreal injection and appropriate capacity for follow-up, monitoring, and re-treatment.[4] Snellen vision assessment of VA is inadequate. The recent increase in awareness of nAMD variants has shown the importance of indocyanine green angiography (ICGA). Stereoscopic photography capability and its interpretation are often neglected but its absence leads to frequent misdiagnosis. Commissioners should insist on the provision of these minimum standards in their providers units.

First review in ophthalmology

A number of clinical decisions need to be taken at the first ophthalmology assessment. The primary diagnostic tool in the assessment of suspected nAMD is FA. The classification of CNV into classic and occult developed for the Macular Photocoagulation Study (MPS) has until

recently been the mainstay of the clinical classification.[10] Its extension based on relative proportions of classic and occult developed after the Treatment of Age-related macular degeneration with Photodynamic therapy (TAP) study allowed the differentiation of responders from non-responders to VPDT:[1] classic no occult, predominantly classic with and without occult, minimally classic with and without occult, occult no classic. The process of lesion classification relies on the accurate identification and delineation of classic and occult CNV (fibrovascular pigment epithelial detachment (FPED) and late leakage of undetermined origin) and its associated lesions, thick haemorrhage, elevated blocked fluorescence, fibrosis, and serous pigment epithelial detachment (SPED). Lesion boundaries are then identified, proportions of CNV calculated and categorisation completed. The competent identification of lesion components and their extent relies on the use of stereoscopic imaging.

The recent increase in identification of retinal angiomatous proliferation (RAP) has coincided with the introduction of video scanning laser angiography and high-quality stereo review capability. The diagnosis and management of RAP is covered in an accompanying article.[11] In brief, RAP should be suspected in patients with intraretinal haemorrhage and disproportionately marked exudates and serous retinal fluid (SRF). On angiography, careful examination of stereo images is required for evidence of sharp changes of direction and dilatation of terminal retinal vessels, and retina–retina anastomosis. Photographers need to be instructed to pay careful attention to focussing on the retinal vasculature in the transit phase of the FA. Leakage is often aggressive and can be multifocal. Beyond stage 1, RAP is associated with SPED and in stages 2B and 3, CNV develops often with retina choroidal communication. The recognition of RAP as part of the neovascular complex has led to a widening of the eligibility criteria to include SRF within the lesion boundary.

Careful determination of lesion components and variants is required in cases of occult-only and minimally classic CNV and any lesion that is atypical in appearance. ICGA, although available for many years, has found an important role in these clinical scenarios. The FA appearance of occult-only CNV can mask polypoidal choroidal vasculopathy (PCV) (Figure 2). PCV should also be carefully considered in patients with juxtapapillary nAMD lesions and cases with extensive subretinal haemorrhage: as haemorrhage clears PCV may become apparent. PCV is covered in more detail in an accompanying article.[12]

A number of conditions can mimic nAMD including macular telangiectasis (MacTel), pattern macular dystrophy, uveitic CNV, myopic CNV, congenital vascular malformations, angioid streaks, and central serous retinopathy (CSR). The role of OCT in the assessment of nAMD is mainly in the determination of lesion activity. However, it can provide additional information in the differential diagnosis especially in MacTel and CSR.

MacTel typically comprises telangiectatic terminal retinal vessels on FA temporally and extending throughout the fovea (Figure 3) with associated crystalline deposits and intraretinal pigmentation on clinical examination. On OCT, there are cystic spaces but little or no thickening of the retina and no outer high-reflectivity band changes. However, there is considerable variation in its appearance and it can easily be confused with RAP; in the late stages the characteristic features may not be apparent. In addition, RAP and CNV can develop in patients with MacTel. Careful examination of the transit and early stereo ICG images is essential.

Central serous retinopathy can be protean in its appearance. The presence of long standing shallow

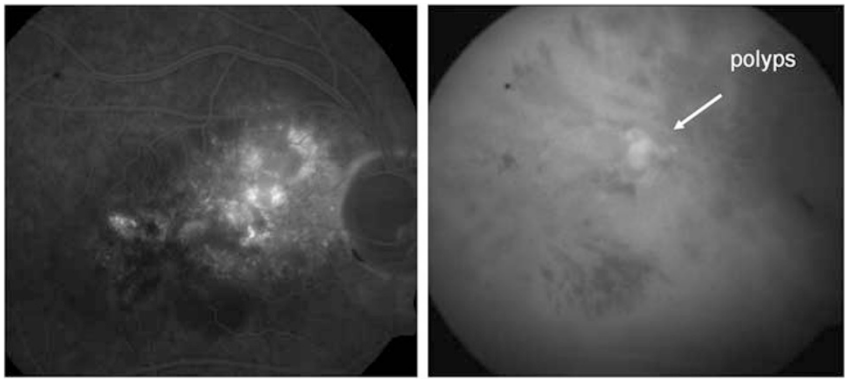

Figure 2 Atypical appearance of choroidal neovascularisation on fluorescein angiography (left panel) with polypoidal choroidal vasculopathy identifiable from indocyanine green angiogram (right panel).

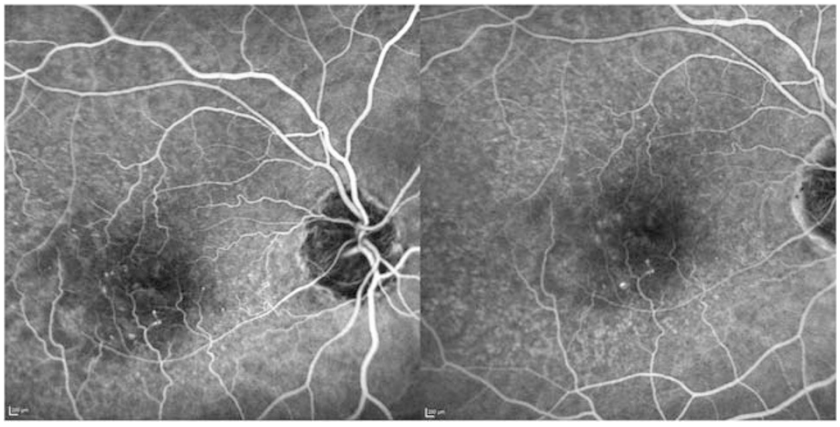

Figure 3 Early (left panel) and mid phase (right panel) fluorescein angiogram illustrating features of macular telangiectasis. This typical appearance is often masked by other pathology include retinal angiomatous proliferation in long standing disease.

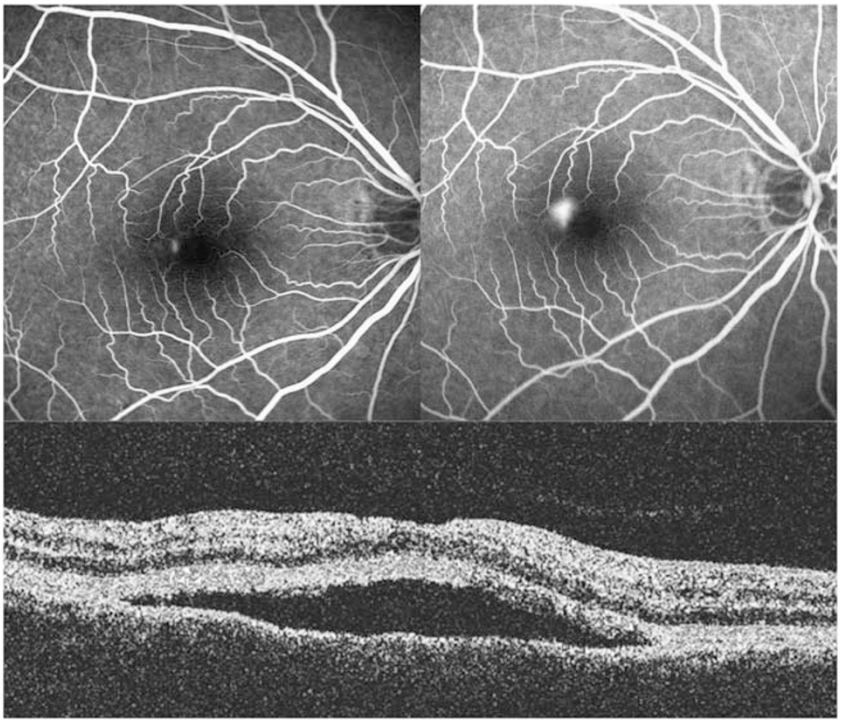

Figure 4 Case of central serous retinopathy showing the typical smoke stack appearance with shallow subretinal fluid on optical coherence tomography.

subretinal fluid with relatively normal retina as observed on OCT (Figure 4) should alert the assessing clinician to the possibility.

In distinguishing the variants and mimics of nAMD examination of the fellow eye can be very informative.

Treatment of neovascular age-related macular degeneration in 2009

At the time of writing the evidence of effectiveness of intravitreal ranibizumab has led to its position as the first-line treatment for nAMD. This evidence has been recently reviewed by Mitchell *et al*.[13] In brief, the ANCHOR study compared ranibizumab with photodynamic therapy in predominantly classic lesions; frequency of visual improvement ($\geqslant$15 letters gained) was 40.3% at 12 months and 41.0% at 24 months, respectively.[14–16] The MARINA study compared ranibizumab with sham treatment in patients with minimally classic and occult no classic lesions. The frequency of vision improvement was 33.8% at 12 months and 33.3% at 24 months, respectively.[17]

Some commissioners of treatment services have opted to provide bevacizumab in preference to ranibizumab on grounds of cost in spite of the lack of randomised controlled trial evidence of its effectiveness.[18] Trials are underway to compare the effectiveness and cost-effectiveness of ranibizumab compared with bevacizumab and will report in 2010/11. These include in the United Kingdom, the Avastin for choroidal neovascularisation (ABC) and Inhibition of VEGF in Age-related choroidal Neovascularisation (IVAN) trial, and in the United States, the Comparison of Age-related Macular Degeneration Treatments Trial (CATT).

Future treatment will require improvements in the regime as the current requirements for monthly review and frequent injections are expensive and unrealistic in an elderly population. Optimised case selection based on genetic evidence of response such as has been evaluated in PDT[19] may improve targeting of therapy to high-risk groups. In one retrospective study of 156 with exudative AMD treated with intravitreal ranibizumab monotherapy were genotyped for the single-nucleotide polymorphism rs1061170 (Y402H) in the *CFH* gene. In a recurrent event analysis, patients homozygous for the CFH Y402H risk allele had a 37% significantly higher risk of requiring additional ranibizumab injections ($P = 0.04$).[20]

Eligibility for anti-VEGF treatment

A number of uncertainties exist in the determination of eligibility for treatment at baseline. Commissioners throughout the world have issued guidelines, which vary and are typically incomplete in their application to individual clinical scenarios creating problems with decision making. This is illustrated by the guidance issued in the United Kingdom by NICE in October 2007.[5] Recommendation 1.1 of this guidance recommends ranibizumab for the treatment of wet AMD if all of the following circumstances apply in the eye to be treated:

- The best-corrected VA is between 6/12 and 6/96.
- There is no permanent structural damage to the central fovea.
- The lesion size is $\leqslant$12 disc areas in greatest linear dimension.
- There is evidence of recent presumed disease progression (blood vessel growth, as indicated by FA, or recent VA changes).

The aim of this type of guidance is that clinicians do not recommend treatment in inactive or involuting lesions. Careful review of the ophthalmoscopic and FA features will help determine whether the lesion is still active. The upper and lower limit of VA gives problem to clinicians in advising their patients. Many recommend treatment for eyes with VA better than 6/12. The definition for permanent structural damage requires clarification. Mitchell *et al*[13] have suggested that advanced subretinal fibrosis or significant geographic atrophy involving the foveal centre is a reasonable definition while others have suggested that large cysts visible on OCT, especially with the destruction of the normal architecture of the fovea, may indicate that therapy will be unsuccessful. It appears wise to advise against treatment for eyes with one or more of these features present and a VA of $<$6/96. One such case is shown in Figure 5. The upper limit of lesion size was adopted by the ANCHOR and MARINA study design. Such large lesions are also unlikely to have much chance of visual gain although evidence is lacking.

The VIP study introduced the concept of presumed recent disease progression important in the determination of eligibility of occult-only lesions for PDT.[2] This comprises any of: loss of five or more letters on a ETDRS chart recorded as letters read at 1 m or increase in GLD of $\geqslant$10% within last 3 months; evidence of haemorrhage from CNV. In considering treatment for occult-only lesions, it seems reasonable not to include lesions that show no evidence of recent progression; this could be extended to minimally classic lesions.

Several components of nAMD lesions present difficulty in advising on eligibility including SPED, retinal pigment epithelial (RPE) tear, and thick blood because of their exclusion from the pivotal RCTs. The treatment of a lesion with a large SPED ($>$50% of the lesion) remains controversial. Limited evidence comes from one retrospective study of 328 patients with SPED associated with CNV or RAP treated with a range of treatment options: 86 patients with bevacizumab, 128 with ranibizumab, 60 with pegaptanib, and 54 with VPDT combined with intravitreal triamcinolone acetonide (IVTA). A small increase occurred in mean logMAR VA by 0.066 from a mean at baseline of 0.78. Eyes receiving bevacizumab or ranibizumab had better functional and morphological outcomes compared with the other therapies. Even with treatment, tears of the RPE or only a partial flattening of the PED always indicated a worse prognosis.[21]

In borderline cases with a long history or evidence of involution, it is reasonable to offer review and re-assessment. Some clinicians recommend a course of three treatments as a 'trial of treatmernt', although in the absence of any supporting evidence this seems unjustified. It is important, however, for the majority of patients to understand that a course of ranibizumab therapy is a long-term commitment requiring frequent visits to the clinic and no clear time to stop. So if patients cannot attend monthly alternative treatment should be offered. Other treatments have a limited place at present

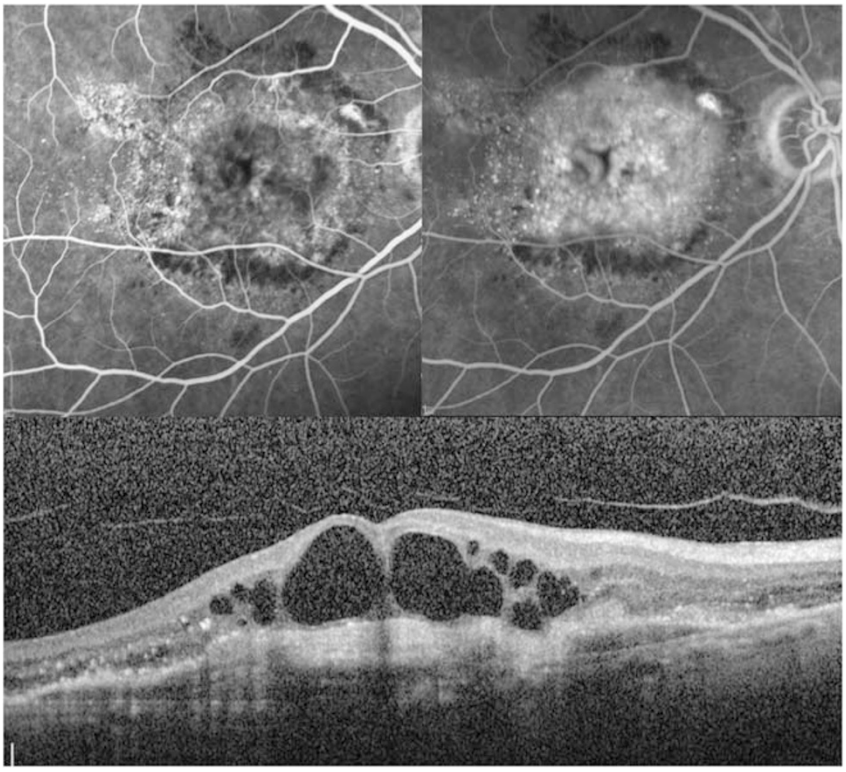

Figure 5 Case of involuting fibrovascular pigment epithelial detachment visible on fluorescein angiography (upper panel) with optical coherence tomography (lower panel) showing development of large cysts and loss of normal foveal architecture. Right eye. Refraction protocol visual acuity = 28 ETDRS letters. This case would be excluded from many eligibility guidelines.

in subgroups for whom treatment with ranibizumab is not indicated or in patients who cannot receive a monthly treatment and include photodynamic therapy[1,2,22,23] and pegaptanib sodium.[24]

Treatment protocols

The principle evidence on treatment regimes for intravitreal ranibizumab comes from the ANCHOR and MARINA trials in which treatment was administered monthly for 24 months in a robust RCT design. However, several study groups have investigated reduced frequency regimes in an attempt to limit the number of treatments and visits. They are based on an initiation or loading phase followed by a maintenance phase with clinician-determined re-treatment. A 3 month initiation or loading phase of monthly injections is based on the findings from MARINA and ANCHOR in which the bulk of improvement in BCVA occurred in the first 3 months. Several maintenance regimes have been studied throughout the world with variation in frequency of treatment, frequency of review, re-treatment protocols, and stopping rules. Phrases that have been applied include: treat and extend, treat and maintain, treat to lesion inactivity, treat until dry, and treat until best VA.

The PIER study[25] tested a reduced frequency regime at a fixed quarterly frequency and showed that the initial benefit at 3 months was lost over the subsequent 21 months and that more frequent observation and treatment is required.

Re-treatment decision making

In variable frequency treatment regimes a key component is clinician-determined re-treatment. There is no consensus on which criteria should be used in making this decision.

Table 1 lists the various factors that should be considered and one approach that can help the clinician to review them systematically.

There is considerable uncertainty regarding a number of other possible criteria for re-treatment that can be included. These include VA loss with cut points of $\geqslant 5$ or $\geqslant 10$, symptoms, quantitative OCT measures such as mean central foveal thickness of centre point thickness and persistence of PED.

The results of a number of retrospective or small uncontrolled prospective clinician-determined re-treatment protocols have been reported. The numbers of treatments delivered has varied as well as the

Table 1 Guidance for decision making in clinician-determined re-treatment protocols

	Consider re-treatment	*Consider not retreating*
Patient symptoms	Worse	Better/no change
Best-corrected visual acuity (BCVA)	5–19 lost	(i) <5 lost (ii) <15 letters on 2 consecutive visits (iii) ⩾20 letters lost
Fresh haemorrhage	Present	
Subretinal fluid	Present	Absent Persistent but unresponsive to previous treatment
Intraretinal fluid	(i) Present and worsening (ii) Present and BCVA dropping	Absent
Structural damage on optical coherence tomography		Present
Fibrosis		>75%
Fluorescein angiography	(i) Extension (ii) Leakage	
Serious adverse event		Present

outcome. The Prospective OCT imaging of patients with Neovascular AMD Treated with intraOcular Ranibizumab (PrONTO) study used a 3 monthly loading dose regime followed by variable dosing and reported a mean increase in VA of 11.1 letters and 15 + letter improvement in 43% with a mean of 9.9 injections.[26] However, the study was in only 37 patients with no controls.

Recent studies have reported the results of variable dosing regimes in routine clinical practise. They suggest that better results are achieved with more frequent treatments. Rothenbeuhler *et al*[27] found ⩾15 letters improvement in 30% of 138 eyes of 138 patients followed prospectively for 24 months and treated with a PRN regime. Mean number of injections per patient was 5.6 and 4.3 from baseline to month 12 and month 12–24 respectively. Michalova *et al*[28] reported a mean VA of 5.5 letters in a retrospective review of 78 patients treated with a similar PRN regime over 12 months but with more frequent a injections (mean 9.2). Cohen *et al*[29] performed a retrospective review of the first 12 months of treatment in 124 eyes of 122 patients treated on a PRN basis after one or three doses at initiation. Mean frequency of IVT injections was 3.8 and mean number of follow-up visits was 8.1. The results showed stabilisation rather than improvement (mean VA change = +0.7 letters) with the number of treatments being fewer than other studies; the authors concluded that the results were less favourable than the RCTs and the Pronto study.

In contrast, a recently published simulation based on pooled data from treated and sham groups in MARINA, ANCHOR and PIER, and pharmacokinetics of ranibizumab in the vitreous suggested that after a three dose loading phase a mean of 5.1 injections until the 12 month visit would on average maintain VA gain achieved at 3 months.[30]

Mitchell *et al*[13] recent review of the available evidence from ANCHOR, MARINA, PIER, SAILOR, SUSTAIN, and EXCITE concluded that treatment initiation with three consecutive monthly injections, followed by continued monthly injections, has provided the best VA outcomes. A flexible strategy appears viable if repeated monthly injections are not feasible and initiation regimes of <3 monthly injections have not been reliably tested.

In the decision process of clinician-determined re-treatment a number of other issues need to be considered. Failure to respond should be considered when ⩾15 letters have been lost from baseline (preferably on two consecutive visits), there has been an increase in SRF or IRF or retinal thickness or the VA has dropped to 20 letters or worse. Discontinuation of treatment should be considered. In these refractory cases, the baseline FA should be reviewed and if not carried out at baseline an ICGA performed to look for PCV. Vitreomacular traction may be apparent on OCT in which case vitrectomy and membrane peel may be justified. Finally, the lesion may have reached an end stage with the development of fibrosis indicating that further treatment will be futile.

With such a wide range of factors to be considered in the management of patients with nAMD and the rapidly changing knowledge base, it is essential to establish clear guidelines and protocols in each unit based on evidence review and consensus. Definitions of activity and non-response should be established and the preferred treatment protocol agreed. Decisions should be reviewed regularly.

In conclusion, present evidence and experience suggests that optimal management of nAMD comprises ranibizumab delivered with an initiation phase of monthly injections for 3 months followed by a variable dosing regime delivered with monthly visits. However, this is likely to change with the addition of new evidence and the introduction of treatments with better efficacy and cost-effectiveness. At a time of frequent difficult decisions, it is important to start from a recognised published guideline and to cautiously extend or modify this in light of collective unit experience in a systematic manner. Clinicians and commissioners should insist on an appropriate service specification. Advanced disease should not be treated.

Conflict of interest

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