

The Royal College of Ophthalmologists interim recommendations for the management of patients with age-related macular degeneration

Introduction

Age-related macular degeneration (AMD) causes severe visual loss and is the commonest cause of blindness in persons ≥ 50 years old in the western world.^{1–4} Two main forms of AMD occur: dry and wet. The dry form accounts for 90%, whereas the wet form occurs in 10% of all AMD. The severe visual loss in 90% of cases is due to the wet form of AMD, which is characterized by choroidal neovascularisation (CNV). The majority of CNVs occur subfoveally.⁵ There is evidence that angiogenic factors, especially vascular endothelial growth factor (VEGF) and fibroblastic growth factor play a significant role in the development and maintenance of CNV. High levels of VEGF have been demonstrated in CNV surgically excised from humans or animal experimental CNV.^{6,7}

It was previously estimated by research commissioned by the Macular Disease Society (MDS) (Fletcher A, Donoghue M, Owen C. Low Vision Services for People with Age-Related Macular Degeneration in the UK: A Review of Service Need and Provision. Macular Disease Society Report, June 2001) that 21 000 new cases of wet AMD occurred in the United Kingdom each year. Current estimates by the Royal National Institute for the Blind (RNIB) and the National Institute of Clinical Excellence (NICE) indicate that there may be 26 000 patients eligible for the new anti-VEGF treatments in the United Kingdom each year (compared with 7000 currently eligible for photodynamic therapy (PDT) (NICE: HTA Ranibizumab and Pegaptanib for the treatment of AMD. Final Scope. 25 April 2006; <http://www.nice.org.uk>).

The management of an individual patient depends on the type of AMD present. Until recently, the management of wet AMD has been limited to laser photocoagulation and PDT where applicable.

Remit of these guidelines

The document aims to provide an update of the management of AMD in the light of recent developments, which supersede the previous AMD guidelines. The situation will continue to evolve over the next several months.

The recommendations provided in this document are aimed mainly at the newer therapies and are temporary as they will change from time to time with the emergence of new evidence and the NICE process. As such, these recommendations will be updated at regular intervals to incorporate new evidence/developments as they arise.

Dry AMD

Unfortunately, there is no medical or surgical treatment currently available for dry AMD. However, patients can be helped by supportive measures such as low vision assessment, provision of and advice on the use of optical aids, and counselling about the condition and prognosis. Smoking is a recognised risk factor for both dry and wet AMD.⁸ Ocular nutritional supplements have been shown (in the Age-Related Eye Disease Study) to slow the

progression of dry AMD to more advanced stages.⁹ Such nutritional supplements should therefore be recommended to patients. Patients should be advised to avoid smoking.

Wet AMD

Laser photocoagulation

Laser photocoagulation with conventional thermal laser is effective for extrafoveal lesions and destroys the CNV before ingrowth to the fovea has occurred.¹⁰ The effectiveness of this treatment is limited by the scotoma it causes in the visual field, by the high recurrence rate, and by the fact that only small classic CNV, which are extrafoveal at presentation, can be treated.^{10,11} Practically, only a few patients present with these small classic extrafoveal lesions; however, it is still the treatment of choice for this small group of patients.

Laser photocoagulation is not recommended for patients with subfoveal or juxtafoveal CNV because of the immediate visual loss that results from foveal photoreceptor and retinal pigment epithelium (RPE) damage, or later encroachment of the scar on the fovea.^{12,13}

Photodynamic therapy with verteporfin

PDT with verteporfin destroys CNV without damaging the overlying neurosensory retina, thereby allowing subfoveal lesions to be treated. Verteporfin PDT acts through occluding newly formed vessels.

PDT with verteporfin was shown to be effective in clinical trials in patients with classic and predominantly classic subfoveal CNV secondary to AMD.^{14,15} In addition, the VIP Study showed that after 2 years, PDT with verteporfin significantly reduced the risk of moderate-to-severe visual loss in patients with occult and no classic CNV.¹⁶ Similar findings have been reported for CNV secondary to myopia.¹⁷

On 24 September 2003, NICE published Guidance (<http://www.nice.org.uk>) on PDT in wet AMD. It recommended PDT for the treatment of wet AMD with a confirmed diagnosis of classic with no occult CNV, and best-corrected visual acuity of 6/60 or better (paragraph 1.1). The other key recommendation in the NICE Guidance was in paragraph 1.2, which 'recommended PDT for the treatment of predominantly classic subfoveal CNV (ie, 50% or more of the entire area of the lesion is classic CNV but some occult CNV is present) associated with wet AMD, only as part of ongoing or new clinical studies that are designed to generate robust and relevant outcome data.

Only retinal specialists should carry out PDT with expertise in the use of this technology.

NICE did not evaluate the efficacy of PDT in treatment of occult CNV as verteporfin was not licensed for the treatment of occult CNV at the time.

To comply with the guidance in paragraph 1.2, the Verteporfin Photodynamic Therapy Cohort Study was set up to collect data on all National Health Service (NHS) patients undergoing PDT in the United Kingdom. The DoH commissioning/implementation document, which accompanied the NICE Guidance allowed for the treatment of all classic without occult, and predominantly classic with occult subfoveal and juxtafoveal CNV of any aetiology. Recently, some primary care trusts (PCTs) have allowed the treatment of occult CNVs, of less than four disc diameters in size, with

recent progression of disease as shown in VIP 2.¹⁶ However, the EU licence for the use of PDT in the treatment of occult CNV has been revoked as the Committee for Medicinal Products for Human Use (CHMP) has recommended the deletion of the indication of Visudyne PDT in patients with occult CNV as the benefit-risk profile is no longer considered favourable following reports from the VIO study (see EU Marketing Authorisation Number: EU/1/00/140/001).

Clinical experience in the United Kingdom is widespread and has produced outcomes similar to those reported in the clinical trials, and with slight reduction in the number of retreatment. This experience, however, indicates that significant visual loss may still result in some patients after PDT for subfoveal CNV, and that multiple repeated treatments may lead to potential cumulative damage to the retina and inner choroid. Furthermore, PDT is not useful in reducing visual loss in some lesion types including minimally classic CNV.

Anti-VEGFs

As VEGF plays a significant role in the development and maintenance of CNV, substances that block VEGF have been developed as treatment for wet AMD. Two specific agents have been developed and investigated for intraocular injection in the treatment of CNV secondary to AMD. These two agents are a major advance in the treatment of wet AMD as they will allow ophthalmologists to treat the wide range of subfoveal CNV lesions, including occult. Both of these agents are given by intravitreal injection, pegaptanib at intervals of 6 weeks and ranibizumab in every 4 weeks. Although there have been no direct comparisons of the different anti-VEGFs, it seems that ranibizumab is the more efficacious of the two products currently available.

A third agent, bevacizumab, which may have similar effects to ranibizumab (from pilot studies) when given intravitreally is licensed for the treatment of colorectal or breast cancer. It is, however, not licensed for the treatment of ocular disease or intraocular delivery.

Anti-VEGF therapies are effective in all CNV lesion types: classic, predominantly classic, minimally classic, and occult lesions including serous retinal pigment epithelial detachments (PEDs) and retinal angiomatous proliferations (RAPs). Lesions of any size are treatable with anti-VEGFs.

The effects of anti-VEGF therapy in pregnancy and breastfeeding are unknown.

Pegaptanib sodium

Pegaptanib (Macugen, Pfizer/OSI Eyetech) is a pegylated modified oligonucleotide, an aptamer, with molecular weight of 20 kDa, which binds isoform 165 of VEGF (VEGF 165) inhibiting its activity. VEGF 165 is thought to be preferentially increased in pathologic neovascularisation, including CNV.

Clinical trials. The VISION Trial¹⁸ was a multicentre, prospective, randomised, dose-ranging double-blind controlled trial of pegaptanib at doses of 0.3, 1.0, and 3.0 mg or sham injections administered every 6 weeks. The study was run in two concurrent arms (FDA regulations) over an initial period of 48 weeks,

subsequently extended to 2 years. The results show that more patients who received pegaptanib 0.3 mg compared to sham injection maintained their vision, and further that severe visual loss was reduced. The vision improved by 15 letters in 6% of patients while it was maintained in 33%. Pegaptanib at 0.3 mg is therefore effective in the treatment of all subtypes of CNV secondary to AMD.

Use of pegaptanib in routine clinical practice. Pegaptanib was licensed for use in the United States in December 2004, and has had widespread use since then. It was licensed by the European Medicines Evaluating Agency (EMA) at a dose of 0.3 mg in February 2006, and launched in the United Kingdom in May 2006. Its use in UK clinical practice is limited as services are yet to be commissioned by PCTs. However, there is substantial experience from clinical trials and private medical practice.

The VISION Study entry criteria may provide a guide for clinical practice.¹⁸ In the trial, pegaptanib was used to treat lesions of any subtypes with the greatest linear diameter of 12 disc diameters, and visual acuities between approximately 6/12 and 1/60. Minimally classic and occult lesions were required to show indicators of progression before treatment.

Safety in clinical practice. The 2-year safety data from the VISION Study have been published and are reassuring. Injection-related endophthalmitis (0.16%/ injection) in the first year was attributed to violations in the injection preparation protocol.¹⁹

There have been a few reports of severe systemic allergic reactions associated with intravitreal pegaptanib injections, and these may occur up to 1 hour following the injection.²⁰ Similarly, there have been a few reports of retinal pigment epithelial tears following treatment with pegaptanib. However, as these can occur spontaneously, or following laser treatment, their occurrence cannot be attributed to the administration of pegaptanib.²¹

Ranibizumab

Ranibizumab (Lucentis, Genentech/Novartis Pharma) is a humanised therapeutic monoclonal antibody fragment, with a molecular weight of 48 kDa, designed to bind to and inhibit all isoforms of VEGF-A. It is thus nonselective.

Ranibizumab was licensed in the United States in 2006 and in the European Union and the United Kingdom in February 2007, at a dose of 0.5 mg per intravitreal injection. The results of routine clinical use are limited but there is extensive clinical experience from trials, as well as treatment on particular patient supply programme before EU licensing of ranibizumab, and recent post-licence experience.

The initial results show that ranibizumab is effective in preventing visual loss but, can also in a significant proportion improve visual acuity, unlike verteporfin PDT or pegaptanib. There is no long-term data and concerns that CNV recurrence may occur after 24 months of ranibizumab treatment has stimulated research into other dosing regimes and combination therapies.

Clinical trials. The MARINA Trial was a multicentre, randomised, double-masked trial to test two doses of

ranibizumab (0.3 and 0.5 mg) in minimally classic and occult CNV in comparison with sham injections. The results showed that ranibizumab was effective in preventing vision loss in 95% of treated patients; however, in 25–35% of patients at 12 and 24 months vision improved by 15 letters.²²

The ANCHOR Study is a 2-year, phase 3, randomised, multicentre double-masked trial comparing efficacy and safety of monthly injections of 0.3 and 0.5 mg ranibizumab combined with sham verteporfin PDT, with sham injections of ranibizumab and verteporfin PDT. The primary end point was loss of less than 15 letters of visual acuity, and at the 1 year results in terms of this and lesion size, the ranibizumab patients fared significantly better than PDT with verteporfin with maintenance of vision in 95% of patients.²³ Vision improved by 15 letters in 35–40% of patients with ranibizumab compared to 5.6% with PDT.

The PIER Study evaluated different injection schedules of ranibizumab in all types of CNV. The results showed that vision outcome was below that achieved with the MARINA and ANCHOR regimes.

Use of Ranibizumab in clinical practice. The results show that ranibizumab, at 0.3 or 0.5 mg delivered intravitreally is effective in preventing visual loss but also in a significant proportion can improve visual acuity, unlike verteporfin PDT or pegaptanib. There is no data beyond 24 months and concerns that CNV recurrence may occur after 24 months of ranibizumab treatment has stimulated research into other dosing regimes (PIER, PRONTO, and SUSTAIN Studies) and combination therapies.

Safety of ranibizumab. Two years safety results from the MARINA Trial indicated that patients treated with repeated ranibizumab injections had a low rate (<1% each) of serious ocular adverse events including endophthalmitis, uveitis, retinal detachment, retinal tear, vitreous haemorrhage, and lens damage.^{22–24} No notable imbalance in nonocular adverse events was observed. Approximately 95% of patients commenced the second year of the study, thus indicating patient satisfaction.

Advantages and disadvantages of ranibizumab. The main advantage of ranibizumab is that like pegaptanib, it can be used in all lesion subtypes of wet AMD, and it has a good safety profile from research data. Unlike pegaptanib, in a significant proportion of patients there is not only a prevention of visual loss but also an improvement in visual acuity.

Bevacizumab

Bevacizumab (Avastin, Genentech/Roche) is a full recombinant humanised monoclonal antibody with a molecular weight of 149 kDa (three times the size of ranibizumab), which binds to all isoforms of VEGF-A (similar to ranibizumab).²⁵ It is glycosylated, and has an Fc fragment unlike ranibizumab. The Fab domain of bevacizumab differs from ranibizumab by six amino acids. The serum and vitreous half-lives of bevacizumab are longer than those of ranibizumab.

The biological similarity of bevacizumab to ranibizumab has led to the widespread 'off-label' use for the treatment of wet AMD. These case series suggest that

bevacizumab may be successful in the short term in limiting visual loss. However, there are no clinical trials available for intraocular use of bevacizumab. As such, there are no safety data and the minimum effective dose, and the optimum dose or dose-frequency are not known. The safety data of bevacizumab cannot be completely inferred from those of ranibizumab. The National Eye Institute (NEI) in the United States has announced that it will fund a trial comparing bevacizumab with ranibizumab. Similar consideration is being given to a comparative study of bevacizumab and ranibizumab by a consortium of UK ophthalmologists.

Combination therapy with PDT and Anti-VEGFs

A combination therapy with PDT may prove to be even more effective than either therapy on its own. Potentially, such combinations will improve efficacy, reduce frequency of retreatments and reduce toxicity. Trials of such combinations are currently on going, including the PROTECT Study,²⁶ FOCUS Study²⁷ (combinations of PDT and ranibizumab), and EOP 1012 (combination of PDT and pegaptanib).

The interim results to date suggest that combination of PDT and pegaptanib does not make a significant difference to visual outcome, although retreatment rates may be slightly reduced. Results from the PROTECT Study and FOCUS Study, however, show that combination of PDT and ranibizumab is safe and that retreatment rates may be reduced with good outcomes.^{26,27}

It is implied that patients who have failed to respond to PDT may be safely transferred to anti-VEGF therapy without any risk.

Recommendations

Patients with dry and wet AMD should be advised to stop smoking. Dry AMD patients should be advised to eat balanced diets, which may be enhanced with ocular nutritional supplements.

Supportive measures such as low vision aid: provision and advice on the use of optical aids, and counselling are helpful in both dry and wet AMD.

Before initiating treatment for wet AMD, it is expected that a firm diagnosis of CNV would have been made. The CNV lesion type, location in relation to the fovea, and the size would be established and recorded in the notes.

Baseline investigations including LogMAR visual acuities, OCT, and FFAs would be undertaken and analysed. Concomitant ocular diseases will be documented. It is advisable to record history of hypertension, cerebrovascular disease—particularly CVA—and ischaemic heart disease, although their presence is not a contraindication to treatment.

It is recommended that ophthalmologists should exercise caution and exercise their own judgement and experience when recommending treatments for wet AMD. The guiding principle should be that whatever treatment is recommended must be in the best interest of patients. Intravitreal injections should only be undertaken by or under the supervision of ophthalmologists experienced in the procedure as there are serious potential adverse events including endophthalmitis, cataracts, retinal detachment, and vitreous haemorrhage (please refer to the RCOphth Guidelines on intravitreal injections on the College website).

Extrafoveal CNV

Patients with extrafoveal CNV should be treated with focal laser photocoagulation as described in the Macular Photocoagulation Study protocol. However, in patients with large extrafoveal classic CNV, or occult CNV with progression, it is justifiable to offer alternative treatment similar to that of juxtafoveal lesions. Where no progression is demonstrable, or vision is not threatened observation is advised.

Subfoveal/juxtafoveal CNV. It is expected that eyes with subfoveal/juxtafoveal CNV of all lesion types will benefit from treatment.

Predominantly classic subfoveal/juxtafoveal CNV. Where funding is available, anti-VEGF therapies may be offered as first-line therapy. However, where such funding is not available, patients with predominantly classic AMD with subfoveal and juxtafoveal location, with GLD < 6400 µm may be offered PDT in the first instance. Where there is poor response to PDT in the eye requiring treatment, or in the other eye described previously, trial of licensed anti-VEGFs are highly recommended. In the absence of such availability, then the use of unlicensed products including bevacizumab may be justified.

Occult subfoveal/juxtafoveal CNV. PDT is no longer recommended as the first choice for occult CNV. Intraocular injections of licensed anti-VEGF are recommended for such lesions as in 5.3.1. However, the risk of RPE tears in fibrovascular PEDs of 20–30% has to be taken into account.

Minimally classic subfoveal/juxtafoveal CNV. PDT is not recommended for such patients. Intraocular injections of anti-VEGFs should be considered as first-line treatment.

Retinal angiomatous proliferations do not respond well to PDT. It is recommended that eyes with RAPs are treated with repeated injections of anti-VEGFs with or without PDT.

When recommending intraocular bevacizumab, it is extremely important to inform patients that it is unlicensed for this indication and that it has not undergone the usual rigorous clinical trials and independent evaluation by regulatory authorities. Adequate follow-up information must also be maintained on these patients, and recorded appropriately.

It is expected that all unwanted ocular effects and systemic adverse events (especially cardiovascular) will be recorded in the patient's notes. The relation of such events to treatment should be determined.

There are significant resources (including staffing), logistical and financial implications, in commissioning anti-VEGF treatments for AMD. The College has convened an AMD Provisions Subcommittee (under the Scientific Committee), which continues to evaluate, among other things, AMD service configurations and distribution, staff and other resource requirements (the recommendations are available on the RCOphth website as 'Commissioning Contemporary AMD Services: guidance to commissioners and clinicians).

Irrespective of the cost of the new anti-VEGF treatments, it is anticipated that the workload for AMD will increase considerably with the introduction of intravitreal therapy. This will impinge on the ability of ophthalmic departments to deliver ophthalmic services overall. Clinicians are, therefore, urged to work with managers and commissioners to make a strong case for increasing the complement of doctors, nurses, optometrists, and technicians to cope with this workload.

NICE has commenced the HTA process of evaluating new treatments for AMD. All stakeholders, including the RCOphth have made their initial submissions to NICE. Decisions are not expected until early 2008. Pegaptanib and ranibizumab will be evaluated. It is anticipated that bevacizumab will not be evaluated as it is not licensed for treatment of AMD.

The Health Service Circular (HSC) 1999/176 advises PCTs to consider available evidence in order to provide funding for new treatments. This advice applies to treatments for AMD. Clinicians should, therefore, seek funding for anti-VEGF treatment from their PCTs. The absence of NICE Guidance should not be accepted as a reason for nonfunding of AMD treatments.

Future developments

The definitive AMD guidelines are being prepared by a group using a clearly defined methodology, which includes consultation of all stakeholders. It is expected that a final draft of the guidelines will be sent out to all consultant ophthalmologists for comments later this year.

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Conflicts of interest

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