



**AMD Interim Guidelines:
The Royal College of Ophthalmologists Interim Recommendations for the Management of
Patients with Age-related Macular Degeneration (AMD)**

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%, whilst 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 (FGF) 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)^a that 21,000 new cases of wet AMD occurred in the UK each year. Current estimates by the Royal National Institute for the Blind (RNIB) and the National Institute of Clinical Excellence (NICE) indicate there may be 26,000 patients eligible for the new anti-VEGF treatments in the UK each year (compared to 7,000 currently eligible for photodynamic therapy [PDT]).^b

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 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 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 in order to incorporate new evidence/developments as they arise.

Dry AMD

There is, unfortunately, 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 AREDS Study) to slow the progression of dry AMD to more advanced stages.⁹ Such

^a 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.

^b NICE: HTA Ranibizumab and Pegaptanib for the treatment of AMD. Final Scope. 25 April 2006. www.nice.org.uk

nutritional supplements should therefore be recommended to patients. Patients should be advised to avoid smoking.

Wet AMD

1. 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 RPE damage, or later encroachment of the scar on the fovea.¹²⁻¹³

2. Photodynamic therapy with verteporfin.

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

PDT with verteporfin was shown to be effective in clinical trials in patients with classic and predominately 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 the National Institute for Clinical Excellence (NICE) published Guidance (www.nice.org.uk) on verteporfin photodynamic therapy (PDT) in wet age-related macular degeneration (AMD). It recommended PDT *for the treatment of wet AMD with a confirmed diagnosis of classic with no occult subfoveal choroidal neovascularisation (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 (that is, 50% or more of the entire area of the lesion is classic CNV but some occult CNV is present) associated with wet age-related macular degeneration, 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.

In order to comply with the guidance in paragraph 1.2 the VPDT Cohort Study was set up, to collect data on all 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 no occult, and predominantly classic with occult subfoveal and juxtafoveal CNV of any aetiology. Recently, some PCTs have allowed the treatment of occult CNVs, of less than 4 disc diameters in size, with recent progression of disease as shown in VIP 2.¹⁶

Clinical experience in the UK is widespread and has produced outcomes similar to those reported in the clinical trials, and with slight reduction in the number of re-treatment. 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.

3. Anti-VEGFs.

As VEGF plays a significant role in the development and maintenance of CNV, substances which 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 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) and is licensed for the treatment of bowel cancer. It is not licensed for the treatment of ocular disease.

3.1 Pegaptanib sodium.

Pegaptanib (Macugen, Pfizer/OSI Eyetech) is a pegylated modified oligonucleotide, an aptamer, with molecular weight of 20 KD, which binds isoform 165 of vascular endothelial growth factor (VEGF 165) inhibiting its activity. VEGF 165 is the isoform of VEGF that is thought to be preferentially increased in pathologic neovascularisation, including choroidal neovascularisation.

3.1.1 Clinical Trials.

The VISION Trial¹⁸ was a multicentre, prospective, randomised, dose-ranging double-blind controlled trial of Pegaptanib at doses of 0.3mg, 1.0mg and 3.0mg or sham injections administered every 6 weeks. The study was run in 2 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 0.3mg 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 whilst it was maintained in 33%. Pegaptanib at 0.3mg is therefore effective in the treatment of all subtypes of choroidal neovascularisation secondary to AMD.

3.1.2 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 0.3mg in Feb 2006, and launched in the UK 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.

3.1.3 Safety in clinical practice

The two 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 one 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

3.2 Ranibizumab

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

Ranibizumab was licensed in the United States very recently and is expected to be licensed in the EU and United Kingdom by end of 2006 or early 2007. 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.

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.

3.2.1 Clinical Trials.

The MARINA Trial was a multicentre, randomised, double masked trial to test two doses of ranibizumab (0.3 and 0.5mg) in minimally classic and occult CNV in comparison with sham injections. The results showed that ranibizumab was effective in preventing vision loss in 95% in treated patients; however, in 25-35% of patients at 12 and 24 months vision improved by 15 letters.²²

The ANCHOR Study is a two year, phase 3, randomised, multicentre double-masked trial comparing efficacy and safety of monthly injections of 0.3mg and 0.5mg 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 one 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%.²³ Vision improved by 15 letters in 35-40% 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.

3.2.2 Use of Ranibizumab in clinical practice.

The results show that ranibizumab, at 0.3mg or 0.5mg 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.

3.2.3 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 non-ocular adverse events was observed. Approximately 95% of patients commenced the second year of the study thus indicating patient satisfaction.

3.2.4 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, it has a good safety profile from research data. Unlike pegaptanib, in a significant

proportion of patients not only is there a prevention of visual loss but also an improvement in visual acuity occurs.

3.3 Bevacizumab (Avastin).

Bevacizumab (Avastin, Genentech/Roche) is a full recombinant humanised monoclonal antibody with a molecular weight of 149KD (3 times the size of ranibizumab) which binds to all isoforms of VEGF-A (similar to ranibizumab).²⁵ It is glycosylated unlike ranibizumab, and has an Fc fragment unlike ranibizumab. The Fab domain of bevacizumab differs from ranibizumab by 6 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, 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 US 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.

4. Combination therapy with PDT and Anti-VEGFs.

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 re-treatments and reduce toxicity. Trials of such combinations are currently on going, including the PROTECT Study (combination of PDT and ranibizumab) and EOP 1012 (combination of PDT and pegaptanib).

5. 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 LVA: provision and advice on the use of optical aids, counselling are helpful in both dry and wet AMD.

5.1 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.

5.2 Extrafoveal CNV: Patients with extrafoveal CNV should be treated with focal laser photocoagulation as described in the MPS 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.

5.3 Predominantly classic subfoveal/juxtafoveal CNV: Presently all patients with predominantly classic AMD with subfoveal and juxtafoveal location may be offered PDT in the first instance. Where there is poor response to PDT in the treated eye, or in the other eye previously, trial of licensed anti-VEGFs may be used where available. In the absence of such availability then the use of unlicensed products including Avastin may be justified.

5.4 Occult subfoveal/juxtafoveal CNV: PDT may be considered for occult no classic CNV if costs are covered by local commissioning arrangements. In the absence of such arrangements then the use of anti-VEGF is recommended as in 5.3.

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

5.6 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.

5.7 There are significant resource (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 will evaluate, amongst other things, AMD service configurations and distribution, staff and other resource requirements.

5.8 Irrespective of the cost of the new anti-VEGF treatments, 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 in order to cope with this workload.

5.8 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 till August 2007, unless the process is especially expedited. Pegaptanib and ranibizumab will be evaluated, with PDT. Currently, it is anticipated that bevacizumab will not be evaluated as it is not licensed for treatment of AMD.

5.9 The Health Service Circular (HSC) 1999/176 advises Primary Care Trusts (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 non-funding of AMD treatments.

6. Future developments.

The definitive AMD guidelines are being prepared by a group using a clearly defined methodology which includes the consultation of all stakeholders. It is anticipated that a final draft of the guidelines will be sent to all consultant ophthalmologists for comment by May 2007.

References

1. Ferris FL III, Fine SL, Hyman L. Age-related macular degeneration and blindness due to neovascular maculopathy. *Arch Ophthalmol* 1984; 102: 1640-2
2. Klein R, Klein B, Linton RL. Prevalence of age-related maculopathy. The Beaver Dam Eye Study. *Ophthalmology* 1992; 99: 933-43.
3. Evans J. Causes of blindness and partial sight in England and Wales: 1990-1991. Her Majesty's Stationery Office, London. 1995.
4. Mitchell P, Smith W, Attebo K, Wang JJ. Prevalence of age-related maculopathy in Australia. The Blue Mountains Eye Study. *Ophthalmology* 1995; 102: 1450-60.
5. Olsen TW, Feng X, Kasper TJ, Rath PP, Steuer ER. Fluorescein angiographic lesion type frequency in neovascular age-related macular degeneration. *Ophthalmology* 2004; 111: 250-5.
6. Kvanta A, Algvere PV, Berglin L, Seregard S. Subfoveal fibrovascular membranes in age-related macular degeneration express vascular endothelial growth factor. *Invest Ophthalmol Vis Sci* 1996; 37:1929-34.
7. Lopez PF, Sippy BD, Lambert HM et al. Transdifferentiated retinal pigment epithelial cells are immunoreactive for vascular endothelial growth factor in surgically excised age-related macular degeneration-related choroidal neovascular membranes. *Invest Ophthalmol Vis Sci* 1996; 37 :855-868.
8. Age-Related Eye Disease Study Research Group (AREDS). Risk factors associated with age-related macular degeneration. A case-control study in the age-related eye disease study : Age-related Eye disease Study Report Number 3. *Ophthalmology* 2000; 107 :2224-32.
9. Age-Related Eye Disease Study Research Group. A randomised, placebo-controlled, clinical trial of high dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss : AREDS report no. 8. *Arch Ophthalmol* 2001; 119 : 1417-36.
10. Macular Photocoagulation Study Group. Argon laser photocoagulation for neovascular maculopathy. Three year results from randomised clinical trials. *Arch Ophthalmol* 1986; 104 :694-701.
11. Macular Photocoagulation Study Group. Recurrent choroidal neovascularisation after argon laser photocoagulation for neovascular maculopathy. *Arch Ophthalmol* 1986; 104:503-512.
12. Macular Photocoagulation Study Group. Laser photocoagulation of subfoveal neovascular lesions in age-related macular degeneration. *Arch Ophthalmol* 1991; 109: 1220-1231.
13. Macular Photocoagulation Study Group. Visual outcome after laser photocoagulation for subfoveal choroidal neovascularisation secondary to age-related macular degeneration. The influence of initial lesion size and initial visual acuity. *Arch Ophthalmol* 1994; 112:480-488.
14. Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularisation in age related macular degeneration with verteporfin: one year results of 2 randomised trials – TAP report 1. *Arch Ophthalmol* 1999; 117: 1329-45.

15. Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularisation in age related macular degeneration with verteporfin: two-year results of 2 randomised clinical trials – TAP report 2. Arch Ophthalmol 2001; 119:198-207
16. Verteporfin in Photodynamic Therapy Study Group. Verteporfin therapy of subfoveal choroidal neovascularisation in age-related macular degeneration: two-year results of a randomised clinical trial including lesions with occult with no classic choroidal neovascularisation – Verteporfin in Photodynamic Therapy report 2. Am J Ophthalmol 2001; 131:541-560.
17. Verteporfin in Photodynamic Therapy Study Group. Photodynamic therapy of subfoveal choroidal neovascularisation in pathologic myopia with verteporfin: one-year results of a randomised clinical trial including lesions with occult with no classic choroidal neovascularisation – VIP Report 1. Ophthalmology 2001; 108:841-52.
18. Gragoudas ES, Adamis AP, Cunningham ET Jr, Feinsod M, Guyer DR; VEGF Inhibition Study in Ocular Neovascularisation Clinical Trial Group. N Engl J Med 2004; 351:2805-16.
19. VISION Clinical Trial Group (D'Amico DJ et al). Pegaptanib sodium for neovascular age-related macular degeneration: two year safety results of the two year prospective, multicentre, controlled clinical trials. Ophthalmology 2006; 113: 992-1001.
20. Steffensmeier AC, Fuller JJ, Muller BA, Russell SR. Severe systemic allergic responses associated with vitreous injections of Pegaptanib sodium. Invest Ophthalmol Vis Sci 2006; 47: E-Abstract 4247.
21. Chang LK, Shah S, Chen J, Sarraf D. OCT imaging of RPE tears in patients receiving treatment with Macugen for AMD-related PED. Invest Ophthalmol Vis Sci 2006; 47: E-Abstract 2185.
22. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS et al for the MARINA Study Group. Ranibizumab for Neovascular Age-Related Macular Degeneration. N Engl J Med 2006; 355:1419-31.
23. Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS et al for ANCHOR Study Group Subgroup Analysis. Ranibizumab vrs Verteporfin for Neovascular Age-Related Macular Degeneration. N Engl J Med 2006; 355:1432-44.
24. Miller JW, Shapiro H, Acharya N and for the MARINA Study Group Randomized, Controlled Phase III Study of Ranibizumab (Lucentis) for Minimally Classic or Occult Neovascular Age-Related Macular Degeneration: Two-Year Safety Results of the MARINA Study. Invest Ophthalmol Vis Sci 2006;47: E-Abstract 3539.
25. Presta LG, Chen H, O'Connor SJ et al. Humanisation of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders. Cancer Res 1997; 57: 4593-4599.

Contributions to this document by Miss Brenda Billington, President, Professor David Wong, Senior Vice-President and Chair of the Scientific Committee, Mr Richard Smith, Chair of the Professional Standards Committee, and Mr Jon Gibson are gratefully acknowledged.

Winfried MK Amoaku
2nd November 2006