

Macular degeneration

— advances in treatment

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This article describes progress in the treatment of age-related macular degeneration, focusing on a new class of drugs which may be able to reverse vision loss. The medicines management considerations of these drugs are also discussed



Visual acuity tests are used to evaluate the effectiveness of new treatments for age-related macular degeneration

Age-related macular degeneration (AMD) is a degenerative disease and is one of the leading causes of sight loss in the UK. There are approximately 26,000 new cases of AMD diagnosed in the UK each year.¹

About 10 per cent of people with AMD have the “wet” type, which is the most severe (see p151).¹ The aim of pharmacological therapy for people with wet AMD is to alter the progression of vision loss. However, the advent of new drugs with the potential to revert the disease (those targeting vascular endothelial growth factor [VEGF]), heralds a new era in treatment.

This article describes the current treatment options for wet AMD, including photocoagulation and photodynamic therapy. It then examines evidence for the effectiveness and safety of the newer drugs, and discusses the medicines management considerations.

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— Photocoagulation therapy

The choroidal neovascular (CNV) lesions (see p151) that occur in wet AMD respond to treatment in the earlier stages of the disease process. In classic CNV lesions the growth of the lesion can be prevented by burning the abnormal vessels with a thermal laser. This is called photocoagulation and it may prevent the lesion from causing further visual deterioration.²

Although photocoagulation can successfully destroy the CNV lesion, the thermal laser also destroys the overlying retina, resulting in a scotoma (a localised defect in the visual field bordered by an area of normal vision).¹ Because of this, photocoagulation treatment is not usually suitable when the CNV lesion is subfoveal (directly beneath the centre of the fovea — the most crucial area for visual acuity) or juxtafoveal (near but not at the centre of the fovea).¹

Photocoagulation can be used to reduce the risk of severe visual loss in the 10–15 per cent of patients with extrafoveal CNV.^{1,2} However, recurrence rates of lesions have been quoted to be as high as 50 per cent over the three years following treatment.²

— Photodynamic therapy

In photodynamic therapy (PDT) a light-sensitive drug is administered by intravenous infusion, and activated by a low powered laser. The laser is calibrated to a specific wavelength which is applied over a circular area slightly larger than the lesion. The light is absorbed and the drug is activated. PDT aims to destroy CNV lesions without damaging the overlying retina so, unlike photocoagulation therapy, it can be used for subfoveal lesions. The only drug currently licensed in the UK for this indication is verteporfin.¹

Verteporfin Light activation of verteporfin in the presence of oxygen results in the formation of cytotoxic free radicals, which cause local damage to the neovascular endothelium, causing vessel occlusion with little or no damage to the overlying retinal pigment epithelium or photoreceptor cells. This process slows or halts the progression of vision loss.

Verteporfin was licensed in the UK in 2000 for predominantly classic or occult subfoveal CNV with evidence of recent or ongoing disease progression, or for subfoveal

Panel 1: Dose and cost of drugs used to treat age-related macular degeneration

Drug	Dose schedule	Cost per patient per year*
Verteporfin	6mg/m ² by intravenous infusion over 10 minutes. Repeated up to four times per year	£850–£3,400 (based on maximum treatment of four times per year) ⁴
Pegaptanib	0.3mg by intravitreal injection every six weeks for as long as the patient is shown to benefit	£4,626 (based on nine treatments per year) ⁴
Ranibizumab	0.5mg given by intravitreal injection once a month for three consecutive months. Patients should be monitored monthly thereafter and given further doses if loss of visual acuity (of more than five letters) occurs. Compared with continued monthly dosing, dosing every three months will lead to an approximate five-letter (one line) loss of visual acuity benefit, on average, over the following nine months.	£9,134 (if given monthly) £4,567 (based on six injections per year — one every month for three months and then three-monthly)
Bevacizumab	The optimum dose is unclear, but most studies have used either 1mg or 1.25mg by monthly intravitreal injection, until macular oedema, subretinal fluid or pigment epithelial detachment has resolved. The number of treatments needed is hard to establish.	£990 (based on monthly injections) The optimum frequency of administration has not been established

*Excluding VAT and add-on costs (eg, photodynamic therapy and delivery costs)

CNV secondary to pathologic myopia. Following publication of National Institute for Health and Clinical Excellence guidance, the licence for verteporfin was extended to include PDT in patients with lesions entirely composed of occult CNV.

Current NICE guidance recommends the use of verteporfin only in confirmed diagnoses of “classic with no occult” subfoveal CNV or “predominantly classic” CNV as part of a clinical trial.

When being assessed for AMD patients’ best-corrected visual acuity is measured, and an ophthalmic examination and fluorescein angiography is carried out. If there is evidence of active leakage from the CNV lesion or an increase in lesion size then PDT treatment is given. Patients undergoing a course of PDT treatment are seen as outpatients, at three-monthly intervals, for two years.

— New treatment options

Two drugs, pegaptanib and ranibizumab, have recently been licensed for the treatment of AMD, and bevacizumab is undergoing trials for treatment of the condition. The drugs are anti-angiogenic, inhibiting the formation of neovascular membranes to prevent further development of the condition and to improve vision. This is thought to happen due to inhibition of VEGF.³

Pegaptanib Pegaptanib is a selective inhibitor of the VEGF₁₆₅ isoform. It does not cure AMD but slows the progression of lesion growth in a proportion of patients.³ Pegaptanib was licensed in the UK for the

treatment of AMD in January 2006. Last July the Scottish Medicines Consortium announced that it had accepted pegaptanib for restricted use within NHS Scotland for the treatment of wet AMD.⁴ NICE is expected to publish a health technology appraisal covering ranibizumab and pegaptanib for the treatment of AMD in September.

Ranibizumab Ranibizumab is a crystallisable fragment of the humanised antibody bevacizumab (see below). It binds to and inactivates all isoforms of VEGF-A. Ranibizumab has been shown to improve vision and prevent ongoing vision loss. Since the antibody has a smaller structure than bevacizumab it may require more frequent administration. However, it also has greater affinity for VEGF than bevacizumab and since it is formulated for intraocular use more of the drug may penetrate all the layers of the retina.⁵

Ranibizumab was licensed in the UK for the treatment of wet AMD in January this year.

Bevacizumab Bevacizumab is a recombinant humanised monoclonal IgG1 antibody, licensed in the UK for intravenous use in the treatment of colorectal cancer. It binds to and inhibits the activity of all isoforms of VEGF-A. Early data suggest improvements in vision with bevacizumab treatment (see p158), although there have been no large controlled studies.

Unlike ranibizumab, bevacizumab is a full-sized antibody and so may stay in the eye for longer. While this may allow for less frequent administration and reduce the risk of injection-related adverse events, the risk

of systemic toxicity may be increased. The half-life of bevacizumab is longer than that of ranibizumab, so bevacizumab could be associated with more systemic toxicity if it leaks into the circulation, but this has not been formally investigated.⁵

Panel 1 summarises the dose and cost per patient per year of the drugs used to treat AMD, and Panel 2 (p158) summarises their adverse effect profiles.

The following section in this article considers evidence for intravitreal use of the anti-VEGF drugs. Trial names are written in full in Panel 3 (p160).

— Pegaptanib

Evidence suggests that pegaptanib is not curative in AMD³ but compared with sham injections it slows lesion growth in a proportion of patients who would otherwise have experienced loss of vision, especially during the first year of treatment.³

Pegaptanib was compared with sham injections in two prospective phase II/III randomised controlled trials involving 1,208 patients.^{3,6} Patients were eligible for inclusion if they were over 50 years of age and had subfoveal sites of CNV secondary to AMD. For ethical reasons, the use of PDT with verteporfin was permitted in patients with predominately classic lesions, at the discretion of the ophthalmologist.

A total of 1,186 patients received a study treatment of varying doses of pegaptanib or sham injections, administered every six weeks for 48 weeks (nine treatments). Combined data from the trials showed that 70 per cent of pegaptanib recipients

(0.3mg, N=294) versus 55 per cent of sham injection recipients (N=296) had a loss of visual acuity (fewer than 15 letters on a visual acuity test) at week 54 ($P<0.001$). An extension of these studies to week 102 showed that pegaptanib was less effective during the second year than during the first year of treatment.^{3,6}

— Ranibizumab

ANCHOR was a phase III, randomised, two-year, controlled study comparing two different doses of ranibizumab (0.3mg and 0.5mg monthly) with PDT (three monthly) in 423 patients with predominantly classic subfoveal wet AMD.⁷ Results showed that 94 per cent of patients treated with 0.3mg ranibizumab and 96 per cent of those treated with 0.5mg ranibizumab lost fewer than 15 letters in visual acuity compared with baseline, compared with 64 per cent of those treated with PDT ($P<0.0001$).

One year results from this study showed a difference in mean change in visual acuity of 18 letters for patients treated with 0.3mg ranibizumab and 21 letters for those treated with 0.5mg compared with those treated with PDT. Patients treated with ranibizumab gained an average of 8.5 letters in the 0.3mg dose group and 11 letters in the 0.5mg dose group compared with patients treated with PDT, who lost an average of 9.5 letters.⁷

The phase III MARINA study was a randomised, two-year, controlled study evaluating the safety and efficacy of ranibizumab in 716 patients with minimally classic or occult wet AMD.⁸ At 24 months, 92 per cent of patients treated with 0.3mg ranibizumab and 90 per cent of those treated with 0.5mg ranibizumab lost fewer than 15 letters compared with baseline, compared with 53 per cent of those treated with sham injections. Patients gained an average of six letters in visual acuity compared with study entry, while those in the control group lost an average of 15 letters.

These results indicate that ranibizumab does not just slow vision loss, but improves vision from baseline in patients with wet AMD. Pegaptanib delays but does not prevent ongoing vision loss.

The PIER study involved 184 patients in the US with AMD.⁹ Ranibizumab was

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Panel 2: Adverse effects of the anti-VEGF agents

Pegaptanib

The most frequently reported adverse effects of pegaptanib (reported in 10–40 per cent of patients) include anterior chamber inflammation, blurred vision, cataract, conjunctival haemorrhage, corneal oedema and eye discharge, irritation or pain.^{3,6} Data from animal studies and *in vitro* experiments suggest the potential for serious systemic adverse effects with VEGF antagonists. However, pegaptanib has been studied for periods of no longer than two years in a relatively small number of patients and some patient groups were excluded from the trials (eg, those with cardiac, cerebral or peripheral vascular disease).^{3,6} Rare reports of anaphylactic reactions, including angioedema, have been highlighted.

Ranibizumab

Common, mild to moderate adverse effects seen with ranibizumab treatment include: conjunctival haemorrhage, eye pain, increased intraocular pressure and vitreous floaters.⁸ Other, less common serious ocular adverse events include endophthalmitis and intraocular inflammation.

Cerebral vascular events and myocardial infarctions were observed in all three arms of the phase III MARINA and ANCHOR studies.^{7,8} In the MARINA trial the rate of arterial thromboembolic events at 24 months was 3.8 per cent in the sham injection group and 4.6 per cent in those on 0.3mg and 0.5mg of ranibizumab.⁸ In the ANCHOR study, arterial thromboembolic events were seen in 2.2 per cent of patients in the 0.3mg group, 4.3 per cent in the 0.5mg group and 2.1 per cent in the verteporfin group.⁷

Bevacizumab

An internet site has been developed to collect global data on adverse events associated with bevacizumab injections in ocular disease.¹⁴ From November 2005 to April 2006, 70 centres responded to the survey, reporting 7,115 intravitreal injections in 5,228 patients. The treatment-related adverse events included corneal abrasion (0.15 per cent), endophthalmitis (0.1 per cent), and retinal detachment (0.01 per cent). The potentially drug-related adverse events included 10 cases of inflammation (0.14 per cent), five cases of acute vision loss (0.07 per cent) 15 blood pressure elevations (0.21 per cent), one transient ischaemic attack (0.01 per cent), five cerebral vascular accidents (0.07 per cent), four episodes of new or increased subretinal haemorrhage (0.06 per cent) and two deaths (0.03 per cent).

administered monthly for the first three months, and then once every three months for a total of 24 months. After an initial increase in visual acuity (following monthly dosing), patients given ranibizumab once every three months on average lost visual acuity, returning to baseline at month 12.⁹

Further studies are ongoing to investigate the effect of different reduced dosing schedules for ranibizumab.

— Bevacizumab

Several trials have examined the use of bevacizumab for AMD although not all are fully published. They have tended to be small, uncontrolled, retrospective trials or individual case reports. There have not yet been any large, prospective, randomised controlled trials conducted that have examined the safety and efficacy of bevacizumab therapy in patients with wet AMD. Several centres throughout the UK are using bevacizumab (off-licence) for AMD, often in private patients or as part of a trial. There is also considerable worldwide use of bevacizumab for AMD and some of the larger studies have been published recently.

A non-randomised, uncontrolled retrospective case study of bevacizumab use in 266 patients (266 eyes) has been published.¹⁰ Each patient received 1.25mg intravitreal bevacizumab. At month 1, the visual acuity of 67 patients had improved, and had worsened in 13 patients.² At month 3, 54 patients had improved visual acuity and 10 had worsened.¹⁰ Mean central macular thickness had improved at month 1 compared with baseline measurements.

In one uncontrolled open label study involving 79 patients (81 eyes) with subfoveal neovascular AMD, intravitreal bevacizumab was investigated for the short term safety, biological effect and possible mechanism of action.¹¹ This study suggested that intravitreal bevacizumab (monthly intravitreal injections of 1.25mg for three months) is well tolerated and associated with improvement in visual acuity, decreased retinal thickness and reduction in angiographic leakage in most patients, the majority of whom had previous treatment with PDT or pegaptanib.¹¹

A retrospective case series report on 48 patients with subfoveal CNV secondary to AMD who received 1.25mg intravitreal bevacizumab suggested a statistically

significant improvement in visual acuity, macular thickness and macular volume.¹²

The National Eye Institute in the US has recently 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.¹³

— Medicines management

Organisations such as the Royal National Institute for the Blind (RNIB) and AMD Alliance UK are considering the implications for the NHS of the new drugs for AMD.¹⁵

A recent statement from the Royal College of Ophthalmologists states: "The guiding principle is that patients with AMD (like any other disease) should receive whatever

treatment is in their best interests. Until NICE makes a definitive ruling on the new treatments for AMD ophthalmologists should use their judgement and experience when recommending treatments. Regional inequalities in NHS provision are unacceptable."¹³

This puts pressure on local providers to deliver therapies but, until the NICE guidance is published, regional inequalities are likely to arise.

Whereas verteporfin has specific indications, the newer agents are likely to have broader indications, with increased numbers of patients being eligible for treatment. Estimates by the RNIB and NICE indicate that there may be 26,000 patients eligible for the new anti-VEGF treatments in the UK each year compared with the 7,000 currently eligible for PDT.¹³ This will increase the capacity pressures on ophthalmology clinics.

The future The notion of combining anti-VEGF treatment with PDT and other treatments is already being explored and the introduction of combination therapies in the future could have a big impact on the number of patients who may benefit.¹³

Despite reports of bevacizumab being used off-license there remains a lack of well designed, controlled prospective studies that have examined its efficacy and safety. There

is also a lack of published safety data on the retinal toxicity of bevacizumab compared with that of pegaptanib or ranibizumab. The unlicensed status of bevacizumab, its cost compared with that of ranibizumab, and the fact that PDT is a payment-by-results exclusion all require consideration now that ranibizumab is licensed.

Pending the publication of NICE guidance, decisions will have to be made by trusts on how such agents should be made available. They must be prescribed with due consideration to pharmaceutical, clinical, ethical, economic and practical issues.

A paper by the RNIB suggests that a dialogue has started among primary care trusts nationally, with regard to developing a common evidence-based approach to the managed introduction of anti-VEGF treatments.¹⁵ The financial consequences for local health economies will be significant and commissioners, PCTs and provider trusts will need to work closely to ensure access to these treatments is introduced in a consistent and equitable way.

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Suggestions for future special features

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Panel 3: Trials of ranibizumab

Acronym	Trial name
ANCHOR	Anti-VEGF antibody for the treatment of predominantly classic choroidal neovascularisation in age-related macular degeneration
MARINA	Minimally classic/occult trial of the anti-VEGF antibody ranibizumab In the treatment of neovascular age-related macular degeneration
PIER	A phase IIIb, multi-centre, randomised, double-masked, sham injection-controlled study of the efficacy and safety of ranibizumab in subjects with subfoveal choroidal neovascularisation with or without classic CNV secondary to age-related macular degeneration

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