Posterior Segment  Age-related Macular Degeneration

Treatments for Age-related Macular Degeneration

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Abstract
Age-related macular degeneration (AMD) is the most common cause of irreversible visual loss in the developed world. There are two types of AMD: dry and wet. The exact cause of the disease is unknown, but it is thought to result from interplay of genetic and environmental factors.

Key words
Macular degeneration, age-related, ocular nutritional supplements, laser photocoagulation, verteporfin, photodynamic therapy (PDT), pegaptanib, ranibizumab, bevacizumab, vascular endothelial growth factor (VEGF), VEGF Trap

Age-related macular degeneration (AMD) is the most common cause of irreversible visual loss in the western world. Broadly, there are two types of AMD: dry and wet. The dry form is characterised by drusen formation and a slow, progressive focal atrophy of the macular retinal pigment epithelium (RPE) and inner choroid. This in turn leads to secondary atrophy of the overlying photoreceptors. Over time, this focal atrophy spreads to involve large parts of the macula, leading to so-called geographic atrophy. The initial symptoms reported by patients include gaps in images or words and slow progressive blurring. With time, these focal defects enlarge to produce a central scotoma.

Wet AMD is characterised by the growth of abnormal new vessels arising from the inner choroid. These new vessels, called choroidal new vessels (CNVs), penetrate Bruch’s membrane and grow under the RPE or, with further penetration of the RPE, to the potential space under the neuroretina (photoreceptors). The clinical features include retinal and subretinal haemorrhages, retinal pigment epithelial detachment (serous or haemorrhagic), exudates and fibrous proliferation in the late stage. The majority of CNVs in AMD involve the subfoveal area and are stimulated by growth factors such as vascular endothelial growth factor (VEGF) and fibroblastic growth factor (FGF). Other growth factors have also been demonstrated to be involved in AMD.

The new treatments for wet AMD are repetitive, and have significant service implications. These implications occur irrespective of which anti-VEGF agent is adopted. Visual rehabilitation is still important in the management of AMD.
of people under 55 years of age had advanced AMD; however, this increased to 18.5% over 85 years of age. It is estimated that there are approximately 215,000 people with wet AMD in the UK, with an estimated incidence of wet AMD in the UK of 26,000. It is further accepted that approximately 10% of patients with wet AMD in the first eye will develop similar pathology in the other eye with every passing year. With current demographic changes with a skew towards a more elderly population, the number of people with AMD is likely to increase even further, with marked health economic implications.

Risk Factors
The exact cause of AMD remains elusive. AMD is probably a multifactorial disease affected by both genetic and environmental factors. This may account for the wide variation in phenotypes.

A number of large epidemiological studies have identified a number of risk factors. Increasing age is an undoubted risk factor; however, this, unfortunately, is not modifiable. Smoking has been shown to increase the risk of AMD by between three- and four-fold. Therefore, smoking cessation regimes offer the prospect of dramatically reducing the incidence of severe visual loss secondary to AMD. The finding of macular hard drusen (small yellow sub-retinal deposits) increases dramatically with advancing age without significant risk of advanced AMD; however, the possession of the large, soft drusen increases the risk of advanced AMD by between five- and 10-fold. In addition, the finding of advanced AMD (e.g. CNV secondary to wet AMD, or geographic atrophy) in one eye means that there is a 50% risk of the fellow eye developing a similar lesion over five years. Other factors such as obesity, diets high in saturated fat content and high alcohol consumption, all of which result in low body antioxidant levels, may predispose to the development and progression of AMD.

In 2000, Mullins et al. demonstrated that drusen in AMD had a significant inflammatory element. This was linked to the major breakthrough in our understanding of the genetic risks of AMD pathogenesis in 2005. The discovery that the complement system in some way played a role in AMD confirmed the existence of an immune-related mechanism in the pathogenesis of the disease. Several genes are now known to play an important role in the pathogenesis of AMD: the complement factor H (CFH) gene on chromosome 1, a region on chromosome 10 harbouring the gene for protein LOCS5715, the serine protease HTRA1 gene, the complement factor B (CFB) and complement component 2 (CC2) genes on chromosome 6 and the complement component 3 (CC3) gene on chromosome 19. Treatments based on genetic modifications in humans are yet to be tested.

Diagnosis
Diagnosis of AMD is dependent on clinical features and ancillary investigations. In particular, retinal imaging with fundus fluorescein angiography (FFA) and optical coherence tomography (OCT) are an integral part of patient management and are required for confirmation of diagnosis and for monitoring response to therapy, especially in wet AMD. As such, treatments should not be initiated in any patient without adequate imaging with FFA and OCT. Indocyanine green angiography (ICG-A) provides information that complements that derived from FFA to optimise the management of AMD patients. Angiographic subtypes of wet AMD include classic, occult or mixed lesions. Retinal angiomatosus proliferations (RAPs) represent anastomoses between the retinal and choroidal vasculature and occur secondary to CNVs, especially of the occult type. Irrespective of whether they arise from the choroidal or retinal vasculature, RAPs leak and alter the behaviour of the CNV lesion to therapy. Idiopathic polypoidal choroidopathy (IPCV) is an atypical form of neovascular AMD in which highly exudative lesions with haemorrhagic pigment epithelial detachments are seen adjacent to the optic disc. These lesions are best visualised with ICG-A, which shows dilated grape-like or polypoidal complexes in the inner choroid.

Treatments for Age-related Macular Degeneration

No treatment exists for dry AMD to date. However, there has recently been growing interest in developing treatments for dry AMD following significant improvements in therapies for wet AMD.

At present, progression of the disease may be modified with ocular nutritional supplements. Subgroup analysis of a large multicentre, randomised, placebo-controlled trial (the Age-Related Eye Disease Study [AREDS]) suggested that progression from early to advanced AMD could be reduced by as much as 25% in high-risk patients by daily supplements of vitamins C (500mg) and E (400IU), zinc (80mg) and beta carotene (15mg). On the basis of these results, the AREDS research group recommend that people over 55 years of age should undergo dilated fundus examinations to determine their risk of developing advanced AMD. Those with high-risk characteristics should consider taking supplements and antioxidants plus zinc. Importantly, however, this formulation is not recommended for smokers because beta carotene has been shown to increase the risk of lung cancer. There is also evidence to suggest that those individuals with a high intake of the macular pigments lutein and zeaxanthin were at reduced risk of AMD. There is an ongoing large international trial investigating the value of lutein/zeaxanthin and omega-3 long-chain polyunsaturated fatty acid supplementation in AMD (AREDS 2 trial); this trial is not expected to report for a number of years.

Treatments for Wet Age-related Macular Degeneration

Until recently, the main modalities for treatment of wet AMD were physical and included focal laser photocoagulation in small extrafoveal CNVs and photodynamic therapy (PDT) for subfoveal/juxtafoveal lesions. Pharmacological treatments have evolved for wet AMD based on our recently improved understanding of the pathophysiology of the disease and similarities to vascular biology in cancer therapy.

Laser Photocoagulation
The Macular Photocoagulation Study Group (MPSG) for wet AMD has shown that laser photocoagulation with conventional thermal laser is effective for extrafoveal lesions, and destroys the CNV before ingrowth to the fovea has occurred. The burns must be confluent, totally covering the lesion, extending into the normal retina surrounding the lesion and of adequate intensity to fully ablate the CNV without rupturing Bruch’s membrane. However, the effectiveness of this treatment is limited by the resultant scotoma in the visual field, by the high recurrence rate of CNV and by the fact that only small classic CNVs that are extrafoveal at presentation can be treated in this way. 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 photoocoagulation is not recommended for eyes with subfoveal CNV because of the immediate visual loss that results from foveal photoreceptor and RPE damage. Laser photoocoagulation is also less useful and not generally recommended for juxtapfoveal CNV. This is because of the potential immediate collateral damage to the fovea from the laser burn, or later encroachment of the scar on the fovea.51,52

### Photodynamic Therapy with Verteporfin

PDT with verteporfin destroys CNV without damaging the overlying neurosensory retina, thereby allowing subfoveal lesions to be treated.53 Verteporfin PDT acts through occlusion of the newly formed, actively growing vessels of the CNV lesion while avoiding damage to the other choroidal blood vessels and the RPE (within limits). In clinical trials, PDT with verteporfin has been shown to be effective in reducing visual loss compared with placebo-treated patients with classic and predominantly classic subfoveal CNV secondary to AMD.54,55 In addition, the Verteporfin in Photodynamic therapy (VIP) study showed that after two years, PDT with verteporfin significantly reduced the risk of moderate to severe visual loss in patients with occult and no classic CNV.56 Similar findings have been reported for CNV secondary to myopia.57 However, the EU licence for the use of PDT in the treatment of occult CNV was subsequently revoked: the Committee for Medicinal Products for Human Use (CHMP) recommended deletion of the indication of visudyne PDT in patients with occult CNV as the risk–benefit profile was no longer considered favourable following reports from the Visudyne PDT in Occult CNV (VIO) study (see EU Marketing Authorisation Number EU/1/00/140/001).

### Anti-vascular Endothelial Growth Factors

Although several growth factors, including FGF, platelet-derived growth factor (PDGF) and placental growth factor (PiGF) have been identified in CNV, VEGF is thought to be the most significant growth factor in the development and growth of CNV in wet AMD.11–17 This has led to the development of molecular inhibitors of VEGF, including pegaptanib (Macugen), ranibizumab (Lucentis) and others, as treatments for wet AMD.

### Pegaptanib Sodium

Pegaptanib (Macugen, Pfizer/Osi Eyetech) is a pegylated modified oligonucleotide, an aptamer, with a molecular weight of 20kD that binds isoform 165 of VEGF (VEGF 165), inhibiting its activity. VEGF 165 is the isoform of VEGF that was originally thought to be preferentially increased in pathological neovascularisations18 and CNV.

#### Clinical Trials

The VEGF inhibition Study in Ocular Neovascularisation (VISION) trial19–27 was a multicentre, prospective, randomised, dose-ranging, double-blind, controlled trial of pegaptanib at doses of 0.3, 1.0 and 3.0mg or sham injections administered every six weeks. The study was run in two concurrent arms (US Food and Drug Administration [FDA] regulations) over an initial period of 48 weeks, subsequently extended to two years. The results showed that more patients who received pegaptanib 0.3mg compared with sham injections maintained their vision and, furthermore, that severe visual loss was reduced. Vision improved by 15 letters in 6% of patients and was maintained in 33%. Pegaptanib (Macugen) at 0.3mg is therefore effective in the treatment of all subtypes of CNV secondary to AMD.

### Use of Pegaptanib in Routine Clinical Practice

Pegaptanib (Macugen) was licensed for use in the US in December 2004. It was licensed by the European Medicines Agency (EMEA) at a dose of 0.3mg in February 2006, and launched in the UK in May 2006. Substantial experience of its use was accrued from clinical trials and private medical practice in the EU and worldwide prior to approvals and subsequently.58–64

The VISION entry criteria may provide a guide for clinical practice.65 In that trial pegaptanib was used to treat lesions of any subtype with the greatest linear diameter of 12 disc diameters or fewer and visual acuities (VAs) between approximately 6/12 and 1/60. CNV lesions of the minimally classic and occult type were required to demonstrate progression (of different indicators) before treatment. Pegaptanib is administered at six-weekly intervals.

### Safety in Clinical Practice

The two-year safety data from VISION are reassuring. Injection-related endophthalmitis (0.16%/injection) in the first year was attributed to violations in the injection preparation protocol.66 Significant reductions in endophthalmitis rates were achieved when these violations were curtailed.

There have been some reports of severe systemic allergic reactions associated with intravitreal pegaptanib injections, which may occur up to one hour following the injection.67 Similarly, there have been a few reports of retinal pigment epithelial rips following treatment with pegaptanib. However, as these can occur spontaneously or following laser treatment, their occurrence cannot be attributed to the administration of pegaptanib.68

The use of pegaptanib has gone into decline recently following the availability of ranibizumab and bevacizumab.

### Ranibizumab

#### Clinical Efficacy and Clinical Trials

Randomised, double-blind, controlled, multicentre phase III trials (ANCHOR, MARINA and PIER) have evaluated the efficacy of intravitreal ranibizumab in the treatment of neovascular AMD.18–24 Other trials include SUSTAIN, SAILOR and EXCITE.

The MARINA study compared ranibizumab 0.3mg/month (n=238) or 0.5mg/month (n=240) with sham injections (n=238) in eyes with minimally classic or occult subfoveal neovascular AMD for two years.69 The ANCHOR study compared ranibizumab 0.3mg/month (n=140) or 0.5mg/month (n=140) with verteporfin PDT at baseline and repeated every three months as required (n=143) over two years in patients with predominantly classic CNV.70–72

The study outcomes were similar in the ANCHOR and MARINA trials: VA was at least maintained in 94–96% of eyes receiving ranibizumab at one year and in 90–92% at two years compared with 62 and 53%, respectively, at one and two years in PDT-treated controls (p<0.001).70–73 VA improved by 15 or more letters in 25–40% of patients receiving ranibizumab at one year and 26–33% at two years in these trials compared with 5–6 and 4% at one and two years, respectively, in the controls (p<0.001).70–73 An overall VA gain of seven to 11 letters at one year and five to seven letters at two years was achieved compared with VA loss of 10 and 15 letters at one and two years, respectively, in the sham injection group and a loss of 10 and 9.8
letters at one and two years, respectively, in the PDT group.\textsuperscript{41–44} Severe VA loss (>30 letters) occurred in <1% of the ranibizumab-treated patients compared with 13% of controls at one year and in 3 and 23%, respectively, at two years in the MARINA study (p<0.001).\textsuperscript{61,65} While in the ANCHOR Study severe visual loss (>30 letters) occurred in only 1.4% of the patients treated with the 0.3mg dose and none in the 0.5mg group compared with 16.1% in the PDT group.\textsuperscript{64}

Subgroup analyses indicated that the VA changes were consistent across all sexes, ages, lesion types and baseline lesion sizes.\textsuperscript{41–44} The most important predictors of VA outcomes were baseline VA score, CNV lesion size and patient age.\textsuperscript{66,67} Angiographic and OCT analyses of the MARINA study have shown consistent improvement in FFA leakage and OCT thickness in eyes treated with ranibizumab compared with sham-treated eyes.\textsuperscript{68}

Quality of life (QoL) analyses in the MARINA study showed that ranibizumab-treated patients had significantly improved QoL after treatment compared with the sham-treated group.\textsuperscript{49} Similarly, QoL was significantly better at up to 24 months in the ranibizumab-treated group compared with the PDT group.\textsuperscript{49} This was especially so for near activities, distance activities and dependency (p<0.001).\textsuperscript{69,70}

The PIER study was designed to determine whether a less frequent dosing regime after initiation with ranibizumab every month for three doses was enough to prevent visual loss in patients with subfoveal wet AMD.\textsuperscript{71} It compared ranibizumab 0.3mg/month (n=60), 0.5mg/month (n=61) and sham injections (n=63) given for three doses, and identical single doses repeated at three-monthly (quarterly) intervals for two years in all types of CNV. The results from this study indicated that the quarterly dosage of ranibizumab after the initial loading was not enough to maintain the VA gain attained after month three compared with continued monthly dosing. However, the VA outcome was still significantly better in the ranibizumab-treated group compared with the 16-letter VA loss in the sham-treated group.\textsuperscript{72}

The SUSTAIN study was an open-label, multicentre phase IIIb/IV trial where ranibizumab at 0.3 or 0.5mg/month was administered for three doses followed by dosing as required based on VA and OCT criteria at monthly intervals for 12 months. The interim analysis (which included 71 patients) showed that the average number of treatments required in the 12 months was 5.3.\textsuperscript{73} Similarly, the final report showed that an average total of 5.6 injections were required over 12 months (Novartis, data on file). However, the VA gain achieved with the SUSTAIN regime was not as impressive as that achieved with regular monthly dosing as in the ANCHOR and MARINA studies.\textsuperscript{74} Subgroup analysis of the SUSTAIN data showed that there were three distinct responder groups: the first group maintained their initial VA gain with no or only minimal re-treatment, the second required more injections to maintain the initial gain, which otherwise deteriorated, and the third group had progressive VA loss in the maintenance treatment phase (Novartis, data on file).

Results from SAILOR, a 12-month phase IIIb study of monthly administration as required of ranibizumab after an initial three monthly doses according to protocol-defined VA or OCT changes, showed that there was reduced benefit at 12 months compared with the monthly dosing regimes. However, as baseline VA decreased, the degree of VA improvement was better.\textsuperscript{75} The results from EXCITE, in which the three initial monthly loading doses of ranibizumab (0.3 or 0.5mg) followed by monthly or quarterly doses of 0.3mg ranibizumab, show that in the quarterly treated group the VA improved by 4.0 letters in the 0.3mg group and 2.8 in the 0.5mg group. Subgroup analysis identified responder groups similar to those in the SUSTAIN study (Novartis, data on file).

When data from the four studies (MARINA, ANCHOR, PIER and SAILOR) were combined, the acute thromboembolic event (ATE) rate\textsuperscript{76} was 2.7%, which was not statistically different from that in the control group.\textsuperscript{77,78} In the second year of the MARINA study, the rate of ATE events was similar in patients treated with ranibizumab 0.5mg (2.6%) and patients in the control arm (3.2%).\textsuperscript{79} Analyses of pooled two-year data from the MARINA, ANCHOR and PIER trials showed that there were no safety concerns as the rate of ATE was 4.1% after year two, which was comparable to that in the control group. There was a non-statistically significant difference towards a higher rate of stroke in the 0.5mg ranibizumab group compared with controls, no such difference was noted for myocardial infarctions (MIs).\textsuperscript{76} In further meta-analysis of the MARINA, ANCHOR, FOCUS, PIER and SAILOR data there was no statistically significant difference in ATEs, although prior stroke was the significant risk factor for stroke in cohort 1 of the SAILOR study.

Bilateral intravitreal administration of ranibizumab has not been formally investigated in trials. Theoretically, bilateral simultaneous administration of ranibizumab could lead to an increased systemic exposure, with a possible increase in the risk of systemic adverse events. So far, post-marketing clinical experience of bilateral simultaneous administration of intravitreal ranibizumab has not highlighted any safety concerns as long as asepsis is observed and instruments are changed between the two eyes.

**Contraindications**

Hypersensitivity to ranibizumab or to any of the excipients in Lucentis is a contraindication. Although not investigated, it is possible that a hypersensitivity reaction to ranibizumab will result in a similar reaction to bevacizumab. Similarly, ranibizumab should be avoided in eyes with active severe intraocular inflammations as such administration may aggravate the inflammation. It is also advised that ranibizumab should not be administered concurrently with other anti-VEGF agents (systemic or ocular) as this will result in increased systemic exposure and potential toxicity. Ranibizumab is also to be avoided in eyes with rhegmatogenous retinal detachment and grade 4 macular holes.\textsuperscript{76}

**Dosage and Administration/Different Regimes**

In the US, the recommended dosing regime for ranibizumab is 0.5mg delivered by intravitreal injection monthly. After the first four doses, treatment may be given quarterly or as required.\textsuperscript{80}

In the EU, including the UK, the recommended dose of ranibizumab in wet AMD is 0.5mg given intravitreally. The recommended regime is initiation with three monthly doses, after which, in the maintenance phase, treatment is given as required based on visual acuity outcomes.\textsuperscript{81} In the UK in particular, the Royal College of Ophthalmologists (RCOphth) guide advises treatment as in the summary of product characteristics, with treatment guided by LogMAR visual acuity and OCT changes.\textsuperscript{82}

**Current Status**

Ranibizumab (Lucentis) has been licensed by the EMEA and FDA for the treatment of neovascular membrane of all lesion types. In the UK,
Posterior Segment  Age-related Macular Degeneration

the National Institute for Health and Clinical Excellence (NICE), after a protracted evaluation, has recommended ranibizumab in the treatment of eyes with subfoveal CNV of all lesion types secondary to AMD.48 The VA restrictions in the guidance were based on the inclusion criteria of the pivotal ranibizumab studies. However, the ROCophth guide advises clinicians to offer treatment in all eyes with VA better than LogMAR 1.2, i.e. there are no upper VA limitations.19 RAPS that occur as part of CNV respond better to ranibizumab than to PDT or focal laser photocoagulation, although there are no randomised controlled trials to date.18,19 The efficacy of ranibizumab in the treatment of IPCV is yet to be fully established; however, The Asia SUMMIT (EVEREST) study suggests that combination therapy with PDT and ranibizumab is more efficacious than monotherapy in the treatment of IPCV (see below) (Novartis, data on file).

Emerging evidence suggests that ranibizumab is also effective in the treatment of subfoveal CNV secondary to causes other than AMD, e.g. myopia, angioid streaks, idiopathic and inflammation.83–85 It is expected that the indication of ranibizumab will be extended to CNV and will be completely inferred from those of ranibizumab.89,90 The biological similarity of bevacizumab to ranibizumab87,95,96 may imply potentially higher ocular and systemic adverse events, including RPE atrophy, subfoveal fibrosis and RPE tears. Recent studies have reported that there are significant differences in the immunoglobulin G (IgG) content in pre-packaged bevacizumab syringes, and that micron-sized protein aggregates increase with the attendant decrease in IgG content of the syringes. Such large aggregates may lead to aqueous outflow obstruction with subsequent intraocular pressure rise.96

In effect, there are no safety data available for intravitreal bevacizumab. Furthermore, there are no formal avenues for reporting adverse events associated with bevacizumab in most countries. Reporting mechanisms for adverse events are unclear, and even where such avenues exist, reports are arbitrary and subject to physician discretion. It is therefore highly possible that there is under-reporting of adverse events.

**Combination Therapy with Photodynamic Therapy and Anti-vascular Endothelial Growth Factors**

It was postulated that combination therapy with PDT and anti-VEGFs may prove to be even more effective than either therapy on its own as the two treatments had different, probably complementary, mechanisms of action. Potentially, such combinations will improve efficacy, reduce frequency of re-treatments and reduce toxicity. However, the combination of pegaptanib and PDT (Macugen, Pfizer/OSI Eyetech EOP1012) has been disappointing as no difference was observed between the monotherapy and the therapy groups, although there were no safety concerns (Pfizer, data on file).

Results from the FOCUS study98 and the PROTECT study99 showed that the combination of PDT and ranibizumab was safe and that re-treatment rates may be reduced, with good outcomes.100 Similar safety studies had been previously reported in monkeys. Randomised controlled trials of such combinations, including the SUMMIT (MONT BLANC, DENALI, EVEREST) combinations of PDT and ranibizumab, have been completed and are awaiting publication. The preliminary data
Treatments for Age-related Macular Degeneration

from these phase III trials of combination therapy of ranibizumab and PDT in wet AMD have not lived up to the promise of significantly reducing the frequency of injections as well as improving visual outcomes, except in EVEREST (for IPCV), where there was a significant difference in treatment frequency and outcome with combination therapy compared with monotherapy with either ranibizumab or PDT.\textsuperscript{101–103} No safety concerns were noted with the combination therapy.

However, it is implied that patients who have failed to respond to PDT may be safely transferred to anti-VEGF therapy without any risk. Similarly, patients unresponsive to ranibizumab monotherapy may benefit from combination therapy with PDT.

Future Developments and Applications

Despite its cost, ranibizumab, especially when given every month, is considered the gold standard in the treatment of CNV secondary to wet AMD. Combination therapy of ranibizumab and PDT is under investigation at present. However, monthly dosing of ranibizumab and other anti-VEGF agents as treatment of AMD presents a significant logistical challenge to clinical services worldwide. Significant strides would be made with treatment regimes that result in reductions in patient traffic through AMD clinics.

Extended-release preparations that will deliver ranibizumab over prolonged periods (three to six months) are as such systems will remove the need for repeated monthly intravitreal injections. Such development will improve the logistical bottlenecks in service delivery, as well as reducing injection-related risks such as endophthalmitis, retinal detachment and cataracts. However, the enthusiasm for such systems has to be tempered with the potential increased risk of the undesirable effects of chronic VEGF antagonism in the neuro-retina, as VEGF is known to be neurotrophic.\textsuperscript{104}

There is hardly any competition from pegaptanib at the moment (at least in the UK), as it is considered less efficacious than ranibizumab in the treatment of wet AMD, and therefore is not recommended by NICE. However, in the presence of very high cardiovascular risk or known/suspected allergy to ranibizumab, it would seem prudent to advise pegaptanib, even in the absence of direct evidence of comparisons.

Afirmecept (VEGF Trap, Regeneron Pharma/Bayer Schering) is a new molecule designed to block VEGF-mediated angiogenesis. It contains immunoglobulin domains of both VEGFR-1 and VEGFR-2 fused to a constant region,\textsuperscript{105} and neutralises VEGF and PI GF. This dual action may be an advantage over simple VEGF blockade. Phase I and II trials indicated no safety concerns, and there were VA gains and OCT reduction in central retinal thickness.\textsuperscript{106–108} It is possible that the treatment intervals may be slightly less frequent than with ranibizumab.

Pre-clinical and phase I studies have indicated that PDGF-B blockage may give increased efficacy in abrogating CNV, especially in combination with anti-VEGFs.\textsuperscript{109} The role of radiotherapy in combination with anti-VEGF therapy is yet to be fully assessed.

Visual Rehabilitation

For patients with advanced dry or wet AMD unresponsive to treatment, visual rehabilitation offers the potential of maximising the use of the patient’s remaining vision. Low-vision clinics are available in most hospital optometry units and some community optometrist services. These services encompass advice on large-print books, optimum lighting and the use and provision of hand- and spectacle-supported magnifying devices and closed-circuit television (CCTV) devices. More recently, a number of training courses have become available for patients to learn to use eccentric fixation outside the area affected by disease for tasks such as reading.

Recommendations for Clinical Practice

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. Antismoking advice must be given to patients with all types of AMD. A healthy lifestyle must be stressed. Supportive measures such as low-vision aids cannot be overemphasised. The provision of, and advice on the use of, optical aids, and also counselling, are helpful in both dry and wet AMD.

It is recommended that ophthalmologists exercise caution and use their own judgement and experience, which must be underpinned by the existing evidence base when recommending treatments for wet AMD. The guiding principle should be that whatever treatment is recommended must be in the best interest of the patient. This clinical judgement should not be over-ridden by the perceived low cost of compounded bevacizumab compared with ranibizumab, pegaptanib or any other licensed product.

Intravitreal anti-VEGF may be used to treat all lesion types: classic, predominantly classic, minimally classic, occult and RAP lesions.
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Posterior Segment
Age-related Macular Degeneration


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