

# Age-related macular degeneration

## Where are we now?

**A**ge-related macular degeneration (AMD) is the most common cause of blindness in the elderly. It accounts for over 54% of all cases of registered blindness in people over 65 years<sup>1</sup> with a prevalence of 20-30% in the western world<sup>2</sup>.

In 2003 in the UK, 124,000 people over 65 years were registered as blind<sup>3</sup> mostly due to AMD. The true figures for actual blindness registrations are likely to be much higher because of under-certification. They may be as high as 64% for blind and 77% for partially-sighted people<sup>4</sup>. As the average life span continues to increase, particularly in developed countries, the incidence of AMD is expected to double within the next 25 years<sup>5</sup>. Demographic projections for the UK indicate that this segment of the 'at-risk' population over the age of 65 will increase by 29% in the next 20 years<sup>2</sup>.

Although not life-threatening, AMD has been judged on the basis of a spectrum of measures of patient disability to be the third most disabling disease in the US population after diabetes and cancer<sup>2</sup>. As the disease progresses, patients become unable to read and write, watch television or even recognise people's faces. As expected, this interferes with work, hobbies, mobility, communication and social interaction. It also leads to an increased risk of falls with hip fractures<sup>6</sup> and social isolation<sup>7</sup>. Choroidal neovascularisation (CNV) is responsible for the majority of cases of severe central visual loss, often sudden in onset with devastating psychological and practical consequences.

### Clinical features and classification

The characteristic ophthalmoscopic lesions of AMD are drusen with areas of increased or irregular pigmentation at the level of the retinal pigment epithelium (RPE). If these are the only lesions present, the condition is best referred to as early age-

related maculopathy (ARM), reserving the terms late ARM or AMD to describe more advanced changes which are likely to be associated with visual impairment. AMD can take two forms: dry AMD, also referred to as geographic atrophy (GA) or non-exudative AMD (seen in 90% of cases); and wet AMD, also known as neovascular, exudative or disciform AMD (seen in 10% of cases).

The dry form of AMD is characterised by thinning of the macular retina with or without drusen, while the wet form is characterised by the growth of abnormal new blood vessels from the choroid beneath the retina. These new vessels (CNV) can leak fluid and blood causing scarring, which can threaten vision. Using fluorescein angiography (Figure 1), these vessels have been classified into 'classic' if they can be seen clearly, and 'occult' if they cannot. If the picture is mixed, they would be then classed as either 'minimally classic' or 'predominantly classic'. Wet AMD usually occurs in people who already have dry macular degeneration and it progresses more quickly with severe visual loss.

The classification and grading of ARM and AMD has been complicated by the large variation in location, size, number and types of lesion that may occur. Over the years, many definitions have been used in epidemiological studies making comparisons difficult. This problem was simplified to some extent by the International Age-related Maculopathy Epidemiological Study Group, which proposed a classification and grading system for ARM and AMD based on detailed assessment of colour fundus photographs<sup>8</sup>.

### Aetiology

#### Genetic factors in AMD

The aetiology for this blinding disease remains elusive. However, a number of studies have implicated both genetic and environmental factors in its aetiology. In addition to age, the evidence for heredity in AMD is compelling and nearly 20% of AMD patients have been shown to have a positive family history<sup>9,10</sup>. Certain clinical features may suggest a genetic causality when present in particular AMD cases (Table 1).

AMD is, however, difficult to study genetically because of its late age of onset and the lack of large families to study. This limits the application of the most successful method of gene discovery, called 'positional cloning'. This method requires three-generation families to be available for study. Genes are then identified by association of affected family members with genetic markers.

Despite these limitations, multiple studies have confirmed that AMD is inherited. These include twin studies (a higher prevalence of AMD is seen among monozygotic twins as compared to their spouses and first-degree relatives<sup>11</sup>), population based segregation analyses<sup>12</sup>, familial aggregation studies, gene variation association studies, studies identifying AMD chromosomal loci by linkage<sup>13</sup> and, recently, AMD genes identified through studies of related dominant macular dystrophies.

Studies of inherited retinal disorders have revealed that AMD is likely to display extensive genetic heterogeneity, involving functional sequence variations in numerous genes, sometimes singly and sometimes in combination. In the past decade, many groups used positional cloning<sup>14</sup> to try to identify genes that caused early onset inherited macular diseases, in the hope that identification of these genes would provide insights into the late-onset forms of diseases like AMD. Several genes were identified (Table 2), but none have convincingly been demonstrated to be involved in a clinically significant fraction of AMD patients<sup>15-22</sup>.

The hereditary macular disease that is clinically most similar to 'typical' AMD is Malattia Leventinese (Doyme's honeycomb

Figure 1  
Fluorescein angiographic appearances of classic (A) and occult (B) types of CNV

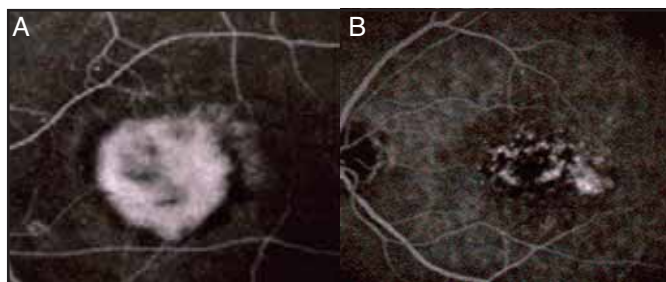


Table 1

#### Features which may point to a genetic cause

1. Age of presentation < 55 years
2. Other affected family members
3. Clinical features - basal laminar drusen, symmetrical changes, lack of environmental risk factors like smoking

Hereditary retinal dystrophy	Implicated gene	Locus	Findings in AMD
Best disease	VMD2	11q13	No significant association
Malattia Leventinese (Doyme's honeycomb dystrophy)	EFEMP1	2p16	No significant association
AMD	Hemicentin-1	1q25-q31	Gene mutated in a single AMD family
Sorsby's fundus dystrophy	TIMP-3	22q12.1	No significant association
AR Stargardt's disease	ABCA4(ABCR)	1p21	No significant association
AD Stargardt's disease	ELOVL4	6q14	No association found
Pattern dystrophy	Peripherin-RDS	6p21	No association found
Batten's disease	CLN3	16p	No association found

➤ Table 2

Hereditary retinal dystrophy candidate genes evaluated in AMD

retinal dystrophy). The authors of this article were part of the group which identified that this is caused by a single mutation (Arg345Trp) in the fibulin-3 gene (also known as EFEMP1)<sup>23</sup>. The discovery that fibulin-3 was mutated in a juvenile form of macular degeneration, focused our attention on the fibulin gene family as potential candidate genes for AMD. We recently reported the results of analysis of the fibulin group of genes in 402 patients with AMD and 429 age matched controls<sup>24</sup>. We identified seven different missense mutations in the fibulin-5 gene. These were seen in 1.7% of patients, but none were found in the control individuals ( $P = 0.006$ ). Fibulin 5, which is essential for elastinogenesis, is also important in the development of AMD.

Genes other than those associated with hereditary retinal dystrophies can also be candidate genes for AMD. Klaver *et al*<sup>25</sup> have reported that the ApoE  $\epsilon 4$  allele is associated with a reduced risk of AMD (odds ratio 0.43) and the  $\epsilon 2$  allele with a slightly increased risk (odds ratio 1.5). ApoE is an important receptor for cholesterol and lipid clearance and transport. In a large AMD family with 10 affected members, Schultz *et al*<sup>26</sup> identified that fibulin-6 (hemicentin-1) was mutated in a single family with AMD but not in simplex cases. Other genes which have been evaluated recently with some positive findings include paraoxonase 1 (PON1), cystatin C (CST3), Superoxide dismutase 2 (SOD2) and angiotensin-converting enzyme (ACE).

Finally, as in other complex diseases, the additional effect exerted by multiple gene variants by their interaction with environmental factors cannot be discounted. Environmental components, such as smoking, therefore could trigger the development of AMD in genetically predisposed individuals. There is also increasing evidence that low grade inflammation is important in AMD; for example, raised serum C-reactive protein levels have recently been associated with AMD<sup>27</sup>.

Even as progress is being made in the molecular mechanisms of AMD, a major AMD gene is still to be found. It now seems unlikely that a single gene variant would be responsible for AMD

development, at least not in the common disease form. The eventual goal is to genetically screen individuals at an early age to assess their genetic predisposition for developing AMD, so that effective interventions can be planned optimally even before the disease develops. Also, modification of behaviour and environmental factors at an early age may prevent or even completely avoid the development of this devastating disease at a later age.

### Role of inflammation in AMD

Recent research suggests that inflammation may also play a causal role in the development of AMD<sup>28-31</sup>. Cell biologists have demonstrated a possible alternative aetiology for the formation of drusen in AMD; namely, a dysregulation of the immune response. Drusen, which are pathognomonic of the AMD disease process, contain proteins which modulate the body's response to inflammation, including vitronectin, complement and immunoglobulins<sup>32,33</sup>. Inflammatory cells including macrophages<sup>34-36</sup>, multinucleate giant cells<sup>35,37,38</sup>, fibroblasts and mast cells have been observed in association with Bruch's membrane in AMD donor eyes<sup>38</sup>. Recently, AMD type changes have been described in ageing mice which were deficient in macrophage associated Chemokine receptor genes<sup>40</sup> – thus, supporting an immunological basis for the development of AMD. A unifying hypothesis to explain both the genetic inheritance of AMD and the role of inflammation in AMD would be that AMD is, at least in part, an immunogenetic disease. Patients with AMD may also have a specific HLA genotype, which makes them genetically susceptible to immune mediated processes which cause AMD and its consequent neovascular sequelae. Recently, significant associations, both predisposing and protective, have been found between particular HLA alleles and AMD<sup>41</sup>.

### Management

#### Recognising treatable lesions

Recognising symptoms is crucial for early diagnosis of CNV in a treatable stage. As usually only one eye is affected initially, patients often do not notice visual loss or

distortion. In these cases, the condition is more likely to be picked up by optometrists or ophthalmologists during a routine examination. Rarely, patients may present with acute symptoms to the optometrist or hospital eye casualties, especially if they have only one effective seeing eye. Telemedicine, as is practised in many parts of the UK for diabetic retinopathy, may have a similar role in streamlining the hospital referral and improving the diagnosis of potentially treatable AMD. This may be difficult to reproduce in AMD referrals, as more specific measures may be needed, in that stereoscopic colour fundus photographs need to be complemented by fluorescein and sometimes indocyanine green angiograms. Also, some aspects such as discussions with patients regarding relevant symptoms and appropriate visual acuity testing are important; these can only be done during a clinic visit.

#### Guidelines for referrals

The Royal College of Ophthalmologists guidelines recommend that mild, early AMD requires no special management and can be managed in the community. Optometrists should continue to carry out routine examinations and refraction in this group of patients. Reassurance and advice about the value of magnification and lighting may be helpful. More importantly, modifying proven risk factors by discontinuing smoking and initiation of nutritional preventive measures, i.e. vitamin supplements, could reduce the risk of progression of AMD. Patients do not necessarily require referral to the Hospital Eye Service (HES). Referral is indicated when there is rapidly developing visual failure or distortion. In these cases, urgent assessment is needed to ascertain whether the patient would benefit from laser treatment or photodynamic therapy (PDT).

Patients with significant visual loss, where there is need for an accurate diagnosis, and those requiring low vision aids and social needs assessment or possibly partially-sighted/blind registration, should be referred to the HES for certification purposes. Since 2003, BD8 forms have been replaced by the Certificate of Vision Impairment (CVI 2003). These forms are generally signed by a consultant ophthalmologist. Alternatively, a Letter of Vision Impairment (LVI 2003) and Referral of Vision Impaired Patient (RVI 2003) can be issued by High Street optometrists and hospital eye clinics respectively, to alert social services in advance of CVI certification. Last but not least, since AMD can often be concurrent with other treatable diseases, such as cataract and glaucoma, these need to be identified for appropriate treatment.

## Prevention strategies

The Age-Related Eye Disease Study (AREDS) reported significant reduction (25%) in the progression of disease from an intermediate stage to advanced neovascular AMD by the use of high-dose antioxidant, vitamin and zinc supplementation given over 6.3 years. There are numerous alternative food supplements ranging from lutein and zeaxanthin to selenium, which claim to reduce the risk of progression of AMD. At present, their efficacy is not well established.

There is conflicting evidence concerning the association between AMD and hypertension<sup>42,43</sup>, raised cholesterol<sup>44</sup> and raised C-reactive protein (CRP)<sup>27</sup>. Among all identified potential environmental factors, only age, diet and smoking are agreed upon by all to increase the risk of AMD. People with AMD should therefore receive lifestyle counselling in relation to these and other known modifiable risk factors of CNV development. For example, in patients who show presence of confluent drusen, Amsler monitoring may be beneficial; smokers should be advised to give up or seek advice from self-help groups or the NHS smoking helpline.

## Treatment of AMD

Argon laser therapy has been traditionally used to coagulate new vessels in wet AMD. However, the procedure itself may permanently impair vision, especially if the vessels are very close to the fovea and recurrence is common. Laser photocoagulation is only effective in cases of classic CNV and is still the treatment of choice for extrafoveal CNV, as described by the Macular Photocoagulation Study (MPS)<sup>45</sup>. Classic subfoveal CNV is best treated with PDT. Juxtafoveal CNV is treated with laser photocoagulation by some physicians, while others would now recommend PDT. Other treatment options for CNV include anti-angiogenic drugs, which suppress new vessel formation, radiotherapy, indocyanine angiography guided laser to feeder vessels, transpupillary thermotherapy and surgery to remove CNV.

Figure 2 shows the current recommended treatment algorithm for AMD.

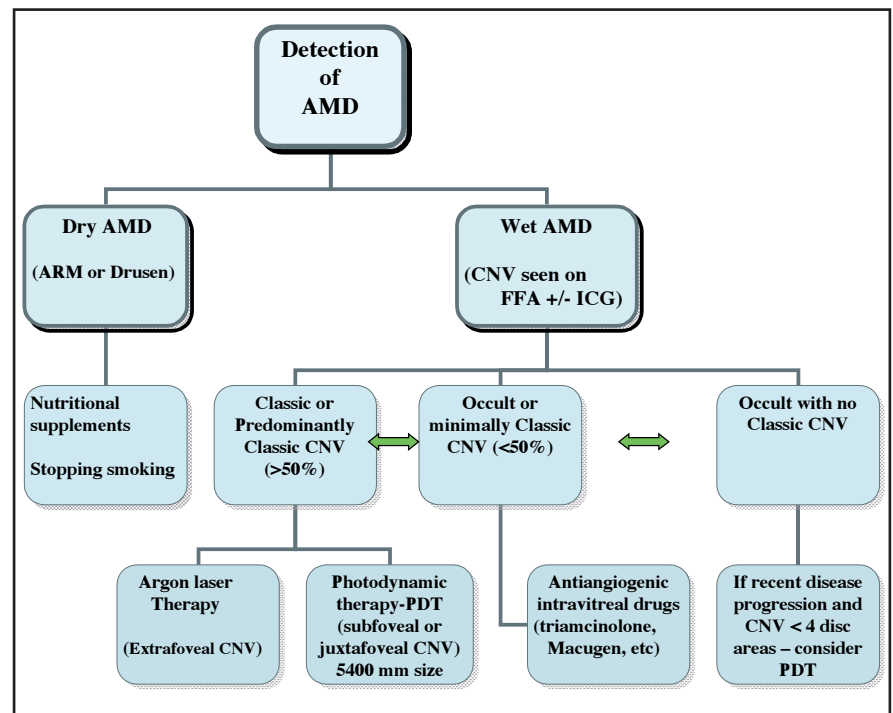


Figure 2

Flow chart summarising current recommended treatment algorithm in AMD

## Photodynamic therapy (PDT)

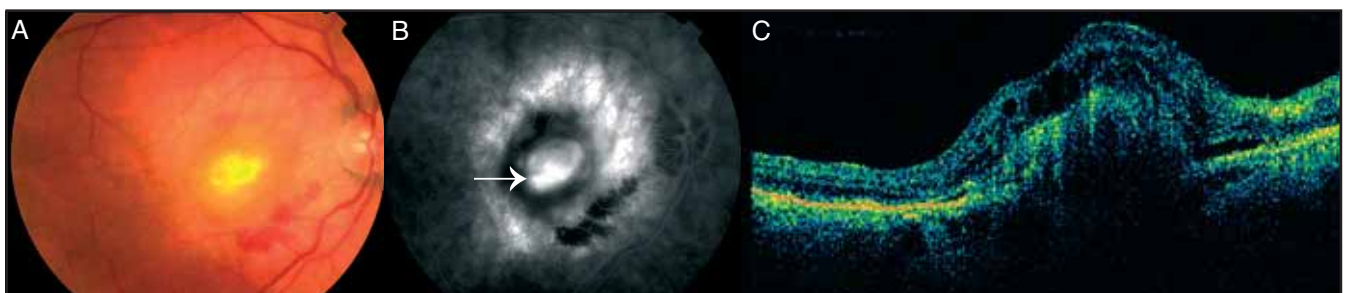
PDT, using a light activated drug, was initially used in dermatology and oncology. The drug currently licensed for use in AMD is verteporfin. Other similar photosensitisers are also being evaluated. PDT for AMD is a two-stage process requiring administration of both verteporfin and non-thermal laser. This is achieved by a 10-minute intravenous infusion of 6mg/kg verteporfin followed by activation five minutes later by a 689nm diode laser for 83 seconds at 50J/cm<sup>2</sup>. Lesions up to 5400mm in greatest linear diameter can be treated. The photosensitive verteporfin is selectively taken up by the rapidly proliferating endothelial cells within the target CNV, reaching its peak concentration at 15 minutes. Microvascular thrombosis of the CNV is then caused by endothelial damage from reactive oxygen radicals generated by the light activated verteporfin. However, animal studies have shown that verteporfin is also present in the normal

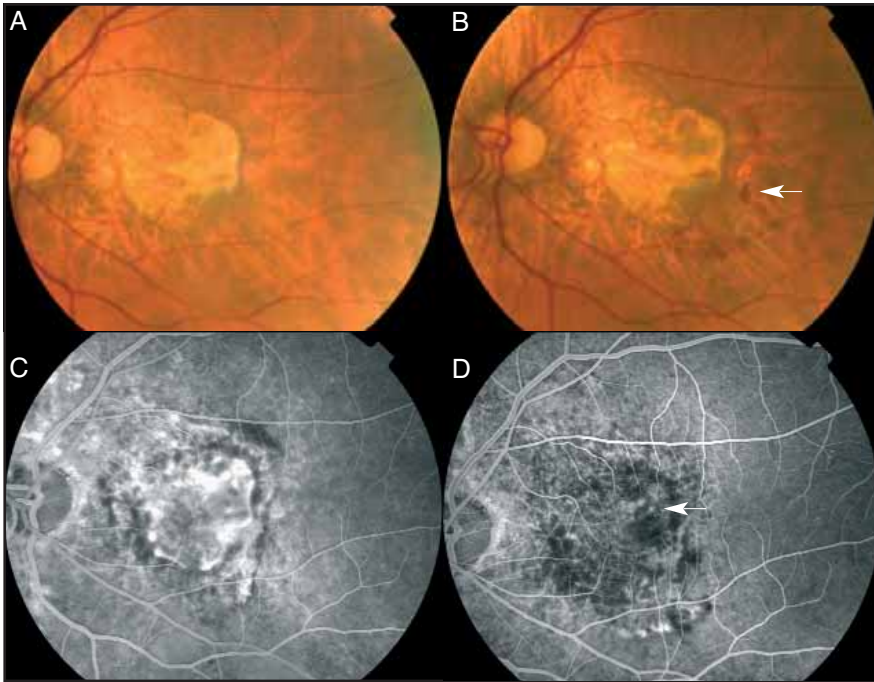
retina, which may lead to collateral damage following photoactivation

Evidence of clinical effectiveness of PDT with verteporfin comes from two major multicentre, randomised controlled clinical trials – the Treatment of AMD with Photodynamic Therapy (TAP)<sup>46,47</sup> and Verteporfin in Photodynamic Therapy (VIP)<sup>47</sup> trials – which showed that vision outcomes were significantly better in treated than in untreated eyes throughout a two-year study period. The TAP trial included 609 patients with subfoveal, predominantly classic CNV having lesions of 5400mm in size, and best corrected visual acuity between 20/40 (6/12) and 20/200 (6/60). Of those patients treated with verteporfin, 59% had lower vision loss compared to 31% of those on a placebo ( $p < 0.001$ ) at 24 months. The VIP study analysed a subgroup of patients with subfoveal lesions composed of occult with no classic CNV. Some benefits were shown in reducing the risk of moderate visual loss in the verteporfin-treated group –

Figure 3

Patient with classic CNV. A. Fundus appearance. B. Fluorescein angiography appearance showing central leakage from CNV (arrow). C. Corresponding optical coherence tomography (OCT) scan showing sub-retinal and intra-retinal oedema from CNV





▶ **Figure 4**

A&C. Classic CNV before treatment with PDT. B&D. Small temporary retinal haemorrhages following treatment are common (arrow), fluorescein angiography shows reduced leakage from CNV (arrow) at six months (after two PDT treatments)

especially in those with recent disease progression (29% in treated versus 47% in placebo,  $P=0.004$ ). No major safety issues have been identified with verteporfin PDT therapy, but potential long-term adverse effects on the RPE are unknown.

Guidance on the implementation of PDT has been issued by NICE (National Institute for Clinical Excellence)<sup>49</sup>. The appraisal recommended the use of PDT for predominantly or wholly classic subfoveal CNV in patients with a visual acuity of 6/60 or better. Retreatments are recommended at three-monthly intervals if there is still angiographic evidence of leakage from the CNV. NICE has not issued any guidance in relation to occult CNV or the more common dry form of AMD.

This treatment of classic CNV has been categorised as, "efficacy established" and "further evaluation required to establish safety" by the Safety and Efficacy Register of New Interventional Procedures (SERNIP) group. PDT treatments are therefore currently being accessed through clinical studies to provide evidence as to the outcome and effectiveness of the treatment. The Department of Health is funding a nationwide PDT cohort study to collect data on optimal PDT treatment regimens, long-term visual outcomes, quantification of PDT benefits with respect to visual functioning and quality of life, and cost-effectiveness/cost-utility analyses for different subgroups of patients. NICE will take results from this study into account when reviewing its guidance on PDT in 2006.

Figures 3 and 4 show the features of

classic CNV, before and after treatment with PDT.

### Integration of PDT into NHS ophthalmic services

There are around 245,000 people in the UK with wet AMD<sup>50</sup>, most of whom already have untreatable end stage AMD. The annual incidence of new cases of wet AMD is currently approximately 21,000 and still rising. Also, the window of opportunity to deliver therapy to eyes with predominantly classic CNV is relatively short, as significant vision can be lost in three months. Of these new cases, NICE guidance estimates that up to 7,500 people each year will present with either classic with no occult CNV, or predominantly classic with occult CNV in England and Wales (approx 55% classic with no occult CNV, and 45% predominantly classic with occult CNV); forming a large target population for PDT.

It is difficult to quantify the total cost of AMD to the UK taxpayer, but the cost of social care due to this disease alone is believed to be in excess of £137m a year; it is therefore likely that the costs to the NHS are in excess of £500m. Cost estimate models from a technology assessment report on PDT by NICE reveal that a single treatment costs about £1,181. Because PDT diminishes the rate at which individuals become blind, there are beneficial cost offsets in medical and social care. This is exclusive of the treatment cost and has been estimated at £6,295 a year (cost of £159 for blindness registration, low vision aids, and rehabilitation services; annual housing and council tax benefit of £1,221;

social security of £1,212; tax allowance of £16; depression treatment of £151; hip replacement of £183; community care of £171; and residential care of £3,340).

A recent cost-effectiveness study<sup>51</sup> suggested that, in terms of QALY gains, treating predominantly classic, subfoveal AMD lesions using PDT with verteporfin had a better chance to be cost-effective when initiated at better levels of visual acuity. Since PDT therapy may be more cost-effective in patients with better visual acuity (and therefore, at an earlier stage of disease), screening those at risk may be a practical method of deploying this technology.

Health authorities and purchasers such as primary care trusts have adopted varying positions on PDT while they consider proposals for service contracts, as the treatment is relatively expensive. Although recommendations have been made for at least 50 PDT centres in England and Wales during the course of the three-year Cohort Study, the provision of PDT is currently patchy with referrals of patients being made on a case-by-case basis to the major retinal centres. This scenario is changing fast with progress being made in establishing rapid PDT referral pathways, development of dedicated angiogram reading centres and specialised PDT centres.

### Treatment with anti-angiogenic drugs

There is now new evidence<sup>52</sup> that CNV is caused by a low grade inflammation, which can be reduced with drug treatment. Steroids are anti-angiogenic drugs, which inhibit fibrovascular proliferation. They inhibit cell mediated inflammation as well as leucocyte adhesion and extravasation, each of which are observed factors in the pathogenesis of AMD<sup>53,54</sup>. Triamcinolone affects vascular endothelial cell extracellular matrix turnover<sup>55</sup>, increases blood-retinal barrier function and down-regulates VEGF<sup>54</sup>. Triamcinolone acetonide has been shown to be safe for intravitreal use in animal models<sup>53</sup> and, recently, in humans also. Previous small clinical trials<sup>56-59</sup> in occult CNV treatment have shown promise and results of larger ongoing trials are awaited.

Another drug which may soon be available for the treatment of CNV is Pegaptanib sodium<sup>60</sup>, a non-immunogenic compound which binds with high affinity and high specificity to VEGF. It has both anti-angiogenic and anti-permeability effects.

Thus, current pharmaceutical research aimed at the treatment of CNV is largely focused on the development of anti-angiogenic drugs that would inhibit further CNV formation, or even reduce existing CNV. However, other lines of treatment are also being explored, including anti-inflammatory agents as well as new PDT agents (Table 3).

### Radiotherapy

Radiotherapy has been used in people with wet AMD where a beam of radiation is carefully directed at the area and is used to destroy the new blood vessels. The aim of this procedure is to slow down the patient's sight loss and so it wouldn't be expected to give immediate improvements. The most common method employed is external beam radiotherapy, others being brachytherapy where sealed radioactive plaques are sutured temporarily to the posterior pole, and stereotactic irradiation techniques which utilise a three-dimensional stereotactic system.

In the past decade, a multitude of small pilot studies using standard fractions of 2-3 Gy with a total dose of 10-20 Gy have been published<sup>61</sup>, some showing better maintenance of visual acuity in treated eyes<sup>62-66</sup>, while others failed to show any benefit<sup>67-70</sup>. Among the randomised controlled trials, three studies demonstrated a significant reduction in visual loss when comparing radiotherapy to very low dose (effectively sham) radiotherapy<sup>71</sup> or observation<sup>72,73</sup>. NICE recognises the modest benefits from radiotherapy, but restricts its usage to ethically approved quality clinical trials only in the UK<sup>74</sup>.

### Transpupillary thermotherapy (TTT)

TTT has recently been used for the management of CNV secondary to AMD. Here, laser energy is used to coagulate vessels in wet AMD using a lower-power diode laser setting, which creates a more diffuse beam than standard laser treatment. It may be used to treat patients with occult new vessels. Although previous studies<sup>75,76</sup> have been relatively small and results inconclusive, recent results presented at the American Academy of Ophthalmology from the prospective, randomised, sham-controlled multicentre clinical trial (TTT4CNV)<sup>77</sup> showed no benefit of this treatment in AMD.

### Macular translocation and submacular surgery

Macular translocation involves moving the macula so that the fovea lies over a healthier part of the choroid. This involves detaching and rotating the retina (macular translocation with 360° retinotomy)<sup>78</sup> or detaching the retina and folding the outer sclera shorter, thus moving the choroid slightly in relation to the macula (limited macular translocation)<sup>79</sup>. Anatomical success is not always associated with visual improvement<sup>79</sup>. However, dramatic improvements have been reported. Current evidence is limited for this procedure and so it is only used in a research setting.

Recently, results from the Submacular Surgery Trials (SSTs) investigating outcomes of surgery for CNV removal were published, where no significant visual improvement was found<sup>81,82</sup>.

Drug name	Pharmaceutical company	Mechanism of action	Current regulatory status for clinical use
Visudyne (verteporfin)	Novartis	Photodynamic	Approved in US, UK, Europe, Japan
Ocuvite Preservision	Bausch & Lomb	Nutritional (Antioxidant)	Approved in US, UK for high risk patients
Macugen	Pfizer/Eyetech	Antiangiogenic	FDA approved in US
Photopoint, SNET	Miravant	Photodynamic	Phase III studies
Anecortave acetate	Alcon	MMP inhibition	Phase III studies
Lucentis	Genentech	Antiangiogenic	Phase II studies
Combretastatin	Oxigene	Antiangiogenic	Phase II studies
Squalamine	Genaera	Antiangiogenic	Phase II studies
Fluocinolone	Bausch & Lomb	Steroid implant	Phase II studies
Celecoxib (with PDT)	GD Searle	Anti-inflammatory	Phase II studies
Triamcinolone acetonide-PF (with/without PDT)	NEI, USA	Steroid-intravitreal	Phase II studies
Kenalog (preserved triamcinolone)	BM Squibb	Steroid-intravitreal	Phase II studies
Lutein	NEI, USA	Nutritional	Phase II studies

» Table 3

Drug treatments available or under investigation for AMD

### Gene therapy and gene directed therapy

Once a human disease gene has been characterised, gene functions can be dissected and biological processes involved in the normal and pathogenic states confirmed. The resulting information can be used to design novel therapies utilising a gene product, vaccine or genetic material. Gene discoveries will lead to more effective therapies for AMD by identifying specific underlying disease mechanisms, which may be corrected by gene therapy or gene directed drug therapy.

Gene therapy encompasses many strategies where genes, gene segments or oligonucleotides are transferred directly into diseased RPE or retinal cells within a patient (*in vivo* gene therapy) using viral vectors<sup>83</sup>, or cells may be removed from the patient and the genetic material inserted into them *in vitro*. Once inside the desired cells, the expressed genes help produce a product that the patient lacks. Currently there is an ongoing human AMD gene therapy trial using pigment epithelium-derived factor (PEDF)<sup>84</sup>. The gene for this potent inhibitor of angiogenesis has been incorporated into an adenoviral vector and delivered into the eye by intravitreal injections to inhibit growth of CNV<sup>85</sup>.

### Conclusion

This is an exciting time for AMD research.

There are novel insights from genetic studies into the basic pathophysiology of the disease and innovative inhibitors of CNV will soon be clinically available. However, more research funding is urgently needed to capitalise on these findings so that we can develop better treatments for our patients.

### About the authors

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### References

For a full set of references, email nicky@optometry.co.uk or visit www.optometry.co.uk/references.



## Age-related macular degeneration: Diagnostic and therapy

Aetiology, risk factors, diagnostics and therapy are covered in this up to date multi-authored book. The volume is well illustrated with tables and summaries.

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