Age related macular degeneration

New developments in treatment

BACKGROUND
Age related macular degeneration (AMD) is a common condition seen in general practice. Over the past few years, new understanding of the condition has seen the rapid development of increasingly effective treatments.

OBJECTIVE
This article discusses the pathogenesis of AMD and how this relates to the most up to date treatments for the disease. It aims to provide general practitioners with timely information regarding these significant advances, which may assist in the management of patients with AMD.

DISCUSSION
Increasingly, AMD sufferers independently source information about the latest treatments. Consequently GPs are likely to hear more questions from their patients regarding treatment options. Antivascular endothelial growth factor drugs show exciting potential for an often debilitating condition. However, early referral and treatment is vital to successful outcomes and GPs can play an essential role in this process. As well, they can serve to provide ongoing information and counselling to their patients with AMD.

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Age related macular degeneration (AMD) is a disorder that usually presents in patients aged over 55 years. The pathology involves the destruction and deterioration of the dense neurosensory layer specific to the macula.[1] The disorder is usually categorised into:

- exudative or 'wet' form, and
- nonexudative or 'dry' form.

The dry form of AMD represents a slow atrophy of the cells within the macula (*Figure 1*). To date, there is no definitive treatment other than risk factor management. These include: reducing consumption of vegetable oils, cessation of smoking, reduction in body mass index (BMI) and taking specific vitamin supplements (eg. antioxidants, omega-3).[1–2] The Age Related Eye Disease Study (AREDS) provided the best evidence for antioxidant supplementation particularly for unaffected eyes or early stage AMD. However, in most instances these measures only slow the progression of the condition. Interestingly, the AREDS formulation also showed a 30% risk reduction in unaffected fellow eyes of patients with wet AMD.

The wet form of AMD presents in a more acute manner with rapid loss of central vision. It may also present on the background of a previously diagnosed dry form. The pathology is related to the process of neovascularisation both below and within the retinal pigment epithelium near the macula. The discrete lesion is referred to as a choroidal neovascular membrane (CNVM) (*Figure 2*). The new growth of these aberrant blood vessels into the retina helps to explain the rapid visual loss experienced by patients. A characteristic of the neovascularisation process is the tendency for abnormal blood vessels to leak exudates and occasionally to haemorrhage. The subsequent inflammatory process that ensues swiftly causes the destruction of the fragile cells of the macula. This process may reoccur multiple times until such a point when the developed scar tissue helps to contain or halt the neovascular process, but leaves a patient with only peripheral vision remaining.

The exact stimulus for the neovascular process is not known, but research has highlighted the role of the vascular endothelial growth factor molecule (VEGF) – a common growth factor expressed in many somatic cells and malignant tumours. Its main function is to promote angiogenesis, permeate endothelial cells and aid in the chemotaxis of leukocytes and macrophages – perhaps in response to tissue hypoxia or oxidative stress.[1]

Initially studies of VEGF have primarily centred on its role in the progression of malignancies. Several treatments specifically designed to inhibit VEGF activity have been approved for the treatment in certain types of cancer. A new development has been the use of these drugs intravitreally for the treatment of AMD.[1,5,6]

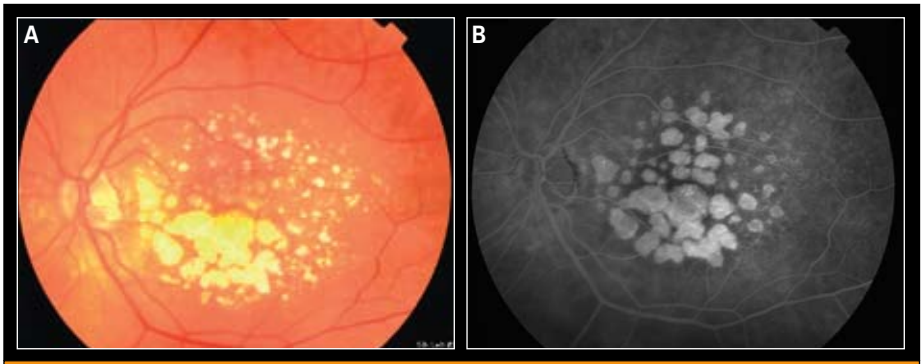

Figure 1. Typical appearance of late stage 'dry' AMD as seen with colour fundus photo (a) and fluorescein angiogram (b). This example shows generalised atrophy more common in the 'dry' form. There is also a large coalescence of drusen (soft exudates) present. These have a different appearance to the scarring and haemorrhage occurring in the neovascularisation process of the 'wet' form

Evolution of exudative AMD treatments

Definitive treatments have been progressing over the past 8–10 years. In earlier stages of treatment, various techniques were applied to help slow the progression of wet AMD. One such treatment was a 'mild' thermal laser (known as transpupillary thermotherapy [TTT]) directed toward the abnormal vessels identified near the macula.[3] In certain situations, specialists have attempted subretinal surgery to manually remove leaking vessels. Another treatment still commonly employed is the intravitreal injection of steroid compound, triamcinolone, hoping to dampen the inflammatory process within the macula.[1] Most if not all of these have proven to be no better than placebo when looking at long term follow up. A more recent and successful approach has been the use of photodynamic therapy (PDT). This involves the systemic administration of the light sensitising medication verteporfin (Visudyne) followed by the use of a special laser directed at the macula. The basic principle is to ablate abnormal vessels without any resulting damage to vital tissues. While the results of PDT have been encouraging (15% showing improvements in visual acuity), in most cases the treatment only offers a slowing in the progression of the disorder (~60% showing less than three lines lost on the Early Treatment of Diabetic Retinopathy Study [EDTRS] chart), and is not suited to all types of wet AMD.[1,4]

New treatments for exudative AMD

Some of the latest and most promising therapies for exudative AMD are the development of anti-VEGF drugs. Initial results seem to suggest that deterioration is arrested in most patients (up to 95% in the phase III MARINA trial of Lucentis) with a significant proportion of patients showing increases in visual acuity (40.3%) from initial presentation.[5,6,10]

In Australia there are only two anti-VEGF drugs currently available, bevacizumab (Avastin) and ranibizumab (Lucentis). Structurally, bevacizumab and ranibizumab are very similar. Bevacizumab is a full size recombinant antibody molecule initially engineered and approved for the treatment of colorectal cancer. Designed for systemic infusion, it has been shown to have a significant side effect profile (mainly hypertension and thromboembolic events). However, the minute intravitreal doses used for treating AMD, to date, have shown essentially no measurable toxicity.[6,10,11] Ranibizumab, in contrast, is derived from its parent molecule, bevacizumab. It consists of the FAB binding fragment of the same antibody molecule targeting VEGF. Ranibizumab is specifically designed for use in the treatment of AMD. In mouse models, FAB binding fragments have been shown to have greater retinal penetration than full size antibody molecules, presumably due to its reduced size.[8] The side effects and administering doses for ranibizumab have been studied in a large randomised controlled trial.[7] These appear to be the only theoretical advantages of one over the other. Both drugs seem to show similar clinical effects when using optical coherence tomography (OCT) images as a guide to treatment responses (*Figure 3*). Optical coherence tomography uses computerised images produced from photons reflected back from light passing through tissue. A computer reconstruction shows the layers of the retina and their relationship.

The actual administration of both drugs is by direct intravitreal injection (~0.05 mL) usually as an outpatient clinic procedure (*Figure 4*). The risks involved are mostly due to the injection itself, ie. raised intraocular pressure, inflammation or introduced infection leading to endophthalmitis. With bevacizumab, the ideal dose and frequency are yet to be established.[6,9,11] Most ophthalmologists are using a protocol similar to that developed for ranibizumab (monthly injections for 3 months then 3 monthly review).

Other new drugs undergoing evaluation outside Australia include pegaptanib (Macugen)

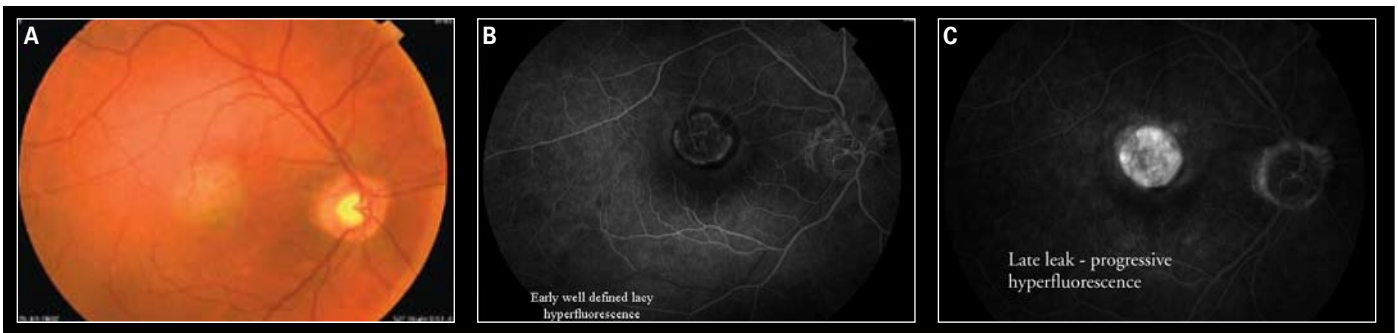

Figure 2. Typical appearance of an eye with an advanced choroidal neovascular membrane (classic type) as demonstrated on colour fundus (a) and fluorescein angiograms (b, c). Figure 2c shows late filling on angiogram, typical of this condition

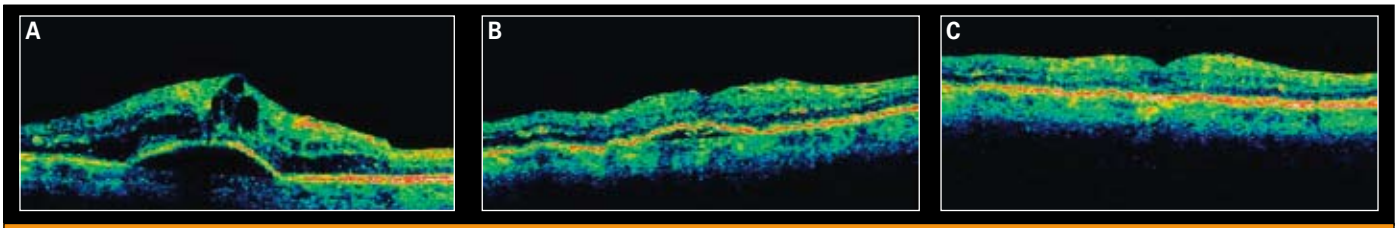

Figure 3. Optical coherence tomography image showing: a) abnormal macular appearance with retinal pigment epithelial defects and subretinal fluid before treatment; b) 1 month after a single intravitreal injection of bevacizumab; c) 3 months after injection showing near normal retinal contour

and anecortave acetate (Retaane). Pegaptanib is another agent directed at inhibiting the specific isoform 165 of VEGF. Its use as an independent agent is confounded by the fact that the majority of initial study eyes had already been treated with verteporfin PDT. The studies did not seem to show the same degree of visual improvements seen with drugs such as ranibizumab.[12] Anecortave acetate is an angiostatic cortisene compound designed to block the migration of proliferating endothelial cells by inhibiting metalloproteinases. Phase III randomised, double masked data showed anecortave acetate to be no better than standard verteporfin PDT.[13] Neither pegaptanib or anecortave acetate are set to be marketed in Australia until further trial data becomes available.

Use of anti-VEGF drugs within Australia

Both bevacizumab and ranibizumab show great improvement over previous therapies for exudative AMD. However, long term data showing sustained treatment benefits for both therapies is still pending. Within Australia and elsewhere, there is some controversy over the use of bevacizumab for ophthalmic conditions.[14] Both bevacizumab and ranibizumab were developed by the same parent company, Genentech. In Australia, bevacizumab is distributed by Roche and ranibizumab by Novartis respectively. Officially the off label usage of bevacizumab for ophthalmic purposes is not recommended. Novartis states that this is due to the lack of safety and efficacy data for bevacizumab as well as the preparation not being designed for intravitreal injection.[14] Despite the warnings and lack of randomised controlled trials, bevacizumab has become the most widely used anti-VEGF drug both in Australia and overseas. The main reasons are its cost effectiveness and seemingly comparable treatment benefits.[15,16] Bevacizuamb is significantly cheaper than ranibizumab. Bevacizuamb is Pharmaceutical Benefits Schedule (PBS) approved for use in patients with colorectal cancer. Available as a larger vial, it can be alloquoted for use in multiple intravitreal injections. Ranibizumab by comparison, is not yet PBS listed, leaving patients to cover a cost of ~$2000 per injection (Novartis caps patient cost after $6000 providing the drug free of charge for subsequent treatments). A single bevacizumab injection costs ~$42. With regards to the safety and efficacy of bevacizumab for AMD, the drugs chemical structure is very similar to ranibizumab and should not be significantly different biologically.[9–11,15,16] Neither Genentech nor Novartis have any incentive to push further research into the use of bevacizumab for AMD. Instead, they have advocated ranibizumab as the most effective treatment for AMD acknowledging their significant research investment.[14] However, the National Eye Institute of the USA has recently granted permission to stage a head to head study between the two drugs.[17] In the short term, intravitreal bevacizumab is likely to be the most cost effective treatment used by ophthalmologists in Australia for the treatment of wet AMD.

Figure 4. Process of direct intravitreal injection with bevacizumab

Conflict of interest: none.

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