Advances in the management of age-related macular degeneration

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Introduction

Age-related macular degeneration is the leading cause of irreversible blindness in those aged 50 years and older.[1,2] It becomes increasingly common with advancing years, and is therefore likely to become even more important as the population ages. The impairment involves central vision (Figure 1). Thus, although navigation vision is usually retained, tasks such as reading and driving become difficult if not impossible, seriously impacting on the patient's quality of life. Fortunately, there are now effective treatments available for wet AMD, the most aggressive form of the disease. This has revolutionised our management of this condition, and in many cases it is now possible to preserve or even improve visual acuity with treatment.

About macular degeneration

The macula, which is specialised for detailed vision, comprises the central part of the retina and is approximately 6mm in diameter. Macular degeneration is divided into early dry AMD, late dry AMD and wet AMD. In early AMD, the patient may have no symptoms or just complain of mild deterioration in their ability to see detailed targets. Changes seen on examination of the fundus at this stage consist of yellow deposits called drusen beneath the retina and sometimes disturbance and clumping of the normal retinal pigment (Figure 2). If the AMD remains dry, the vision loss is typically very slow and the patient may retain reasonable vision for many years.

When the disease has developed more serious vision threatening characteristics it is considered late AMD. This may be either due to late dry AMD which consists of the development of areas of atrophy known as geographic atrophy (Figure 3) or to wet AMD, which occurs when there is abnormal development of blood vessels under the retina that lead to haemorrhage and scarring (Figure 4). In the Beaver Dam study, early AMD was found in about 30% of people aged 75 years or older.[3] Of these, the five-year incidence of late AMD was 11.7%, of whom 7.1% had wet AMD, and 4.6% had geographic atrophy.[4]

As well as being a numerically greater cause of late AMD, wet AMD is important to recognise, as untreated it can cause rapid and irreversible loss of central vision over a few weeks to months. Symptoms that should suggest the diagnosis include rapid deterioration of central vision and new onset or worsening of distorted vision. If these are present an urgent ophthalmological assessment is warranted. If the disease is diagnosed early it is now possible to prevent serious visual loss in the majority of cases of wet AMD.

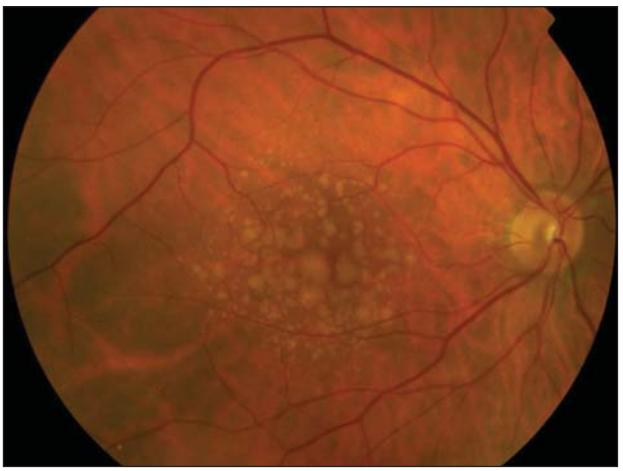
Management of wet AMD

Prior to the advent of the broad spectrum anti VEGF drugs, bevacizumab (Avastin) and ranibizumab (Lucentis), treatments for wet AMD were moderately successful in limiting visual loss, but seldom resulted in improved vision. The first treatment to become available was argon laser photocoagulation. This has been shown to reduce the risk of severe visual loss, but the modest long-term benefit was at the expense of immediate reduction in vision when the centre of the macula (the fovea) was treated,[5] and the treatment was therefore not often recommended. Occasionally this treatment is still used if the choroidal neovascular lesion is small, well defined, and well away from the fovea.

In 1999, the results of the TAP study[6] were published, demonstrating successful results at one year with photodynamic therapy (PDT). This treatment consists of giving the patient an infusion of a dye, verteporfin, which preferentially binds to the neovascular complex. The dye is then activated with a low power laser, releasing free radicals and selectively damaging the new blood vessels while leaving the nor-

Figure 1. Visual loss in advanced AMD primarily affects central vision.

Figure 2. Right eye showing multiple drusen in the macula, characteristic of early AMD.



mal retina relatively undamaged. This resulted in a reduction of moderate visual loss of about 30% without the loss of vision caused by conventional laser treatment. Because of a tendency for the new vessels to reopen, the treatment needed to be repeated several times in most cases. Unfortunately, treated patients still lost vision on average, but the outcomes were better than natural history and, for the next five years or so, PDT became the gold standard management for wet AMD.

A new avenue being explored for treatment in the early 2000s was blockage of vascular endothelial growth factor (VEGF). By blocking VEGF it was hoped that the abnormal blood vessels would close down and regress. The first agent in this class to be released was Pegaptanib, an aptamer that selectively blocks the $VEGF_{165}$ isoform. This had demonstrated efficacy in reducing visual loss in wet AMD,[7] but was similar to PDT in having a failure rate of 30– 40%. Pegaptanib is, however, effective for a wider variety of types of choroidal neovascularisation than PDT and for this reason it was registered for use by the United States FDA in 2004. It has never been registered for use in New Zealand.

The publications of the results of the MARINA[8] and ANCHOR[9] trials on the use of ranibizumab in the treatment of AMD marked a major turning point in the management of this condition. Ranibizumab is an antibody fragment with broad spectrum activity against all of the biologically active forms of VEGF-A. In these studies, the previously defined goal of avoidance of three line visual loss was achieved in 90% of patients, compared with 66% of those treated with PDT in the ANCHOR trial and 53% of those receiving sham treatment in the MARINA trial, where the lesions were unsuitable for PDT. However, what was really exciting for ophthalmologists was that for the first time with a treatment for AMD, the average vision in the treated group increased after treatment (Figures 5, 6). This has been a huge change in treatment outcomes in wet

Figure 3. Geographic atrophy, characteristic of late dry AMD, in a patient's left eye.

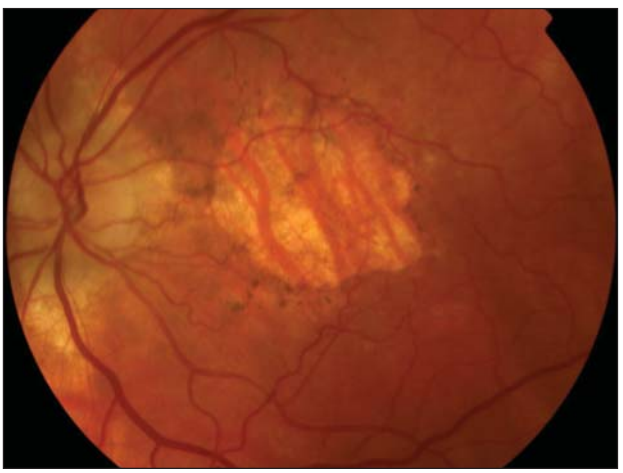


Figure 4. Haemorrhage, exudate and subretinal fluid in the left macula, indicating the presence of wet AMD.

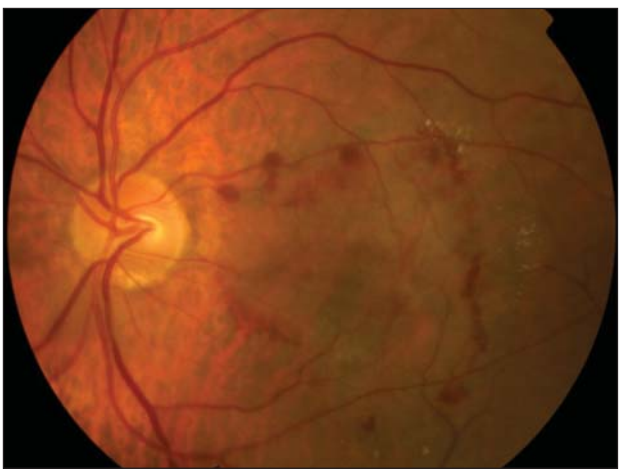
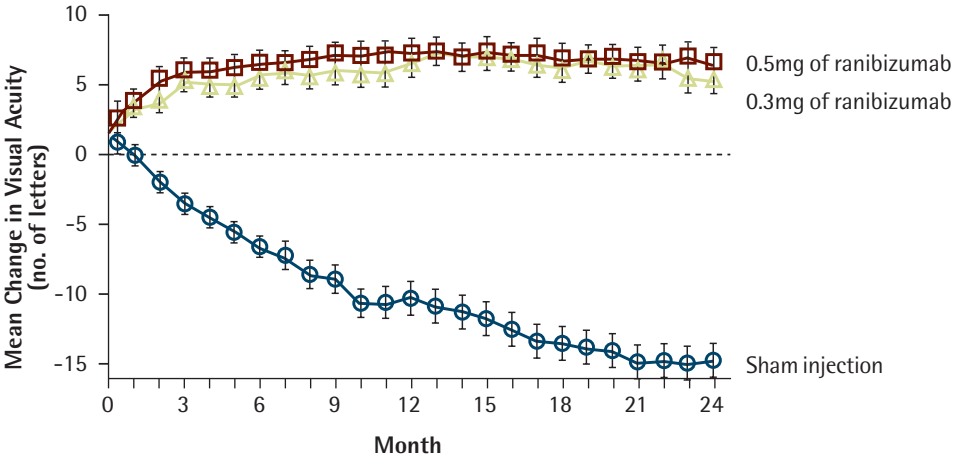


Figure 5. Changes in vision over time in the MARINA trial, comparing monthly ranibizumab injections with sham.



Mean Change from Baseline	(Day 7)								
0.5mg of ranibizumab	+2.6	+5.9	+6.5	+7.2	+7.2	+7.4	+6.8	+6.7	+6.6
0.3mg of ranibizumab	+2.3	+5.1	+5.6	+5.9	+6.5	+6.9	+6.1	+6.2	+5.4
Sham injection	+0.6	-3.7	-6.6	-9.1	-10.4	-11.8	-13.6	-15.0	-14.9

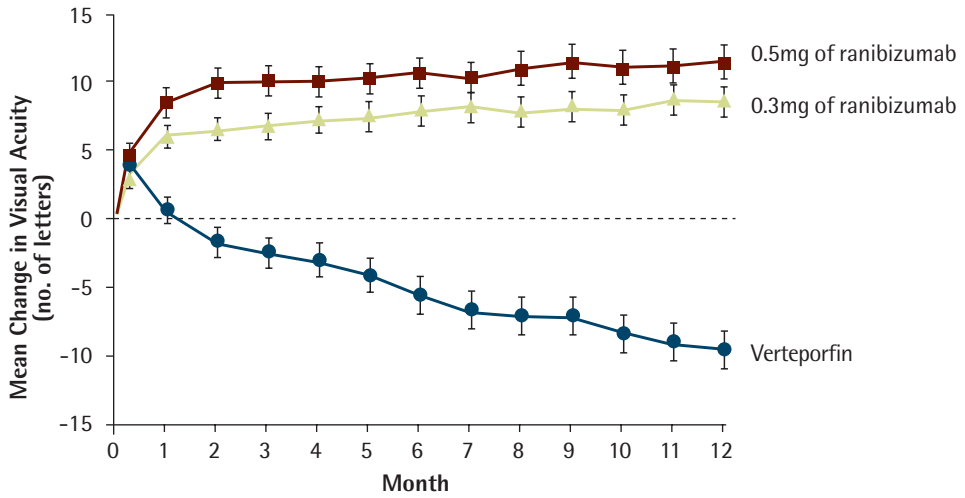
AMD, and future trials will now focus on change in visual acuity rather than simply which group has less severe visual loss.

Ranibizumab was administered in the original trials by monthly intravitreal injections for 24 months. While this was found to be safe, with a serious adverse event rate of only 1–2%, it was a regime which few patients and clinicians are keen to commit to. The PIER study[10] used a three month induction to reach peak effect and then followed with quarterly maintenance dosing for one year. Unfortunately, this was not as successful as the more intensive monthly treatment schedule, with patients having improved vision in the first three months of treatment, but then slipping back to baseline by 12 months. A more successful approach seems to be that adopted by Rosenfeld in the PrONTO study,[11] where patients were treated monthly until there was no evidence of macular fluid on optical coherence tomography (OCT) scanning, and then on a PRN basis according to a number of criteria designed to indicate activity of the disease. Using this method, which is in fact the approach taken by most practitioners, the researchers were able to demonstrate equivalent results at one year to those found in MARINA[8] and ANCHOR.[9]

There was a lag between the initial reports of ranibizumab's effectiveness, and it becoming commercially available, during which time the only licensed treatments were clearly inferior. This lead to the off label use of another broad-spectrum antibody to VEGF, bevacizumab, which was already on the market as an agent for treating metastatic colon cancer. Bevacizumab (Avastin) is the full length antibody from which ranibizumab was developed, and initially it was felt that it was too large a molecule to penetrate the retina and have a therapeutic effect. However, in 2005, Rosenfeld et al.[12] published a report of its successful use as an intravitreal injection in a patient who had failed other treatment modalities. From this starting point, numerous other case series and animal studies followed, demonstrating safety and efficacy of intravitreal bevacizumab which appeared similar to Ranibizumab.[13-18] While the use of bevacizumab in this way does not have the rigorous research behind it that ranibizumab does, it has a major cost advantage as it is possible to aliquot a single intravenous dose in a compounding pharmacy to treat up to 20 patients at an approximate cost of $100 per dose compared to a retail price for ranibizumab of $2193. Currently, there are trials recruiting in the UK and the USA to directly compare ranibizumab and bevacizumab. However, in the meantime in NZ, with neither drug funded by Pharmac, most patients are opting for bevacizumab.

The injection procedure is identical whichever agent is used, although there may be minor variations between practitioners. Essentially, the eye is anaethetised with local anaesthetic drops and possibly also a subconjunctival lignocaine injection. The lids and lashes are cleaned with povodine iodine, and a povodine iodine solution is also dropped onto the eye itself. The lids and lashes are then

Figure 6. Changes in vision over time in the ANCHOR trial, comparing monthly ranibizumab injections with PDT treatment.



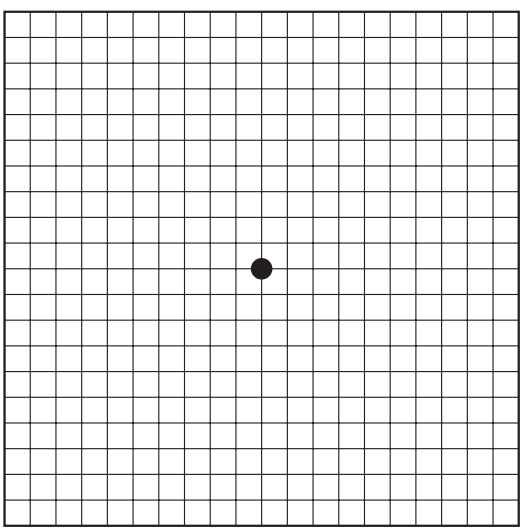
Mean Change from Baseline	(Day 7)												
0.5mg of ranibizumab	+4.6	+8.4	+9.8	+10.0	+9.9	+10.2	+10.6	+10.2	+10.9	+11.4	+10.9	+11.1	+11.3
0.3mg of ranibizumab	+2.9	+5.9	+6.4	+6.8	+7.2	+7.4	+7.9	+8.2	+7.7	+8.1	+7.8	+8.6	+8.5
Verteporfin	+3.9	+0.5	-1.8	-2.5	-3.1	-4.1	-5.6	-6.8	-7.1	-7.1	-8.3	-9.1	-9.5

secured with a speculum and the injection is given through the sclera at a distance of 3–4mm posterior to the limbus. A volume of 0.05ml is injected. Following the injection the patient's vision is confirmed to be at least light perception (indicating that the central retinal artery is perfused). The patient is then instructed to use antibiotic drops or ointment for three to four days afterwards while the eye heals. The rate of presumed endophthalmitis from repeated injections in the MARINA trial[8] was 1%, which corresponds to a per injection rate of 0.05%.

Management of dry AMD

Although dry AMD causes much slower and usually less severe visual loss, there are some patients who develop significant loss of central vision from geographic atrophy and, unfortunately, the treatment options for them are much more limited. Currently there are no treatments that reverse the loss caused by geographic atrophy. The Age Related Eye Disease Study (AREDS)[19] investigated whether both dry and wet late AMD could be prevented by supplementation with high dose antioxidant vitamins and zinc. The subjects were given placebo, antioxidant vitamins, zinc, or both antioxidants and zinc. The benefits were modest, and only statistically significant for the groups who had at least moderate disease at baseline and who received both zinc and antioxidants. Nevertheless, the five-year risk of a three line drop in vision in either eye was reduced by the treatment from 29% in the placebo group to 23% in the treated group. The AREDS formulation consists of vitamin C 500mg, Vitamin E 400IU, beta carotene 15mg, zinc oxide 80mg and cupric oxide 2mg. In New Zealand it is available on prescription as Ocuvite Preservision, but is not funded. High doses of beta carotene are not recommended in smokers because of an increased risk of lung cancer.[20,21] An alternative

Figure 7. The Amsler grid. To perform the test, the patient wears their usual reading glasses and holds the grid at a comfortable reading distance. They cover one eye and look at the central dot. Any distortion, blurred or missing patches on the grid should be noted. When printed the grid should be about 10x10cm.



formulation exists with lutein instead of beta carotene, but this has not yet been tested in a clinical trial setting. Whether or not a patient chooses to take the high dose supplements, worthwhile steps to decrease the risk of late AMD include avoidance of cigarette smoking[22] and a diet rich in fruit and vegetables.[23] This is also a good policy for those who have no disease themselves, but may be at increased risk due to family history.

Conclusions

It is now more important than ever to recognise AMD, in particular wet AMD. New treatments for wet AMD are available in the form of bevacizumab (Avastin) and ranibizumab (Lucentis). These treatments can usually prevent visual loss and may even improve vision, but are most effective if employed before too much damage has occurred. Any patient with new or worsening distortion of their central vision should therefore be referred urgently for an ophthalmology assessment. A useful test for distortion is the Amsler grid (Figure 7). This can be used in the GP surgery, and at-risk patients can also be instructed to check their own vision by using it regularly. Antioxidant vitamins, such as Ocuvite are modestly useful in preventing visual loss in those with moderate disease, or those who have already lost vision in one eye. Currently they are the only treatment available for the dry form of AMD.

Competing interests

Dr Barnes has attended symposia hosted by Novartis (agents for Lucentis in Asia/Pacific).

Key Points

- AMD is a major cause of blindness in NZ.
- Bevacizumab (Avastin) and ranibizumab (Lucentis) are very effective in preventing blindness from wet AMD.
- Early referral is crucial – new onset of visual distortion requires urgent assessment.
- Antioxidant vitamins and zinc give a modest benefit in prevention of visual loss.
- Other than vitamins as above, no treatment yet exists for advanced dry AMD.

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