Advances in the management of age-related macular degeneration

Age-related macular degeneration (AMD) is a progressive disorder of the retina in older adults. Dry AMD, characterised by deposits in the fundus, does not cause significant vision loss. But if it progresses to advanced AMD, it can cause severe vision loss if left untreated. Laser therapy, which itself can damage the retina, was standard therapy during 1980 and 90s. However, a class of drugs that inhibit vascular endothelial growth factor has revolutionised outcomes for many patients

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Age-related macular degeneration (AMD) is a progressive degenerative disorder of the retina in older adults. The hallmark of AMD is the presence of yellowish deposits called drusen in the fundus of the eye along with pigment abnormalities, which alone do not cause significant visual loss. At this early stage, the condition is called dry AMD (approximately 90% of patients have this type of AMD). Some patients with dry AMD develop a confluent atrophy known as geographic atrophy, which is associated with a slow and progressive visual decline.

There are no effective treatments that prevent or delay the development of this form of late AMD. The most important cause of vision loss is the development of choroidal neovascularisation—another manifestation of late AMD. When choroidal neovascularisation is present, the condition is termed wet, exudative, or neovascular AMD. There is sudden deterioration in vision because the new vessels are leaky and exude fluid and blood. Patients will complain of distortion in the affected eye and, over time, severe vision loss will occur if it is left untreated.

Because of the ageing population, neovascular AMD has become more common. Its prevalence among Western populations is around 3·0% in people aged 75 and older.[1,2] The exact cause of neovascular AMD is not known, but a combination of environmental and genetic factors are thought to play a role. Smoking is the most consistently identified environmental risk factor[3] while genetic variations in complement factor H, factor B, and C2 genes have been identified in 50–70% of cases of neovascular AMD.[4,5]

Antioxidants may play a role in preventing progression to neovascular AMD. The Age-Related Eye Disease Study (AREDS)[6] trial established that people at high risk of developing neovascular AMD who were treated with a combination of specific antioxidants (vitamin C, vitamin E, and β-carotene) and zinc had a 22% reduced risk of progression to advanced AMD (ie, when vision is affected).

The AREDS 2 study,[7] which is ongoing, is investigating the possible benefits of lutein, zeaxanthin and omega 3 fatty acids supplementation in patients at high risk of developing neovascular AMD.

Diagnosis and treatment

Fluorescein angiogram is used for both diagnosing neovascular AMD and targeting laser therapy. Sodium fluorescein, a non-toxic vegetable dye, is injected into a suitable peripheral vein and reaches the ocular blood vessels. This dye allows choroidal neovascular membranes to be easily imaged using a fundus camera. Images are taken over a period of 10 minutes immediately after the intravenous injection. Depending on the spatial and temporal characteristics of the pattern of fluorescence seen in the fundus images, various morphological neovascularisation types are recognised.

The term classic neovascularisation is applied if abnormally increased fluorescence, which is indicative of leakage from new vessels, is seen within the first 30 seconds of the angiogram and if this area is well demarcated. But in most eyes, leakage occurs in the later phases of the angiogram and the margins of the leaky area are poorly delineated. This type of leakage is called occult neovascularisation.

Most patients will have a mixture of classic and occult neovascularisation, and it is common practice to describe the membranes based on the proportion of classic neovascularisation. Therefore the terms predominantly classic

(>50% of the leakage is classic), minimally classic (<50%), and occult with no classic (0%) are used. Membranes that are entirely classic are more easily targeted and effectively treated by Argon laser therapy than other types, but only 5% of patients have this type of neovascularisation.

Laser therapy

Argon laser ablation was the first treatment developed for laser therapy and is carried out in a short outpatient visit. A thermal laser delivers bursts of energy that destroys both the neovascular membrane and the overlying retina, which can result in the development of blind spots (scotomas) in the patient's vision. Despite the trauma to the retina, this treatment was better than none and became standard practice during the 1980s and 90s. However, prognosis after laser therapy is poor, with 50–70% of treated eyes developing recurrent new vessels within a 2-year period. Visual outcomes after thermal laser therapy are therefore poor with most eyes experiencing moderate or severe vision loss.[8]

The next major advance in the treatment of neovascular AMD was photodynamic therapy, which exploits the properties of a non-toxic photosensitiser drug (verteporfin) that preferentially accumulates in the choroidal neovascular membrane. The drug is activated by a non-thermal infrared laser (different from the Argon laser described previously) and the subsequent release of free radicals results in thrombosis of the neovascular membrane.[9]

However, the occlusive effect is not permanent and multiple treatments are needed at 3-month intervals for up to 2 or 3 years. Trials have shown that photodynamic therapy results in better visual outcomes compared with no treatment in patients with wholly classic or predominantly classic neovascular AMD. Fewer patients who received this treatment experienced moderate or severe visual loss than placebo-treated patients (37% versus 65%).[10] Unfortunately, on average, photodynamic therapy can only slow the progression of vision loss rather than provide any vision gain.

Biological agents

The introduction of biological agents that can influence the micro environment of affected ocular tissues has ushered in a new era of treatment. In particular, one class of agents that inhibit vascular endothelial growth factor (VEGF) have revolutionised outcomes for many patients with neovascular AMD. VEGF causes blood vessels to become very permeable and it is 50,000 times more potent than histamine. It is also required as a survival factor for new vessels,[11] and has been shown by immunohistochemistry to be expressed in the blood vessels of choroidal neovascular membranes.[12] There are nine different isoforms of VEGF, and VEGF 165 is the major angiogenic form.

Three anti-VEGF agents are available: pegaptanib, ranibizumab, and bevacizumab. They are administered intravitreally thus avoiding the problems of excessive systemic dosing. Pegaptanib (manufactured by Pfizer) is a ribonucleic acid blocking molecule that specifically targets VEGF 165.[13] The VEGF Inhibition in Ocular Neovascularisation (VISION)[14] studies showed that pegaptanib injections given every 6 weeks over a 2-year period limited visual acuity loss compared with placebo or cessation of therapy at 1 year. Visual acuity is measured on the Early Treatment of Diabetic Retinopathy Study (ETDRS) acuity charts where a fall of 3 lines is equal to 15 letters. Fewer pegaptanib-treated eyes lost more than 15 letters compared with placebo ($p<0{\cdot}001$). However, few patients experienced any improvement in vision.

Agents that inhibit vascular endothelial growth factor (VEGF) have revolutionised outcomes for many patients with neovascular AMD

Ranibizumab (developed by Genentech) is an antibody fragment that blocks all active forms of VEGF.[15] Two pivotal studies, MARINA[16] and ANCHOR,[17] showed that injections of ranibizumab given every 4 weeks over a 2-year period were superior to both no treatment and photodynamic therapy. Around a third of ranibizumab treated eyes experienced at least 3 lines of visual gain and more than 90% remained within 3 lines of presenting acuity. This was the first time that any treatment for neovascular AMD resulted in an improvement in vision.

Bevacizumab (also developed by Genentech) is a full-length monoclonal VEGF antibody and is used to treat colorectal cancer.[18] Changes to the structure of bevacizumab, along with an improved affinity for VEGF, resulted in the development of ranibizumab. Although there have been no large clinical trials on the efficacy or safety of bevacizumab for neovascular AMD, more than 7,500 patients have received it for this condition.[19] Its popularity stems from the fact that it was shown to have similar benefits to ranibizumab in a series of small uncontrolled clinical studies when administered intravitreally in roughly equimolar concentrations to ranibizumab.[18]

Compared with ranibizumab, which costs £761.20 per dose, bevacizumab is cheap. A single vial of bevacizumab for oncological use is approximately £500 and this can yield around 50 doses for intraocular use, costing approximately £10 per injection. Improvements in vision and morphological appearance have been

found with varying doses of the drug from 1 mg to 1·25 mg.[20] Two major trials, one in the USA and one in the UK, have been designed to compare the efficacy of bevacizumab versus ranibizumab. The ophthalmic community awaits with interest the results of these trials.

VEGF is essential for angiogenesis and might therefore be required for the development of accessory blood vessels in the myocardium or ischaemic limbs. While ocular administration of such drugs results minimal systemic exposure, elderly people—who are already at an increased risk of cardiovascular events such as stroke and myocardial infarction—may still be at an increased risk if VEGF is blocked systemically.

The longest prospective follow-up of 3 years on VEGF inhibition has been with pegaptanib and to date no systemic safety concerns have been raised.[20] Since ranibizumab and bevacizumab block all forms of VEGF, they might pose a larger risk than pegaptanib. An analysis[16,17] looking at the first year data for the MARINA, ANCHOR, and PIER trials found no undue concerns about the incidence of arterial thromboembolic events (based on definitions from the Antiplatelets Trialists Collaboration[21]) with ranibizumab compared with the expected number of arterial thromboembolic events in this predominantly elderly population.

Adherence to standardised protocols employing asepsis, correct injection technique, and use of appropriately trained clinical staff markedly reduces the rate of injection-related complications.

In January 2007, Genentech advised clinicians that ranibizumab increased susceptibility to stroke in patients who had previously had a stroke.[22] An interim analysis of the SAILOR[22] study of 5000 patients recorded an incidence of stroke of 1·2% in the 0·5 mg group compared with 0·3% in the 0·3 mg group (p=0·02). Clinicians need to remain vigilant and report all adverse events so that if an association exists, it can be quickly identified and recommendations made regarding treatment. Since bevacizumab has not been studied in any controlled trials to date and the safety results from the ranibizumab trials cannot be extrapolated to bevacizumab, it remains to be seen whether the larger bevacizumab molecule has a different safety profile.

Ocular side-effects are largely from the procedure itself. Repeated injections into the eye carry a risk of infective or sterile endophthalmitis (a sight-threatening eye infection occurring in approximately 1 in 1000 patients), traumatic retinal detachment and traumatic cataract. Adherence to standardised protocols employing asepsis, correct injection technique, and use of appropriately trained clinical staff markedly reduces the rate of injection-related complications.[14] It is unknown whether chronic inhibition of VEGF will have significant long-term ocular side-effects since VEGF is a known neuroprotectant.[23]

There is also a concern that VEGF blockade may be simply putting on hold the inevitable decline in vision when treatment is withdrawn. Since VEGF inhibition appears to act by reducing the permeability of existing vessels and possibly by preventing development of new vessels, it seems sensible to combine this treatment with photodynamic therapy. Such a strategy may minimise the frequency of treatments needed and perhaps also limit the duration of treatment. Promising results from some preliminary small clinical trials suggests that this avenue deserves further investigation.[24-25]

National guidance

In December 2007, The National Institute for Health and Clinical Excellence (NICE) published a second appraisal document[26] concerning the use of ranibizumab and pegaptanib for the treatment of neovascular AMD. It recommends ranibizumab for all patients with neovascular AMD with best-corrected vision better than 6/60. This is a marked change from its first appraisal document, which recommended treatment only for patients with onset of disease in the second eye and even limited the treatment to those with classic and predominantly classic types of neovascular AMD.

Interestingly, it also suggests that the pharmaceutical company behind the drug should meet the cost of treatment if it extends beyond 14 injections. These preliminary recommendations will be reviewed in February 2008, with the final decision expected in March. Until this guideline is finalised, clinicians need to discuss funding arrangements for this expensive technology with their commissioning authorities because the absence of NICE guidance should not mean patients are excluded from treatment.

Summary

The future for patients suffering from neovascular macular degeneration looks promising. New randomised controlled trials comparing different drugs and combination therapies will hopefully continue to improve outcomes and identify optimum therapeutic strategies.

Professor Chakravarthy has been on the scientific advisory boards of Novartis, Pfizer, Genaera, Jerini and Eyetech, all of whom have proprietary interests in agents that inhibit VEGF. She was a member of the VISION Trials study group and has received financial assistance from some of the above for speaking at conferences. Miss McAvoy was involved in clinical trials sponsored by Novartis and Pfizer.

References

1. Klein R, Klein BE, Jensen SC, Meuer SM. The five-year incidence and progression of age-related maculopathy: the Beaver Dam Eye Study. *Ophthalmology* 1997; **104**: 7–21
2. Owen CE, Fletcher AE, Donoghue M, Rudnicka AR. How big is the burden of visual loss from age-related macular degeneration in the United Kingdom. *Br J Ophthalmol* 2003; **87**: 312–17
3. Chakravarthy U, Augood C, Bentham G, et al. Cigarette smoking and age-related macular degeneration in the EUREYE study. *Ophthalmology* 2007; **114**: 1157–63. Epub ahead of print
4. Edwards AO, Ritter R 3rd, Abel KJ, et al. Complement factor H polymorphism and age-related macular degeneration. *Science* 2005**; 308**: 421–24
5. Hughes AE, Orr N, Esfandiary H, et al. A common CFH haplotype with deletion of CFHR1 and CFHR3 is associated with a lower risk of age-related macular degeneration. *Nat Genetics* 2006; **38**: 1173–77
6. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch Ophthalmol* 2001 **119**: 1417–36
7. Coleman H, Chew E, Nutritional supplmentation in age-related macular degeneration. *Curr Opin Ophthalmol* 2007; **18**: 220–23
8. Macular Photocoagulation Study Group. Laser photocoagulation for juxtafoveal choroidal neovascularisation. Five-year results from randomized clinical trials. *Arch Ophthalmol* 1994; **112**: 500–09
9. Bakri SJ, Kaiser PK. Verteporfin ocular photodynamic therapy. *Expert Opin Pharmacother* 2004; **5**: 195–203
10. Bressler NM; Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: two-year results of 2 randomized clinical trials-TAP report 2. *Arch Ophthalmol* 2001; **119**: 198–207
11. Ferrara N. Vascular endothelial growth factor: basic science and clinical progress. *Endocr Rev* 2004; **25**: 581–611
12. Kvanta A, Algvere PV, Berglin L, et al. Subfoveal fibrovascular membranes in age-related macular degeneration express vascular endothelial growth factor. *Invest Ophthalmol Vis Sci* 1996; **37**: 1929–34
13. Bell C, Lynam E, Landfair DJ, et al. Oligonucleotide NX1838 inhibits VEGF165-mediated cellular responses in vitro. *In Vitro Cell Dev Biol Anim* 1999**; 35**: 533–42
14. VEGF Inhibition Study in Ocular Neovascularization (V.I.S.I.O.N.) Clinical Trial Group; Chakravarthy U, Adamis AP, Cunningham ET Jr, et al. Year 2 efficacy results of 2 randomized controlled clinical trials of pegaptanib for neovascular age-related macular degeneration. *Ophthalmology* 2006; **113**: 1508–21
15. Gaudreault J, Fei D, Rusit J, et al. Preclinical pharmacokinetics of ranibizumab (rhuFabV2) after a single intravitreal administration. *Invest Ophthalmol Vis Sci* 2005; **46**: 726–733
16. Rosenfeld PJ, Brown DM, Heier JS, et al. Boyer DS, for the MARINA Study Group. Ranibizumab for neovascular age related macular degeneration. *N Engl J Med* 2006; **355**(14); 1419–31
17. Brown DM, Kaiser PK, Michels M, et al; ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med* 2006; **355**: 1432–44
18. Ranieri G, Patruno R, Ruggieri E, et al. VEGF as a target of bevacizumab in cancer. From biology to the clinic. *Curr Med Chem* 2006;**13**: 1845–57
19. Lynch SS, Cheng CM. Bevacizumab for neovascular ocular diseases. *Annals of Pharmacotherapy* 2007; **41**: 614–24
20. VEGF Inhibition Study in Ocular Neovascularization (V.I.S.I.O.N.) Clinical Trial Group; Chakravarthy U, Adamis AP, Cunningham ET Jr, et al. Pegaptanib sodium for neovascular age-related macular degeneration: two-year safety results of the two prospective, multicenter, controlled clinical trials. *Ophthalmology* 2006. **113**: 992–1001
21. Antiplatelets Trialists Collaboration. Collaborative overview of randomised trials of antiplatelet therapy. Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994; **308**: 81–106
22. Genentech Release on Safety Lucentis http://www.fda.gov/medwatch/safety/2007/Lucentis_DHCP_01-24-2007.pdf (accessed: 13/02/08)
23. Storkebaum E, Lambrechts D, Carmeliet P. VEGF: once regarded as a specific angiogenic factor, now implicated in neuroprotection. *Bioessays* 2004; **26**: 943–54
24. Schmidt-Erfurth UM, Gabel P, Hohman T, PROTECT Study Group. Preliminary results from an open-label, multicenter, phase II study assessing the effects of same-day administration of ranibizumab (Lucentis(TM)) and verteporfin PDT (PROTECT Study). Program and abstracts of the Association for Research in Vision and Ophthalmology; April 30-May 4, 2006; Fort Lauderdale, Florida. Abstract 2960
25. Fung AE, Lalwani GA, Rosenfeld PJ, et al. An optical coherence tomography-guided, variable dosing regimen with intravitreal ranibizumab (Lucentis) for neovascular age-related macular degeneration]. *Am J Ophthalmol* 2007;**143**: 566–83
26. The National Institute for Health and Clinical Excellence. Macular degeneration (age-related)—pegaptanib and ranibizumab http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11700 (accessed: 31/01/08)