Bevacizumab: a new hope?

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EDITORIAL

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The introduction of vascular endothelial growth factor (VEGF) antibodies has markedly improved the visual prognosis for patients with neovascular age-related macular degeneration (AMD). Patients presenting with good vision, can now look forward to near normal quality of life, with sufficient vision to drive and read. The results of anti-VEGF therapy stand in sharp contrast to those of argon laser treatment or photodynamic therapy.^{1–6}

Pegaptanib sodium (macugen; a pegylated oligonucleotide modified to bind VEGF₁₆₅) was the first intravitreal treatment. The VISION trials, of pegaptanib on neovascular AMD, found 70% of treated eyes had stable vision, compared to 55% in the sham group.¹ Late in 2006, the ANCHOR and MARINA trials, demonstrated the efficacy of ranibizumab (a monoclonal antibody fragment binding VEGF-A) for neovascular AMD.^{2,3} These reported visual stabilisation in 94–96% and improvement in vision in 40% of eyes. Both pegaptanib and ranibizumab have a European licence for neovascular AMD and the National Institute for Health and Clinical Excellence (NICE) have considering their use in the NHS, in the meantime, some primary care trusts are already funding ranibizumab or pegaptanib treatment. This is good news for the 25 000 patients, who develop neovascular AMD in the United Kingdom each year.

However, before licensing of ranibizumab, ophthalmologists started to use bevacizumab (Avastin), a full-length anti-VEGF antibody, licenced for colorectal carcinoma treatment. Dr Rosenfeld first used this drug as an intravenous infusion, finding similar results to intravitreal ranibizumab.⁷ He subsequently gave it intravitreally, again with positive results.⁸ Within 12 months, bevacizumab use had become international and several reports on its efficacy and safety were published.^{9–13}

In this edition of EYE, Cleary *et al*¹⁴ contribute to the literature, reporting on the effect of intravitreal bevacizumab on occult and classic

CNV in 112 eyes. Overall vision improved from 0.84 Log MAR (6/41) at baseline to 0.69 Log MAR (6/30) at 9 months after an average of 1.69 injections. There was a reduction in macular thickness and some adverse events such as retinal pigment epithelial rip, submacular haemorrhage, and endophthalmitis. These results are similar to others published about intravitreal bevacizumab. Avery *et al*¹¹ reported a series of 79 patients, finding a reduction in macular thickness in 55% at 1 week, with an improvement in vision from 20/200 to 20/125 at 1 month. Similarly, Rich *et al*¹⁰ observed improvements in visual acuity and macular thickness at 1 week. At 3 months, the visual acuity improved from 20/160 to 20/125 and the mean central retinal thickness decreased by 99.6 microns after an average 2.3 injections of intravitreal bevacizumab.

At the 2007 Association for Research in Vision and Ophthalmology (ARVO) meeting, the interest in bevacizumab was intense with 154 presentations. Key papers again came from Dr Rosenfeld's group. They presented data from a group of 403 patients treated with bevacizumab;¹⁵ of these, eight (1.9%) did not achieve a fluid-free macula. These eight were treated with ranibizumab; five had improved optical coherence tomogram (OCT) measurement, but only three (0.74%) had an improvement in vision. Another paper looking at patients switched from bevacizumab therapy to ranibizumab therapy, found a 2–3 letter improvement of vision ($P > 0.05$).¹⁶ This may, however, be due to an ongoing improvement in macular function (personal communication). Others found significantly better results with bevacizumab and ranibizumab when compared to pegaptanib sodium.¹⁷ For some bevacizumab has become a 'generic ranibizumab'¹⁸ but to fully assess the difference between the two drugs, the US and UK governments have set up head-to-head trials to determine the safety and effectiveness of these treatments.

As with many new treatments, there are several unresolved issues over the use of intravitreal anti-VEGF therapy. Monthly

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ranibizumab injections may cost up to 0.5% of the total NHS budget (£500 million). There are several trials looking at reducing the dosage frequency (to save cost and reduce complications), however results from the PIER trial, found that the initial improvement in vision was not sustained, with vision returning to baseline at 1 year.^{18,19} More positive data have come from the PrONTO study (40 patients), which suggests that OCT-guided treatment of patients can improve the visual prognosis while avoiding monthly ranibizumab injections.²⁰ The dosage (0.3 or 0.5 mg) and frequency of ranibizumab are still an issue. There is some evidence that 0.5 mg is more effective than 0.3 mg,^{2,3} but the SAILOR (a safety) trial suggests it may also cause more stroke than the 0.3 mg dose (1.2 vs 0.3%; $P = 0.02$).²¹ The total stroke rate is however lower than expected for that population making this data difficult to interpret. Bevacizumab, a larger molecule, is given less frequently than ranibizumab, reducing the potential of systemic side effects and the risk of endophthalmitis.²² As such, some countries currently support the use of only bevacizumab, excluding ranibizumab on cost grounds.

In summary, anti-VEGF treatment has revolutionised the management of neovascular AMD, worldwide. Stabilisation or improvement in vision is achieved for the majority of patients treated with either bevacizumab or ranibizumab. Identification and appropriate referral of patients, before irreversible loss of vision occurs is now a clear priority. Research is being focused on the head-to-head clinical trials of bevacizumab and ranibizumab and developing treatments for the underlying dry AMD, which now determines the visual prognosis for the majority of our patients with macular degeneration.

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