By Nick Lane PhD

New VEGF antagonists in AMD – new quandaries abound

Effective vascular-endothelial growth-factor (VEGF) antagonists have been a long time coming, after first being proposed back in the 1970s; but now, like London buses, three have arrived at once for the treatment of wet AMD. Far from being just 'me-too' drugs in the same class, the VEGF antagonists have called attention to difficult issues relating to cost, efficacy, quality of evidence, share value, and a potential split between industry, regulators and practicing clinicians. The issues have repercussions throughout medicine.

The first VEGF antagonist to be approved for AMD was pegaptanib (Macugen®, Pfizer/Eyetech), which received FDA fast-track approval last December. Despite this good news, it's fair to say that the results were disappointing, no doubt for the co-developers. While unquestionably effective at slowing the progression of neovascular AMD, and the accompanying loss of visual acuity, hopes for a treatment substantially better than verteporfin PDT (Visudyne®, Novartis) were dashed.

Some 70% of patients receiving pegaptanib lost fewer than 15 letters VA compared with 55% of placebo-injected patients at one year; but only 6% or 7% of patients gained more than 15 letters compared with 2% in the control group. These results are similar to verteporfin PDT, both in terms of efficacy and treatment cost, no snippet for pegaptanib at around $1000 per injection.

Higher hopes turned instead to ranibizumab (Lucentis®), developed by Genentech in partnership with Novartis, and still in phase III trials. In May 2005, Genentech announced good one-year data directly to the press, two months before giving ophthalmologists a chance to judge for themselves at the American Society of Retinal Specialists meeting in Montreal at the end of July. I call attention to this deliberately: giving shareholders priority over clinicians is a trend that should not be encouraged.

But the data do seem to be genuinely extremely encouraging. In the MARINA trial, 95% of patients treated with ranibizumab maintained or improved their vision (defined as <15 letters loss of VA on the ETDRS charts), versus 62% of placebo-injected patients. If the control group seems to have done particularly well, this is partly attributable to the patient population, who had minimally classic or occult CNV lesions, which are generally less aggressive than the classic or predominantly classic CNV most suitable for treatment with verteporfin PDT.

Even so, despite the relatively slow disease progression, patients treated with ranibizumab experienced a mean increase of seven letters VA at 12 months, while patients in the control group had a mean decrease of 10.5 letters. Some 34% of the 0.5 mg-treatment group experienced a better than15-letter gain in VA, compared with 4.6% in the control group.

On behalf of the MARINA Study Group, Joan Miller MD (Massachusetts Eye and Ear Infirmary), told delegates at the ASRS meeting in Montreal, "These data are very compelling because, for the first time, we have a potential treatment which has been shown to improve vision in a significant number of patients with wet AMD as opposed to just slowing progression of vision loss."

Another trial (FOCUS, phase I/II) compared verteporfin PDT plus ranibizumab with PDT alone in patients with predominantly classic CNV. The results were similarly encouraging (also presented first directly to the press in May): 90% of patients receiving combination therapy had stable or improved vision (<15 letters loss) compared with 62% of patients receiving PDT alone.

What may be hidden in the small print is still unpublished. In September the FDA notified Genentech that it would not grant the company's request for fast-track review, which allows for a rolling BLA (Biologics Licence Application). However, Genentech plans to file for approval this December, and still have the potential to obtain priority review status for ranibizumab.

Genentech in Competition with Itself

So far, so good. The only surprise, a positive one, is that ranibizumab looks substantially better than pegaptanib. Is this a fluke or real? It might well be real. There are five or six different isoforms of VEGF, with differing molecular weights and properties. The heavier isoforms are membrane-bound, whereas the lighter isoforms diffuse through the vasculature. Ranibizumab is a humanised antibody that binds to all the isoforms of VEGF, whereas pegaptanib is a ribonucleic aptamer (a molecule that binds with an affinity that depends on its shape), which binds only to VEGF165. While this is thought to play an important role in AMD, it is nonetheless just a single isoform. So differences in both mechanism of action and target could account for the observed differences in efficacy.

But here is the rub. Ranibizumab is a molecular cousin of a larger antibody, known as bevacizumab (molecular weight 148 kDa), marketed by Genentech as Avastin®. Engineered on the DNA level, ranibizumab has several specific base changes that increase its affinity to VEGF. The FDA approved bevacizumab for treating advanced colorectal cancer in February 2004, and it is still in trials for other forms of cancer.

Of course, in both advanced cancer and wet AMD, angiogenesis is an important factor in determining outcome. Genentech felt that bevacizumab was too big to penetrate the retina by intravitreal injection; and while life-threatening adverse events (a higher risk of thromboembolic events such as stroke and MI) might be acceptable in treating advanced cancer, systemic treatment with bevacizumab for AMD seemed to be using a sledgehammer to crack a nut. The risk of such adverse

What is a cost-effective drug?

Many new medicines, such as pegaptanib (Macugen, Eyetech/Pfizer) or indeed verteporfin PDT (Visudyne, Novartis), seem prohibitively expensive, with prices often in excess of $1000 per treatment. As probably the best treatment so far, ranibizumab (Lucentis, Genentech) seems certain to follow a similar path. But when does it become simply too expensive to reimburse?

Verteporfin PDT has been mired in cost-effectiveness issues for almost its whole time on the market, but newer drugs rarely face the same problem. Their cost-effectiveness is virtually guaranteed to be close to the threshold accepted by society. How so? By wielding the weapon of ICERs per QALY backwards.

The term ICER means incremental cost effectiveness ratio. The most common definition is simply the ratio of cost to outcome. Outcome is usually given as a QALY, or quality-adjusted life-year gained. QALYs range from 1, for a full additional year in perfect health, to zero, for death. It's also possible to score negative QALYs, for fates considered worse than death. A QALY of, say, 0.5, implies that lifespan may not be extended, but quality of life is improved; or that lifespan is extended, but quality of life is poor.

Because quality of life is subjective, QALYs are also obviously somewhat subjective. QALYs are often high in ophthalmology, because people value their sight so highly. For example, a recent poll (www.costofblindness.org) revealed that 69% of Canadians would rather lose the use of their legs, or their hearing, than their vision; and those already legally blind were willing to accept a 50% cut in their remaining years to recover sight.

The advantage of using an ICER, or cost per QALY, is that it is a standard measure that can give a comparison across different areas of medicine. Should a cash-strapped health system fork out for a new cancer drug, or ranibizumab, and when should it refuse to pay? While rarely stated in as many words, a presumed 'threshold' cost-effectiveness of $50,000 per QALY is generally thought worth paying by reimbursement agencies; any more may well not get reimbursed.

Given a known efficacy and QALY, this means that a pharma company can hardly get it wrong now. Simply plug in the number of QALYs gained and calculate the cost effectiveness threshold. A recent paper by Sanjay Sharma et al (Can J Ophthalmol, 2005), on anecortave acetate (Retaane, Alcon) shows how it is done. They calculate that the threshold cost effectiveness for anecortave works out at $2986 per vial. The producers, Alcon, can argue that at that price it is just as cost-effective as other products that have been reimbursed in the past.

Of course there is still plenty of scope for dispute. One factor is the time span considered. This is a problem that has frustrated verteporfin PDT. In the UK, the NHS Health Technology Assessment calculated an ICER of £150,000-180,000 per QALY, but this was based on a two-year period (then the limit of RCT data), during which time the re-treatment costs are maximum and the benefits are limited to the two-year period. If the treatment benefit persists beyond two years (which it does), but fewer treatments are needed (which they are), then the cost per QALY falls.

events would be virtually eliminated by intravitreal injection of a smaller antibody that could penetrate the retina, so Genentech developed ranibizumab for intravitreal injection.

Then in June 2005, Drs Stephan Michels, Philip Rosenfeld and their colleagues at the Bascom Palmer Eye Institute, University of Miami, published an uncontrolled case series using systemic bevacizumab for treating AMD in Ophthalmology. With 12-week data for only nine patients, they still found that patients receiving bevacizumab had marked improvements in VA from as early as a week – results that, on the face of it, were comparable with ranibizumab.

"There are potential advantages to treating AMD systemically. In particular, the treatment effect of two to three initial infusions is quite durable, lasting six months in the majority of our patients, so we may not need to treat as often; and secondly, active AMD is often bilateral, and we treat both eyes at once with systemic treatment. We are seeing improvements in VA in the fellow eye as well as the study eye," Dr Michels told *EuroTimes*.

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So far, Dr Michels and colleagues (who are continuing their case series at the University of Vienna, Austria) have found no serious adverse events, beyond a small and reversible rise in blood pressure (about 12 mm Hg); but that is a moot point. Just this September, Genentech halted a phase II trial of bevacizumab in platinum-refractory ovarian cancer after a higher rate of gastrointestinal perforations (5/43 patients enrolled). Safety is certainly an issue.

Dr Michels emphasised that systemic treatment for AMD is not comparable with cancer treatment.

"In treating advanced cancer, bevacizumab is combined with multiple chemotherapy regimens and given every two weeks for months or even years. This is not the case for AMD, so the risks are very different. Even so, in treating AMD it's important that patients are regularly seen by their internal specialist."

In the meantime, however, it seems that bevacizumab is also effective by intravitreal injection. Philip Rosenfeld MD and colleagues announced strikingly good, albeit very preliminary, VA, optical coherence tomography and angiographic findings at the same ASRS meeting in Montreal, and published a case series in Ophthalmic Surgery, Lasers and Imaging, in July 2005.

In an accompanying editorial, Elias Reichel MD, of the New England Eye Centre, Tufts University, concluded, "Bevacizumab is a readily available drug that costs a fraction of the proposed alternatives. The dramatic findings of Rosenfeld et al demand that further studies be done to assure safety and confirm treatment benefit."

Rosenfeld and colleagues have now treated more than 200 patients with intravitreal bevacizumab, but have yet to publish detailed longer-term results; and the FDA would hardly deem this a clinical trial. Even so, more and more ophthalmologists are trying intravitreal bevacizumab, ostensibly with very encouraging results, mainly on patients who did not benefit from other treatments such as verteporfin PDT or pegaptanib – a refractory group.

The trend has become so marked that analysts SG Cowen recently revised their financial projections for ranibizumab: "Our checks indicate growing demand for intravitreous Avastin for the treatment of wet age-related macular degeneration. Positive clinical experience and its low cost should enable the drug to rapidly capture and maintain significant share in the wet AMD market. We expect Avastin and Lucentis to dominate the AMD market, but have reduced our Lucentis estimates to account for increasing competition from Avastin."

In fact they lowered their projected revenues from $1.1 billion to $600 million, anticipating nearly a 50% reduction in the peak sales potential of ranibizumab.

Cost versus Efficacy

A 100 mg vial of bevacizumab costs around $700, but only 1.0 mg is needed for intravitreal injection, giving an estimated treatment cost for AMD of around $40 to $75. While ranibizumab has not yet been priced, pegaptanib costs around $1000 per vial, and it's a fair bet that ranibizumab would cost more. Mike King, an analyst with Rodman and Renshaw, estimates that the cost will be in the order of $1,200 per injection, totalling $14,000 a year for treatment.

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This raises several major issues, notably cost, efficacy, and quality of data. The high cost of modern medicines is a serious challenge to health systems, even in the US, where Medicare is teetering on the brink of bankruptcy. In other countries, including much of the EU, reimbursement is a major issue.

Verteporfin PDT, for example, has been stalled at the National Institute for Clinical Excellence (NICE) in the UK for several years, pending the resolution of interminable cost-effectiveness arguments. In the circumstances, a safe, cheap, effective medication that is widely available, albeit off-label, is a huge boon. But is it safe and effective?

According to Dr Michels, very preliminary results have convinced many retina specialists.

"We have tried to get funding from pharmaceutical companies to conduct clinical trials with ranibizumab, but there has been no interest. It is very likely that larger case series with longer follow-up, including VA, angiography and optical coherence tomography will be the only data available for some time. The situation is to some extent comparable to the off label use of intravitreal steroids in combination with verteporfin therapy for neovascular AMD," he told *EuroTimes*.

For many surgeons, deprived of the double-blind approach, this would also be enough; how many effective procedures in ophthalmic surgery have been adopted, to the undoubted benefit of patients, without exhaustive and time-consuming clinical trials data?

But if clinicians are to prescribe new medicines widely on an off-label basis, this is not just vulnerable to the charge of double-standards – why should only pharmaceutical companies go to the trouble of paying for proper clinical trials – but also has the potential to put patients at risk. This would place clinicians at odds with regulators, with price, rather than efficacy, a driving force.

According to Genentech, bevacizumab was never designed for intravitreal injection. Its safety and efficacy are simply unknown. This might sound a little disingenuous, for Genentech did not test the pharmacokinetics of bevacizumab by intravitreal injection. Instead they compared a molecule of similar size (Herceptin, also of molecular weight148 kDa) against an antibody fragment similar to ranibizumab. A cynic might be forgiven for wondering whether Genentech had nothing to gain and everything to lose from testing bevacizumab directly.

But the real world is rarely as black and white as a good conspiracy theory. When *EuroTimes* put this question directly to Genentech, spokeswoman Dawn Kalmer came back with a reasonable answer.

"The tests we did were on rhesus monkeys, because we needed an animal model that was much closer to the human eye than the rabbit. The trouble was, at the time we did not have humanized antibodies for either bevacizumab or ranibizumab – this work was done back in 1996, before either had been developed. So we worked with what we had, humanised antibodies of differing molecular weights, which is the most important parameter of retinal penetration. And this work clearly showed that only the smaller antibody fragments could penetrate the retina. On that basis, we developed ranibizumab for intravitreal injection."

She noted that in addition to retinal penetration, the company considered a number of other factors based on pre-clinical studies as it made the decision to develop Lucentis. These included: the systemic half life which is significantly shorter for Lucentis (21 days for Avastin compared to four hours for Lucentis; elimination of the Fc portion of the full-length antibody, a portion known to cause inflammation; and the 100 times higher affinity of Lucentis to VEGF enabling use in smaller quantities than Avastin.

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So what should be done now? According to Dr Reichel the cost issue is a non-issue, at least in the US.

"The data behind ranibizumab are so good that I think it will certainly be cost effective to prescribe it here. In the MARINA trial, 75% of patients showed some improvement and 40% of patients had excellent vision (20/40 or better) at the end of one year. These are outcomes that society would consider worth paying for."

And for the poor relations, who simply can't afford ranibizumab?

"I think it's very important that we have good properly controlled, double-blinded data for both safety and efficacy. I can see that pharma companies may not be interested in funding this work, but it seems an ideal opportunity for governments to get involved. After all, they could save a lot of money if bevacizumab really is proved to be equivalent. So perhaps the NEI, or a European organisation like the MRC in the UK, could organise a head-to-head trial," Dr Reichel told *EuroTimes*."