Avastin vs Lucentis

The drug reimbursement dilemma of the century

Governments are increasingly reliant on health technology assessment (HTA) to help ensure that patients have access to the medicines they need while curbing healthcare spending. But in the current economic climate, policy makers are having to make some difficult decisions – even reinterpreting existing procedures.

A case in point involves an approved drug for wet age-related macular degeneration (AMD) and a similar drug that appears to be effective against AMD but which is not approved for this indication. Depending on where it is sold, the unlicensed drug may cost less than 10% of the approved drug. This saddles bodies that inform healthcare policy, such as the UK's National Institute for Health and Clinical Excellence (NICE), with a vexing dilemma. NICE is expected to uphold the law that says medicines intended for widespread use must have a marketing authorisation for that use. At the same time, it has a responsibility for obtaining "good value for money, weighing up the cost and benefits of treatments".

The debate is over the use of Avastin (bevacizumab) or Lucentis (ranibizumab) in the treatment of wet AMD – a common cause of visual loss that affects about half a million elderly people in the UK. The incidence of the disease is significant in other developed countries as well. Both drugs were developed by Genentech (part of the Roche Group) but Lucentis is indicated for wet AMD whereas Avastin is not. Nonetheless, Avastin is often used off-label to treat the condition. In the UK and many other countries, doctors have the discretion to use off-label drugs (ie drugs that have not been approved by a regulatory agency for a particular indication) on an individual patient basis.

The tension over the issue is such that the UK National Institute for Health Research (NIHR), a government body, has funded the so-called IVAN trial to compare the effectiveness of the two drugs in treating wet AMD. This is remarkable not only because Avastin is licensed for cancer, but also because NICE has given Lucentis its stamp of approval in the form of technology appraisal guidance recommending that the National Health Service (NHS) only use this drug for treating wet AMD.[1]

The NIHR is directed by the Department of Health (DoH), which now has confirmation on just how high the stakes are. On releasing IVAN's one-year results in May 2012, researchers suggested that the NHS could save about £85 million annually if it switched from Lucentis to Avastin for wet AMD and administered the treatment on an as-needed (rather than the standard monthly) basis. They said that there was "no functional difference in the effects of both drugs".[2]

To add fuel to the fire, some hospitals and clinicians have taken matters into their own hands. Last year, for example, the Southampton, Hampshire, Isle of Wight and Portsmouth primary care trusts (SHIP PCT Cluster) made a radical policy decision to go against NICE guidance and offer patients Avastin for wet AMD on the NHS. This prompted Lucentis's European Union (EU) marketing authorisation holder, Novartis, to seek judicial review.[3]

The policy dilemma

Wet AMD occurs when abnormal changes affect the retina causing swelling, leaking fluid and abnormal blood vessels to form in the back of the eye. A class of drug called vascular endothelial cell growth factor (VEGF) inhibitors can be injected directly into the eye to alter the growth of the blood vessels and reduce the swelling at the back of the eye. Both Lucentis and Avastin are VEGF inhibitors, but only Lucentis was developed for intraocular (intravitreal) use.

Considering the two drugs' very different indications, the decision about which one to use in wet AMD should be straightforward. But there are some issues that UK policy makers have been unable to ignore.

- **Price:** Lucentis is about 10 times more expensive than Avastin per injection. (Only a tiny dose compared with amounts used in cancer is required.) Moreover, Avastin was being used routinely in the UK and across the EU as an off-label treatment for wet AMD before Lucentis came onto the market two years later, in 2007. Despite the cost differential, widespread off-label use of Avastin on the NHS was curtailed following NICE's 2008 guidance.
- **Clinical trials:** On 30 April 2012, the US National Eye Institute published the two-year results of IVAN's sister study entitled, 'Comparison of AMD Treatments Trials' (CATT). CATT researchers concluded that Avastin and Lucentis are equivalent in treating AMD.[4] Though IVAN's one-year results showed a somewhat higher rate of arterial thromboembolic events or heart failure in patients treated with Lucentis, when combined with CATT's one-year results, there was no difference between the two drugs in this area. Both IVAN and CATT researchers did observe a "slightly higher" rate of other serious adverse events with Avastin, but they said this may not even be attributed to Avastin for various reasons. Nonetheless, Novartis has said that both CATT and IVAN data support Lucentis as being safer and more effective in the treatment of wet AMD.
- **Acceptance abroad**: Other countries such as the US routinely use Avastin for wet AMD. Medicare, a public insurance programme available to Americans aged 65 years or older, has been reimbursing the off-label ophthalmic use of Avastin for years. It is estimated that Avastin injections account for about 60% of the American wet AMD market.[5]

Given the worldwide pressure mounting in favour of Avastin, the UK DoH decided that it was worth exploring the drug's routine use to treat wet AMD. One way to do this was by funding the IVAN trial. The other was by asking NICE to look into the feasibility of doing a technology appraisal on Avastin for wet AMD without the support of Roche, the drug's EU marketing authorisation holder.

NICE reported back to the DoH in 2010 saying that there was support for such an appraisal, but that it "would need to be conditional on, or incorporate the assessment of, the safety and quality of intravitreal bevacizumab by a regulatory body or through the involvement of regulatory experts".[6]

The DoH has yet to ask NICE to do an appraisal; it says that NICE will not normally appraise a drug unless it is licensed for the indication in question.[7] NICE, however, has said that there have been cases where the DoH has asked it to do an appraisal for an unlicensed indication, such as the off-label use of immunosuppressive drugs for renal transplantation in children and adolescents.

The judicial review

Recognising that "any formal change in NICE guidance would probably take years to implement", the SHIP PCT Cluster Board decided in 2011 that, based on existing evidence, Avastin was suitable to use in AMD patients as long as potential product contamination risks were addressed.[8] Because Avastin is sold in the dose size for cancer treatment and is not manufactured for intravitreal use, it has to be broken down into much smaller 'eye dose' sized vials. Conditions are not always sterile enough, which has led to infections in some patients.

"PCTs would not ordinarily deviate too far from NICE guidance unless there are exceptional circumstances. The exceptional circumstance here is one of cost, with no noticeable reduction in benefit by using Avastin", the board noted in a report. Though it said doctors would not pressure patients into choosing Avastin over Lucentis, it noted that switching could save the cluster about £5 million annually.

Novartis says that it is not attempting to prevent clinicians from using Avastin off-label for individual patients should they deem it clinically appropriate. However, a spokesperson told *MedNous* in an email that the company was compelled to take legal action because the cluster board's policy "undermines the fact that any medicines intended for widespread use are required to have a marketing authorisation for that use".

Novartis further said that the policy does not properly take into account the restrictions placed on the use of unlicensed medicines, namely that they can only be produced and supplied in relation to requests for individual patients. It also noted that the board failed to inform or consult with the company prior to making the decision.

The cluster board believes that its decision was made lawfully and says it intends to "defend its position vigorously".[9] The Administrative Court is due to hear the case later this year.

What else does the future hold?

Although the future can never be predicted with certainty, some things are clear. One is that Roche has no plans to seek a marketing authorisation for Avastin in wet AMD.[10] Another is that from a regulatory perspective, Avastin has 10-year data exclusivity (it was approved in 2005). This means that the European Medicines Agency cannot accept an application for a biosimilar product from a third party referring to Avastin until the exclusivity period ends.[11] In the interim, if a third party wanted to apply for a product containing the active substance bevacizumab, it would have to submit results of its own pharmaceutical, pre-clinical and clinical data to fully support the application.

Furthermore, the NICE guidance that recommends Lucentis as the only treatment for wet AMD is not due to be considered for review until 2014. That said, NICE amended the guidance in May 2012 to reflect a new patient access scheme (PAS) for the drug, which comes into effect on 1 July 2012. According to Novartis, the PAS "removes complexity and burden on NHS resources".

The DoH says that it has no immediate plans to refer Avastin for the treatment of wet AMD to NICE for appraisal, but that it will "keep the evidence on the issue under review".

If the DoH changed its mind and NICE approved Avastin for wet AMD, this would be a major policy shift. Some HTA experts believe that such a change could impact reimbursement decisions beyond the UK, given that NICE is recognised as a global leader in technology assessment and its guidelines are followed worldwide.

Furthermore, they caution that policy makers should look at the potential long-term implications as well as the short-term economic gain. For example, this type of public health decision could result in companies avoiding the UK market until they have reimbursement secured in other countries. Companies might also refrain from developing valuable new products to steer clear of another Lucentis/Avastin-type conundrum.

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