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Provider, Patient, and Public Benefits from a NICE Appraisal of Bevacizumab (Avastin)

Abstract

There are several good reasons for UK Department of Health to recommend appraisal of bevacizumab for treatment of eye conditions by the National Institute for Health and Clinical Excellence. These reasons will extend to other drugs when similar situations arise in future.

“Doing nothing and leaving the situation as it currently stands would be to the detriment of many people, including patients, clinicians and healthcare decision makers.”^{1(p9)}

Where there is a treatment that is apparently vastly more cost-effective, with a similar safety profile to an existing licensed treatment, there is no good reason that those in charge of resource allocation decisions within healthcare systems (be they public, private, or mixed) and those responsible for delivering treatment should not be able to opt for the cheaper alternative. They should certainly not be blocked from collating full information allowing comparison of treatment options. The [INSTITUTIONAL NAME REMOVED] fully supports NICE’s view that an appraisal of bevacizumab (Avastin) would be beneficial and supports the conduct of government funded comparative clinical studies. We would suggest that Roche, which owns both bevacizumab and the existing licensed drug ranibizumab, (and other pharmaceutical companies who may be involved in similar cases) should be more supportive of and cooperative with such processes. In what follows we explain why.

NICE and Feasibility of an Appraisal of Bevacizumab for wet-AMD

At the request of the Department of Health, NICE (the National Institute for Health and Clinical Excellence) undertook an investigation of whether it would be appropriate for it to appraise bevacizumab for treatment of wet age-related macular degeneration (AMD). NICE reported in December 2010, supporting an appraisal: “Patients, clinicians and healthcare commissioning groups would benefit from an appraisal, or appraisals, of the clinical and cost-effectiveness of intravitreal bevacizumab in eye conditions.”^{1(p1)} and suggesting that it be “conditional on, or incorporate assessment of, the safety and quality of intravitreal bevacizumab... by a regulatory body or through the involvement of regulatory expertise.”^{1(p10)}

The next stage, as recently reported in the BMJ,² is for the Department of Health (DoH) to decide whether to refer bevacizumab to NICE for appraisal of its use in treatment of wet-AMD and other eye conditions.

Bevacizumab, Ranibizumab and the Treatment of Wet-AMD

Bevacizumab is licensed for treatment of some metastatic cancers, but not for treatment of eye conditions. It is unusual for NICE to appraise unlicensed drugs, but an exception is being considered because bevacizumab appears to produce comparable results at a substantially lower cost than the licensed treatment ranibizumab (Lucentis).

Wet-AMD is a leading cause of severe vision loss. Bevacizumab and ranibizumab have been demonstrated to be superior to previous treatments for wet-AMD, being more effective at

stabilisation and resulting in vision improvement for many patients.³ The 'off-label' or unlicensed use of bevacizumab in the treatment of wet-AMD appears to have emerged in the United States in 2005, and to have rapidly become a widespread practice among ophthalmologists worldwide.⁴ Ranibizumab was approved for treatment of wet-AMD in the US in June 2006, the EU in January 2007, and by NICE in 2008.^{5,6,7}

Bevacizumab, Ranibizumab and Cost-Effectiveness

Although ranibizumab is a licensed and approved treatment, many ophthalmologists in the UK and worldwide wish to continue prescribing bevacizumab and would like its clinical and cost-effectiveness to be properly assessed. Roche – the company that owns both drugs – has indicated that it does not intend to submit bevacizumab for licensing for use in treatment of eye conditions.^{1(p7)} This situation has produced many calls for clinical studies to be conducted to directly compare the two treatments. (Avastin and Lucentis are manufactured by Genentech, a subsidiary of Roche; Roche markets Avastin in the UK; Novartis is licensed to market Lucentis in the UK and most of Europe.)

For wet-AMD treatment, ranibizumab is effective, licensed, and has gone through trials to study its safety and efficacy. Bevacizumab has been observed to be effective, with few adverse effects reported, but – at least until very recently – has not been subject to large-scale, randomised clinical trials. Two major studies are now underway directly comparing the two drugs and different dosing regimes: CATT (Comparison of Age-Related Macular Degeneration Treatments Trial) funded by the US National Eye Institute and expected to report late 2011; and IVAN (randomised controlled trial of alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularisation), funded by the NHS and due to report early 2012. Not only is Roche unwilling to submit bevacizumab for licensing for eye conditions, it is also resistant to continued off-label use, to the conduct of these clinical studies, and views an appraisal as infeasible and inappropriate.^{1(p7)}

Ranibizumab costs substantially more per injection than bevacizumab. Relative costs per dose are estimated at \$1950 to \$50 in the US and £750 to £50 in the UK.^{1(p6)}⁸ (Intravitreal injections of bevacizumab are produced by splitting doses of the cancer drug.) A study by Raftery et al,⁸ indicated that when compared to bevacizumab, given their cost difference, ranibizumab would have to be two and a half times as clinically effective to meet NICE's threshold of £30,000 per QALY. While the results of the CATT and IVAN trials are yet to be released, observations from ophthalmologists, a small-scale trial,⁹ and the fact that the drugs are very similar, indicate that, while there may be a small difference in efficacy and/or in frequency of side-effects this is highly unlikely to represent anything like the scale of effect necessary to make ranibizumab the more cost-effective option.

Our Opinion

Companies should not be in the position to block moves to more cost-effective treatments in order to maximise their profits. They should recognise and be responsive to the social and economic context in which they operate – while health systems in some countries may be able to afford treatment at the higher cost, this will inevitably divert resources from other areas, with negative results for patients, societies and the system as a whole.

The case of ranibizumab and bevacizumab is unlikely to be isolated – indeed it has strong parallels to cases in which incremental modifications are made to drugs that will soon be off-patent, so that market position can be maintained. It should be a cause for concern that many other more cost-effective treatments might be being held back as companies pursue and market those that are expected to bring most profit. The fact that they may lack commercial incentive for pursuing cheaper alternatives does not justify actively blocking

others from doing so, and points to the need for alternative incentive mechanisms to be provided for drugs that companies will otherwise undersupply.

Private and public healthcare providers have an obligation to support their staff in providing best achievable care for their patients within severe financial constraints and it is legitimate for them to take actions such as appraising and approving unlicensed treatments which are significantly more cost-effective. In this context NICE's advice on the feasibility of an appraisal is admirable and timely, and we hope that the DoH will take this up and soon request NICE to conduct an appraisal. This move does not occur in isolation, there is increasing pressure from healthcare professionals and commissioners in several countries to resolve the issue. Austria, Finland, Germany, Italy and New Zealand already formally recommend the use of bevacizumab over ranibizumab and its use is supported by regional Medicare providers in the US.⁴¹⁰

Hope for the future?

The case of bevacizumab and ranibizumab has brought drug licensing and pricing issues to the attention of many governments, healthcare providers and medical professionals. Their pressure to enable full assessment and use of the more cost-effective option in the absence of industry cooperation indicates that such practices are no longer unquestionably accepted, and the example provided by this case will hopefully promote earlier interventions by these groups as similar cases arise in the future.

Pharmaceutical companies operate with different incentive structures and motivations to those involved in running healthcare systems and delivering treatment to patients. Clashes between these groups on drug pricing are to be expected. Operation of commercial incentives does not, however, excuse the often obstructive behaviour of the companies involved in cases such as this. For example: Novartis initiated a legal case in Germany against health insurers and ophthalmologists due to their policy promoting off-label use of bevacizumab¹¹; Genentech moved to block supply of bevacizumab to compounding pharmacies in the US¹²; and industry representatives have criticised the comparative clinical trials.¹³

Perhaps this case points to the need to implement schemes similar to that proposed in the Ethical Pathway Act 2010 (a bill before the US Senate relating to data exclusivity)¹⁴ – so that there would be a mechanism in such cases to ensure a fair and reasonable fee be paid to the manufacturer to incentivise licensing of its cheaper product. However, given that Roche has already achieved significant income flows from bevacizumab, and Novartis from ranibizumab (sales of 6.461 billion and 1.458 billion Swiss Francs respectively in 2010^{15(p30)}), and the companies would generate further income from a substantial and expanding market for bevacizumab in eye conditions it would appear that corporate concern may be less for the loss of profit for this particular drug, than for the precedent that might be set.

More importantly this case adds weight to the already substantial call for fundamental rethinking of the structures and incentives that dominate research and development, production, marketing and pricing of pharmaceuticals. These not only impose unnecessary financial costs on healthcare systems, they have detrimental effects on hundreds of millions of people, and for too many remain literally a matter of life and death.

The licensing system also needs to be rethought. It should not be left to companies to decide whether a particular product is submitted for licensing as this can clearly operate against the public and patients' interests.

It should be recognised that there is no general right to freedom of trade, it is a dimension of political and moral liberty and is justly constrained in familiar and obvious ways. A combination of general morality, the nation state's obligation to protect its citizens and to promote the public interest, and what George Orwell memorably termed "decency",¹⁶ combine to provide the moral and political force behind all justifiable restrictions on freedom and capture the distinction drawn by Ronald Dworkin between "liberty as licence" and "liberty as dignity"¹⁷. Since the Factory Acts¹⁸ in England in the Nineteenth Century put an end to the licence of manufacturers to produce goods at substantial danger to their own workers, it has been generally accepted that commercial freedom stops at the point where it puts citizens' life or health at risk and where it severely compromises the public interest.

The Factory Acts were a milestone in the history of both ethics and regulation. We have the possibility today to take a comparable step to ensure that the life and health of citizens receives comparable priority when weighed against personal and corporate financial interests. No one finds it acceptable to see their health damaged or their lives compromised by the failure to regulate industry or profits. We are here suggesting the equal recognition of interests of comparable importance.

The philosophical roots of such an approach are to be found in Thomas Hobbes, Jeremy Bentham, and John Stuart Mill and Karl Marx. Whatever their origins, we scarcely need to be reminded that moral duties are general, owed, *inter alia*, to all other moral subjects, and not simply to shareholders, fellow citizens or patent holders. In respecting what is equally owed to all we have to take account of what each party stands to lose by the compromise of their interests. It is surely totally implausible to think that marginally reduced profits can equate to real and palpable protection for the rights of citizens, and all the limitations on both freedom of movement and of choice, not to mention quality of life that compromised sight entails.

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