



Ranibizumab (Lucentis) versus bevacizumab (Avastin): modelling cost effectiveness

James Raftery, Andrew Clegg, Jeremy Jones, et al.

Br J Ophthalmol 2007 91: 1244-1246 originally published online April 12, 2007

doi: 10.1136/bjo.2007.116616

Updated information and services can be found at:

<http://bjo.bmj.com/content/91/9/1244.full.html>

These include:

References

This article cites 17 articles, 8 of which can be accessed free at:

<http://bjo.bmj.com/content/91/9/1244.full.html#ref-list-1>

Article cited in:

<http://bjo.bmj.com/content/91/9/1244.full.html#related-urls>

Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic collections

Articles on similar topics can be found in the following collections

[Retina](#) (1002 articles)

[Editor's choice](#) (493 articles)

Notes

To order reprints of this article go to:

<http://bjo.bmj.com/cgi/reprintform>

To subscribe to *British Journal of Ophthalmology* go to:

<http://bjo.bmj.com/subscriptions>

PERSPECTIVE

Ranibizumab (Lucentis) versus bevacizumab (Avastin): modelling cost effectiveness

James Raftery, Andrew Clegg, Jeremy Jones, Seng Chuen Tan, Andrew Lotery

Br J Ophthalmol 2007;**91**:1244–1246. doi: 10.1136/bjo.2007.116616

Two new drugs provide startling benefits in the treatment of age-related macular degeneration (AMD). The clinical and cost effectiveness of ranibizumab (Lucentis) was compared to that of bevacizumab (Avastin), which costs up to 100 times less. A cost effectiveness model was developed to assess the cost per quality adjusted life year (QALY) over 10 years. For predominantly classic AMD, the efficacy of bevacizumab relative to ranibizumab would have to be around 40% for the latter to achieve £30k per QALY, a NICE threshold. Similar but worse results applied to the other main forms of AMD, minimally occult and occult with no classic lesions. The price of ranibizumab would have to be drastically reduced for it to be cost effective. Continued unlicensed use of bevacizumab raises ethical, legal and policy questions. Public pressure may be the most potent weapon in persuading Genentech to license bevacizumab for AMD.

The natural history of disease progression, applied in the model once treatment had ceased, was based on an indirect comparison with another trial³ with a relevant control arm, since the ANCHOR trial did not include a sham treatment arm. For patients with MC/OC lesions, data on efficacy, dosing and side effects were taken from the MARINA trial, in which ranibizumab was compared with sham injections and treatment continued for a maximum of 2 years.⁴ Post-treatment disease progression was based on outcomes reported for the patients in the sham arm of the trial.

Lacking clinical trial data for bevacizumab, we employed a range for its efficacy relative to ranibizumab. Having estimated the incremental cost per QALY for each level of relative efficacy, we changed side effects and prices in sensitivity analysis.

MODEL STRUCTURE

We developed a Markov model, based on two previous models,^{5,6} amended to allow for gains as well as losses in visual acuity. The model had six health states, five defined by visual acuity plus a death state. Transition probabilities for vision loss and vision gain were based on the relevant ranibizumab trial.^{2,4} Utilities for each health state were based on a study⁷ linking visual acuity and utilities.

Patients entered the model at 75 years of age with follow-up to 85 or death. They started in the second least severe state to allow improvement. Two groups of patients were modelled, those gaining and those losing visual acuity, based on the licensing trials.^{2,4} Treatment was continued monthly as in licensing trials, for 1 year in PC and 2 years in MC/OC. After treatment, disease progression for untreated patients was applied. The most severe states (visual acuity less than 6/60) had an annual cost based on the cost of near-blindness.^{8,9} Patient mortality reflected UK averages for the relevant ages,¹⁰ with a 50% increased mortality risk assumed for the more severe health states.¹¹ The model was simulated for 1000 patients in 3-month cycles.

The price ratio of ranibizumab to bevacizumab was 39:1, based on the US price of US\$1950 (£1025) per injection for ranibizumab and (a high) US\$50 (£26) for bevacizumab. NHS costs were estimated for drug administration and monitoring

New drugs for age-related neovascular macular degeneration (AMD) reverse the disease process, usually leading to gains in visual acuity. Two new drugs are available, one licensed for AMD, the other not. Ranibizumab (Lucentis), licensed in the USA in 2006 (and in the EU in 2007), costs almost US\$2000 per injection. Bevacizumab (Avastin), its close relative, is licensed for cancer but not for macular degeneration. It costs between US\$17 and US\$50 per injection, based on splitting up doses licensed for cancer into minute amounts for injection into the eye.¹ Roche/Genentech owns both drugs but has no plans to license the cheaper.

Bevacizumab has been widely used globally off-license, although currently there is no clinical trial evidence of its efficacy in treating AMD compared with sham treatment (placebo) or ranibizumab. Given it costs 1–3% of the price of ranibizumab,¹ we modelled how much better the dearer drug would have to be to meet NICE's threshold of £30k per quality adjusted life year (QALY).

Ranibizumab is licensed in the USA for two forms of AMD (predominantly classic (PC) and minimally classic or occult (MC/OC) lesions) and shows similar visual acuity gains with each form. We mainly report results for PC, the scenario most favourable to ranibizumab, but also provide results for MC/OC. For patients with PC lesions, data on efficacy, dosing and serious ocular side effects are from the licensing trial which compared ranibizumab to photodynamic therapy with verteporfin.²

See end of article for authors' affiliations

Correspondence to: James Raftery, Wessex Institute for Health R&D, Mailpoint 728, Medical School, University of Southampton, Southampton SO16 7PX, UK; raftery@soton.ac.uk

Accepted 14 March 2007
Published Online First
11 May 2007

Abbreviations: AMD, age-related macular degeneration; MC, minimally classic; OC, occult; PC, predominantly classic; QALY, quality adjusted life year

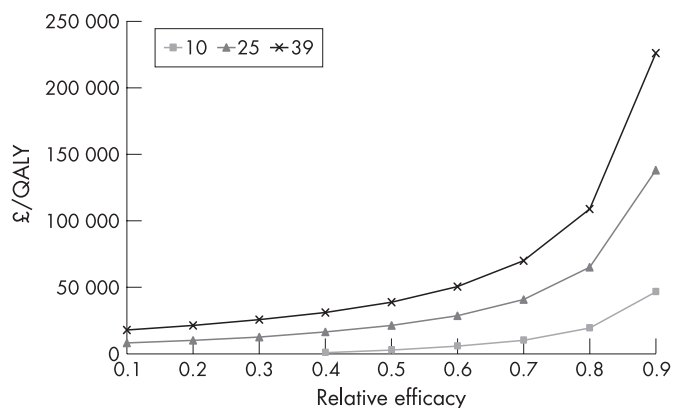


Figure 1 Cost per QALY of ranibizumab versus bevacizumab, by relative efficacy and price ratio (10, 25 and 39) in patients with PC lesions.

of patients as well as treatment of side effects using NHS Reference Costs.¹² NHS and personal social services costs for near-blindness were based on previously published estimates.⁹ The efficacy of bevacizumab relative to ranibizumab was varied from 0.1 to 0.9. The perspective of the analysis was that of the NHS and personal social services. Both cost and utilities were discounted at an annual rate of 3.5%.

In the base case for each form of the disease, the side effect profile of the two drugs was equal. Sensitivity analyses doubled the side effect profile of bevacizumab and reduced the price ratio to 25 and 10.

RESULTS

The results (fig 1) indicate that the efficacy of bevacizumab relative to ranibizumab in PC would have to be low for the latter to achieve an acceptable level of cost effectiveness. Only when relative efficacy was reduced to 0.4 did the cost per QALY fall to £31 092. At 0.8 the cost per QALY was well over £100 000.

Doubling event rates for serious ocular adverse effects for bevacizumab had minimal (<1%) effect on the cost per QALY.

Reducing the price ratio improved the cost per QALY as expected. Relative efficacies of 0.65 and 0.85 would be required to meet the NICE threshold at price ratios of 25 and 10, respectively.

Similar results applied to MC/OC, as shown in fig 2, which differs only in being less favourable to ranibizumab, due mainly to 2 years of treatment being required.

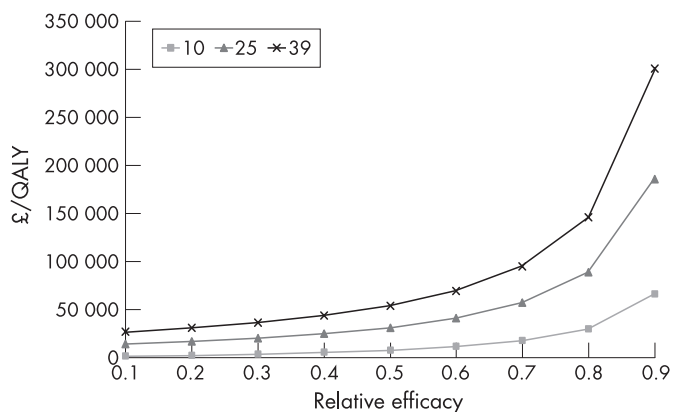


Figure 2 Cost per QALY of ranibizumab versus bevacizumab, by relative efficacy and price ratio (10, 25 and 39) in patients with MC/OC lesions.

DISCUSSION

Ranibizumab is not cost effective compared to bevacizumab at current prices unless it is at least 2.5 times more efficacious. However, in observational studies bevacizumab appears to have similar efficacy.^{13–18}

Given our model, like all others, combined data from a variety of sources, what might the main biases be? The main deficiency, lack of head-to-head data on relative effectiveness, was solved by assuming a full range of possible values. Although we used data from a different trial for natural disease progression in PC, any bias would apply equally to both drugs compared to this baseline. Side effect data were taken from the licensing trials for ranibizumab, but lacking similar data for bevacizumab, the assumption that its side effect profile was twice as bad made minimal difference in sensitivity analysis. The available data indicate its side effect profile is similar to that of ranibizumab.¹⁹ In translating changes in visual acuity to quality of life scores, we relied on previous work which we acknowledge was small scale. More generally, when in doubt we have biased our assumptions favourable to ranibizumab so that our estimates are conservative.

Some 25 000 new UK cases of neovascular AMD might be eligible for treatment each year. A year of treatment, with monthly injections of ranibizumab at £1000 each, costs £300m. Treatment with bevacizumab, as modelled above, would cost 2.6% of that. The difference of £292m represents the opportunity cost.

NICE will issue guidance in late 2007 on ranibizumab compared to best supportive care and photodynamic therapy where appropriate, for patients with the subfoveal choroidal neovascularisation (CNV) associated with wet AMD. Bevacizumab has been omitted from the appraisal as it is unlicensed. A recommendation in favour of ranibizumab would make recruitment to any UK head-to-head trial of ranibizumab and bevacizumab impossible for these patients. The Department of Health should arguably have broken with precedent to refer bevacizumab to NICE as part of its review, widened to include the relevant forms of AMD.

Ownership of the two drugs by a single company unwilling to license the cheaper one points to policy limitations. The separation of licensing (based on safety and efficacy) from cost effectiveness means that the company can avoid assessment of the latter by refusing to license. Although use of an unlicensed drug is not illegal, prescribers may feel pressured to use the more expensive licensed alternative. Even if a clinical trial showed the two drugs to be equivalent, it is not clear how bevacizumab could be authorised for use given the refusal by its owner to license it.

Roche and its subsidiary Genentech own almost half the global market in monoclonal antibodies. Besides bevacizumab and ranibizumab, similar highly priced drugs from this company include trastuzumab (herceptin) and rituximab. These drugs have the potential to treat different diseases, as shown by the use of bevacizumab for cancer and macular degeneration. The response by health systems to this problem of differential pricing of very similar drugs for different diseases is of major importance.

Authors' affiliations

James Raftery, Andrew Clegg, Jeremy Jones, Seng Chuen Tan, Wessex Institute for Health R&D, Medical School, University of Southampton, Southampton, UK

Andrew Lotery, University of Southampton, Southampton Eye Unit, Southampton General Hospital, Southampton, UK

Competing interests: None declared.

REFERENCES

- 1 Steinbrook R. The price of sight - ranibizumab, bevacizumab, and the treatment of macular degeneration. *N Engl J Med* 2006;**355**(14):1409–12.

- 2 **Brown DM**, Kaiser PK, Michels M, *et al*. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med* 2006;**355**(14):1432–44.
- 3 **Bressler NM**, Arnold J, Benchaboune M, *et al*. Verteporfin therapy of subfoveal choroidal neovascularization in patients with age-related macular degeneration. *Arch Ophthalmol* 2002;**120**(11):1443–54.
- 4 **Rosenfeld PJ**, Brown DM, Heier JS, *et al*. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* 2006;**355**(14):1419–31.
- 5 **Sharma S**, Brown GC, Brown MM, *et al*. The cost-effectiveness of photodynamic therapy for fellow eyes with subfoveal choroidal neovascularization secondary to age-related macular degeneration. *Ophthalmology* 2001;**108**(11):2051–9.
- 6 **Smith DH**, Fenn P, Drummond M. Cost effectiveness of photodynamic therapy with verteporfin for age related macular degeneration: the UK case. *Br J Ophthalmol* 2004;**88**(9):1107–12.
- 7 **Brown GC**, Sharma S, Brown MM, *et al*. Utility values and age-related macular degeneration. *Arch Ophthalmol* 2000;**118**(1):47–51.
- 8 **Meads C**, Salas C, Roberts T, *et al*. Clinical effectiveness and cost-utility of photodynamic therapy for wet age-related macular degeneration: a systematic review and economic evaluation. *Health Technol Assess* 2003;**7**(9):98.
- 9 **Meads C**, Hyde C. What is the cost of blindness? *Br J Ophthalmol* 2003;**87**(10):1201–4.
- 10 **Government Actuary's Department**. *UK Interim Life Tables 2002–2004*. London: GAD, 2005.
- 11 **Zhou S**, Javitt J, Zlateva G, *et al*. Evaluating the risk of mortality for exudative (wet) AMD patients compared to a control group. *Invest Ophthalmol Vis Sci* 2006;**47**:E-Abstract, 2213.
- 12 **Department of Health**. NHS Reference Cost 2005. London: Department of Health, 2006, Available from [http://www.dh.gov.uk/PublicationsAndStatistics/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT_ID=4133221&chk=TxHkqo](http://www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT_ID=4133221&chk=TxHkqo) (accessed 29 June 2007).
- 13 **Avery RL**. Regression of retinal and iris neovascularization after intravitreal bevacizumab (Avastin) treatment. *Retina* 2006;**26**(3):352–4.
- 14 **Avery RL**, Pieramici DJ, Rabena MD, *et al*. Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. *Ophthalmology* 2006;**113**(3):363–72.
- 15 **Iturralde D**, Spaide RF, Meyerle CB, *et al*. Intravitreal bevacizumab (Avastin) treatment of macular edema in central retinal vein occlusion: a short-term study. *Retina* 2006;**26**(3):279–84.
- 16 **Kahook MY**, Schuman JS, Noecker RJ. Intravitreal bevacizumab in a patient with neovascular glaucoma. *Ophthalmic Surg Lasers Imaging* 2006;**37**(2):144–6.
- 17 **Spaide RF**, Laud K, Fine HF, *et al*. Intravitreal bevacizumab treatment of choroidal neovascularization secondary to age-related macular degeneration. *Retina* 2006;**26**(4):383–90.
- 18 **Spaide RF**, Fisher YL. Intravitreal bevacizumab (Avastin) treatment of proliferative diabetic retinopathy complicated by vitreous hemorrhage. *Retina* 2006;**26**(3):275–8.
- 19 **Fung AE**, Rosenfeld PJ, Reichel EZ. Intravitreal Avastin safety survey: results from the world wide web. *Invest Ophthalmol Vis Sci* 2006;**47**(5):5251.

bmjupdates+

bmjupdates+ is a unique and free alerting service, designed to keep you up to date with the medical literature that is truly important to your practice.

bmjupdates+ will alert you to important new research and will provide you with the best new evidence concerning important advances in health care, tailored to your medical interests and time demands.

Where does the information come from?

bmjupdates+ applies an expert critical appraisal filter to over 100 top medical journals. A panel of over 2000 physicians find the few 'must read' studies for each area of clinical interest.

Sign up to receive your tailored email alerts, searching access and more...

www.bmjupdates.com