Northern Treatment Advisory Group

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Bevacizumab (Avastin®) and ranibizumab (Lucentis®) in the management of neovascular age-related macular degeneration: Updated appraisal

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Summary

- Neovascular age-related macular degeneration (AMD) is a common bilateral condition that affects people aged 50 years and older, and causes severe impairment of central vision.
- Ranibizumab (Lucentis®) and bevacizumab (Avastin®) are both used in the management of AMD. However, Ranibizumab (priced at £742.17 per injection, but reduced under the patient access scheme)[1] is significantly more expensive than bevacizumab (priced at £51 per injection)[2]. Ranibizumab is licensed and approved by NICE for the treatment of AMD whereas bevacizumab is not.
- The North of England Treatment Advisory Group (NETAG) has previously undertaken appraisals of bevacizumab in the management of AMD. In 2011 the appraisal recommendation was 'The North East Treatment Advisory Group recommends bevacizumab (Avastin®) 1.25 mg intravitreal injection as a cost-effective treatment option for age-related macular degeneration'[3]. This report is a further update, in light of the publication of additional clinical evidence.
- Combined data from the CATT trial[4] and IVAN trial[5] 2-year findings provide the most informative contemporary clinical evidence. Bevacizumab was found to be non-inferior to (i.e. 'as good as') ranibizumab concerning its clinical effect on visual acuity. With regard to safety, these studies found that there is no difference between the two drugs in deaths or thrombotic events at 2 years, and inconsistent results on other serious adverse events.
- A decision to favour the use of bevacizumab over ranibizumab in the treatment of AMD presents the potential for significant cost savings for the NHS. A recent cost-effectiveness study reported that 'even after considering the potential for differences in risks of serious adverse events and therapeutic effectiveness, bevacizumab confers considerably greater value than ranibizumab for the treatment of neovascular macular degeneration'[6].

Introduction

Neovascular age-related macular degeneration (AMD) is an eye condition that affects people aged 50 years and older, and is a major cause of severe sight loss.

Intravitreal treatment with ranibizumab (Lucentis®), an antibody to vascular endothelial growth factor (anti-VEGF), is an effective treatment for neovascular AMD, compared with photodynamic therapy or no treatment. Ranibizumab is recommended as a possible treatment for people with neovascular AMD if certain conditions apply (NICE Guidance TA 155)[7]. More recent guidance recommends another anti-VEGF aflibercept injection as a possible treatment for some people with neovascular AMD, in accordance with the same recommendations for ranibizumab (NICE Guidance TA 294)[8]. Anti-VEGF drugs are thus an established treatment for neovascular AMD.

Bevacizumab (Avastin®) is an antibody to VEGF that is licensed for treatment of bowel cancers. It is the parent molecule from which ranibizumab was developed. Small non-randomised studies done while ranibizumab was awaiting marketing authorisation suggested that bevacizumab had similar effectiveness to ranibizumab for treatment of neovascular AMD. The dose at which bevacizumab is supplied is sufficiently large to allow dividing into many smaller fractions for intra-ocular administration, thus offering large cost savings. Its use off licence, given in a similar way to ranibizumab, has spread rapidly across the world[5].

In April 2009, the NETAG conducted an appraisal on the use of bevacizumab in an unlicensed indication for the treatment of AMD. The conclusion was not to recommend the use of bevacizumab for neovascular AMD in preference to ranibizumab unless within the context of a prospective, comparative, randomised study with ranibizumab**Error! Bookmark not defined.**. An updated appraisal was undertaken in July 2011[3], based on further evidence relating to the use of bevacizumab in AMD. The appraisal recommended bevacizumab (Avastin®) 1.25 mg intravitreal injection as a cost-effective treatment option for age-related macular degeneration.

Since the last NETAG review, further evidence on the efficacy and safety of bevacizumab and ranibizumab for the treatment of neovascular AMD has been published. This report summarises this evidence. The scope of the report is limited to the use of bevacizumab and ranibizumab for the treatment of neovascular AMD and does not include the use of other treatments for AMD, such as aflibercept.

Efficacy

The publication of 2-year findings from the IVAN trial has been a key development in the evidence base since the last NETAG appraisal in 2011. The 2 year results from CATT and IVAN have been pooled[5]. The combined results show that bevacizumab and ranibizumab have similar efficacy with no significant difference in best corrected distance visual acuity between the two drugs. Table 1 shows the pooled data from the CATT and IVAN studies at 2 years for the change in best corrected distance visual acuity.

Table 1 Change in best corrected distance visual acuity in CATT and IVAN at 2 years

	Bevacizumab		Ranibizumab		Weighted mean difference (95% CI)
	N =	Mean change (SD)	N =	Mean change (SD)	
CATT	380	5.95 (17.1)	398	7.41 (15.0)	-1.46(-3.73 to 0.81)
IVAN	249	4.1 (13.5)	268	4.9 (15.0)	-0.80(-3.26 to 1.66)
Overall	**629**		**666**		**-1.15(-2.82 to 0.51)**

Safety

Pooled estimates of safety outcomes from CATT and IVAN at 2 years showed no differences by drug for deaths or arterial thrombotic events. There was a significant increased risk of any systemic serious adverse event in the bevacizumab group (p=0.008; Table 2). The pooled analysis masks the inconsistency between the two trial estimates. Findings from the IVAN trial show no significant difference with an OR almost at unity.

Table 2 Safety outcomes in CATT and IVAN at 2 years

	Bevacizumab		Ranibizumab		
	N =	No. of patients with at least one serious adverse event	N =	No. of patients with at least one serious adverse event	Odds ratio (95% CI)
Death					
CATT	586	36	599	32	0.86(0.53 to 1.41)
IVAN	296	15	314	15	0.94(0.45 to 1.96)
Overall	**882**	**51**	**913**	**47**	**0.89(0.59 to 1.33)**
Arterial thrombotic event					
CATT	586	29	599	28	0.94(0.55 to 1.60)
IVAN	296	10	314	13	1.24(0.53 to 2.86)
Overall	**882**	**39**	**913**	**41**	**1.02(0.65 to 1.60)**
≥ serious systemic event					
CATT	586	234	599	190	0.70(0.55 to 0.89)
IVAN	296	80	314	81	0.94(0.65 to 1.35)
Overall	**882**	**314**	**913**	**271**	**0.76(0.63 to 0.93)**

Cost-effectiveness

Three studies were conducted to identify the cost implications of using bevacizumab and ranibizumab in the treatment of neovascular AMD. In their comparative study, Jackson et al[31] reported the highest 3-year cumulative treatment costs for treatment naïve patients as those associated with ranibizumab (£25,658), followed by bevacizumab (£16,177). Patel et al[32] used a Markov model to undertake a cost-utility analysis of bevacizumab versus ranibizumab in neovascular AMD. The cost-effectiveness ratios for bevacizumab and ranibizumab were found to be $1,405 per QALY and $12,177 per QALY, respectively. Probabilistic sensitivity analysis

revealed a 95% probability of bevacizumab being more cost-effective than ranibizumab at a willingness to pay (WTP) threshold of $50,000 per QALY gained. Stein et al[33] studied the cost-effectiveness of monthly and PRN regimens of bevacizumab and ranibizumab treatment for newly diagnosed neovascular AMD, again using a Markov model. Compared with PRN bevacizumab, the incremental cost-effectiveness ratio of monthly bevacizumab was found to be $242,357 per quality-adjusted life year (QALY). In sensitivity analyses assuming a WTP of $100,000 per QALY, the authors stated that the annual risk of serious vascular events would have to be at least 2.5 times higher with bevacizumab than that observed in the CATT trial for as-needed ranibizumab to have an incremental cost-effectiveness ratio of <$100,000 per QALY. The authors concluded that even after considering the potential for differences in risks of serious adverse events and therapeutic effectiveness, bevacizumab conferred considerably greater value than ranibizumab.

Cost analysis

A cost comparison of ranibizumab and bevacizumab was conducted using local data applied to the NICE costing template for aflibercept for treating neovascular age-related macular degeneration (TA 294)[34].

The incidence of neovascular AMD for the UK as a whole, in people aged 50 and over, is estimated to be around 0.11%[35]. This is approximately 20,000 cases per year in England and 1,379 for the North East and Cumbria. The NICE costing template assumes that 80% of this number will be eligible for treatment and of these 19% will need treatment in the second eye. The model assumes that over time the number of injections for this cohort will decline as patients either die or stop treatment for other reasons. Taking these factors into account, the model estimates that the number of patients in this theoretical cohort will reduce from 1,278 to 662 over 5 years. The model also assumes that the number of injections per patient per year will fall from 8 to 4 over 5 years. Based on these assumptions, the model estimates that the numbers of injections per year needed in the North East and Cumbria for this theoretical cohort of new patients will be 10,200 rising to 27,500 after 5 years.

In the NICE costing template the cost per injection for ranibizumab is the current list price of the drugs per eMC dictionary of medicines and devices browser 2013 at £742.17. Ranibizumab is recommended by NICE Technical Appraisal 155 only if the drug price is reduced under the patient access scheme. The discounted drug price as supplied to the NHS is subject to commercial confidentially and we are therefore unable to publish these figures. There is no equivalent source for the cost per injection of bevacizumab. In this model we have used the cost of £51 per injection as this is the price of the drug used for patients entered into the TANDEM study. Table 3 shows the costs of ranibizumab and bevacizumab for this hypothetical cohort of new patients for all Clinical Commissioning Groups (CCGs) in the North East and Cumbria. The figures do not include any other treatment costs.

The potential cost savings through the use of bevacizumab would amount to over £70 million over 5 years for hypothetical cohorts of newly diagnosed patients. If future changes in disease prevalence and a decrease in cost of bevacizumab due to scaling, are factored into the calculations these savings would be even greater. It is unlikely that this scale of savings is achievable in the short term. However, if patients were offered a choice and 50% of patients were treated with bevacizumab, this still

represents a significant saving to the NHS. The accompanying Commissioning Guide provides a more detailed analysis of the potential savings for CCGs.

Table 3 Comparative drug costs for ranibizumab and bevacizumab over 5 years for CCGs in the North of England

	Ranibizumab	Bevacizumab	Cost difference
Year 1	£7,585,268	£521,240	£7,064,028
Year 2	£13,075,106	£898,487	£12,176,619
Year 3	£16,050,598	£1,102,956	£14,947,643
Year 4	£18,469,674	£1,269,188	£17,200,485
Year 5	£20,436,382	£1,404,335	£19,032,046
Total	**£75,617,028**	**£5,196,206**	**£70,420,822**

Relevant guidance

Ranibizumab[7] and aflibercept[8] are recommended by NICE as options for treating neovascular age-related macular degeneration if specified criteria apply the eye being treated the manufacturers provide the drugs with the discount agreed in the patient access scheme. NICE is not currently, nor planning to, conduct an appraisal of intravitreal bevacizumab for any indication.

There is a legal duty on CCGs to consider NICE guidance. However, CCGs are entitled to depart from NICE guidance if it has a good reason to do so. Previous case law (R v North Derbyshire Health Authority, ex parte Fisher, 1998) found that a decision not to follow national policy in the form of guidance from the Secretary of State was not unlawful if there was some 'special factor' which 'exceptionally justified departure'.

There is nothing in the statutory duties of CCGs that prevent them from commissioning a treatment for neovascular AMD that included bevacizumab as long as patients who are within the NICE Technology Appraisal Guidance for ranibizumab and aflibercept can choose these treatments as well.

Licensing

Bevacizumab is a licensed drug, although it is not licensed for any ophthalmic treatments. Due to the additional compounding of bevacizumab when used in ophthalmology, NICE classify its use as unlicensed, whereas ranibizumab is licensed for the management of neovascular AMD. A consequence of this is that there is very little use of bevacizumab in NHS patients with neovascular AMD[2]. In other eye conditions for which there is no licensed treatment available, for example non-AMD choroidal neovascularisation, intra-vitreal bevacizumab is more commonly used in the NHS. There are two major suppliers of intra-vitreal bevacizumab in the UK that hold specials licenses originally set up to provide this drug for clinical trials within the NHS. The use of intra-vitreal bevacizumab is even more widespread in private practice and in other health care systems including Medicare is the US.

The General Medical Council has published professional guidance on the use of unlicensed medicine (see Appendix). In the NHS, bevacizumab is not used for the

treatment of neovascular AMD as it is not licensed for this indication and there are licensed drugs available. GMC guidance does not absolutely preclude the use of an unlicensed drug in these circumstances providing specific governance issues are properly adhered to. Bevacizumab could also be used as part of a properly approved research project.

Author's declaration. The lead author has no relevant interests to declare.

Appendix: GMC Prescribing guidance: Prescribing unlicensed medicines

67. The term ‘unlicensed medicine’ is used to describe medicines that are used outside the terms of their UK licence or which have no licence for use in the UK. Unlicensed medicines are commonly used in some areas of medicine such as in paediatrics, psychiatry and palliative care. They are also used, less frequently, in other areas of medicine.

68. You should usually prescribe licensed medicines in accordance with the terms of their licence. However, you may prescribe unlicensed medicines where, on the basis of an assessment of the individual patient, you conclude, for medical reasons, that it is necessary to do so to meet the specific needs of the patient.

69. Prescribing unlicensed medicines may be necessary where:

a. There is no suitably licensed medicine that will meet the patient’s need, for example, where:

i there is no licensed medicine applicable to the particular patient. For example, if the patient is a child and a medicine licensed only for adult patients would meet the needs of the child; or

ii a medicine licensed to treat a condition or symptom in children would nonetheless not meet the specific assessed needs of the particular child patient, but a medicine licensed for the same condition or symptom in adults would do so; or

iii the dosage specified for a licensed medicine would not meet the patient’s need; or

iv the patient needs a medicine in a formulation that is not specified in an applicable licence.

b. Or where a suitably licensed medicine that would meet the patient’s need is not available. This may arise where, for example, there is a temporary shortage in supply; or

c. The prescribing forms part of a properly approved research project.

70. When prescribing an unlicensed medicine you must:

a. be satisfied that there is sufficient evidence or experience of using the medicine to demonstrate its safety and efficacy

b. take responsibility for prescribing the medicine and for overseeing the patient’s care, monitoring, and any follow up treatment, or ensure that arrangements are made for another suitable doctor to do so

c. make a clear, accurate and legible record of all medicines prescribed and, where you are not following common practice, your reasons for prescribing an unlicensed medicine.

71. You must give patients (or their parents or carers) sufficient information about the medicines you propose to prescribe to allow them to make an informed decision.

72. Some medicines are routinely used outside the terms of their licence, for example in treating children. In emergencies or where there is no realistic alternative treatment and such information is likely to cause distress, it may not be practical or

necessary to draw attention to the licence. In other cases, where prescribing unlicensed medicines is supported by authoritative clinical guidance, it may be sufficient to describe in general terms why the medicine is not licensed for the proposed use or patient population.‡ You must always answer questions from patients (or their parents or carers) about medicines fully and honestly.

73. If you intend to prescribe unlicensed medicines where that is not routine or if there are suitably licensed alternatives available, you should explain this to the patient, and your reasons for doing so.

References

[1] Joint Formulary Committee. British National Formulary (online) London: BMJ Group and Pharmaceutical Press. Available from: http://www.medicinescomplete.com (Accessed: 01/07/14)
[2] National Institute for Health and Care Excellence Decision Support Unit. Bevacizumab in eye condition: Issues related to quality, use, efficacy and safety. University of Sheffield, August 2012
[3] Horsley W. Bevacizumab (Avastin®) in the management of neovascular age-related macular degeneration: Updated appraisal. NHS North East Treatment Advisory Group, July 2011
[4] Martin DF, Maguire MG, Fine SL, et al, and the Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. Ophthalmology 2012; 119: 1388–98.
[5] Chakravarthy U, Harding SP, Rogers CA, Downes SM, Lotery AJ, Cullifod LA, Reeves BC, on behalf of the IVAN study investigators. Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial. Lancet 2013; 382: 1258-67.
[6] Stein JD, Newman-Casey PA, Mrinalini T, Lee PP, Hutton DW. Cost-effectiveness of bevaizumab and ranibizumab for newly diagnosed neovascular macular degeneration. Transactions of the American Ophthalmological Society 2013; 111: 56-69
[7] NICE TA 155 Ranibizumab and pegaptanib for the treatment of age-related macular degeneration August 2008 (Updated May 2012) http://www.nice.org.uk/guidance/TA155
[8] NICE TA 295 Aflibercept solution for injection for treating wet age-related macular degeneration. July 2013 http://www.nice.org.uk/guidance/TA294/chapter/1-guidance