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CONTROVERSY

Should avastin be used to treat age-related macular degeneration in the NHS? – Yes

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Yes, because the available evidence shows that it is as good but at 1–2% of the price! The two drugs are 'almost identical'.[1] Both owned by the same company—Roche/Genentech, the main difference is that one is highly profitable for treating AMD, the other not. Unless and until the main head-to-head trials,[1,2] currently recruiting, report to the contrary, avastin should be preferred.

The evidence for avastin versus lucentis is weak for one very simple reason: the company refused to license it. Whether this was because of cock-up or conspiracy does not matter. Cock-up in that Roche/Genentech may not have realised it would work in humans. Or the conspiracy in that once avastin was licensed in high doses for colorectal cancer, the cost of the small doses for AMD was going to be low. Either way, avastin has not been properly trialled for AMD. This is why publicly funded trials are now in progress, due to report around 2010/11. In the meantime, clinicians and funders must decide which drug to use.

Given the lack of trial data, we must rely on observational data for evidence. The perils of such data are well recognised. The observational studies are uncontrolled case series of avastin over time. In order to compare these with lucentis, we searched for studies that (a) investigated the effect of avastin on visual acuity in patients with wet-AMD, (b) using a dose of avastin from 1 to 1.5 mg, (c) measured visual acuity using the ETDRS protocol, (d) published up to March 2008. The nine studies[3–11] meeting these criteria, for which we were able to access data, all showed improvements in visual acuity on average at 3 months, as shown in Figure 1.

How do these improvements compare with lucentis? The profile of lucentis is well established from the pivotal trials,[12,13] the results up to 6 months are shown in Figure 2. Compared with placebo, lucentis improved visual acuity in the first 3 months on average and then leveled off. This was true for both the Marina and Anchor trials. By comparison, the untreated group in these trials suffered diminished visual acuity. When the meta-analytic effect (random) over time of the observational studies for avastin is plotted on this graph, its short term 'signature' is similar to that of lucentis as shown in Figure 1. Given the similarity of the two drugs, this is hardly surprising.

What of the safety profile? The safety of avastin has been shown in two ways. First, the pioneering international intravitreal bevacizumab safety survey[14] initiated by Rosenfeld, who pioneered the use of both drugs, showed avastin to be relatively safe in the treatment of AMD. Second, the widespread use of avastin in cancer has not indicated any serious lack of safety. As overall fewer patients have probably been exposed to lucentis than avastin, the latter may well be safer.

What of price? The British National Formulary has bevacizumab as a 400 mg vial priced at £924.40, which means that a 1.5 mg dose would cost £3.50. By contrast, Lucentis costs £761.20 for a 3 mg vial.[15] The ratio of prices is 218 : 1! Even granting some costs incurred in breaking down the avastin vial, a price ratio of between 50 and 100–1 applies. Avastin costs 1–2% of lucentis.

In terms of cost effectiveness, for lucentis to meet the NICE threshold for cost per QALY of £30k, it would have to be more than twice as good as avastin in terms of visual acuity.[16] Although this seems unlikely, the truth will be revealed when the independent trials are completed.

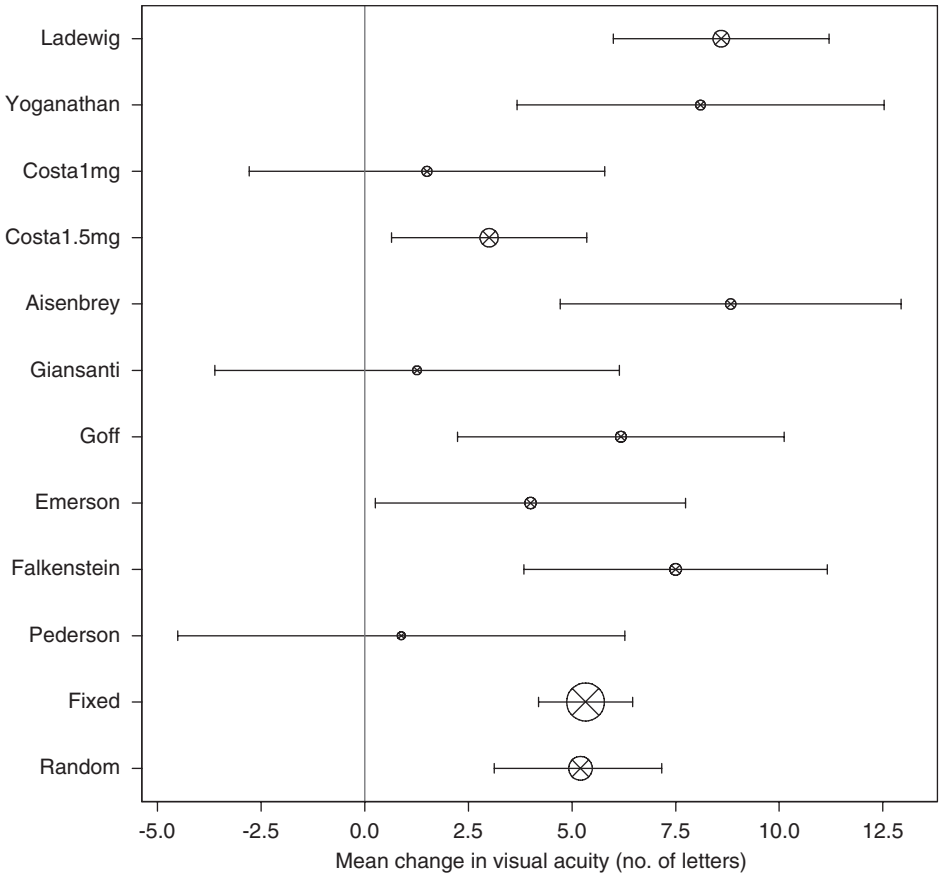

Figure 1 Forest plot of nine observational studies of avastin in wet AMD; results at 3 months.

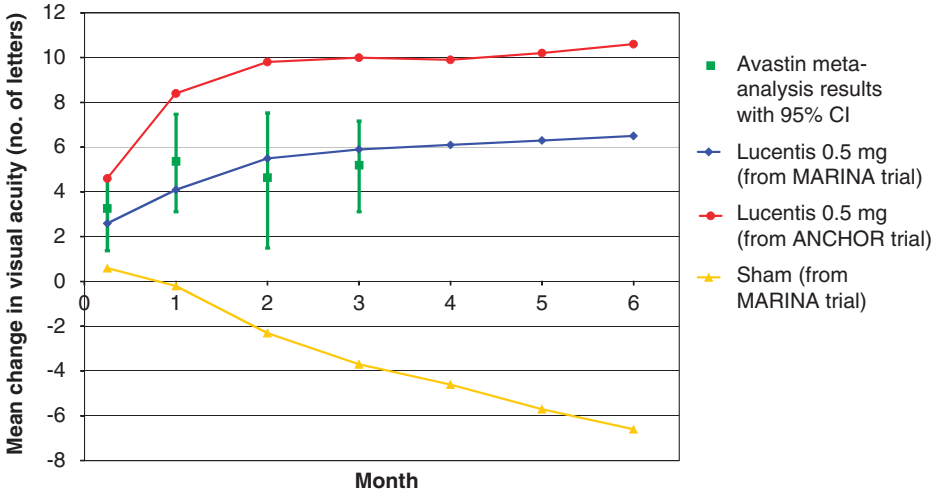

Figure 2 The effects of lucentis and avastin versus non treatment on visual acuity over time.

The price difference between avastin and lucentis means that in poor countries avastin will continue to be the most widely used treatment of AMD. One danger is that the richer countries will use lucentis, whereas the poor use avastin. This would be undesirable in that the relative merits including safety of both drugs need to be established. This can only be established by the richer countries, ensuring that the relevant studies are carried out.

The international reaction to the avastin/lucentis dilemma has been interesting with some countries

favouring avastin despite legal constraints. Italy's AIFA authorised the use of avastin.[17] In Germany, a low tariff for funding treatment of macular degeneration incentivised the use of avastin in place of lucentis after a court case by the European owner of avastin; Novartis was rejected.[18] New Zealand's PHARMAC rejected lucentis but recommended avastin subject to patient consent.[19] Several countries are reported to have initiated clinical trials, including Holland, France, and Spain. However, others recommended lucentis over avastin due to the latter not being licensed. These included England's NICE,[20] Canada's CADTH,[21] and Australia's PBAC.[22] Ironically, these countries with more formal HTA processes tended to favour lucentis because of the non-licensed status of avastin. At the very least, it can be concluded that internationally, no consensus exists in favour of lucentis!

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References

1 CATT comparison of age-related macular degeneration treatments trials: lucentis-avastin trial. http://www.med.upenn.edu/cpob/studies/CATT.shtml.
2 Ivan trial England & Wales. http://www.ivan-trial.co.uk/Default.aspx.
3 Aisenbrey S, Ziemssen F, Völker M, Gelisken F, Szurman P, Jaissle G *et al*. Intravitreal bevacizumab (Avastin) for occult choroidal neovascularisation in age-related macular degeneration. *Graefe's Arch Clin Exp Ophthalmol* 2007; **245**: 941–948.
4 Costa RA, Jorge R, Calucci D, Cardillo JA, Melo LAS, Scott IU. Intravitreal bevacizumab for choroidal neovascularisation caused by AMD (IBeNA study) results of a phase I dose-escalation study. *Invest Ophthalmol Vis Sci* 2006; **47**: 4569–4578.
5 Emerson VM, Lauer AK, Flaxel CJ, Wilson DJ, Francis PJ, Stout JT *et al*. Intravitreal bevacizumab (Avastin) treatment of neovascular age-related macular degeneration. *Retina* 2007; **27**: 439–444.
6 Goff MJ, Johnson RN, McDonalds HR, AI E, Jumper JM, Fu A. Intravistreal bevacizumab for previously treated choroidal neovascularisation from age-related macular degeneration. *Retina* 2007; **27**: 432–438.
7 Ladewig MS, Ziemssen F, Helb HM, Scholl HPN, Eter N, Bartz-Schmidt KU *et al*. Intravitreales bevacizumab bei der neovaskulären alterabhängigen maculadegeneration. *Ophthalmologe* 2006; **103**: 463–470.
8 Yoganathan P, Deramo VA, Lai JC, Tibrewala RK, Fastenberg DM. Visual improvement following intravitreal bevacizumab (Avastin) in exudative age-related macular degeneration. *Retina* 2006; **26**: 994–998.
9 Falkenstein IA, Cheng L, Morrison VL, Kozak I, Tammewar AM, Freeman WR. Standardized visual acuity results, associated with primary versus secondary bevacizumab (Avastin) treatment for choroidal neovascularization in age-related macular degeneration. *Retina* 2007; **27**: 701–706.
10 Pedersen R, Soliman W, Lund-Andersen H, Larsen M. Treatment of choroidal, neovascularization using intravitreal bevacizumab. *Acta Ophthalmol Scand* 2007; **85**: 526–533.
11 Giansanti F, Virgili G, Bini A, Rapizzi E, Giacomelli G, Donati MC *et al*. Intravitreal bevacizumab therapy for choroidal neovascularization secondary to age-related macular degeneration: 6-month results of an open-label uncontrolled clinical study. *Eur J Ophthalmol* 2007; **17**: 230–237.
12 Rosenfeld PJ, Brown DM, Heijer JS. Ranibizumab for neovascular age-related macular degeneration. *N Eng J Med* 2006; **355**: 1419–1431.
13 Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med* 2006; **355**: 1432–1444.
14 Rich M, Rosenfeld PJ, Puliafito CA, Dubovy SR, Davis JL, Flynn HW *et al*. Short-term safety and efficacy of intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. *Retina* 2006; **26**: 495–511.
15 Joint Formulary Commitee. *British National Formulary*. 55 edn. London: British Medical Association and Royal Pharmaceutical Society of Great Britain, 2008.
16 Raftery J, Clegg A, Jones J, Chen ST, Lotery A. Ranibizumab (lucentis) versus bevacizumab (avastin): modelling cost effectiveness. *Br J Ophthalmol* 2007; **91**: 1244–1246. http://bjo.bmj.com/cgi/content/full/91/9/1244.
17 AIFA: Ophthalmology Time Europe 2007.
18 Germany. http://www.clinicaltrials.gov/ct2/show/NCT00559715?term=Avastin&cond=AMD&rank=26,http://www.bfarm.de/nn_1199492/DE/Arzneimittel/3__nachDerZulassung/offLabel/offlabelnode.html__nnn=true,http://retinologie.org/index.php?option=com_docman&task=doc_view&gid=10&Itemid=19.
19 NZ: personal communication from PHARMAC.
20 NICE. Macular degeneration (age-related) — ranibizumab and pegaptanib. Technology Appraisal 155. 2008. http://www.nice.org.uk/Guidance/TA155.
21 Canada. http://www.cadth.ca/index.php/en/publication/813.
22 Australia. http://www.health.gov.au/internet/main/publishing.nsf/Content/8273CE4F07D2021FCA2572F800047B3B/$File/Ranibizumab.pdf.

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