Some ethical considerations for the "off-label" use of drugs such as Avastin

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Is off-label use of drugs legal?

Anyone who has attended ophthalmology conferences recently cannot fail to notice the enthusiasm of retinal specialists in adopting the new treatment, Avastin. Avastin is a humanised monoclonal antibody against vascular endothelial growth factor: an important growth factor for angiogenesis. The labelled indication of Avastin is for the treatment of colon cancer. Its use in the eye is therefore off label; no robust scientific data exist on its safety and efficacy; all the positive reports have short follow-ups. The clamour to introduce this treatment raises several ethical issues.

IS IT LEGAL?

Off-label use of drugs is not illegal. Physicians and surgeons are allowed to do this. It is not uncommon. In a paediatric hospital ward setting, almost half the prescriptions are unlicensed or are off label.[1] Intravitreal Triamcinolone, tissue plasminogen activators, intracameral Vancomycin or Lignocaine are just a few off-label drugs used in ophthalmology. The fact that it is common practice does not make it safe. There may be a risk of unexpected adverse outcomes, but this is also true of labelled use of new drugs. Some adverse effects do not become apparent until after several years of use or many thousands of prescriptions; Vioxx[2] is a good example.

APPROVED AND PROVEN

Approved and proven are not synonymous terms, especially with new treatment. A treatment can be proven effective and safe but not be approved because it is too costly. Good evidence from randomised control trials (RCT) shows that photodynamic therapy (PDT) compared to no treatment is effective in predominantly classic lesions.[3] The National Institute for Health and Clinical Excellence (NICE) does not recommend PDT for predominantly classic lesions, except in the context of a study.[4] Good evidence shows that PDT is also effective in treating small occult lesions and deteriorating vision.[5] NICE has not approved this because it has not considered it. In most European countries PDT for occult lesions is approved. Equally, Macugen is a licensed and proven effective treatment, but its approval is pending an appraisal process that is not due to report for more than 12 months. In the USA, the Food and Drug Administration (FDA)-approved treatments are PDT and Macugen. A recent survey indicated that most ophthalmologists believe Avastin to be equally or more effective than the FDA-approved treatment. The American Academy of Ophthalmology has asked the insurance companies to approve and pay for Avastin, even though it is not a treatment proven by RCT (http://www.aao.org/news/release/20060420.cfm)

ETHICS AND RANDOMISED CONTROLLED TRIALS

For dramatically effective treatment, randomised trials are not necessary. Many well-known examples of such treatments exist: penicillin for bacterial infections; smallpox vaccination; thyroxine for hypothyroidism; vitamin B12 replacement; insulin for insulin-dependent diabetes; anaesthesia for surgical operations; and the immobilisation of fractured bones. In all these examples, observational studies were adequate to show effectiveness.[6] Equipoise is the only justification for randomisation. If a treatment is clearly superior, randomisation will put one group of patients at a disadvantage. Randomisation is necessary to avoid bias in case selection and interpretation of the results. In wet age-related macular degeneration (AMD), good objective measures of outcome are seen. In the UK, the only NICE-approved treatment for AMD is PDT, and this is limited to classic lesions with no occult lesions. Is it irresponsible to use an unproven treatment instead of an approved treatment? If it is not, is it ethical to perform a randomised trial of PDT versus Avastin? Some think the only ethical trial is between Lucentis and Avastin.

IS IT FAIR AND TO WHOM?

We are grateful to drug companies that have invested large amounts of research money and effort on developing new treatment. In the case of Avastin, its use initially was based on the first-year results of Lucentis.[7] Avastin is in fact the mother molecule and Lucentis a fragment of this, with the active binding sites. Lucentis was developed because it was thought that Avastin would not penetrate the full thickness of the retina and might not be effective in choroidal neovascularisation.[8] Case series of Avastin showed results that were comparable to Lucentis. It is difficult to estimate, but Avastin has probably been used on >10 000 patients worldwide, with few documented complications.[9–16]

In divided doses, Avastin may cost only a few pounds per injection. Lucentis, when licensed, is not likely to be cheap. If Herceptin or Macugen provides a guide, then the cost might be several thousands of pounds per patient per year. Both Lucentis and Avastin are produced by the same company, Genentech, San Francisco, USA. Assuming that Lucentis gets a licence in 6 months, doctors will have the dilemma of a choice between the two: with an expensive and proven treatment on the one hand and a cheap treatment with many unanswered questions on the other. Is it fair that Genentech should lose out? What of the patients (or countries) who cannot afford Lucentis? Is it fair that treatment is available to only those who are wealthy?

RIGHTS AND DUTY

No one has any right (to a treatment) unless someone else has a duty to provide it. In modern societies the duty to provide healthcare is established by law on the government. The NHS is free at the point of delivery. This does not mean that all treatments can be afforded and funded out of taxation. The courts stated that "the (European) Convention (on human rights) does not give applicants the right to free healthcare in general," and emphasised the right of the government to determine healthcare priorities.[17] No patient has any legal right to an expensive treatment until NICE recommends it and charges the primary care trusts (PCT) to fund the treatment. NICE undoubtedly needs time to appraise and consult. In the meantime, what is the duty of care of the doctor?

''IS MY EYE TREATABLE, DOCTOR?''

To the next patient with a minimally classic lesion, what should we say?

Do we say, ''No! there is no approved treatment''?

Do we say, ''Yes, there is a proven treatment, but you are not entitled to it as the government has not agreed to fund this expensive treatment. We can try and apply to your local health authority for funding. It is unlikely that every patient applied for will be funded.''

Or, do we say, ''There is an unapproved treatment, which seems to be effective, safe and affordable, but the evidence is not of the highest order. Like any new treatments, there is no long-term safety and efficacy data.''

DUTY OF CARE: WHO CARES?

The introduction of Avastin has created a dilemma. Doctors are torn. We are constantly urged to practice evidence-based medicine. Equally importantly, doctors need to practise medicine compassionately and ethically. Difficult decisions are often reduced to simple bottomline type analyses: what would you do if the patient sitting in front of you is your mother and she is losing vision fast? The present difficulties over Avastin echo the fuss made when another apparent wonder drug, Steptomycin, was introduced for treatment of tuberculosis. There was resistance to randomisation (a novel concept then) as benefits of treatment were obvious and compelling, but randomisation won the day. The only way a patient could receive the drug was to agree to enter the trial (this in itself was ethically questionable). An exception was the case of a physician who contracted tuberculosis while the trial was still running. He was not entered into the trial but received the new drug anyway.[18]

Some doctors opt to advise the patient to pay for the drug and to have private treatments. A few doctors genuinely try to seek research funding and mount studies to treat patients. Yet others write a case of needs, apply to hospital medicine committees, write to PCTs and plead for funding on a case-by-case basis. The work required to introduce a new treatment is substantial; the standard ethics application form is 60 pages long; a pathway of care includes several nights on the computer; a case of needs requires many meetings with managers and colleagues.

It is becoming increasingly difficult for a doctor to discharge his or her duty of care. But unless the doctor is willing to do so, who else will be the patient's advocate?

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REFERENCES

1 **Conroy S**, Choonara I, Impicciatore P, *et al*. Survey of unlicensed and off label drug use in paediatric wards in European countries. European Network for Drug Investigation in Children. *BMJ* 2000;**320**:79–82.
2 **Bombardier C**, Laine L, Reicin A, *et al*. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. *N Engl J Med*. 2000;343: 1520–8, 1530.
3 **Treatment of age-related macular degeneration with photodynamic therapy (TAP) study group**. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: two-year results of 2 randomized clinical trials—TAP report 2. *Arch Ophthalmol* 2001;**119**:198–207.
4 **National Institute for Clinical Excellence**. Guidance on the use of photodynamic therapy for age-related macular degeneration. Technology Appraisal 68, September, 2003.
5 **Treatment of age-related macular degeneration with photo-dynamic therapy study group, Verteporfin in photodynamic therapy study group**. Photodynamic therapy of subfoveal choroidal neovascularization with verteporfin: fluorescein angiographic guidelines for evaluation and treatment—TAP and VIP report no. 2. *Arch Ophthalmol* 2003;**121**:1253–68.
6 **Black N**. Why we need observational studies to evaluate the effectiveness of healthcare. *BMJ* 1996;**312**:1215–18.
7 **Reichel E**. Intravitreal bevacizumab for choroidal neovascularization and cystoid macular edema: a cost-effective treatment? *Ophthalmic Surg Lasers Imaging* 2005;**36**:270–1.
8 **Mordenti J**, Cuthbertson RA, Ferrara N, *et al*. Comparisons of the intraocular tissue distribution, pharmacokinetics, and safety of 125I-labeled full-length and Fab antibodies in rhesus monkeys following intravitreal administration. *Toxicol Pathol* 1999;**27**:536–44.
9 **Spaide RF**, Laud K, Fine HF, *et al*. Intravitreal bevacizumab treatment of choroidal neovascularization secondary to age-related macular degeneration. *Retina* 2006;**26**:383–90.
10 **Kahook MY**, Schuman JS, Noecker RJ. Intravitreal bevacizumab in a patient with neovascular glaucoma. *Ophthalmic Surg Lasers Imaging* 2006;**37**:144–6.
11 **Avery RL**. Regression of retinal and iris neovascularization after intravitreal bevacizumab (Avastin) treatment. *Retina* 2006;**26**:352–4.
12 **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**:279–84.
13 **Spaide RF**, Fisher YL. Intravitreal bevacizumab (Avastin) treatment of proliferative diabetic retinopathy complicated by vitreous hemorrhage. *Retina* 2006;**26**:275–8.
14 **Avery RL**, Pieramici DJ, Rabena MD, *et al*. Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. *Ophthalmology* 2006;**113**:363–72 e5.
15 **Rosenfeld PJ**, Fung AE, Puliafito CA. Optical coherence tomography findings after an intravitreal injection of bevacizumab (avastin) for macular edema from central retinal vein occlusion. *Ophthalmic Surg Lasers Imaging* 2005;**36**:336–9.
16 **Rosenfeld PJ**, Moshfeghi AA, Puliafito CA. Optical coherence tomography findings after an intravitreal injection of bevacizumab (avastin) for neovascular age-related macular degeneration. *Ophthalmic Surg Lasers Imaging* 2005;**36**:331–5.
17 Northwest Lancashire Health Authority v A, D &G [2000] 1 WLR 977.
18 **Yoshioka A**. Use of randomisation in the Medical Research Council's trial of streptomycin in pulmonary tuberculosis in the 1940s. *BMJ* 1998;**317**:1220–3.