THE INTRAVITREAL USE OF BEVACIZUMAB (AVASTIN) IN AGE RELATED MACULAR DEGENERATION

There have been developments on this subject. Please refer to our statement 'Bevacizumab (Avastin) use in medical ophthalmology' dated 14th December 2011

Bevacizumab (Avastin, Genentech/Roche) is a full recombinant humanised monoclonal antibody with a molecular weight of 149KD (3 times the size of ranibizumab) which binds to all isoforms of Vascular Endothelial Growth Factor A (VEGF-A) (similar to ranibizumab). It is glycosylated unlike ranibizumab, and has an Fc fragment unlike ranibizumab. The Fab domain of bevacizumab differs from ranibizumab by 6 amino acids. The serum and vitreous half-lives of bevacizumab are longer than those of ranibizumab. It is licensed for the treatment of metastatic colorectal and breast cancer.

The European Medicines Agency (EMEA) gives the following summary on the use of **bevacizumab (Avastin)**. Full information can be found on the web site http://www.emea.europa.eu/

Therapeutic Indication
Avastin (bevacizumab) in combination with intravenous 5-fluorouracil/folinic acid or intravenous 5-fluorouracil/folinic acid/irinotecan is indicated for first-line treatment of patients with metastatic carcinoma of the colon or rectum. Avastin in combination with paclitaxel is indicated for first-line treatment of patients with metastatic breast cancer.
Date of issue of Marketing Authorisation valid throughout the European Union
12 January 2005

The intravitreal use of bevacizumab is off label. There is no long-term information on safety and efficacy, although the preliminary data are very encouraging. When used on patients with wet age-related macular degeneration (AMD) who continued to deteriorate anatomically or visually after photodynamic therapy (PDT) with or without pegaptanib (Macugen), a non-randomised trial showed highly significant improvement in vision at 4 and 8 weeks after treatment with intravitreal bevacizumab.[1] A recent international survey of over 7000 injections in more than 5000 patients indicated hypertension at a rate of approximately 2 in 1000 and other systemic complications less than 1 in 1000 for each (cerebrovascular accidents, myocardial infarctions, and thromboembolic event); these complications might or might not be related to the intravitreal use of bevacizumab.[2] However, such surveys of self-reported complications are likely to under-report their occurrence. There are several other case series, and a pilot RCT with short follow-up supporting the role of bevacizumab in the treatment of wet AMD.[3,4] A systematic review on the use of bevacizumab in wet AMD has been undertaken by Schouten et al

(2009).[5] However, it remains unlicensed, and there are no large randomised trials to date. There are no true dose escalating/ranging studies for intravitreal bevacizumab. As such the optimum dose and dose-frequency for intravitreal bevacizumab remain unknown. Data from long term studies with pegaptanib and ranibizumab indicate that localised VEGF-A inhibition does not appear to increase the risk of systemic adverse events (arterial thromboembolic events) in treated patients compared with placebo for choroidal neovascularisation.[6,7] However, this scenario cannot be directly extrapolated to bevacizumab as the plasma half lives of the two anti-VEGF agents are very different. As such, the medium to long term safety of bevacizumab are unknown.

Genentech, and partner Roche, the manufacturers of Avastin, recently raised concerns about the compounding of Avastin into smaller doses for intraocular use as it is not designed, manufactured or approved for such use. It advised that compounding may contaminate the product. The company also noted the absence of formal, randomised controlled clinical trials for the intraocular use of their product. [8,9]

In a 'Dear Doctor' letter dated 9th Feb 2009, Roche UK issued an Important Safety Information on 'Reports of severe eye inflammation and sterile endophthalmitis following off label intravitreal use of Avastin (bevacizumab) in Canada.'[9] This follows an earlier one issued by Genentech on 19th Dec 2008. It advised of 2 clusters of spontaneously reported severe ocular inflammation following the off-label intravitreal administration of aliquots of Avastin Lot B3002B028. There were no culture-positive cases of in this series. The reports seem to be confined to Canada. There were no adverse events in oncology patients with the same lot. The report further indicated that a small number of spontaneous reports of similar adverse events have been received from other countries including the EU. Additional notifications have been posted on the websites of the Canadian Ophthalmological Society and The Royal Australian and New Zealand College of Ophthalmologists. [10,11]

Roche advised that the causal relationship between Avastin and the said adverse events have not been established but there are ongoing investigations. It further advised that 'the production methods, formulation, and dosages for Avastin were specifically developed for intravenous use in the oncology setting', and that 'the use of Avastin in the ophthalmology setting has not been authorised by any Health Authority worldwide.'

The treatment options for patients with wet AMD have changed rapidly as two anti-VEGF drugs - ranibizumab (Lucentis) or pegaptanib (Macugen) – are now licensed in this country. Ranibizumab is currently considered the gold standard in the treatment of CNV secondary to wet AMD. Emerging evidence suggests that anti-VEGFs may also be effective in the treatment of subfoveal CNVs secondary to causes other than AMD e.g. myopia. Both drugs have been approved by the Scottish Medicines Consortium (SMC) for use in the treatment of patients with wet AMD in Scotland. NICE has recommended the use of ranibizumab in the treatment of eyes with subfoveal CNV of all lesion types secondary to AMD for the remainder of the UK. Pegaptanib has not been recommended by NICE. This guidance became binding on the 26th November 2008. For CNV secondary to AMD, therefore, there should be no barriers to the use of ranibizumab. As such there should be no restrictions from Primary Care Trusts (PCTs) on the use of ranibizumab in wet AMD.

The NICE evaluation of ranibizumab and pegaptanib did not include the treatment of CNVs secondary to other causes e.g. myopia, inflammatory disease or idiopathic cases. Some PCTs have allowed the use of ranibizumab on particular patient applications, based on the specialist consultants' recommendation. This is similar to extension of photodynamic therapy (PDT) to non-AMD CNV indications in 2004. Policies of some PCTs have restricted the freedom of clinicians to treat such cases with ranibizumab (Lucentis) or pegaptanib (Macugen). Some PCTs are beginning to authorise bevacizumab for non-AMD CNV. It is appreciated that some patients' condition is such that they cannot wait until these drugs become freely available and that there are difficult ethical considerations at present for the doctor who is trying to act in the patients' best interest. [12] It is recognised that cost can be a barrier and can effectively make certain drugs unavailable to patients. It is, however, unfortunate for PCTs to use drug cost as the main determinant of treatment in these patients who face potentially more blind years than AMD patients if untreated, and cumulative adverse events over time.

For CNV secondary to other causes, in areas where PCTs impose limitations on the prescribing of ranibizumab, the only option for patients not eligible for NHS treatment may be to seek treatment privately. For many patients in this situation, the relatively low cost of bevacizumab in comparison with ranibizumab may be the main factor which influences the choice of treatment. .

The General Medical Council has this to say about off label prescribing:

Prescribing medicines for use outside the terms of their licence (off-label)
You may prescribe medicines for purposes for which they are not licensed...when prescribing a medicine for use outside the terms of its licence you must:

- Be satisfied that it would better serve the patient's needs than an appropriately licensed alternative
- Be satisfied that there is a sufficient evidence base and/or experience of using the medicine to demonstrate its safety and efficacy. The manufacturer's information may be of limited help in which case the necessary information must be sought from other sources
- Take responsibility for prescribing the medicine and for overseeing the patient's care, monitoring and any follow up treatment, or arrange for another doctor to do so.
- Make a clear, accurate and legible record of all medicines prescribed and, where you are not following common practice, your reasons for prescribing the medicine.[13]

What information must I give patients about the licence for their medicines?

1. You must give patients, or those authorising treatment on their behalf, sufficient information about the proposed course of treatment including any known serious or common side effects or adverse reactions. This is to enable them to make an informed decision (for further advice, see GMC guidance Seeking patients' consent: the ethical considerations). [14]

2. Some medicines are routinely used outside the scope of their licence, for example in treating children. Where current practice supports the use of a medicine in this way it may not be necessary to draw attention to the licence when seeking consent. However, it is good practice to give as much information as patients, or those

authorising treatment on their behalf, require or which they may see as significant. Where patients, or their carers express concern you should also explain, in broad terms, the reasons why medicines are not licensed for their proposed use. Such explanations may be supported by written information, for example, the leaflet on unlicensed medicines produced by the Royal College of Paediatrics and Child Health.

3. However, you must explain the reasons for prescribing a medicine that is unlicensed or being used outside the scope of its licence where there is little research or other evidence of current practice to support its use, or the use of the medicine is innovative. [15]

Under the heading, **Doctors' interest in Pharmacies**, the Good Practice in Prescribing Medicine points out clearly that, "you should not accept any inducement which may affect or be seen to affect the advice you give patients".[13]

It is now obvious that large randomised control trials are required to determine the safety, efficacy and optimal dosing of intravitreal bevacizumab. The IVAN trial funded by the NHS for this purpose has commenced and will last 2 years. See the trial web site www.ivan-trial.co.uk A similar study (The CATT Study) is ongoing in the US.

The Royal College of Ophthalmologists calls for full implementation of the NICE guidance TA155. It also supports more research on the ocular use of bevacizumab, and for ophthalmologists to promote good clinical practice as set out by the General Medical Council.

However, at the present time, the College does not recommend the routine use of intravitreal bevacizumab for choroidal neovascularisation over anti-VEGFs which are already licensed for that indication, and recommended by NICE. There is currently insufficient data on the optimum dose and dose-frequency, as well as medium to long term efficacy and safety of bevacizumab. This is especially so in light of the recent warnings of the manufacturer. Whilst the College recognises the financial pressures experienced by many Primary Care Trusts, it cannot endorse the commissioning of Avastin services on the basis of current evidence.

Should intravitreal bevacizumab be used, the College advises such use must either be part of a research programme (as in the IVAN Study) or be documented by robust ongoing audit, with systematic prospective data collection. Special attention should be paid to reporting possible systemic side effects (particularly cardiovascular, neurologic and thromboembolic), as well as ocular adverse events. The treating physician must discuss with the patient alternative treatments and obtain appropriate consent in accordance with GMC guidance. Responsibility for prescribing drugs outside the terms of the product licence remains that of the prescriber i.e. the clinician.

References

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