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The Royal College of Ophthalmologists response to the NICE Decision Support Unit (DSU) report on ranibizumab for the treatment of macular oedema caused by retinal vein occlusion (RVO)

1. Quality

Pharmaceutical quality of reformulated bevacizumab as used in eye conditions in general.

The DSU report suggests that the major supply of compounded bevacizumab in the UK came from 2 Specials pharmacies – Moorfields Pharma and Royal Liverpool and Broadgreen University Hospital. This report suggests that the quality of compounded bevacizumab from these 2 suppliers is satisfactory for periods up to 3 months. However, no evidence or data was supplied to support this statement. The DSU survey, further, indicated that approx. 30% of the supplies come from elsewhere: local pharmacies or other compounding pharmacies. Again, no data is provided on the quality of these supplies.

Bevacizumab (Avastin, Roche/Genentech) as supplied by the manufacturer is manufactured to the standards for intravenous injection. It does not meet the standards for intravitreal injections as recommended by the US Pharmacopea (USP 788 and USP 789). A recent analysis of re-packaged bevacizumab from 5 UK Specials pharmacies (including the above 2) intended for intravitreal administration (Kamali et al, 2012 ARVO) showed that compounded bevacizumab supplied by these compounding pharmacies, within their expiry date, did not meet the USP 788 and 789 standards. There were variable microparticles (visible and subvisible) in different batches of bevacizumab obtained from each supplier, and the different suppliers. There were significant differences ($p<0.001$) in particle density on day 1 (day of acquisition) between the different batches from the five suppliers. Furthermore, there was a significant increase in particle density (particles/ml) over the 14 day period (test 1 to test 2) for the repackaged bevacizumab from the five different suppliers ($p<0.03$ for all comparisons). Particle size was also significantly different ($p<0.001$) between each batch tested at day 1 and 14 days. Whether these variations in re-packaged bevacizumab supplied for intravitreal injrection have any impact on clinical efficacy or safety are unknown.

The quality of bevacizumab used in UK clinical practice is both variable and different from that used in various clinical trials. As an example, in the CATT trial, bevacizumab

was supplied in glass vials. In the UK, compounded bevacizumab is supplied in non-standardised plastic syringes with different stoppers.

The risks of intraocular inflammation and infections are covered by the DSU report and cannot be overlooked.

Should NICE support the use of compounded bevacizumab, it is suggested that the manufacturing should be restricted to a small number of Special licensed pharmacies supported by rigorous internal as well as external quality assurance. Each of these compounding pharmacies should produce their internal quality assurance data, such as shell life, contamination, storage etc.. Each should also have a pharmacovigilence programme in place.

2. How widespread is Intravitreal Bevacizumab (IVB) used in the UK?

The review of commissioning policies from different PCTs demonstrates the varied nature of interpretation of the efficacy and safety of bevacizumab throughout the UK. These policy statements do not give any estimation of the actual use of bevacizumab in practice by clinicians.

The recent survey of ophthalmologists on their use of bevacizumab gives no actual numbers of patients treated with intravitreal bevacizumab throughout the UK. Neither does it gives reasons for such use. In addition, the recent NICE recommendation on Ozurdex as a treatment option in macular oedema secondary to retinal vein occlusion (RVO) (NICE TA 229) most likely would have reduced the off-license use of bevacizumab in this condition.

It is important to note that when a licensed and funded treatment (ranibizumab) is available as in the case of neovascular AMD the use of bevacizumab as an alternative is very limited by UK ophthalmologists. For non-AMD choroidal neovascular membrane (of different aetiologies including myopic CNV) for which there are currently no licensed anti-VEGF agents, bevacizumab is used off-license. Although ranibizumab has marketing authorisation in the EU for the treatment of diabetic macular oedema (DMO) it is currently not recommended by NICE. This means, therefore, that there are currently no licensed drugs available for the treatment of DMO in UK NHS practice. As such, some clinicians may resort to the use of unlicensed bevacizumab. For macular oedema secondary to RVO, dexamethasone implant (Ozurdex) is recommended by NICE. The use of bevacizumab in the treatment of macular oedema secondary to RVO has therefore declined considerably over the past several months, except in Trusts where NICE guidelines have not been implemented, in contradiction to the binding guidelines.

When faced with a patient with visual loss, an ophthalmologist would wish to treat the patient if possible. The treatment needs to be effective and safe. The level of effectiveness and safety required are relative to the severity of the problem and what treatment options are available. These options are weighed from the doctors', and patients' points of view, and the treatment decision may also be influenced by availability of funding. There are many clinical circumstances where drugs are used

off- label, or unlicensed but the such use of a drug which has not undergone any regulatory scrutiny, and where the data supporting safety and efficacy in the eye are limited, and where there is a licensed alternative cannot be viewed as “best practice”. The use of bevacizumab,identified in the survey, therefore reflects the fact that funding is not available for ranibizumab rather than it being an endorsement by doctors that bevacizumab is an entirely satisfactory treatment. Given a choice the majority of doctors would rather use a drug which has been formulated for intraocular use and had regulatory approval for such an indication.

Pegaptanib (Macugen) is used occasionally by clinicians as deemed necessary on clinical grounds, despite its non-recommendation by NICE (NICE TA 155). Such use of pegaptanib would similarly not be considered routine use in the UK NHS or private sector.

The GMC rule on the use of an unlicensed alternative in the treatment of any condition in the presence of available licensed products has not changed, despite the recent review. It states, inter alia, that before a prescriber uses a medicine off label or outside its licence he/she must be satisfied: “that it would better serve the patient's needs than an appropriately licensed alternative” and “that there is a sufficient evidence base and/or experience of using the medicine to demonstrate its safety and efficacy.” This guideline, therefore, is against the use of an unlicensed alternative in the presence of a licensed drug (2 agents in the case of RVO, and 1 in case of DMO).

It should be concluded that bevacizumab use in UK NHS or private practice is inconsistent, not routine and certainly not considered best practice.

3. What is the evidence for efficacy of IVB in adults with RVO and DMO specifically?

Most evidence for the use of bevacizumab exists for the treatment of CNV in neovascular AMD as reported by the CATT and IVAN studies.

The evidence for efficacy of bevacizumab in DMO and RVO is less robust than that for CNV, as rightly pointed out by the DSU report. There is evidence for efficacy of bevacizumab in DMO, as the existing data seems to favour vision improvement with bevacizumab compared with laser therapy. However, the data was often heterogeneous or not comparable with clinical practice. The trial designs (of available reports) often preclude inter-study comparisons to those of licensed anti-VEGF drugs. In patients with RVO, bevacizumab appears to provide some improvement in best corrected visual acuity (BCVA); however, the evidence is currently only limited, and comparison amongst the available data is difficult. Furthermore, the 2 types of RVO (branch and central) have different outcomes. As such, bevacizumab treatment outcomes from these 2 RVO types cannot be pooled. More rigorous studies are needed before valid conclusions on the efficacy of bevacizumab in macular oedema secondary to RVO are reached.

In summary, the evidence of efficacy of bevacizumab in macular oedema secondary to RVO is currently limited, whilst in DMO there is some, but limited clinical trial evidence

of efficacy. Efficacy of bevacizumab in DMO cannot be extended to macular oedema in RVO. Head to head non-inferiority studies of bevacizumab vrs ranibizumab would be helpful in the long term in making reasoned comparisons. Furthermore, as diabetics (Campbell et al, 2012) and RVO patients are more susceptible to cardiovascular events, clinicians may be reluctant to proceed to widespread use of bevacizumab as the recommended treatment option for DMO or macular oedema secondary to RVO, especially if there are licensed alternatives. (See below).

4. Adverse events

None of the published or currently running trials comparing bevacizumab with ranibizumab administered intravitreally are robustly powered to determine differences in safety between the 2 drugs. The DSU document identifies " Of particular note is the fact that in head to head comparisons of IVR and IVB (CATT and IVAN trials), when results are meta-analysed, there is a statistically significantly higher rate of 1 or more serious systematic adverse event (RR 1.27, 95% CI 1.09 to 1.47) in the IVB group." It is of critical importance that the adverse events that noted were considered serious adverse events. This recent analysis prompted the Data Safety Monitoring Committee of the IVAN study to send out a warning letter to all investigators and patients. The results of the CATT (at 2 years) and IVAN (1 year) show no difference between the drugs in rates of death or thromboembolic events. Both studies however report more systemic serious adverse events with bevacizumab; these events were across many different systemic conditions, the majority of which were not reported as being associated with systemic bevacizumab use in cancer trials (where a much higher dose of the drug was used). The reasons for the increased incidence of serious adverse events in patients treated with bevacizumab in these two trials are unclear. A recent population-based, nested case-control study by Campbell et al (2012) reported that intravitreal injections of bevacizumab and ranibizumab were not associated with significant increased risk of ischemic stroke, acute myocardial infarction, heart failure or thromboembolism. There was no difference in the safety profile of the two drugs used for the treatment of AMD. Thus overall the two drugs appear to have a similar safety profile in respect of cardiovascular and thromboembolic events but both the IVAN and CATT studies reported an overall increased risk of serious adverse events with the use of bevacizumab. These findings are currently unexplained and require further study.

It is accepted that the AMD population is different from that in DMO and RVO. The serious adverse events that may be predicted to be associated with the use of anti-VEGF agents include cardiovascular and arterio-thrombolic events (ATEs) occur more commonly in patients with diabetes and RVO. It is therefore possible that there will be an increased rate of SAEs in diabetics and RVO patients treated with anti-VEGF agents compared with that seen in neovascular AMD. In the recent population-based, nested case-control study by Campbell et al (2012) subgroup analysis showed no difference between diabetics and patients without diabetes in the incidence of cardiovascular and arterio-thrombotic events with intravitreal injections of either anti-VEGF agent. However in the subgroup with diabetes the authors found a significant association between exclusive bevacizumab use and myocardial infarction when using exclusive ranibizumab use as the comparator. Since hypertension, diabetes,

hypercholesterolemia are risk factors for retinal vein occlusion, patients with macular oedema secondary to vein occlusion are also likely to be more at risk of heart disease and ATEs following anti-VEGF use.

There have been few studies that have investigated the effect of systemic anti-VEGF agents on serum VEGF levels but current evidence suggests that the use of both anti-VEGF agents is associated with reduction in serum VEGF levels (Ivan study; Carneiro et al). Bevacizumab is associated with a significantly greater effect on serum VEGF levels. The clinical significance of this is as yet unknown and further studies are needed.

5. Regulation

There are significant issues about the adoption of bevacizumab as standard treatment in eye diseases as it remains unlicensed. In order to use bevacizumab as a comparator for licensed therapies in ocular disease, NICE has to decide whether to bypass the enshrined licensing process for new drugs and support its use instead of a licensed product for the same indication. Presumably this may require some discussion with the MHRA and EMA. Under those circumstances, service providers and treating physicians will have to be assured that there are no legal or practice regulatory consequences of providing such unlicensed treatment in the presence of licensed drugs for the particular indications.

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