

NICE Health Technology Appraisal Ranibizumab and Pegaptanib for the Treatment of Age-related Macular Degeneration

Personal Statement

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Expertise

I am a currently practising specialist and clinical researcher in medical retinal diseases. The study and care of patients with macular degeneration caused by a range of diseases including ageing form a large part of my current work. I have extensive clinical experience of laser photocoagulation and verteporfin photodynamic therapy (PDT) for macular degeneration, recent experience in the use of pegaptanib in clinical practice and limited experience of ranibizumab in clinical trials. I was an investigator in the TAP and VIP studies which investigated the efficacy of verteporfin PDT and am lead investigator in the Verteporfin PDT Cohort Study, a HTA/DH funded clinical study of the effectiveness and cost effectiveness of PDT in routine clinical practice in the UK. I am a lead member of the executive team for the Intravitreal Anti-angiogenesis in Neovascular Age-related Macular Degeneration (IVAN) study. This is a randomised clinical trial recently funded by the HTA to investigate the relative effectiveness and cost-effectiveness of ranibizumab and bevacizumab (Avastin). I am co-chair of the Medical Retina Group, an association of medical retina specialists in the UK.

Current clinical practice in the UK

At present PDT is widely available on the NHS in England and Wales for the treatment of classic no occult and predominantly classic with or without occult choroidal neovascularisation (CNV). Treatment is provided in designated centres by specialists in the assessment and treatment of macular disease as recommended by NICE and the RCOphth in relevant guidance. Treatment is included for CNV caused by any aetiology. The diagnosis and accurate classification of disease is a complex process requiring high levels of technical support and clinical expertise. Clinical experience is that PDT effectiveness is similar for classic no occult and predominantly classic subgroups and this is supported by research data.

AntiVEGF therapies are being introduced into the NHS in a number of areas, with pegaptanib being more widely available than ranibizumab at present. Developing clinical experience suggests that the frequency of adverse events is low, but the true incidence remains unclear. Intravitreal injections are increasingly being administered in designated clean rooms while the use of operating theatres/day case facilities is declining. A number of patients are unable to commit to the frequent visits required and opt for PDT. Many PCTs have contingency plans in place to fully commission antiVEGF therapy, mainly after NICE has produced its guidance.

The role of PDT if/when antiVEGF therapies are introduced is unclear. The VPDT cohort study is likely to identify patients who will benefit from PDT and some patients will select it because of difficulty with 4 or 6 weekly visits. The role of combined therapy is unclear.

Comments on Committee Papers

Overview

The overview provides a detailed and comprehensive review of the current research data and lists a number of important uncertainties. It does mix up the use of Snellen and ETDRS charts for the assessment of vision. There is no place for Snellen vision in the assessment and management of patients with AMD.

Cost-effectiveness Models

All the cost-effectiveness models report generally encouraging ICERs for both drugs with ranibizumab appearing to be superior to pegaptanib. However in the Pfizer and Southampton HTA models of cost-effectiveness of pegaptanib and ranibizumab there appears to be a significant underestimate of the costs of delivery of therapy and the Novartis model includes no details of unit costs.

Both models that do include this information use an extended outpatient visit of around £96 and a standard outpatient visit of around £50 to cover the costs of the delivery of care. None of the 3 models includes VAT. This data has resulted in a significant underestimate: the fact is supported by both drug and treatment delivery for AMD being currently excluded by the PBR team of the DH.

The business case from St. Paul's Eye Unit has used an ingredient approach built up from 10 years of experience of delivering macular degeneration screening and treatment. It uses known activity levels and the staff /consumable/overhead costs of providing optometry vision assessment, OCT and FA imaging, clinical assessment, treatment, supportive care, clerical and administration and transport costs to elderly patients attending with carers for time consuming and extensive investigation. The 2006/7 first year costs agreed with Trust Finance Directors, Regional Specialised Commissioners and PCT Directors of Finance and assuming trial-based dosing are: pegaptanib £10,764 and ranibizumab £20,104. Reviewing these costs to reflect likely reduced frequency throughout years 1 and 2 based on experience with pegaptanib and the revised Novartis license gives: pegaptanib year 1 £9,474, year 2 £6,450, total £15,924; ranibizumab year 1 £13,552, year 2 £10,164, total £23,716. These costs are around 50% higher than used in the models presented to the Appraisal committee.

Final Scope

There is an error in Appendix A which states that PDT was approved by NICE in its guidance of 2003 for the treatment of classic no occult CNV secondary to AMD. The guidance also approved the use of PDT for predominantly classic CNV with or without an occult component within clinical studies. This was the basis for inclusion of both classic no occult and predominantly classic with occult CNV in clinical practice throughout England and Wales within the context of the VPDT Cohort Study.

Royal College of Ophthalmologists Submission

This provides a detailed review of the state of service provision in the UK and the ophthalmologists' perspective of ranibizumab and pegaptanib. The report from the Medical Retina Group indicates widespread support amongst medical retina specialists for the introduction of ranibizumab into NHS practice. The need to develop new centres for the service delivery is highlighted with an estimated tripling of capacity being required. A hub and spoke approach to service organisation is discussed. Since this report was prepared further models have been considered including the development of local networks of care

Personal assessment of AntiVEGF therapy

Pegaptanib

Data from the VISION trials of pegaptanib indicates that this therapy appears to be roughly as efficacious as PDT but its efficacy is not restricted to the subgroups of classic/no occult and predominantly classic CNV. The therapy appears to be effective in clinical practice across the range of lesion subtypes and offers potential benefits over current care for patients with minimally classic and occult/no classic CNV.

In the RCTs pegaptanib was administered 6 weekly for 2 years and it remains unclear how long patients should be treated for, or the rate of recurrence/reactivation. Clinical practice is limited to date in the UK, but in the US there are reports of patients receiving therapy for up to 5 years. Clinical guidelines on when to stop pegaptanib therapy are yet to be developed. The frequency of discontinuation of the required frequent intravitreal injections remains unclear – patients recruited into the RCTs were a selected group.

Ranibizumab

Data from the MARINA and ANCHOR studies indicates that this therapy appears to be more efficacious than PDT and pegaptanib. It offers a significant chance of improvement in vision in between 30 and 40% of patients depending on lesion subtype and also better rates of stabilisation of vision. These results indicate important benefits to patients and a major step forward in care for affected patients.

Clinical experience in the UK to date is limited and largely confined to the private sector. In the RCTs ranibizumab was administered every 4 weeks for 2 years. Novartis have understandably reduced this in their revised license appreciating the difficulty for patients and funders of 24 injections over 2 years. The reduced dosing frequency is based on data modelled from three of the RCTs and based on subgroup analyses of the predominantly classic group only. There is no trial data to support this although 8 applications in year one and 6 in year 2 does seem reasonable. As is the case with pegaptanib, stopping rules have yet to be developed. Significant numbers of injections will be required beyond year 2. There is likely to be a significant proportion of patients who will not be prepared to attend regularly for 4 weekly treatment.

The recently funded IVAN study will answer questions about drug dosing regimes as well as comparing efficacy with bevacizumab but is not expected to report until 2009. It will give some useful information on safety but has not been powered to detect infrequent and rare adverse events. A surveillance programme will be required to detect rare adverse events.

The Novartis license describes the re-treatment decision making based on visual acuity alone. This is oversimplified. Other important parameters of disease activity need to be included such as clinical features, OCT and FA, all of which are routinely used in clinical trials and clinical practice.

Service delivery

The optimum model of service delivery needs to be developed. Models will need to build on the diagnostic expertise of existing centres. The most appropriate appear to be a local network containing at least one established PDT centre or some sort of “hub and spoke” model. Current accuracy of diagnosis is unsatisfactory. In a recently completed audit of 155 cases referred to St. Paul’s Eye Unit between July and December 2006 the interpretation of fluorescein angiograms was correct in only 39% of cases with several cases being recommended for treatment that did not have CNV. Only 51% of angiograms were deemed of good quality. There was wide variation between units. Significant training will be required to ensure that treatment is

delivered to the correct group of patients. The use of the existing network of AMD grading centres in the UK could offer training and external diagnostic support.

Recommendation to NICE

1. Ranibizumab should be introduced into the NHS for the treatment of all subtypes of subfoveal choroidal neovascularisation due to age-related macular degeneration.
2. Pegaptanib may be considered by purchasers to be more cost-effective than ranibizumab and therefore have a role in the treatment of cases not currently suitable for verteporfin photodynamic therapy.
3. Treatment should be delivered in dedicated facilities by experts in the management of macular disease supported by ETDRS vision assessment, optical coherence tomography and stereoscopic fluorescein angiography.
4. Data should be collected on adverse events and outcomes in routine clinical practice.
5. Research should be undertaken to establish the effectiveness and cost-effectiveness of alternative dosing regimens and the effects beyond 2 years.

Declaration of interests

I have received departmental support for participating in clinical trials sponsored by Novartis and Pfizer. I have also received personal and departmental support for serving on various advisory boards for both companies.