Submission from the Royal College of Ophthalmologists

to

the National Institute for Health and Clinical Excellence.

Health Technology Appraisal

Ranibizumab and pegaptanib

for the treatment of Age related Macular Degeneration.

1st August 2006

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1. How is Age related Macular Degeneration currently treated in the NHS in England and Wales?

Patients with Age related macular degeneration (AMD) are currently treated in all ophthalmology departments in the NHS in England and Wales, where it is one of the main causes of outpatient referral. In most units NHS consultants with a special interest in medical retina have taken the lead in organising and providing these services.

The management of an individual patient will depend on the type of AMD present which is broadly divided into dry and wet types.

Dry AMD

Patients with early manifestations of AMD are currently offered advice by hospital eye departments on cessation of smoking, the importance of a healthy diet and lifestyle and the potential value of nutritional supplements for prevention of progression to advanced AMD (1)

For one form of advanced AMD (otherwise known as Geographic Atrophy) there is unfortunately no medical or surgical treatment that is currently available. However patients can be helped by supportive measures such as low vision assessment, provision of and advice on the use of optical aids and counselling about the condition and prognosis. In most cases the Hospital Eye Services (HES) work closely with local optometrists and social services, and have good links with local patient support groups. Registration as blind or partially sighted is a valuable process for the more severely visually handicapped patients.

Wet AMD.

The other form of advanced AMD is known as wet or exudative . Wet AMD can give rise to rapid deterioration in central vision and is associated with the subretinal ingrowth of choroidal new vessels (CNV), with resultant damage to the fovea. The majority of patients registered blind with AMD have the wet type (2). CNV is assessed by clinicians using fundus fluorescein angiography and categorised into two main types termed “classic and occult”. The location of CNV in relation to the centre of the fovea is also important, being categorised into “extra-“ ($\geq$200μ), “sub-“ (1-199μ) and “subfoveal”.

The options for treatment are currently limited to laser photocoagulation with thermal laser to extrafoveal lesions and photodynamic therapy with verteporfin to juxta- and subfoveal lesions. A further type of treatment, transpupillary thermotherapy (TTT) has proved of limited value and is not in widespread use in the UK.

2.Current relevant guidelines published by the Royal College of Ophthalmologists

The management of age related macular degeneration (2000). Currently under review

Guidelines for Photodynamic Therapy (2001)

PDT Update (February 2004)

Establishing Photodynamic Therapy Services – Guidance for Commissioners

3.Treatment options for neovascular AMD

3.1 Laser photocoagulation.

Laser photocoagulation with conventional thermal laser is currently used for treating well delineated extrafoveal CNV lesions , and destroys the neovascular membrane. In a proportion of eyes, treatment limits the area of CNV growth and prevents involvement of the fovea. The effectiveness of this treatment is limited by the scotoma it causes in the visual field, the high recurrence rate and the fact that only small classic CNV which are extrafoveal at presentation can be treated. In practice few patients meet these criteria, but in the UK in 2006 it is still the treatment of choice for this small group of patients. (3,4)

3.2 Photodynamic therapy with verteporfin

Photodynamic therapy with verteporfin (PDT) acts by inducing thrombosis within the CNV without damaging the overlying neurosensory retina. Thus subfoveal lesions can be treated.
In two controlled clinical trials, PDT with verteporfin was shown to be effective in limiting vision loss in patients with classic subfoveal CNV secondary to AMD (5-7). In addition a further contolled clinical trial the VIP Study showed that after 2 years, PDT with verteporfin significantly reduced the risk of moderate to severe visual loss in patients with occult and no classic CNV. (8)

3.3 Combined verteporfin PDT and intravitreal triamcinolone.

Reports from Germany have shown that verteporfin PDT combined with intravitreal triamcinolone acetate (IVTA) may improve the outcome of standard verteporfin PDT, and reduce the number of retreatments. (9)

This has encouraged many treating ophthalmologists in England and Wales to offer this combination treatment to patients in the following categories; patients with aggressive predominantly classic CNV that are not responding to conventional verteporfin PDT; patients with retinal angiomatous proliferation (RAP) a subgroup of wet AMD that is not responsive to verteporfin PDT alone: some occult CNV (less than 4 disc diameters) with rapid reduction in vision. Many of these patients do not receive funding for treatment in the NHS and therefore seek treatment in the private sector.

IVTA has potential complications that include cataract progression, increased intraocular pressure and rarely endophthalmitis. Clinical trial evidence for the use of IVTA in combination with PDT is limited but a number of RCT are currently underway and should report their findings within the next 12 months.

Combination therapy of PDT verteporfin and periocular triamcinolone injection may be safer but clinical trial evidence of the efficacy is limited and RCT are currently underway.

4. NICE PDT technology evaluation

In England and Wales the current model of care for the treatment of AMD is based on the National Institute for Clinical Excellence (NICE) guidance of 2003 and the guidance for commissioners published by the Department of Health and available on the RCOphth website (**www.rcophth.ac.uk**).

On 24 September 2003 the National Institute for Clinical Excellence (NICE) published Guidance (**www.nice.org.uk**) on verteporfin photodynamic therapy (PDT) in wet age-related macular degeneration (AMD). The key recommendations in the NICE Guidance are set out below.

NICE Guidance on the use of PDT for age-related macular degeneration

1.1 Photodynamic therapy (PDT) is recommended for the treatment of wet age-related macular degeneration for individuals who have a confirmed diagnosis of classic with no occult subfoveal choroidal neovascularisation (CNV), and best-corrected visual acuity of 6/60 or better. Only retinal specialists should carry out PDT with expertise in the use of this technology.

1.2 PDT is not recommended for the treatment of people with predominantly classic subfoveal CNV (that is, 50% or more of the entire area of the lesion is classic CNV but some occult CNV is present) associated with wet age-related macular degeneration, except as part of ongoing or new clinical studies that are designed to generate robust and relevant outcome data, including data on optimum treatment regimens, long-term outcomes, quality of life and costs.

1.3 The use of PDT in occult CNV associated with wet age-related macular degeneration was not considered because the photosensitising agent (verteporfin) was not licensed for this indication when this appraisal began. No recommendation is made with regard to the use of this technology in people with this form of the condition.

1.4 Patients currently receiving treatment with PDT could experience loss of well-being if their treatment is discontinued at a time they did not anticipate. Because of this, all NHS patients who have begun a course of treatment with PDT at the date of publication of this guidance should have the option of continuing to receive treatment until their clinical condition indicates that it is appropriate to stop.

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4.1 Practical Implications of NICE guidance.

NHS treatment is theoretically limited to patients fulfilling 1.1 criteria. However virtually all treating units in England and Wales are also collecting and submitting data for the VPDT Cohort Study under category 1.2, and are therefore also treating patients that fulfil 1.2. Based on the guidance from commissioners many units are treating patients with CNV that are unrelated to AMD and these include CNV secondary to high myopia, trauma, post-inflammatory, angioid streaks, retinal angiomatous proliferation, retinal dystrophies and idiopathic.

Some patients that have small occult CNV (<4 disc diameters), with rapid deterioration of vision and best corrected vision of 6/60 or better, have also been funded by PCT's on an individual basis. (JM Gibson, SP Harding, personal communications, 2006)

Patients with classic juxtafoveal CNV are treated with PDT in most treating units in England and Wales, and very few patients would receive laser photocoagulation for these lesions.

4.2 Verteporfin in PDT (VPDT) Cohort Study for the UK.

In order to comply with the guidance in paragraph 1.2 the VPDT Cohort Study was set up, to collect data on all NHS patients undergoing PDT in the United Kingdom. Up to July 2006 52 designated provider centres had been identified and were submitting data, with details of 5600 patients submitted for data collection. (VPDT Data Management Centre, July 2006. (**www.lshtm.ac.uk/hsru/vpdt)**.

All PDT treating units in the UK have made use of participation in the VPDT Study to treat predominantly classic CNV (1.1 and 1.2) and CNV due to rare causes. Although in theory funding for the VPDT Cohort Study has been provided by the relevant Primary Care Trusts, in practice many Trusts have not provided adequate resources to support the large amount of required data collection and submission, including of digital images. This has proved to be an unpopular burden for several units with busy outpatient services already struggling to meet demand.

4.3 Hub and Spoke Model for PDT

NHS commissioners have ensured that the number of treating centres in England and Wales providing PDT services are limited to from 40-50 "hub sites" to which peripheral units refer for treatment. In the majority of cases assessment with fluorescein angiography is performed at the referring centre and these are sent with the patient to the hub unit. The advantages of this model is that the PDT is kept under the remit of a small number of units, that treatment is easier to standardise and that data collection for the VPDT Study is facilitated.

The major disadvantage of the hub and spoke model is that there is considerable geographic variation in the provision of PDT services, with some patients having to travel large distances for treatment and subsequent retreatment at 3 monthly intervals. An extreme example of this is that for patients in Cornwall the nearest treating unit is situated at Torbay , which results in an unacceptably long and arduous journey for patients who in the most part are elderly and frail and who rely on family and friends for transportation.

Another disadvantage is the difficulty in ensuring that patients are seen rapidly at the hub for treatment to be performed whilst patients still retain sufficient central visual function. There is only a narrow window of opportunity for treatment in most types of CNV as visual function frequently deteriorates rapidly.

5. Pegaptanib and ranibizumab.

These two agents are a potential major advance in the treatment of wet AMD as they will allow ophthalmologists to treat a wide range of subfoveal lesions, including occult CNV. In addition combination therapy with PDT may prove to be more effective / cost-effective. Both of these agents are given by intravitreal injection, pegaptanib at intervals of 6 weeks and ranibizumab every 4 weeks.

A third agent, bevacizumab, which has a similar mode of action to ranibizumab and is licensed for bowel cancer is not being considered in this appraisal as the manufacturers do not intend to apply for licensing for ocular use.

Pegaptanib (Macugen, Pfizer Ltd.) is an oligonucleotide that binds the 165 isoform of vascular endothelial growth factor (VEGF) inhibiting its activity. VEGF165 is the isoform of VEGF that is thought to be preferentially involved in CNV.

Ranibizumab (Lucentis, Genentech/Novartis Pharmaceuticals Ltd.) is a humanised therapeutic antibody fragment designed to bind to and inhibit VEGF-A.

5.1 Current status in the UK

Pegaptanib is licensed for use in the UK and ranibizumab is expected to be by early 2007. However neither of these agents are in widespread NHS use and so evidence from UK clinical practice is very limited. At least one NHS Trust has already received agreement from local PCTs to commence a service with pegaptanib restricted to “exceptional cases”. (SP Harding, personal communication, July 2006).

6. Pegaptanib

6.1 Clinical Trials

The V.I.S.I.O.N Trial (10) consisted of 2 concurrent, was a multicentre, prospective, randomised, dose-ranging double-blind controlled trial of Pegaptanib at doses of 0.3mg, 1.0mg and 3.0mg or sham injections administered every 6 weeks over a period of 48 weeks. The trial was subsequently extended to 2 years. The results show that more patients who received pegaptanib 0.3mg compared to sham injection maintained their vision ($p=0.003$), and further that severe visual loss was reduced ($p <0.001$).

6.2 Use of Pegaptanib

Pegaptanib was licensed for use in the United States in December 2004, and has had widespread use since then. The VISION Study entry criteria have provided a guide for clinical practice(10).

- lesion of any subtype

- vision 20/40 (6/12) to 20/240 (5/60) in the study eye and 20/800 (1½/60) 0r better in the fellow eye
- lesion size less than or equal to 12 disc diameters
- minimally classic
- patients with occult/ were required to have the following indicators of recent progression: subretinal haemorrhage associated with the lesion but <50% of the lesion; the presence of lipid exudates; the loss of 15 letters or more on the logMAR visual acuity chart in the preceding 3 weeks.

6.3 Safety in clinical practice

The two year safety data from the VISION Study have been published and are reassuring. There were no reports of any injection related endophthalmitis in year 2 , compared to 12 events , (0.16%/ injection) in year one, and this difference has been attributed by the study authors to violations in the injection preparation protocol. (11)

There have been case reports of severe systemic allergic reactions associated with intravitreal pegaptanib injections, which occur up to one hour following the injection. (12) There have also been case reports of retinal pigment epithelial rips following treatment with pegaptanib. Since these can occur spontaneously or following laser treatment, the significance of these latter findings are unclear so far. (13)

6.4 Combination therapy with pegaptanib.

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The efficacy of Pegaptanib (Macugen) has been described as improved when used in conjunction with bevacizumab, a pan VEGF isoform inhibitor. This drug has been under investigation for the treatment of a number of ocular neovascular disorders. In a small pilot series bevacizumab has been shown to act as a ”booster shot” in enhancing the effect of pegaptanib.
Macugen has also been tried in combination with IVTA and also with verteporfin PDT in small pilot studies and appears to have no untoward side effects when used in this manner. Further studies are underway.

6.5 Advantages and Disadvantages of using Pegaptanib

Pegaptanib appears to be an effective therapy in all lesion subtypes of wet AMD and has been shown to limit the risk of visual loss compared to the placebo group. Unlike PDT it its efficacy appears to extend across all lesion subtypes including minimally classic and occult lesions (10). The effective use of pegaptanib seems to translate well from research trials to routine clinical practice, at least in the US (14).

The main disadvantages of pegaptanib are that it is given by 6 weekly intravitreal injection, and the period of treatment may need to continue for two years or more, there being no long term data to guide clinicians on when to stop treatment. There is no long term safety data on the use of pegaptanib but the safety profile from the clinical trials is reassuring, with injection related side effects being much rarer in the second year compared to the first. (see above)

7. Ranibizumab

Ranibizumab was licensed in the United States very recently and is expected to be licensed in the EU and United Kingdom by early 2007. The results of routine clinical

use are therefore limited but multiple clinical trials have yielded highly similar visual outcomes in treated eyes suggesting that the observed benefit is robust.

Both one and two year data indicate that ranibizumab is not only effective in preventing visual loss but improves visual acuity in some one-third of all treated eyes. Furthermore overall mean visual acuity in treated eyes is improved by at least 1 line. This is in contrast to the findings following verteporfin PDT or pegaptanib therapy where mean visual acuity showed a steady drop.

Although the visual outcomes following ranibizumab therapy have exceeded all expectations and set a revised standard of care in the management of exudative AMD there are remaining concerns. Firstly there are no long term data and many believe that CNV recurrence can be expected when therapy is stopped after 24 months of ranibizumab treatment. Secondly there are potential systemic adverse effects. Thirdly the optimal dosing regime and intervals between treatment have not yet been identified. Fourthly, the likelihood that combination therapies may prove to be more cost-effective strategies minimising the need for monthly long term administration of ranibizumab has to be explored.

7.1 Clinical Trials.

The MARINA Trial was a multicentre, randomised, double masked trial to test two doses of ranibizumab (0.3 and 0.5mg) in minimally classic and occult CNV and compare with sham injection. (Ref) Data from the one and two year time points reported that ranibizumab was effective in preventing vision loss and in many patients vision also improved (15).

The ANCHOR Study is a two year, phase 3, randomised, muliticentre double-masked trial comparing efficacy and safety of monthly injections of 0.3mg and 0.5mg ranibizumab combined with sham verteporfin PDT, with sham injections of ranibizumab and verteporfin PDT. The primary end point was loss of less than 15 letters of visual acuity, and at the one year results in terms of this and lesion size the ranibizumab patients fared significantly better than PDT with verteporfin ($p<0.0001$) (16).

The PIER study findings are important. This study evaluated an alternate dosing regimen of 0.3 or 0.5 mg of ranibizumab for neovascular AMD. The trial was designed to determine the safety and efficacy of a modified dosing regimen consisting of intravitreal dosing every month for 3 doses, then an additional injection mandated every 3 months. All lesion types were eligible if the active choroidal neovascular membrane accounted for at least 50% of the lesion size. Overall, both doses of ranibizumab that were tested showed a significant benefit over sham in the management of wet AMD. However, quarterly dosing did not appear as effective as monthly dosing, as illustrated by the results of the MARINA and ANCHOR trials.

The PRONTO Study is a small prospective study using optical coherence tomography (OCT) imaging to determine when re-treatment with ranibizumab is necessary with a variable dosing regimen, rather than a rigid monthly injection protocol. Each patient received 3 initial consecutive monthly injections of ranibizumab and then was followed up by OCT and visual acuity. Re-treatment was performed only if one of the following was observed: an increase in OCT central thickness of at least 100um, a loss of 5 letters in conjunction with recurrent fluid by OCT, new onset classic CNV, or a new macular haemorrhage. The study is on going and forty patients have been recruited (17,18).

7.2 Combined treatment regimes with ranibizumab.

Ranibizumab combined with verteporfin PDT appears to be a safe and effective combination (19). The PROTECT Study is an open label, multicentre , phase II, 9 month trial in patients with predominantly classic or occult subfoveal CNV secondary to AMD. Ranibizumab 0.5mg was administered at baseline within 1 hour of PDT therapy, and then at months 1, 2 and 3. Verteporfin PDT is administered at baseline and then at months 3, 6 and 9. Preliminary results suggest that same day administration of ranibizumab and lucentis did not reveal any new safety concerns and visual acuity findings appear similar to monthly ranibizumab monotherapy with significantly lower re-treatment rates (20).

7.3 Safety of Ranibizumab.

First year safety results from the MARINA trial indicate that patients treated with repeated ranibizumab injections have a low rate of serious ocular adverse events including endophthalmitis, uveitis, retinal detachment, retinal tear, vitreous haemorrhage, and lens damage (<1% each). No notable imbalance in non-ocular adverse events was observed. 683 patients (95%) commenced the second year of the study and were followed for safety and efficacy outcomes (21).

Recently there have been several reports of cardiovascular adverse events (one MI and one death) following intraocular administration of ranibizumab. While it is difficult to attribute causality, the treating clinicians believed that the temporal association suggested a causal relationship.

7.4 Advantages and disadvantages of ranibizumab.

The main advantages of ranibizumab are its lack of selectivity and broad use in all lesion subtypes of wet AMD and its safety profile. In terms of visual outcome, it is clearly superior to pegaptanib as patients receiving ranibizumab showed an overall improvement in mean visual acuity whereas with the former, there was a mean reduction in vision from baseline.

By far the most important disadvantage is that the standard dosing regime consists of monthly intravitreal injections. Clinical trial data suggest that increasing the treatment interval or stopping therapy at the end of year 1, would compromise the impressive visual outcomes seen in ANCHOR and MARINA New dosing regimes with less frequent injections and combination treatments are being investigated but these data are unlikely to be in the public domain before 2008..

8. Professional Opinion in the UK – The Medical Retina Group.

The Medical Retina Group is a forum for medical retina specialists that meets annually as a satellite meeting to the Oxford Congress. This year over 150 delegates registered making it the most representative body of medical retina consultants in the UK. In the past the Medical Retina Group was responsible for coordinating and running the SERNIP database on PDT before the VPDT Study was set up, and has been responsible for discussing and testing guidelines on the diagnosis and management of diabetic retinopathy and various retinovascular diseases.

The meeting in July 2006 was themed to discuss the role and introduction of anti-VEGF agents into the NHS. As part of this a post-meeting survey has been conducted to gauge current attitudes amongst UK Medical Retina Specialists. Several questions were put to members regarding anti-VEGF agents (see below).

1. Do you believe that the evidence from the ANCHOR and MARINA trials is sufficient to support Ranibizumab being made available for all patients with neovascular AMD meeting the clinical trial inclusion criteria?

Yes 27 No 1 Unsure 3

2. Do you believe that the evidence from the ANCHOR and MARINA trials is sufficient to support Ranibizumab being made available on the NHS for all patients with CNV?

Yes 18 No 6 Unsure 6

3. Bevacizumab is unlikely to ever receive a licence for ocular use. Do you believe that the use of bevacizumab off label is justified in patients with CNV now?

Yes 26 No 1 Unsure 3

4. Do you believe that the use of bevacizumab off label will be justified in patients with CNV before NICE guidance is issued but after Ranibizumab is licenced?

Yes 21 No 4 Unsure 4

5. Do you believe that the use of bevacizumab off label will be justified in patients with CNV after NICE guidance is published on ranibizumab?

Yes 11 No 11 Unsure 8

Comment

Although only a small number of participants have so far replied to our questionnaire, we believe that due to the time constraints of the submission they are worthy of inclusion and that they are in fact representative of the meeting as a whole.

<u>The overwhelming response from the meeting is that medical retina consultants wished to see anti-VEGF agents introduced for NHS use as soon as possible.</u>

9. Implementation in the NHS

The current hub and spoke model for the PDT service in the NHS was created so that each PDT treating centre would serve a population of approximately 1 million, with patients attending the hub unit every 3 months for PDT treatment. This model will need to be modified for the following reasons.

1. The numbers eligible for treatment with anti-VEGF agents will include minimally classic and occult lesions, which are currently not treated by PDT in the NHS.
2. Assuming that PDT treatment with verteporfin is used for 100% classic and predominantly classic subfoveal lesions this only accounts for approximately 45% of patients. The remaining lesions, minimally classic and progressing occult will account for an additional 55% of patients attending in addition to the PDT clinics. The new workload for the hub units if all treatment is continued there will be the existing PDT workload plus 55/45 x 2-3 (depending on frequency of visit), which will equate to an approximate tripling of existing clinics to provide a wet AMD service. The existing hub units may not be able to provide all these clinical services.
3. Patients receiving ranibizumab and pegaptanib will require 4 weekly and 6 weekly visits respectively and it may not be feasible to ask these patients to travel long distances for repeat treatments at these intervals.
4. It is likely that most patients in the future will be treated with a combination of PDT and anti-VEGF and this may allow less treatment revisits. However if this is the case the central hub unit offering PDT will need to remain, although the hub units may need to take on an enhanced role, particularly in rural areas.

9.1 Proposed Model for the NHS.

This will require considerable thought and planning if NHS units are to meet the expected increased workload. Planning for these services should start as soon as possible so that hub and spoke units can develop their infrastructure. However it is difficult to be too detailed at present until guidance on the indications for treatment , the frequency of treatment and the recommendations for stopping treatment are in place. The Royal College of Ophthalmologists will expect to play the leading role in developing these.

9.2 Additional Resources.

To provide this service greater personnel resources will need to be provided at both hub and spoke units.
Ophthalmologists
Specialist nurses
Optometrists
Imaging technicians
Technician for OCT
Data collection clerks
Administration staff

The injections will need to be performed by staff familiar with and capable of treating the rare but serious complications that can arise from such injections. This in particular will include the ability to manage an anterior chamber paracentesis (the

release of aqueous humour from the anterior chamber) which may need to be done in an emergency if the intraocular pressure becomes elevated after the injection and occludes the central retinal artery. In practice this will mean that these injections will need to be performed by experienced ophthalmologists.

9.3 Capital Investment.

A clean environment is required to give intravitreal injections and guidelines being prepared by the Royal College of Ophthalmologists will be instructive for units wishing to set up these services. In general terms the facility used may be an operating theatre or a special clean room facility in the outpatient clinic. It is estimated that for a typical NHS Ophthalmology Unit serving a cluster of PCOs of 300,000 population 2-3 injection lists will be required per week.

9.4 Retinal Imaging

Fluorescein angiography services will need to be enhanced at the spoke units. OCT may allow the requirement for fundus fluorescein angiograms (FFA) to be reduced and is quicker and non-invasive compared to FFA. Most spoke units do not currently have this facility.

9.5 Education and Training

Staff at both the hub and spoke units will require additional specialised training. In particular this will include OCT scan acquisition and interpretation and injection technique.

9.6 Surveillance register

The frequency of adverse events associated with intravitreal antiVEGF therapy in routine clinical practice is unknown. Patients recruited into the RCTs for licensing purposes were a selected group excluding those with intercurrent severe medical illnesses. Therefore an adverse event registry is required. This should be a requirement of all treating centres. A minimum dataset might include the following: date, NHS number, visual acuity, diagnosis, treatment administered, ocular adverse event, systemic adverse event, did not attend including reason. This should be linked to national datasets on death to allow for an early warning for any unexpected increase in adverse events. A baseline FFA should be submitted to the register and subsequently graded for lesion characteristics and diagnosis.

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11. Appendix .

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