National Institute for Health and Clinical Excellence

Ranibizumab and pegaptanib for the treatment of age-related macular degeneration

Comments provided by Jenny Nosek and Sandy Taylor on behalf of the Royal College of Nursing Ophthalmic Nursing Forum

Introduction

With a membership of over 390,000 registered nurses, midwives, health visitors, nursing students, health care assistants and nurse cadets, the Royal College of Nursing (RCN) is the voice of nursing across the UK and the largest professional union of nursing staff in the world. The RCN promotes patient and nursing interests on a wide range of issues by working closely with Government, the UK parliaments and other national and European political institutions, trade unions, professional bodies and voluntary organisations. Thank you for the opportunity to comment on the review of this guidance.

The Royal College of Nursing welcomes the opportunity to submit evidence to inform the appraisal of the use of ranibizumab and pegaptanib for the treatment of age-related macular degeneration.

Background

'The eye is the window of the human body through which it feels its way and enjoys the beauty of the world. Owing to the eye the soul is content to stay in its bodily prison, for without it such bodily prison is torture'. Leonardo da Vinici (1452-1519)

This may be a poetic way to start a formal document, but one we believe appropriate when discussing a sight threatening eye disease such as age-related macular degeneration (AMD).

AMD can 'imprison' the sufferer', it causes progressive, irreversible loss of central vision with resulting profound visual disability. Patients have difficulty with many everyday activities important for independent living, including reading, recognising faces, handling money and driving. Quality of life is worse with AMD than with other eye diseases affecting a similar

population (glaucoma, cataract, diabetic retinopathy) and levels of emotional distress are as high as for patients with AIDS or cancer (Barker et al 1998, Williams 1998, Liams,1998).

Patients may suffer with neovascular 'wet' or atrophic 'dry' AMD. Wet AMD is associated with the growth of abnormal blood vessels under the retina (choroidal neovascularization (CNV). The disease forms a scar by which time there is profound irreversible loss of central vision. This is the most aggressive form of AMD in terms of both rate of progression and degree of loss of vision and is responsible for 90% of the severe visual disability associated with AMD (Bressler 1988)

Despite advances in recent years with the introduction of Photodynamic therapy (PDT) and the 'National eye care pathway' (DOH 2004), the 'Ophthalmic Specialist Nurses Forum' members report a continuing geographical diversity in provision of care both for access to treatment and visual rehabilitation, due to a lack of NHS resources.

This may some what be due to restrictions imposed by NICE guidance (2003). The guidance limited the provision of PDT to wet AMD lesions confirmed on fluorescien in angiography (FFA) to have 'classic with no occult subfoveal choroidal neovascularisation (CNV), and best-corrected visual acuity of 6/60 or better. Only Retinal specialists with expertise in the use of this technology should carry out PDT.

PDT was 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. No recommendation was made with regard to the use of PDT for occult CNV associated with wet age-related macular degeneration as there was no licensed for this indication when this appraisal began. Therefore, within the NHS if one is to reflect on the epidemiology presented by Owen (2003) there is still an unmet need for approximately 50% of this cohort of AMD suffers.

In addition there are currently only 52 designated NHS provider centres that have been identified and are submitting data to the Verteporfrin Photodynamic therapy Study (VPDT Users Group Newsletter July 2006), a national study that resulted as a recommendation of NICE (2003). There is growing concern amongst nurses that the long distances that some of their patients have to travel to reach these centres is unacceptable and needs addressing in this review.

The only other evidence based treatment in current NHS use for wet AMD is Laser photocoagulation However; it is not widely used due to its limitations. The Macular

Photocoagulation Study (MPS) group showed that it can delay loss of visual acuity, only in a small proportion of patients who meet strict eligibility criteria (MPSG 1982; MPSG 1994).

Dry AMD usually develops slowly, often over years, and there is as yet no medical or surgical treatment, although there is evidence suggesting that food supplements containing vitamins, minerals and carotenoids such as lutein, zeaxanthin and beta-carotene can help slow the progression of AMD (AREDS Research Group 2001; Richer *et al* 2004) For the majority of patients this means the only option is visual rehabilitation including provision of low vision aids, training and coping strategies. The majority of eye units work closely with local optometrists and social services, to provide this care.

Loss of vision, a poor visual prognosis and fears of a loss of independence can be highly stressful for patients and their families. Coming to terms with chronic visual disability is a depressing and arduous process. Explaining the management of AMD requires patience and sympathy. Clinicians in particular, our nursing members, provide emotional support and reassurance to patients through careful patient education and encouraging links with patient support groups.

Again this is another area that needs careful consideration when addressing 'resource issues' within the scope of new treatment modalities. It is expected that the time taken to counsel patients and explain treatment options will increase.

What is the place of the technology in current practice?

The evidence reviewed on the two new agents in question:

Pegaptanib (Macugen, Pfizer Ltd) an oligonucleotide that binds vascular endothelial growth factor (VEGF 165) inhibiting its activity. VEGF 165 is the isoform of VEGF that is thought to preferentially involve choroidal neovascularisation.

The main body of evidence is from the V.I.S.I.O.N Study (Gragoudas et al 2004) Patients were recruited from all subgroups of Wet AMD whose vision ranged from 20/40 to 20/240 in the study eye and 20/800 or better in the fellow eye. Patients with minimal classic or occult lesions needed to demonstrate recent progression in the disease.

In this study, patients received either intravitreal pegaptanib sodium (0.3 mg, 1 mg, 3 mg) or sham injections every 6 weeks for 54 weeks. Those initially assigned to pegaptanib were re-randomized (1:1) to continue or discontinue therapy for 48 more weeks. The study demonstrated that intravitreal injection was well accepted by both patients and physicians. In the first year of the study, patients received a mean of 8.5 out of 9 injections across all treatment groups.

Pegaptanib responder rates (loss of 15 letters of visual acuity) were 76% and 80% in treatment Groups 1 and 2 versus 50% and 57% for sham group Groups 1 and 2 (*P* 0.03 and *P* 0.05), respectively. On reflection this is approximately the clinical effectiveness profile of the current NHS treatment PDT (TAP study group 2001)

The most common ocular adverse events were transient, mild to moderate in intensity, and attributed to the injection preparation and procedure. The safety data improved in the second year of the study with no reported cases of endophthalmitis. The reported 0.16% of endophthalmitis in year one was attributed to violations of the injection preparation protocol.

Ranibizumab (Lucentis, Genentech/Novartis Pharmaceuticals Ltd.) a humanised therapeutic antibody fragment designed to bind to and inhibit VEGF-A.
The two main studies informing our evidence base on ranibizumab are the 'ANCHOR 'and 'MARINA' studies.

The ANCHOR study is an ongoing two year phase 3, study comparing two different doses of ranibizumab to verteporfin photodynamic therapy (PDT) in 423 patients with predominantly classic wet AMD. Approximately 94 percent of patients treated with 0.3 mg of ranibizumab and 96 percent of those treated with 0.5 mg of ranibizumab maintained or improved vision (defined as a loss of les than 15 letters in visual acuity) compared to approximately 64 percent of those treated with PDT. Data from the ANCHOR study also showed a difference in mean change in visual acuity of 18 letters for patients treated with 0.3 mg of ranibizumab and 21 letters for patients treated with 0.5 mg of ranibizumab from study entry compared to those treated with PDT at 12 months. In the first year of this two-year study, patients treated with ranibizumab gained an average of 8.5 letters in the 0.3 mg dose group and 11 letters in the 0.5 mg dose group compared to patients treated with PDT, who lost an average of 9.5 letters (Brown et al 2006)

The MARINA study is also a Phase III clinical study of 716 patients with the subgroup minimally classic or occult lesions (Miller 2006). The results show that, at 12 months, approximately 95 percent of patients treated with ranibizumab maintained or improved vision (defined as a loss of less than 15 letters in visual acuity on the Early Treatment of Diabetic Retinopathy (ETDRS) chart, regardless of whether they received 0.3 mg (94.5 percent, 226/238) or 0.5 mg (94.6 percent, 225/240) of ranibizumab, compared with 62.2 percent (148/238) of those in the sham control group (p0.0001) Vision improved by more than 15 letters in 24.8 percent (59/238) of patients treated with 0.3 mg of ranibizumab and 33.8 percent (81/240) of patients treated with 0.5 mg compared to approximately 4.6 percent (11/238) of patients in the control group (p 0.0001).

Potentially in ranibizumab, we have a treatment which has been shown to improve vision in all

subgroups but additionally in a subgroup of patients that are not currently eligible to receive treatment under current NHS guidance which is a very exciting prospect.

None of these studies have defined the optimum treatment regime required for implementation into daily clinical practice but an open labelled multicenter study PROTECT (Schmidt 2006) reports that combination of same day ranibizumab and PDT appears to be as effective as ranibizumab monotherapy with significantly lower re-treatment rates.

This approach of combination therapy reduces the number of visits thus the burden on the NHS, yet delivering the visual benefits and would certainly be a very favourable model for the NHS to adopt.

Additional information relating to quality of life

As previously discussed, AMD can have profound effects on the patient's quality of life and is a major concern to nurses. Nurses are often the ones that have to support patients and carers in the traumatic time following referral and diagnosis. Fagerstrom (1992) has demonstrated that impairment of vision in older people (71 to 76 years) affects their ability to concentrate on tasks of memory and learning, due to a continuous sense of abnormalness, thus leading to further social isolation.

Quality of life is often difficult to measure, so any methodology that quantifies the patient's view of a disease and its effect on quality-of-life must be taken into consideration to complete the assessment of treatment effectiveness.

In the ANCHOR and MARINA trials, the US National Eye Institute VFQ-25 questionnaire was used to record vision-related function and the impact of vision-related problems on patient quality-of-life. The VFQ-25 was developed more than 6 years ago from the VFQ-51 questionnaire (Mangione CM,et al,1999). The questionnaire has 12 subsections and consists of 25 questions. Subsections are: General vision; near activities; distance activities; driving; peripheral vision; colour vision; ocular pain; vision-specific role difficulties; vision-specific dependency; vision-specific social function; vision-specific mental health; and general health. It has good internal consistency and test-retest reliability and therefore is an excellent tool to use in this cohort of patients.

The clinical relevance of visual function is related to the effect of visual acuity on the ability to undertake vision-related activities. With near-normal vision, patients may have difficulty reading printed materials and require stronger reading lenses, and there may be some restrictions on driving. With moderate to low vision, patients may have difficulty reading large printed pages and have their driving licences restricted.

With 20 / 200 vision, or legal blindness, patients suffering with AMD may have extreme difficulty identifying facial features or reading road signs, they read more slowly than normal, and listen to the news on the radio rather than read it in newspapers. Once they reach profound low vision, patients experience a number of activity limitations around reading, having to rely on others to complete everyday activities.

Clinical trials of patients treated with ranibizumab showed in both studies that there was a statistically significant improvement in near and distance vision which is the first time in any AMD study that we have this clinically meaningful finding (Chang et al 2006)

Another outcome measure that has not previously been discussed in this paper, but ultimately affects the quality of life of these patients, is the residual scaring left on resolution of the disease process. When the macular scotoma affects the fovea, the visual system uses 1 or more preferred retinal loci (PRLs) as a "pseudofovea" to perform visual tasks. (Schuhard R, 2005)

Generally, in the low-vision population with central scotomas, there is no consistent retinal location relative to the scotoma for the PRLs so the size of the scotoma will have an effect on the patient's ability to adapt to directing the eye towards the visual target, which is a requirement to perform even simple tasks of every day activities of living.

It is with interest that we read that Wagner et al (2006) found that at day 90, in ranibizumab treated patients with predominantly classic CNV, absolute scotoma did not increase in any eye. Severe relative scotoma improved or remained stable in 80% and mild relative scotoma improved or stabilized in 60%. In general, pre-existing scotomas became less intensive. Areas of normal macular function decreased in 0%, i.e. no loss in retinal sensitivity occurred in normal retina by combination therapy. In patients with occult CNV, absolute scotoma decreased or remained stable in 83%. Severe relative scotoma also decreased or remained stable in 83% and mild relative scotoma had increased in 50% of patients. Areas of normal macular function improved or stabilized in 83%. One can assume that for AMD patients this will enhance their ability in relation to visual rehabilitation and possibly preserve their dignity and independence.

Implementation issues

Work load

The introduction of anti-VegF intravitreal treatments will be a challenge for current PDT centres, but one they will rise to, given adequate support. The workload will inevitably double as only patients with predominantly classic lesions are currently receiving treatment and

mindful that some patients may receive up to 17 anti-VegF treatments over two years if used as a mono therapy.

It is reported from one eye unit in a district general hospital providing a fast track macular and PDT service, that the unit will be unable to sustain an AMD service that requires patients to attend possibly every four weeks for intravitreal therapy, unless additional staff are employed. (J.Nosek, Specialist Retinal Nurse, personnel communication 2006)

It is also anticipated that time for consultation will need to increase as giving patient information with regards to what is available for them can be a long and complex discussion.

Reducing risk of complications

The literature highlighted that there is an increased risk of endophthalmitis. This will mean that additional theatre lists or 'clean minor procedure rooms' need to be made available to cope with the demand. Capital investment costs need to be 'ring fenced' to develop the infra structure, as most units do not have the current theatre capacity to accommodate additional lists. The general feeling amongst clinicians is to adapt an out patient consulting room to meet infection control standards for this type of procedure. This will also make the patient flow more stream-lined at the point of need.

Nurses will also need to spend additional clinical time educating patients on the signs of infection and Increased IOP and as best practice currently recommends phoning the patients three days after the procedure to check on their progress and the comfort of the eye.

Patient acceptability

The future promises a number of therapeutic options in the treatment of Wet AMD. As the patient's advocate, nurses will be keen to see that all available treatment options are available on the NHS so that the patient and their carers can engage in the most acceptable option both from an effective and social perspective. We know from the evidence that anti-vegF therapies were well tolerated, but there may be social and health reasons why a patient does not opt for this mode of treatment. One factor which must be considered by the NICE appraisal committee, and has been previously mentioned, is the distance some patients have to travel to current PDT centers.

It is possible that the prospect of enduring long journeys more frequently for intravitreal injections may dissuade patients from choosing what could be the most effective treatment option.

Therefore we would encourage a wider distribution of treatment centers providing some, if not all of the patient's treatment pathway. This will also go a long way to easing the burden on existing PDT centers and offering a more local service to our elderly population.

Staff Training

As with any new treatment there will be the inevitable learning curve for all involved. Training around administration of intravitreal injections may be required for staff supporting the experienced ophthalmologist in preparing the room, instruments and the patient's eye prior to the injection to ensure a smooth flow and best use of man power.

Changes in use of imaging technology such as the increased use of Optical Coherence Tomography (OCT) is also a training consideration. Technicians may need to develop enhanced skills to ensure they provide the retinal specialist with optimal images.

Summary

There is clearly good clinical evidence that the anti-VegF drugs in question, in particular ranibizumab, have a beneficial effect on visual function. Thus, they have the potential not only to preserve vision and independence in patients with wet AMD but in some cases improve it.

The Royal College of Nursing urges the NICE appraisal team to recommend that anti-VegF treatment be made available on NHS for all Wet AMD patients. It also requests that the appraisal committee advices funding bodies to make financial provision that will enable current PDT units and other eye units with retinal expertise to expand and provide AMD services for their locality.

The appraisal committee can be reassured that over the past few years, ophthalmic nurses along side their Retinal Specialist colleagues, have endeavoured to implement the recommendations of the NICE, despite what in hindsight was an unrealistic expectation requesting that every patient with subfoveal predominantly classic WET AMD should be recruited into a national study. Should NICE report that both therapies are cost-effective, we hope that a national study would not be required as this would divert resources required for study administration away from front-line clinical care.

We look forward to the future and the opportunity that this new treatment modality will offer to improve the quality of care for AMD sufferers. We hope the recommendations of this appraisal committee gives greater freedom to the clinical experts that have the knowledge and skills to make appropriate decisions.

References:

Age-Related Eye Disease Study Research Group (2001) A randomizied, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no.8. Arch Ophthalmol. 119: 1417-1436.

Alexander LJ. (1993) Age-related macular degeneration: the current understanding of the status of clinicopathology, diagnosis and management. J Am Optom Assoc; 64; 822-837.

Baker M, Winyard S (1998) Lost Vision: Older visually impaired people in the UK. RNIB.

Bressler NM, Bressler SB, Fine SL (1998). Age-related macular degeneration. Surv Ophthalmol; 32: 375-413.

Brown D, Shapiro H ,Schneider S and ANCHOR Study Group (2006) Subgroup Analysis of First–Year Results of ANCHOR: A Phase III, Double–Masked, Randomized Comparison of Ranibizumab and Verteporfin Photodynamic Therapy for Predominantly Classic Choroidal Neovascularization Related to Age–Related Macular Degeneration. Invest Ophthalmol Vis Sci 47: E-Abstract 2963

Department of Health (2004) National Eye Care Pathway. www.dh.gov.uk/policy

Chang T, Fine J, Bressler N (2006) Self reported vision-specific quality of life at 1 year in patients with neovascular age-related macular degeneration in phase 2 phase1ii randomised trails of Ranibizumab. Invest Ophthalmol Vis Sci 2006;47: E-Abstract 5252.

Fagerstrom, R. (1992) "Correlations of memory and learning with vision in aged patients before and after a cataract operation", Psychological Reports, 1992, 71, 675-686).

Gragoudas ES, Adamis AP, Cunningham ET Jr, Feinsod M,Guyer DR (2004) VEGF Inhibition Study in Ocular Neovascularisation Clinical Trial Group. Pegaptanib for Neovascular Age-Related Macular Degeneration. N England J Med; 351(27) :2805-16

Mangione CM,Lee PP,Gutierrez PR,et al (1999) Development of the 25-Item national eye Institute visual function questionnaire.

Macular Photocoagulation Study Group (1982) Argon laser photocoagulation for senile macular degeneration. Results of a randomized clinical trial. Arch Opthalmol; 100: 912-918.

Miller J. W, Shapiro H, Acharya N and for the MARINA Study Group (2006) Randomized, Controlled Phase III Study of Ranibizumab (Lucentis) for Minimally Classic or Occult Neovascular Age–Related Macular Degeneration: Two–Year Safety Results of the MARINA Study. Invest Ophthalmol Vis Sci:47: E-Abstract 3539.

MPSG Macular Photocoagulation Study Group(1994) Laser photocoagulation for juxtafoveal choroidal neovascularization. Five-year results from randomized clinical trials. Macular Photocoagulation Study Group, Archives of -Ophthalmology, Apr; 112(4): 500-9.

Nice technology appraisal 68 (2003) Guidance on the use of photodynamic therapy for age-related macular degeneration.

Owen C et al (2003) How big is the burden of visual loss caused by age related macular degeneration in the United Kingdom? Br J Ophthalmology 87:312-317

Richer S et al (2004) Double-masked, placebo-controlled, randomized trial of lutein and antioxidant supplementation in the intervention of atrophic age-related macular degeneration: the Veterans LAST study (Lutein Antioxidant Supplementation Trial). Optometry. 75(4): 216-30.

Schmidt-Erfurth U.M, Gabel P, Hohman T, and PROTECT Study Group (2006) Preliminary results from an open-label, mulicentre, phase II Study Assessing the effects of same-day administration of ranibizumab and verteporfin PDT (PROTECT Study). Invest Ophthalmol Vis Sci; 47: E-Abstract 2960

Schuhard R (2005) Preferred retinal loci and macular scotoma characteristics in patients with age-related macular degeneration Can J Ophthalmology; 40:303–12

Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group (2001) Photodynamic therapy of subfoveal choroidal neovascularisation in age-related macular degeneration with verteporfin. Two-year results of 2 randomized clinical trials – TAP Report 2. Arch Ophthalmol. 119: 198-207.

Vingerling JR et al (1995) Epidemiology of age-related maculopathy. Epidemiol Rev. 17: 347-60.

VPDT Newsletter March 2006 -http://www.lshtm.ac.uk/hsru/vpdt

Wagner J, et al (2006) changes in functional mapping in patients with neovascular Age-related macular degeneration receiving combination of verteporfin and Randibizumab therapy Invest Ophthalmol Vis Sci 2006;47: E-Abstract 363

Liams RA et al (1998) The psychosocial impact of macular degeneration. Arch Ophthalmol. 116(4): 514-20.