

Ranibizumab and pegaptanib for the treatment of age-related macular degeneration: a systematic review and economic evaluation

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Executive summary

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Executive summary

Background

Age-related macular degeneration (AMD) causes loss of central vision and is one of the leading causes of irreversible sight loss among adults registered blind. The decrease in vision is associated with a loss of independence, an increased risk of depression, falls and fractures and a decrease in health-related quality of life. There are different types of AMD, which have different manifestations, prognoses and treatment strategies. Neovascular or wet AMD has a more variable course than other types and can progress much more quickly. Neovascular AMD is due to choroidal neovascularisation (CNV), which can be subdivided into different disease types according to its appearance on fluorescein angiography: 100% classic, predominantly classic (>50% classic), minimally classic (<50% classic) or occult with no classic. AMD lesions can also be classified according to where they occur in relation to the fovea: subfoveal, juxtafoveal or extrafoveal. Geographic atrophy (or dry AMD) is associated with gradual, progressive loss of visual function, and is not considered in this report.

Treatment options for AMD are limited. Photocoagulation therapy may be used for those with extrafoveal CNV, but only a small proportion of patients have extrafoveal lesions. Photodynamic therapy (PDT) with verteporfin has been recommended by the National Institute for Health and Clinical Excellence (NICE) for those with classic no occult subfoveal CNV and may be used in patients with predominantly classic lesions as part of clinical studies. Although these treatments may be effective in treating established lesions, they do not prevent new CNV formation and are limited to certain subgroups of patients. Ranibizumab and pegaptanib aim to alter the progression of vision loss in patients with subfoveal CNV, and may improve vision in some patients.

Objectives

The objectives of the study were to assess the clinical effectiveness and cost-effectiveness of ranibizumab and pegaptanib for subfoveal CNV associated with wet AMD.

Methods

Data sources

Electronic databases, including MEDLINE, EMBASE, The Cochrane Database of Systematic Reviews and 10 others, were searched from inception to September 2006. Bibliographies of included studies and related papers were checked for relevant studies. Experts were contacted for advice and peer review and to identify additional studies. Manufacturers' submissions to NICE were reviewed.

Study selection

Titles and abstracts were screened for eligibility by two reviewers. Inclusion criteria were applied to the full text of selected papers by one reviewer and checked by a second reviewer, with differences resolved through discussion. The inclusion criteria were as follows:

- Patients: subfoveal CNV associated with wet AMD.
- Interventions: ranibizumab, pegaptanib, combinations of these with photodynamic therapy where the licensed indication allows.
- Comparators: best supportive care, photodynamic therapy with verteporfin for the subgroup with classic no occult lesions. If insufficient evidence was found using these comparators, sham injection was to be included for all subgroups, and photodynamic therapy with verteporfin was to be included for the subgroup with predominantly classic lesions.
- Outcomes: visual acuity, contrast sensitivity, adverse effects, adherence to treatment, health-related quality of life, costs, cost per quality-adjusted life-year (QALY).
- Types of studies: randomised controlled trials (RCTs), systematic reviews and meta-analyses of RCTs, economic evaluations. Abstracts were considered if sufficient information was presented. Non-English language studies were excluded.

Data extraction and quality assessment

Data extraction and quality assessment were undertaken by one reviewer and checked by a second, with differences resolved through discussion. The quality of included studies was

assessed using criteria by the NHS Centre for Reviews and Dissemination (CRD).

Data synthesis

The clinical effectiveness data were synthesised through a narrative review with full tabulation of results. Meta-analysis was not undertaken due to differences in study populations and comparators.

Cost-effectiveness

A model was developed to estimate the cost-effectiveness of ranibizumab and of pegaptanib (separately), compared with current practice or best supportive care, from the perspective of the NHS and Personal Social Services. Two time horizons were adopted for each model. The first adopted time horizons determined by the available trial data. The second analysis extrapolated effects of treatment beyond the clinical trials, adopting a time horizon of 10 years.

The proportions of patients gaining and losing visual acuity reported in the clinical trials were converted to 3-month transition probabilities in the model and combined with published estimates of health state utilities to estimate the QALYs associated with each intervention.

Costs included in the model were drug costs, drug administration and patient monitoring while on treatment and management of treatment-related adverse events. Since the cost-effectiveness analysis adopted an NHS and Personal Social Services perspective, costs of services provided to people with visual impairment were included in the model.

Results

Number and quality of studies

The systematic review identified 266 citations, of which 28 were retrieved in full for further inspection. Subsequently, 23 were excluded from the review as they did not meet the inclusion criteria. The combined analysis of two RCTs of pegaptanib [0.3 mg (licensed dose), 1.0 mg and 3.0 mg] versus sham injection in patients with all lesion types was reported by three publications (the VISION study). Three published RCTs of ranibizumab were identified (MARINA, ANCHOR, FOCUS), and an additional unpublished RCT was provided by the manufacturer (PIER). The ranibizumab trials compared:

- 0.3 and 0.5 mg ranibizumab versus sham injection in patients with minimally classic or occult lesions (MARINA)

- 0.3 and 0.5 mg ranibizumab versus PDT with verteporfin in patients with predominantly classic lesions (ANCHOR)
- a reduced dose frequency regimen of 0.3 and 0.5 mg ranibizumab versus sham injection in patients with any lesion type (PIER, unpublished)
- 0.5 mg ranibizumab plus PDT versus PDT plus sham injection in patients with predominantly classic lesions (FOCUS).

The quality of reporting in the trials was generally good.

Summary of benefits and harms

Pegaptanib

- *Visual acuity.* Statistically significantly more pegaptanib patients (0.3 mg: 70% of patients; 1.0 mg: 71% of patients; 3.0 mg: 65% of patients) lost less than 15 letters of visual acuity at 12 months than sham injection patients (55% of patients). Doses of 0.3 or 1.0 mg also showed statistically significant improvements in all secondary measures of visual acuity, but the 3.0-mg dose was not consistent in producing a statistically significant difference. The proportion of patients gaining 15 letters or more was statistically significantly greater in the 0.3-mg (6%, $p = 0.04$) and the 1.0-mg group (7%, $p = 0.02$), but not the 3.0-mg group (4%, $p = 0.16$) compared with the sham injection group (2%). A gain of 15 letters in visual acuity is a clinically important outcome and would have a significant impact on quality of life. Pegaptanib patients lost statistically significantly fewer letters after 12 months of treatment than the sham group [mean letters lost: 7.5 (0.3 mg), 6.5 (1.0 mg) or 10 (3.0 mg) vs 14.5 (sham)].
- *Legal blindness.* Significantly fewer pegaptanib patients deteriorated to legal blindness [38% (0.3 mg), 43% (1.0 mg), 44% (3.0 mg) versus 56% (sham), $p < 0.001$].
- *Adverse events.* Most adverse events were mild to moderate transient events. Endophthalmitis was experienced by 1.3% of patients receiving pegaptanib in the first year.

Ranibizumab

- *Visual acuity.* Significantly more patients receiving ranibizumab (0.3 mg: 94.3–94.5%; 0.5 mg: 94.6–96.4%) lost less than 15 letters of visual acuity after 12 months compared with sham injection (62.2%, $p < 0.0001$) or PDT (64.3%, $p < 0.0001$). A 0.5-mg dose of ranibizumab plus PDT significantly increased the proportion losing less than 15 letters compared with PDT plus sham injection (90.5 versus 67.9%, $p < 0.001$) ►

in patients with predominantly or minimally classic lesions. The proportion of patients gaining 15 letters or more of visual acuity was statistically significantly higher in the ranibizumab groups (MARINA and ANCHOR, 0.3 mg: 24.8 and 35.7%; 0.5 mg: 33.8 and 40.3%, respectively) compared with sham injection (4.6%, $p < 0.0001$) or PDT (5.6%, $p < 0.0001$). This was also statistically significant for patients receiving 0.5 mg ranibizumab plus PDT compared with PDT plus sham injection (23.8 versus 5.4%, $p = 0.003$). In the MARINA and ANCHOR trials, ranibizumab patients gained letters of visual acuity at 12 months whereas patients with sham injection or PDT lost about 10 letters ($p < 0.001$). In the PIER study, patients lost on average 0.2 letters (0.5 mg) compared with a loss of 16.3 letters in the sham injection group ($p < 0.0001$).

- **Legal blindness.** Significantly fewer patients receiving ranibizumab deteriorated to legal blindness (MARINA and ANCHOR, 0.3 mg: 12.2 and 22.1%; 5 mg: 11.7 and 16.4%, respectively) versus sham injection (42.9%) or PDT (60.1%), $p < 0.0001$. Similarly, fewer patients receiving 0.5 mg ranibizumab plus PDT deteriorated to legal blindness compared with PDT plus sham injection (29.5 versus 46.4%, $p = 0.006$).
- **Adverse events.** Adverse events were common but most were mild to moderate. Endophthalmitis was reported by very few patients in the active treatment arms of the ranibizumab trials and none in the control arms.

Summary of costs

Drug acquisition costs for 1 year of treatment were estimated as £4626 for pegaptanib and £9134 for ranibizumab. Non-drug treatment costs (for administering injections and also patient monitoring while on treatment) accounted for an additional £2614 for pegaptanib (36% of total treatment costs) and £3120 for ranibizumab (25% of total treatment costs).

Further costs are associated with the management of injection-related adverse events – although the proportion of injections associated with adverse events is low, costs of managing each event range from £1200 to £2100. Injection-related adverse events are also associated with significant risks of severe loss of visual acuity.

Summary of cost-effectiveness

The incremental cost-effectiveness ratio (ICER) for pegaptanib compared with usual care in the short-term model is £163,603. This high ICER arises

due to a relatively small QALY gain at 2 years and because treatment costs are realised in the first 2 years. The QALY gain is greater in the long-term model. By this stage, costs of services for visual impairment comprise the largest proportion of total costs, and although the difference in these costs between the pegaptanib-treated and usual care cohorts is not large enough to offset treatment costs fully, the ICER is reduced to £30,986.

For ranibizumab we undertook separate analyses for patients with predominantly classic lesions and for patients with minimally classic and occult no classic lesions. Total costs and the QALYs associated with each intervention were estimated. The incremental cost per QALY gained for ranibizumab against best supportive care, for all lesion types, and against PDT for patients with predominantly classic lesions was estimated.

The ICERs in the trial-based analyses are between £150,000 and approximately £200,000. Again, the high ICER arises due to relatively small QALY gains and treatment costs being concentrated in the first 2 years (with little opportunity to offset these costs by reducing costs of services for visual impairment). The QALY gain at 10 years is larger and incremental costs have reduced (since reduced costs of services for visual impairment in the ranibizumab-treated cohorts have offset some of the costs of treatment). The ICERs reduced to £15,638 for the comparison with PDT and £11,412 for the comparison with best supportive care. The ICER for patients with minimally classic and occult no classic lesions is £25,098 at 10 years.

Sensitivity analyses

Deterministic sensitivity analysis showed that the cost-effectiveness estimates in the base case were sensitive to the model time horizon and visual acuity of the cohort at baseline. Cost-effectiveness estimates were also sensitive to assumptions over post-treatment effects (with the ICER for pegaptanib reducing to £26,896 if the post-treatment effect was included in the model only for the year after treatment ceased and to £20,467 if the effect was assumed to persist for the patient's lifetime).

The cost-effectiveness estimates were particularly sensitive to assumptions over the cost of services for visual impairment and the uptake of these services. Using extreme values produced a situation where treatment with pegaptanib or ranibizumab was cost saving over a 10-year time ►

horizon (assuming high cost and high uptake) or alternatively could be associated with a 30–70% increase over the base case estimate for incremental cost (assuming low cost and low uptake). Further analysis suggested that the cost-effectiveness estimates were most sensitive to assumptions over uptake, estimated as the proportion of eligible cases receiving services.

In a probabilistic sensitivity analysis for pegaptanib, the majority of simulations produced incremental cost-effectiveness estimates that were in the north-east quadrant of the cost-effectiveness map. That is, the majority of simulations were associated with increased QALYs but also increased costs. In this analysis, pegaptanib had a probability of being cost-effective (compared with usual care) of 17% at a willingness to pay threshold of £20,000 per QALY and 58% at a willingness to pay threshold of £30,000 per QALY.

In a probabilistic sensitivity analysis for ranibizumab (conducted separately for lesion types and alternative comparators), the majority of simulations were associated with increased QALYs but also increased costs. Ranibizumab for patients with predominantly classic lesions had a probability of being cost-effective (compared with PDT) of 72% at a willingness to pay threshold of £20,000 per QALY and 97% at a willingness to pay threshold of £30,000 per QALY. The equivalent values for the comparison with best supportive care were 95% at a threshold of £20,000 per QALY and 97% at a threshold of £30,000 per QALY. For patients with minimally classic and occult no classic lesions, the probabilistic sensitivity analysis shows a 15% probability of ranibizumab being cost-effective at a willingness to pay threshold of £20,000 per QALY and 81% at a willingness to pay threshold of £30,000 per QALY.

Conclusions

Patients with AMD of any lesion type benefit from treatment with pegaptanib or ranibizumab on measures of visual acuity when compared with sham injection and/or PDT. Patients who continued treatment with either drug appeared to maintain benefits after 2 years of follow-up. When comparing pegaptanib and ranibizumab, the evidence was less clear due to the lack of direct comparison through head-to-head trials and the lack of opportunity for indirect statistical comparison due to heterogeneity.

The cost-effectiveness analysis showed that the two drugs offered additional benefit over the comparators of usual care and PDT but at increased cost. For pegaptanib compared with usual care, the ICER ranged from £163,603 for the 2-year model to £30,986 for the 10-year model. Similarly, the ICERs for ranibizumab for patients with minimally classic and occult no classic lesions, compared with usual care, ranged from £152,464 for the 2-year model to £25,098 for the 10-year model. The ICER was influenced by the model's time horizon, the patient's baseline visual acuity, the disease-modifying effect of the treatment, whether injections were costed as an outpatient or day case procedure and assumptions over the cost and uptake of services for visual impairment.

Recommendations for further research

Suggested further research priorities are as follows:

- A trial to compare pegaptanib with ranibizumab and bevacizumab as well as the role of verteporfin PDT in combination with these drugs.
- A study to assess adverse events outside the proposed RCTs.
- Studies to determine the optimal dosing regimes of these drugs and the benefits of re-treatment after initial treatment.
- More detailed costing work, for example an independent survey of the costs associated with vision loss.
- Health state utilities and their relationship with visual acuity and contrast sensitivity. Further research is also required to reduce uncertainty over the relationship between duration of vision loss and the quality of life and functional impact of vision loss.
- Studies to assess whether the identification of being genetically at risk will alter behaviour, for example, inspire people to stop smoking.

Publication

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NIHR Health Technology Assessment Programme

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