EXTENDED REPORT

Pegaptanib and ranibizumab for neovascular age-related macular degeneration: a systematic review

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Aims: To assess the clinical effectiveness of pegaptanib sodium and ranibizumab for neovascular age-related macular degeneration (AMD).

Methods: A systematic review of randomised controlled trials (RCTs) identified through searching 12 electronic databases, bibliographies and consultation with experts and manufacturers. RCTs were eligible if they assessed the effects of pegaptanib or ranibizumab with best supportive care, sham injection or photodynamic therapy (PDT) on patients with subfoveal choroidal neovascularisation associated with wet AMD and examined outcomes including visual acuity and adverse events.

Results: Three RCTs of ranibizumab (MARINA, ANCHOR, FOCUS) and two of pegaptanib (VISION study) met the inclusion criteria. The RCTs included patients with different lesion types. The studies showed statistically significant benefit on different measures of visual acuity for patients receiving pegaptanib, ranibizumab or ranibizumab with PDT compared to control (sham injection, PDT or sham injection with PDT) after 12 months. These differences appeared to be clinically significant. Although adverse events were common among those receiving pegaptanib or ranibizumab, they were considered mild to moderate in nature. Meta-analysis of ranibizumab trials and indirect comparison of the two drugs were not possible due to differences in the study populations' lesion types. However, results from the RCTs of ranibizumab tended to show a greater effect on visual acuity than results from the RCT of pegaptanib.

Conclusions: Pegaptanib and ranibizumab appear to slow or stop the progression of neovascular AMD. Uncertainty remains over the relative benefits of pegaptanib compared with ranibizumab and other unlicensed drugs (eg, Avastin), due to the nature of the evidence. Head-to-head RCTs and economic evaluations comparing these alternatives are needed.

Age-related macular degeneration (AMD) is one of the leading causes of irreversible sight loss among adults registered blind.¹ Some two thirds of people with AMD have the neovascular (or wet) form of the disease, which can progress quickly causing irreversible sight loss within days or weeks. It is thought that there are 250 000 people in the UK with neovascular AMD, with between 25 000 and 30 000 new cases occurring annually.² Treatment options for people with neovascular AMD are limited. Although laser photocoagulation and photodynamic therapy (PDT) with verteporfin could be effective in treating established lesions for specific subgroups of patients, they do not prevent new choroidal neovascularisation (CNV) formation. For most people, management consists of social support, visual rehabilitation and provision of low vision aids.

Two new drugs have recently received marketing authorisation for the treatment of neovascular AMD. Pegaptanib sodium (Macugen, Pfizer, Tadworth, Surrey, UK) is a pegylated modified oligonucleotide that binds with extracellular vascular endothelial growth factor (VEGF165), inhibiting its activity. Ranibizumab (Lucentis, Genentech, CA, USA/Novartis Pharmaceuticals UK, Frimley/Camberley, Surrey, UK) is a humanised therapeutic antibody fragment designed to bind and inhibit vascular endothelial growth factor A (VEGF-A).

The systematic review summarised in this report synthesised the clinical trial evidence for the use of pegaptanib and ranibizumab in the treatment of age-related macular degeneration. The National Institute for Health and Clinical Excellence considered this independent systematic review and other evidence to issue guidance to the health service in England and Wales on treatment for patients with this condition.

MATERIALS AND METHODS

Our systematic review followed accepted principles and procedures.^{3,4} An information scientist developed a search strategy and searched 12 electronic databases from inception to September 2006, including: the Cochrane Database of Systematic Reviews; the Cochrane Central Register of Controlled Trials; Medline (Ovid); Embase (Ovid) and Web of Science ISI Science Citation Index. The full search strategy is available from the authors on request. All searches were restricted to the English language. Additional sources included abstracts from recent ophthalmology conferences (from 2004 to September 2006), bibliographies of retrieved papers, and consultation with experts and manufacturers.

We included RCTs that compared pegaptanib or ranibizumab (or a combination of the drugs with PDT, where appropriate) with best supportive care, sham injection or PDT for the treatment of patients with CNV associated with wet AMD. Studies were included if they assessed measures of visual acuity or adverse effects. The titles and abstracts of studies identified by the search were screened independently by two reviewers, who then retrieved the full text of eligible papers. Predefined inclusion criteria were applied to the retrieved papers by one reviewer, with decisions checked by a second reviewer. Data were extracted using a standard form, and methodological quality and quality of reporting were assessed using recommended standard quality criteria³ by a reviewer, with decisions checked by a second reviewer. Any differences in opinion

Abbreviations: AMD, age-related macular degeneration; CNV, choroidal neovascularisation; PDT, photodynamic therapy; RCT, randomised controlled trials; VEGF, vascular endothelial growth factor

between reviewers were resolved through discussion or consultation with a third reviewer. Clinical effectiveness was assessed through a narrative comparison of different outcomes. It was not appropriate to pool the results of included studies in a meta-analysis, owing to differences in the patient groups and comparator treatments.

RESULTS

Quantity and quality of studies identified

The numbers of studies identified at each stage of the systematic review are shown in fig 1. Five RCTs met the inclusion criteria,^{5–10} with two RCTs assessing pegaptanib,^{5–7} and three RCTs assessing ranibizumab.^{8–10} The key characteristics of these studies are summarised in table 1. The two RCTs assessing pegaptanib were part of the VEGF Inhibition Study in Ocular Neovascularisation (VISION) study. Although the VISION study included three doses of pegaptanib (0.3 mg, 1.0 mg, and 3.0 mg), we focused on evaluating the licensed dose of 0.3 mg at 12⁵ and 24 months.^{6,7} The three RCTs assessing ranibizumab were: the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA)⁸ study; the Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularisation in Age-Related Macular Degeneration (ANCHOR)⁹ study and the FOCUS¹⁰ study. These studies evaluated doses of 0.3 mg^{8,9} and 0.5 mg^{8–10} over 12^{8–10} and 24 months.⁸ As with pegaptanib, we focussed on results for the licensed dose (0.5 mg).

In the VISION study, patients were re-randomised after 12 months to continue, change or discontinue the initial treatment received (table 1). However, patients re-randomised to discontinue pegaptanib or sham injection were able to resume their initial treatment at any point if they had demonstrated benefit in the first 12 months but then lost ten or more letters of visual acuity during the second year. Some 21% of people randomised to discontinue 0.3 mg pegaptanib resumed therapy, compared with 15% of the sham injection group.⁷ For efficacy analyses, these patients were included in their year two re-randomised groups.

The methodological quality and the quality of reporting of the RCTs were judged to be reasonably good (table 2), with only adherence to intention to treat analysis and reporting of withdrawals a concern. MARINA analysed data on an

intention-to-treat basis, but ANCHOR, FOCUS and VISION excluded one or more patients from analyses who did not receive at least one dose of the study drug, or did not have a sufficiently standardised assessment of visual acuity completed at baseline. The rate of withdrawal was approximately half as high in the 0.5 mg ranibizumab arm of the MARINA trial as in the sham injection arm (10.4% versus 20.2%, respectively).⁸ Similarly, the rate of withdrawals was 7.0% in the ANCHOR trial's PDT group but approximately half this in the 0.5 mg ranibizumab group (3.6%).⁹ A slightly higher percentage of ranibizumab and PDT patients than sham injection and PDT patients discontinued treatment in the FOCUS trial (11.3% versus 8.9%).¹⁰ In the VISION study, withdrawals were similar in both treatment arms, reducing the risk of attrition bias.⁵

Visual acuity

Key visual acuity outcomes are reported in table 3.

Loss of fewer than 15 letters

Loss of fewer than 15 letters was the primary outcome measure for all the RCTs. Treatment with pegaptanib or ranibizumab was shown to be statistically significantly more likely to lead to a loss of fewer than 15 letters of visual acuity at 12 months compared to control. Differences in proportions of patients benefiting ranged from 15% for pegaptanib compared to sham injection, to between 22% and 32% for ranibizumab or ranibizumab plus PDT compared with sham injection or sham injection plus PDT. The benefit of ranibizumab over sham injection was maintained at 24 months, with over 37% more patients losing less than 15 letters from baseline. Comparisons at 24 months in the VISION study were limited due to the re-randomisation of patients after 12 months (table 1). However, similar data are available for those patients who were re-randomised into the same groups in the second year.

In the VISION study, reduction in the proportion of patients losing less than 15 letters ranged from 3% for 0.3 mg pegaptanib and 19% for the sham injection or usual care group in one RCT (study 1004), to 12% for 0.3 mg pegaptanib and 9% for the sham injection or usual care in the other RCT (study 1003).⁷ The paper did not report whether or not the difference between the trials was statistically significant.

Chakravarthy and colleagues reported that the difference of 22% between studies 1003 and 1004 sham/usual care groups at end point (56% versus 34%, respectively) was consistent with the chance imbalance between the groups' proportions of people who had lost fewer than 15 letters at week 54 (65% versus 53%).⁷

Gain of 15 or more letters

Statistically significant gains of 15 letters or more were shown for those receiving pegaptanib or ranibizumab compared to the respective control groups (table 3). Differences in proportions of patients gaining 15 or more letters ranged from 4% for pegaptanib compared to sham injection, to between 18% and 35% for ranibizumab or ranibizumab plus PDT compared with sham injection or sham injection plus PDT. The differences for ranibizumab over sham injection continued to 24 months.⁸

The apparent benefits of ranibizumab over pegaptanib were reflected in the mean change in visual acuity as measured through the mean change in the number of letters at 12 and 24 months (table 3). Although patients receiving pegaptanib lost significantly fewer letters than those receiving sham injection (mean difference 7.0 letters, $p < 0.002$),⁵ those patients receiving ranibizumab or ranibizumab plus PDT experienced statistically significant gains in mean number of letters (ranging between gains of 4.9 and 11.3 letters) compared with losses for the sham injection or sham injection plus PDT

Figure 1 Flowchart of progress through the systematic review.

Table 1 Characteristics of included studies

Study	Intervention	Participants
VISION study year 1 ⁵ VISION year 2 ^{6,7}	(1) 0.3 mg pegaptanib (n = 297) [†] (2) Sham injection (n = 304)	Target population: All angiographic subtypes of lesions
Two concurrent multicentre RCTs (1003 and 1004)	Frequency: injections every 6 weeks, total of 9 treatments. Patients re-randomised after 54 weeks [†] Year 1–Year 2	Angiographic subtype of lesion at baseline PC: (1) 24%, (2) 26% MC: (1) 38%, (2) 34% ONC: (1) 38%, (2) 40%
Primary outcome: proportion losing <15 letters at week 54.	0.3 mg: 0.3 mg n = 133 discontinue n = 132	
Length of follow-up: 54 weeks, plus 48 weeks after re-randomisation.	Sham: 0.3 mg n = 53 sham n = 53 discontinue n = 54	Angiographic subtype of lesion for re- randomised groups in year 2 not reported
MARINA ⁸	(1) 0.5 mg ranibizumab (n = 240) [†] (2) Sham injection (n = 238)	Target population: Occult CNV or minimally classic CNV
Multicentre RCT	Frequency: monthly injections	Angiographic subtype of lesion at baseline PC: (1) 0%, (2) 0%* MC: (1) 37.9%, (2) 36.6%* ONC: (1) 62.1%, (2) 63.4%* Missing data: (1) 0, (2) 0.4%
Primary outcomes: proportion losing <15 letters at 12 months; safety and tolerability		
Length of follow-up: 24 months		
ANCHOR ⁹	(1) 0.5 mg ranibizumab + sham PDT (n = 140) [†] (2) Sham injection + verteporfin PDT (n = 143)	Target population: Predominantly classic lesions
Multicentre RCT	Frequency: injections given monthly, PDT every 3 months if needed	Angiographic subtype of lesion at baseline PC: (1) 96.4%, (2) 98.6% MC: (1) 3.6%, (2) 1.4% ONC: (1) 0, (2) 0
Primary outcome: proportion losing <15 letters		
Length of follow-up: 24 months (ongoing)		
FOCUS ¹⁰	(1) 0.5 mg ranibizumab [‡] + PDT (n = 106) (2) Sham injection + verteporfin PDT (n = 56)	Target population: Predominantly classic lesions
Multicentre RCT (phase I/II)	Frequency: injections given every 30 days, starting on day 7; verteporfin PDT 7 days prior to initial study drug administration Subjects were allowed to receive further verteporfin PDT if deemed necessary by the investigator at any of the evaluation visits.	Angiographic subtype of lesion at baseline PC: (1) 65.7%, (2) 66.1%, MC: (1) 30.5%, (2) 26.8% ONC: (1) 1.9%, (2) 7.1% Unclassified: (1) 1.9%, (2) 0%
Primary outcome: proportion losing <15 letters Length of follow-up: 24 months (ongoing)		

PC, predominantly classic ($\geq 50\%$ classic); MC, minimally classic ($< 50\%$ classic); ONC, occult with no classic.

*Patients in sham injection group total n = 239 rather than 238 in original paper⁸.

[†]See full papers for data on other dose groups.

[‡]A lyophilised formulation of ranibizumab was used for the first 12 months.

(ranging between losses of 8.2 and 10.4 letters).^{8–10} Again, for patients receiving ranibizumab compared to sham injection the difference persisted during the second year of treatment. For patients in the VISION study who were re-randomised to continue to receive the 0.3 mg pegaptanib during the second year, the losses in letters were less than for those who were randomised to discontinue their treatment with 0.3 mg pegaptanib. Those continuing on 0.3 mg pegaptanib experienced

a mean decrease of 0.6 letters, compared to a decrease of 3.04 letters for those who discontinued treatment in the second year ($p = 0.0041$).⁷

Visual acuity 6/60 or worse

All four studies reported that the percentage of people with visual acuity of 6/60 or worse at follow-up was statistically significantly lower in the pegaptanib or ranibizumab groups

Table 2 Quality assessment of included studies

VISION ⁵	MARINA ⁸	ANCHOR ⁹	FOCUS ¹⁰
Adequate	Adequate	Unclear	Unclear
Adequate	Adequate	Unclear	Unclear
Reported	Reported	Reported	Reported
Adequate	Adequate	Adequate	Adequate
Adequate	Adequate	Adequate	Inadequate*
Adequate	Adequate	Adequate	Inadequate
Adequate	Adequate	Adequate	Adequate
Adequate	Adequate	Adequate	Adequate
Inadequate	Adequate	Inadequate	Inadequate
Partial	Adequate	Adequate	Adequate

Please see CRD reference for explanation of assessment criteria³.

*the VA assessor was masked to treatment assignment, but an unmasked investigator performed treatments and all other evaluations.

Table 3 Changes in visual acuity

Outcome	VISION study year ⁵ Lesion type: all		MARINA ⁸ Lesion type: occult/MC		ANCHOR ⁹ Lesion type: PC		FOCUS ¹⁰ Lesion type: PC/MC	
	0.3 mg PEG (n = 294)	sham (n = 296)	0.5 mg RAN (n = 240)	Sham (n = 238)	0.5 mg RAN + sham PDT (n = 139*)	Sham + PDT (n = 143)	RAN + PDT (n = 105)	Sham + PDT (n = 56)
Mean $\pm$ SD no. letters VA at baseline	52.8 $\pm$ 12.6	52.7 $\pm$ 13.0	53.7 $\pm$ 12.8	53.6 $\pm$ 14.1	47.1 $\pm$ 13.2	45.5 $\pm$ 13.1	45.1 $\pm$ 13.8	48.5 $\pm$ 14.1
95% CI	51.4 to 54.2	51.2 to 54.2	52.0 to 55.3	51.8 to 55.4	44.9 to 49.3	43.4 to 47.6	42.5 to 47.7	44.8 to 52.2
Loss of <15 letters at 54 weeks ⁵ or 12 months ⁸⁻¹⁰	206 (70%)	164 (55%)	227 (94.6%)	148 (62.2%)	134 (96.4%)	92 (64.3%)	95 (90.5%)	38 (67.9%)
95% CI	64.8 to 75.2	49.8 to 61.0	91.7 to 97.4	56.0 to 68.3	93.3 to 99.5	56.5 to 72.2	84.9 to 96.1	55.6 to 80.1
p Value	p<0.001		p<0.0001		p<0.0001		p<0.0001	
Loss of <15 letters at 24 months			216 (90.0%)	126 (52.9%)				
95% CI			86.2 to 93.8	46.6 to 59.3				
p Value			p<0.0001					
Gain $\geq$ 15 letters at 54 weeks ⁵ or 12 months ⁸⁻¹⁰	18 (6%)	6 (2%)	81 (33.8%)	12 (5.0%)	56 (40.3%)	8 (5.6%)	25 (23.8%)	3 (5.4%)
95% CI	3.4 to 8.9	0.4 to 3.6	27.8 to 39.7	2.3 to 7.8	32.1 to 48.4	1.8 to 9.4	15.7 to 32.0	-0.5 to 11.3
p Value	p = 0.04		p<0.0001		p<0.0001		p = 0.003	
Gain $\geq$ 15 letters at 24 months			80 (33.3%)	9 (3.8%)				
95% CI			27.4 to 39.3	1.4 to 6.2				
p Value			p<0.0001					
Mean change in VA (number of letters) at 54 weeks ⁵ or 12 months ⁸⁻¹⁰	-7.5†	-14.5†	7.2	-10.4	11.3	-9.5	4.9 (SD 14.7)	-8.2 (SD 16.3)
p Value	p<0.002		p<0.0001		p<0.0001		p<0.001	
Mean change in VA at 24 months			6.6	-14.9				
p Value			p<0.0001					
VA 6/60† or worse at baseline	-	-	31 (12.9%)	32 (13.4%)	32 (23.0%)	46 (32.2%)	40 (37.7%)	15 (26.8%)
95% CI			8.7 to 17.6	9.1 to 17.8	16.0 to 30.0	24.5 to 39.8	28.5 to 47.0	15.2 to 38.4
VA 6/60 or worse at 54 weeks ⁵ or 12 months ⁸⁻¹⁰	111 (38%)	165 (56%)	28 (11.7%)	102 (42.9%)	23 (16.4%)	86 (60.1%)	31 (29.5%)	26 (46.4%)
95% CI	32.2 to 43.3	50.1 to 61.4	7.6 to 15.7	36.6 to 49.2	10.4 to 22.7	52.1 to 68.1	20.8 to 38.2	33.4 to 59.5
p Value	p<0.001		p<0.0001		p<0.0001		p = 0.006	
VA 6/60 or worse at 24 months			36 (15.0%)	114 (47.9%)				
95% CI			10.5 to 19.5	41.6 to 54.3				
p Value			p<0.0001					

PC, predominantly classic; MC, minimally classic; PEG, pegaptanib; RAN, ranibizumab; VA, visual; acuity (measured in letters); -, not reported. Numbers are n (%) unless otherwise stated. All p values are for comparison between pegaptanib/ranibizumab treatment arm and control arm. The authors calculated 95% CI where sufficient data were presented in publications.

*Only 139 of the 140 patients were observed at baseline.

†Estimated from graph.

‡The studies included in this systematic review reported Snellen measures in feet, and these have been converted to the UK standard of metres.

compared with the sham injection or PDT groups (table 3). Difference appeared greater for those receiving ranibizumab or ranibizumab plus sham PDT compared with sham injection or sham injection plus PDT (range in difference 31% to 44%) than for those receiving ranibizumab plus PDT compared with sham injection plus PDT (difference 16%) or those receiving pegaptanib compared with sham injection (difference 18%).

The benefit of ranibizumab over sham injection continued to 24 months with 33% fewer patients having a visual acuity of 6/60 or worse.⁸ In the VISION study, fewer patients re-randomised to continue 0.3 mg pegaptanib for a second year deteriorated to 6/60 vision or worse than did those re-randomised to discontinue treatment (1% versus 14%, respectively).⁷

However, it should be noted that differences in baseline proportions of patients with visual acuity less than 6/60 could have affected outcomes reported at 12 and 24 months (table 3). In the ANCHOR trial, 23.0% of the 0.5 mg ranibizumab group and 32.2% of the verteporfin PDT group had baseline acuity of 6/60 or worse. Although the higher proportion of PDT patients with low visual acuity at baseline could influence outcomes at follow-up, the magnitude of the difference between the treatment groups at 12 months suggests that the benefits of ranibizumab are unlikely to be an artefact of the differences at baseline. In the FOCUS trial, the imbalance in the proportion of patients with 6/60 vision or worse at baseline favoured the control group. Despite this, those receiving the sham injection had a higher proportion of people with 6/60 vision or worse at the end of the first year (difference 16.9%).

Adverse events

Adverse effects were common, but most were mild to moderate transient events and serious ocular events were rare. Endophthalmitis was experienced by 1.3% of patients receiving pegaptanib in the first year, and by none of the patients who continued with pegaptanib for a second year.⁵⁻⁶ Endophthalmitis occurred in 1.4% and 1.9% of patients receiving 0.5 mg ranibizumab in the ANCHOR⁹ and FOCUS¹⁰ trials, respectively. The rate per injection was 0.05% in the MARINA trial.⁸ Statistically significantly higher proportions of pegaptanib patients than sham injection patients experienced vitreous floaters (33% versus 8%), vitreous opacities (18% versus 10%) and anterior chamber inflammation (14% versus 6%) in the first year of the VISION study ($p \leq 0.001$).⁵

DISCUSSION

This systematic review has synthesised the RCT evidence for the effectiveness of ranibizumab and pegaptanib for subfoveal CNV associated with AMD. It found five RCTs that were judged to be of good quality on criteria assessing methodological quality and quality of reporting.⁵⁻¹⁰ The RCTs showed that patients with AMD of any lesion type benefited from treatment with 0.3 mg pegaptanib or 0.5 mg ranibizumab on measures of visual acuity when compared to sham injection and/or PDT. The benefits of pegaptanib and ranibizumab were shown to be statistically significant and, depending on the starting point for each patient, likely to be clinically significant. People with AMD receiving pegaptanib or ranibizumab were less likely to lose 15 letters, which could mean being able to live independently, drive, read or watch TV, or not to deteriorate to the level of legal blindness (visual acuity of 6/60 or less) than those receiving sham injection and/or PDT. The benefits of continued treatment with pegaptanib or ranibizumab appeared to be maintained after 2 years follow-up. Although adverse events were evident for both drugs, the RCTs showed that these tended to be mild to moderate short-lived events and that serious ocular events were rare.

When comparing pegaptanib and ranibizumab, the evidence was less clear due to the lack of direct comparison in a head-to-head RCT, and the lack of opportunity for statistical indirect comparison due to the heterogeneity of the studies (difference in patient subgroups by lesion subtype, different comparators in some trials and different outcome measures). Although formal comparison of the two drugs was not possible, we calculated 95% confidence intervals for the different measures of visual acuity to provide a crude comparison of the two drugs (table 3). Whilst acknowledging the differences between studies and interpreting the findings cautiously, it appears that ranibizumab compares favourably with pegaptanib when assessed indirectly on measures of visual acuity. On the outcome measures of loss of fewer than 15 letters and gain of 15 or more letters, the 95% confidence intervals did not overlap, with the patients receiving ranibizumab appearing to experience greater benefit compared to patients receiving pegaptanib. On other measures of visual acuity differences were more equivocal.

When evaluating the effectiveness of pegaptanib and ranibizumab, other factors should be considered. Whereas 3-monthly attendances are required for PDT treatment, patients are required to attend every 6 weeks for pegaptanib treatment or once a month for ranibizumab with possible effects on costs and compliance. The ongoing, 24 month PIER study is investigating whether reduced frequency ranibizumab injections are effective. Patients were randomised to receive monthly 0.3 mg ranibizumab, 0.5 mg ranibizumab or sham injection for three months, after which ranibizumab patients received additional doses at months 5, 8 and 11. At the time of writing, no published results were available, although conference abstracts described methodology.¹¹⁻¹² A Genetech press release¹³ indicated that people receiving ranibizumab lost less visual acuity at month 12 on average than those in the sham injection group. However, patients in the clinical trials included in this systematic review who received monthly injections gained letters of visual acuity. This suggests that the majority of patients benefit from monthly injections rather than the reduced frequency used in the PIER trial. Results from a small clinical trial suggest that optical coherence tomography could be useful in determining a variable dosage regimen for ranibizumab injections.¹⁴

Other treatments have emerged, the effectiveness of which should be considered. The off-label use of bevacizumab (Avastin) for AMD has received increasing attention recently,¹⁵ but as it is unlicensed it was outside the remit of this systematic review. Although there is no RCT evidence on the efficacy of bevacizumab compared with standard treatment, nor any long-term safety data, it is thought that it should have similar benefits to those of ranibizumab, given that ranibizumab is a fragment of bevacizumab with minor modifications. The Royal College of Ophthalmologists indicated that single treatments with Avastin could potentially cost as little as £3.00,¹⁶ compared to £761.20 per vial for ranibizumab.¹⁷ This has led to calls for the necessary research to be commissioned for market authorisation to be sought and for pressure to be applied to manufacturers to obtain such authorisation.¹⁸ The US National Eye Institute of the National Institutes for Health announced in October 2006 that it will be funding a new multicentre clinical trial to compare ranibizumab and bevacizumab for AMD. In the UK, the HTA Clinical Trials Programme is considering funding a trial of bevacizumab versus ranibizumab with further randomisation to PDT. These trials should establish whether bevacizumab is a clinically and cost-effective alternative to ranibizumab.

This independent systematic review has applied consistent methods, limiting the opportunity for bias. An advisory group

of clinical experts informed the project from its initiation, through the development of the research protocol and completion of the review. Although we did not consistently follow-up with authors of the primary studies to clarify methodological details and results, contact with experts and manufacturers provided additional information and clarification. Inclusion was limited to English language, which could have led to publication bias affecting the review. Our review found that pegaptanib and ranibizumab are clinically effective in the treatment of subfoveal CNV related to AMD. Fewer patients appear to show an improvement in vision with pegaptanib than with ranibizumab, but no head to head RCTs have been conducted. Several areas for research have emerged. A trial comparing pegaptanib with ranibizumab and bevacizumab should be undertaken, including a broad range of lesion types of AMD and undertaking an economic evaluation with prospective collection of data on quality of life, utilities, resources and costs.

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