North East Treatment Advisory Group

Anti-vascular endothelial growth factor therapies (bevacizumab and ranibizumab) for diabetic macular oedema

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Summary

- There is an expanding evidence base demonstrating the benefit of using aVEGF therapies in treating diabetic macular oedema, a significant cause of blindness. The current standard of care is laser therapy which is used to halt further loss of visual acuity.
- Much of the evidence relating to bevacizumab is of low quality but consistent in its outcomes. The evidence relating to ranibizumab is generally of higher quality but much of it is unpublished. Again, the evidence is consistent, with both therapies demonstrating significant gains in visual acuity.
- Evidence relating to bevacizumab is from non-commercial sources and is therefore sometimes inconsistent in the nature of the patients recruited and the treatment regimens applied. The most common dose used is 1.25 mg.
- The majority of the evidence relating to ranibizumab has been supported by commercial parties. The most common regimen is a dose of 500 micrograms administered monthly for three to four months, with subsequent doses determined by specific clinical criteria.
- No new safety issues arose during studies of intravitreal aVEGF therapies in the treatment of diabetic macular oedema. The incidence of severe adverse events is low. Minor complications generally associated with the mode of administration were relatively common.
- The therapies are costly both in terms of purchase and admission costs. The cost per admission is £591 regardless of the treatment (aVEGF or laser). The cost per dose of bevacizumab is about £105, and about £920 for ranibizumab. The overall cost of treatment per patient is highly sensitive to the number of treatments administered. The estimated cost per patient in the first year of treatment is between £1,600 and £6,300 with bevacizumab and about £10,500 with ranibizumab. Total patient numbers are estimated at up to 400 per annum with additional accumulation of some patients over two to three years.
- If it is assumed that either aVEGF therapy is to be administered at the same frequency then bevacizumab will always be less costly than ranibizumab due to the difference in drug costs. Difference in cost-effectiveness are less striking as the evidence indicates that ranibizumab is more effective than bevacizumab although there is no direct comparison between the treatments.
- Bevacizumab is not licensed for any ophthalmic indication. Ranibizumab is licensed for other ophthalmic indications and is expected to gain a license for diabetic macular oedema in the first quarter of 2011. NICE is expected to issue guidance via a single technology appraisal for ranibizumab in diabetic macular oedema before the end of 2011.

Introduction

Macular oedema is the swelling of the retina resulting from the seepage (exudation) and accumulation of extracellular fluid and proteins in the macula (one of the most highly sensitive parts of the eye) due to the breakdown of the blood-retina barrier and an increase in vascular permeability (i.e. 'leaky' blood vessels in the back of the eye). Diabetic patients are particularly susceptible to such microvascular changes and are therefore at greater risk of macular oedema, giving rise to the distinct condition of diabetic macular oedema (DMO). The microvascular changes that result in DMO are progressive and the incidence of DMO increases with duration of diagnosis. DMO is often accompanied by macular ischaemia due to capillary loss. The severity of the ischaemia has a bearing on the prognosis of vision loss. [1-3]

DMO has been defined by the Royal College of Ophthalmologists based on a minimum level of thickening of the macula (500 micrometres), the proximity of the oedematous area to the centre of the macula, and the presence of hard exudates in the macula. [3]

DMO can affect one or both eyes at different times or concurrently, and to differing degrees. The most common initial symptom of DMO is usually blurred vision but other symptoms include image distortion, floaters, distorted contrast sensitivity, light intolerance, and distorted colour perception. Initial symptoms will progress to reduction in visual acuity that may be reversible in the short-term but can cause irreversible damage leading to blindness if prolonged. [1]

The current standard of care for DMO is laser photocoagulation, and this is supported by a large body of evidence. Often a single treatment is not sufficient and one or more repeat laser treatments may be required. The aim of laser treatment is to delay progression of visual loss and resolve the macula oedema. The evidence does not indicate that laser treatment will result in reversal of visual loss (i.e. regain of vision) or prevent eventual progression. [3-5]

There has been considerable interest in the use of anti-vascular endothelial growth factor (aVEGF) therapies for DMO. [5] Both bevacizumab (Avastin® Roche) and ranibizumab (Lucentis® Novartis) are recombinant aVEGF proteins with the same cellular targets and mode of action. [6,7] Bevacizumab is a full-length antibody derived from the same murine monoclonal antibody precursor as ranibizumab, a humanised antibody fragment. Ranibizumab is produced via a bacterial vector and bevacizumab via mammalian cells resulting in glycosylation of the bevacizumab molecule but not ranibizumab. Ranibizumab has a molecular mass of 48 kilo-Daltons (kD) and bevacizumab has a larger mass of 149 KD. Ranibizumab was specifically developed for ocular use and is currently licensed for the treatment of age-related macular oedema. [6-8]

Bevacizumab is licensed only for a number of neoplasms but has been extensively investigated for several ophthalmic indications. [6] Use of these drugs in DMO currently represents an off-license indication for both drugs however ranibizumab is expected to obtain licensed approval for treatment of DMO during

the first quarter of 2011. [9] Both are administered via intravitreal injection, a procedure that is commonly carried out but which does carry some risks of its own. Ranibizumab requires preparation immediately prior to administration with the drug extracted from single-use vials. Bevacizumab is usually prepared in pre-filled syringes compounded in an aseptic unit prior to administration with multiple doses being extracted from a single vial.

The North East Treatment Advisory Group has been requested by a regional ophthalmology unit and separately by a member primary care organisation to conduct an appraisal of, and issue a recommendation regarding, the use of the aVEGF therapies bevacizumab or ranibizumab as adjuncts to laser therapy in the management of DMO.

This appraisal report will consider the relevant evidence for the safety and efficacy of bevacizumab or ranibizumab as adjunct therapy for the treatment of DMO.

Clinical Evidence

Efficacy

Bevacizumab

There is a substantial volume of evidence regarding the use of bevacizumab in the management of DMO however this evidence is largely of poor quality or difficult to interpret for a number of different reasons: [10]

- No consistently applied dose or regimen
- Short duration or follow-up (< 24 weeks)
- Non-comparative case series
- Retrospective
- Small number of patients or treated eyes
- No pre-defined end points or outcome measures

A Cochrane review of 'antiangiogenic therapy with anti-vascular endothelial growth factor modalities for diabetic macular oedema' was published in 2009 with data collected up to and including February 2008. This included three studies of bevacizumab (involving 91 eyes treated with 1.25 mg and 13 eyes treated with 1.5 mg), none with ranibizumab and one with pegaptinib. The conclusion of this review was that: [1]

> *There is not sufficient high quality evidence from large RCTs supporting the use of either single or multiple anti-VEGF intravitreal injections to treat DMO. Results from ongoing studies on several compounds should assess not only treatment efficacy but also, if a benefit is found, the number of injections needed for maintenance and long-term safety.*

Since the data collection period of the Cochrane review only one important new study of the use of bevacizumab for DMO has been published.

The BOLT study (Bevacizumab Or Laser Therapy) was a prospective randomised study of two-year's duration for which twelve-month interim results have recently been published. [11] The study was conducted at a single UK centre. Patients had BCVA in the study eye of 35 to 69 letters on the ETDRS chart (Snellen equivalent between 6/60 and 6/12) and HbA1c ≤ 11%. Patients were randomised to standard treatment with laser therapy (n = 38) or intravitreal bevacizumab 1.25 mg at weeks 0, 6 and 12 and then repeat injections if clinically indicated based on macular thickness at maximum frequency of once every six weeks (n = 42). Therefore patients could receive between three and nine doses of bevacizumab in the first year. Although patients and study clinicians were not blind to treatment allocation ancillary study staff, such as optometrists and technical personnel, were blinded. Patient groups were well matched although there was a greater proportion of patients of Asian origin (45% vs. 19%), with a corresponding reduction in the proportion of White patients (40% vs. 57%), in the

laser group. Mean age was about 64 years, the majority of patients were male (about two-thirds), the majority had type 2 diabetes (about 90%), and diabetes was relatively well-controlled with a mean HbA1c of 7.5%. The patient group was specifically those with centre-involving clinically significant macular oedema who had received at least one prior episode of laser therapy. [11]

The primary outcome measure was BCVA at 12 months which demonstrated a mean change of +5.6 in the bevacizumab group and -4.6 in the laser group, a difference of 11.2 ($p = 0.0006$). The proportion of patients achieving a gain of ≥ 15 letters was 12% and 5% respectively ($p = 0.43$). The severity of retinopathy was also assessed using an accepted measure ranging through five levels from mild non-proliferative to moderate (non high-risk) proliferative diabetic retinopathy. The results demonstrated that the majority of patients in both groups (73% and 77% respectively) had no change in retinopathy severity, however a greater proportion of the bevacizumab group experienced improvements compared with the laser group ($p = 0.13$). The mean reduction in central macular thickness after 12 months was 130 and 68 micrometres respectively ($p = 0.06$). The median number of bevacizumab injections was nine and the median number of laser treatments was three. [11]

Two other studies with at least 24 week's follow-up also provide useful evidence for bevacizumab in DMO and are described briefly. [12,13]

A comparative non-blinded non-randomised study in patients with severe bilateral DMO investigated the effects of a single injection of bevacizumab 1.25 mg and triamcinolone 4 mg in different eyes of the same patients (n = 14, i.e. 28 eyes). The 24 week results demonstrated a non-significant improvement in bevacizumab-treated eyes compared with triamcinolone-treated eyes which did demonstrate significant improvements in BCVA and macular thickness. Both treatments showed greater initial responses with the effects diminishing over the course of the study. Triamcinolone-treated eyes were significantly improved in terms of BCVA and macular thickness at 24 weeks than bevacizumab-treated eyes. [12]

A brief report of a small and non-randomised study comparing bevacizumab 1.5 mg (n = 12) with triamcinolone 25 mg (n = 15) in patients with diffuse DMO found significant improvements in visual acuity and central macular thickness after six months compared with baseline in each group although without significant differences between groups. The authors speculate that differences may have emerged with longer follow-up as the expected duration of effect of high-dose triamcinolone is six to eight months whereas the duration of effect of bevacizumab could be longer. [13]

Ranibizumab

A lesser volume of evidence for ranibizumab in DMO has been published compared with bevacizumab. [10] Indeed, the Cochrane review published in 2009 did not include any studies of ranibizumab. [1] However the majority of that which has been published, and a large volume of unpublished evidence, does originate from studies of greater methodological quality compared with studies of bevacizumab. In particular the studies are prospective, randomised and blinded trials. The pivotal studies are considered separately.

The READ-2 study (Ranibizumab for Edema [sic] of the mAcula in Diabetes) was an open-label phase two randomised study of 24 months duration which compared ranibizumab with laser treatment with both in 126 patients with DMO. [14] The majority of patients were white (about 70%), female (about two-thirds), had a mean age of 62 years and reasonably well-controlled diabetes (mean HbA1c was 7.6%). Baseline mean BCVA was about 25 letters on the ETDRS chart (Snellen equivalent 20/80). Patients were randomised to one of three groups (n = 42 in each group): a total of four doses of ranibizumab 500 micrograms at baseline, one, three and five months; or laser treatment at baseline and again at three months if indicated; or ranibizumab 500 micrograms followed by laser therapy one week later at baseline and at three months. After six months, all patients were eligible for treatment with ranibizumab at a maximum frequency of two-months or laser treatment if indicated according to foveal thickening. The primary endpoint was the change in BCVA from baseline to six months. Observed changes in visual acuity are demonstrated in table 1.

Table 1. Summary results, including longer-term outcomes, of the READ-2 study

	Improvement in visual acuity (number of letters on ETDRS chart)		
	Six months	Twelve months	Twenty-four months
Ranibizumab	7.2	6.5	7.6
Laser	-0.4	4.5	5.0
Ranibizumab plus laser	3.8	2.1	6.4

This table includes longer term results obtained from abstract data [15]

The proportion of patients with an improvement of ≥ 3 or more lines on the ETDRS chart was 22%, 8% and 0% respectively. Thirty-two patients randomised to the laser only group received an additional laser treatment.

The RESOLVE study was also a phase two randomised controlled study in patients with DMO. This was a placebo-controlled study in which patients were randomised to monthly treatment for 12 months with ranibizumab 300 micrograms (n = 51), 500 micrograms (n = 51) or placebo (sham) injection (n = 49). [redacted].
Change in mean BCVA (ETDRS letters) at 12 months was +10 in ranibizumab patients and -1 in sham-treated patients, [redacted]
Ranibizumab also demonstrated a markedly greater effect on retinal thickness compared with sham injections. [16]

The RESTORE [redacted]
design was similar to that of the READ-2 study involving a randomised, blinded comparison of ranibizumab 500 micrograms with laser and combined therapy. [redacted]
Therefore the groups consisted of ranibizumab plus sham laser (n = XXX), ranibizumab plus laser (n = XXX) and sham injection plus laser (n = XXX). [redacted]. [16,17]

The primary outcome measure was the mean change in BCVA (number of letters) over 12 months, which demonstrated significantly greater improvements in ranibizumab groups than with laser treatment alone (+6.1 and +5.9 vs. +0.8 respectively, $p < 0.0001$ for each comparison with laser monotherapy). [redacted] [16,17]

[redacted]. [16]

[redacted] The proportions of patients with at least a 10 letter gain in visual acuity after 12 months were 37% with ranibizumab, 43% with ranibizumab plus laser and 16% with laser. [redacted] [16]

The largest published study of ranibizumab in DMO was an independent four-way comparison in which two groups received ranibizumab 500 micrograms with concurrent laser therapy. [18] The DRCR.net study randomised 293 patients to sham (placebo) injections plus prompt laser therapy (commenced within three to ten days of injection), ranibizumab 500 micrograms plus prompt laser therapy (n = 187), and ranibizumab 500 micrograms plus deferred laser therapy (commenced ≥ 24 weeks after first injection, n = 188). Patients had visual acuity between 24 and 78 letters (mean 63 letters) and retinal thickness ≥ 250 micrometres (mean 405 micrometres). Patients had generally well-controlled diabetes with a mean HbA1c of about 7.4%, a mean age of about 63 years, about 42% were female and about 70% were white. After the first treatment a specific re-treatment protocol defined whether patients would receive further treatment with ranibizumab or laser therapy. The primary outcome measure was visual acuity at one year and demonstrated a mean improvement compared with baseline of three letters with laser plus placebo injections, and nine with each of the ranibizumab regimens ($p < 0.001$ for each ranibizumab vs. placebo). The proportions of patients with ≥ 15 letter gain in visual acuity from baseline were 15%, 30% and 28% respectively. Changes in retinal thickness showed significant reductions in all groups which were larger, on average, in the ranibizumab groups (micrometre reduction in baseline 102, 131 and 137 respectively). [18]

Longer term (≥ 12 month) outcomes in DMO

Reports on longer term outcomes beyond 12 months with aVEGF therapies in DMO are not yet widely available.

Bevacizumab evidence ≥ 12 months

The PACORES study investigators report the two-year outcomes of 115 patients with DMO treated with either bevacizumab 1.25 mg (n = 74 eyes) or 2.5 mg (n = 65 eyes) in a non-comparative case series. Results are reported here from the 1.25 mg group only: patients received a mean of 4.4 injections in two years (range 1 to 11); BCVA improved from 20/150 to 20/107 at one month to 20/75 at 24 months ($p < 0.001$ compared with baseline). The mean gain in BCVA lines at 6, 12 and 24 months was 2.4, 3.8 and 2.4 respectively ($p < 0.001$ compared with baseline). Macular thickness demonstrated progressive reduction throughout the study and was substantially and significantly reduced at 24 months compared with baseline. [19]

Kook et al report the 12-month results of a non-comparative case series of 59 treatment refractory patients (n = 59 eyes) with DMO treated with bevacizumab 1.25mg. These patients received a mean of 2.7 injections in 12 months. Mean visual acuity (ETDRS letters) increased from 40.4 at baseline to 45.4 after 12 months ($p < 0.05$). Central retinal thickness progressively and significantly ($p < 0.05$) reduced throughout the study. [20]

Twelve-months results are also reported for a small (n = 10) prospective case series in patients with DMO and severe capillary loss, a group considered to have more severe disease and for whom laser therapy is known to be less effective. Patients received a mean of 2.9 injections (range 1 to 4) of bevacizumab 1.5 mg in 12 months. The results demonstrated a significant improvement in BCVA from 20/125 at baseline to 20/80 at all subsequent check-ups to 12 months ($p < 0.01$ compared with baseline). Mean improvement in BCVA from baseline to 12 months was 2.3 letters. Central macular thickness progressively reduced throughout the study and was substantially reduced at 12 months compared with baseline ($p < 0.01$). [21]

Ranibizumab evidence ≥ 12 months

Other than the results presented in table 1, longer term data for ranibizumab in DMO with follow-up ≥ 12 months is reported in the DRCR.net study and the two-year results of the READ-2 study.

In the READ-2 study, after the initial six months, patients were continued with their original treatment allocation except that patients randomised to laser therapy alone could receive ranibizumab if this was deemed clinically appropriate. The number of patients who completed, or for whom a relevant outcome was available at, 24 months was 100. Twenty-eight patients withdrew by month 24; withdrawals were evenly distributed across groups. The mean number of doses of ranibizumab administered over 24 months in group 1 (ranibizumab monotherapy) was 9.3 of a maximum possible value of 13. The mean number of ranibizumab injections at 24 months in group 2 (laser monotherapy) was 4.4 of a maximum possible nine, plus a mean number of laser treatments of less than two. The mean number of ranibizumab injections in group 3 (ranibizumab and laser therapy combination) was 2.9 of a maximum possible six, plus a mean of < 4 laser treatments. The mean gain in BCVA from baseline was 7.7, 5.1, and 6.8 letters respectively (all between group $p > 0.05$). Thus the striking differences between treatments observed after six months have largely disappeared. Although the mean letter gain after 24 months for the ranibizumab monotherapy group is about the same as it was after six months, this hides a large degree of individual variation. It is crucial to observe that after the initial six-month period of the study all groups were treated principally with ranibizumab, with laser treatment becoming the minor component of therapy. This could explain the convergence of mean treatment effects. It is intriguing to note that longer-term changes in foveal thickness did not mirror the observed changes in BCVA, with ranibizumab monotherapy demonstrating initial reductions which subsequently increased again, although not to the same initial level. Conversely, patients who also received laser therapy demonstrated a gradual but consistent decline in foveal thickness to 24 months such that mean values were ultimately clearly less than those of the ranibizumab monotherapy group. [22]

In the DRCR.net study, the numbers of patients completing the first year of the study and entering the second-year open-label phase were 274, 171 and 178 respectively. [17] This demonstrated that initial results were more or less maintained with mean VA gain compared with baseline of 2, 7 and 10 letters respectively. The proportion of patients with ≥15 letter gain from baseline was 17%, 26% and 29% respectively. The median number of ranibizumab injections administered up to two years was 11 in the prompt and 13 in the deferred laser groups. The mean number of laser treatments administered in each group was 3.7, 3.0 and 0.9 respectively. [18]

In addition, three longer-term studies are underway, known as RISE, RIDE and RELIGHT. The first two are due for completion in 2012 and will obtain outcomes up to 24 months. [16,23] The RELIGHT study will be a UK-only study and will recruit over 100 patients with DMO and follow them up for 18 months. This study has not commenced yet. [16]

Summary of the clinical evidence for efficacy

In terms of robust evidence for the use of bevacizumab, there is only one additional and relatively small study available since publication of the Cochrane review, although encouragingly it is UK-based with an appropriate comparator group and with one-year results. This demonstrated that a fairly intensive regimen of bevacizumab was more effective than laser therapy for a narrowly defined group of patients with DMO. It is not clear whether the results of the BOLT study would be sufficient to alter the conclusion of the Cochrane review, which did not support the use of aVEGF therapies for DMO. Longer term results extending up to two years with bevacizumab provide evidence that initial efficacy results are at least maintained if not further improved. The sum of evidence would indicate there is no discernible difference between the different doses of bevacizumab investigated, with most studies utilising a 1.25 mg dose. Evidence for the optimal regimen of bevacizumab is less clear with most patients across studies receiving three loading doses at four to six week intervals followed by *pro re nata* dosing. However it is not clear whether this is any more effective than one initial dose followed by *prn* dosing.

The data for ranibizumab is more robust with greater patient numbers and more consistently applied doses and regimens. The sum of evidence would point to a dose of 500 micrograms although, as with bevacizumab, it is less clear with respect to the optimum regimen. It is also not clear whether treatment should be used sequential to laser therapy, as in the RESTORE study, or concurrent as in the DRCR.net study. Overall, the results obtained from studies of ranibizumab tend to be better than those seen with bevacizumab although it is not clear whether this might be due to differences in cases. Certainly ranibizumab-treated patients appear to undergo more intensive treatment regimens typically requiring more than six doses of ranibizumab in the first year. Evidence from the pivotal RESTORE study has not yet been published in a peer reviewed journal and therefore the data must be interpreted with a degree of caution.

It is reassuring the small amount of longer term evidence consistently demonstrates that initial results are generally maintained, although with continued but decreasing need for therapy.

Despite the relative improvements of aVEGF therapies over laser therapy it must still be remembered that average treatment effects are still fairly modest, equating to, on average, one or two lines of a sight chart, with more than half of patients still failing to achieve a gain of at least three lines.

Safety

The safety of, and adverse effects associated with, intravitreal aVEGF therapies have been established through their extensive use in practice, particularly in the management of age-related macular degeneration. The effects can be distinguished between those relating to the drug, which are often limited due to the localised nature of administration, or due to the intravitreal technique of administration which carries some inherent risks.

Although currently neither bevacizumab nor ranibizumab are licensed for the treatment of DMO, ranibizumab is licensed for the treatment of other ophthalmic conditions and was developed and formulated specifically for intravitreal administration. Bevacizumab is not licensed for any ophthalmic indications and the small doses used in ophthalmology must be extracted from vials of much larger quantity or compounded by special units.

Bevacizumab

The most common adverse effects seen in the BOLT study with bevacizumab include eye pain or other irritation (19%), red eye or subconjunctival haemorrhage (17%) and transient raised intraocular pressure (7%). Other than measures relating to efficacy outcomes, no ocular adverse effects are reported with laser treatment in the BOLT study. The total number of adverse effects and serious adverse effects observed in the BOLT study is 27 in the bevacizumab group and 18 in the laser treatment group. [11] Adverse effects reported in other studies concur with these and generally demonstrate a relatively high rate of minor and transient ocular effects with a low rate of more serious complications. [10-13,19-21]

Ranibizumab

Safety outcomes from ranibizumab studies also do not highlight any unexpected effects. The most common adverse effects were consistent across studies and included transient local irritation effects (visual impairment, blurred vision, itching, tears) and local effects related to administration (pain, minor bleeds, paraesthesia). The incidence of more serious complications such as endophthalmitis is low (< 1%). [14-18]

Safety events up to two years in the READ-2 study are not available. [23] However longer-term safety data is available from the DRCR.net study with safety outcomes of up to two years. [18] The incidence of endophthalmitis was low at 1% in each group. There was one report of a retinal detachment in a ranibizumab patient. The incidence of elevated intraocular pressure was low and less than 10% in each group. Severe increases in pressure occurred in about 2 to 3% of patients. [18]

Summary of safety data

On balance, the intravitreal administration of aVEGF therapies, specifically bevacizumab and ranibizumab, appears to be a low-risk treatment with most effects attributable to the mode of administration than to the pharmacological action of the drugs. However, there is an absence of longer-term outcomes beyond a few years which could be important for those patients who might receive repeated episodes of treatment. The use of bevacizumab does, theoretically, pose a greater risk than use of ranibizumab due to the product requiring some level of compounding from much larger volumes prior to administration, further compounded if multiple doses are to be obtained from the same source (i.e. vial). However, this does not appear to be borne out in practice. A recently published systematic review on the use of aVEGF therapies for DMO concluded that 'although intravitreal delivery of aVEGF agents is a relatively safe procedure, the long-term local and systemic effects of these agents in the diabetic population remain unknown'. There was no evidence of any systemic effects with bevacizumab or ranibizumab in the studies reviewed in this report.

Cost analysis

All costs include VAT at 20% unless otherwise indicated

The cost of treatment considered in this analysis will consist of the drug purchase costs and tariff admission costs only. The cost of additional administration hardware and ancillary equipment is considered to be accounted for within the tariff admission cost. No additional cost is considered necessary for training or equipment purchases. No allowance is made for any differences in follow-up outpatient appointments or in handling adverse effects of treatment as the evidence is not sufficient to reliably estimate these factors.

The tariff cost of admission for a laser treatment session or for an intravitreal injection is defined by the payments-by-results item code BZ23Z 'vitreous retinal procedures – category 1', which is £591 per day case admission for the current year. The market forces factor, typically 2% to 3% for acute trusts within NHS North East, has not been applied. [24]

The mean cost per bevacizumab (Avastin®) 1.25 mg pre-filled syringe purchased from Moorfields Pharmaceuticals is £105, adjusted to include an estimate of delivery costs. [25] Local acute hospitals may be able to manufacture (compound) bevacizumab pre-filled syringes of the same quality at reduced cost as the drug represents only about £4 of the cost per syringe, assuming maximal drug extraction per Avastin® vial. [26] Ranibizumab (Lucentis®) is provided in single-use vials which require preparation into a suitable syringe immediately prior to use. The cost per vial is £913. [26]

Therefore the cost per dose is £696 with bevacizumab, £1,504 with ranibizumab and £591 per episode of laser treatment. [24-26]

The total cost per patient will vary depending on how often they are treated with each of the treatment modalities and estimates of this frequency vary depending on the source/study. Estimates for the cost per patient per therapy for the first 12 months are demonstrated in table 2. For bevacizumab these estimates range from £1,600 to £6,300 per annum. These figures are skewed by the results of the BOLT study in which patients would receive a minimum of three and a maximum of nine injections in the first year. The mean results are not reported, and the median value fell on the maximum. The actual mean value will be less than nine injections, however this is not reported and so the median has been used to estimate annual cost per patient. For ranibizumab the equivalent range is £6,000 to £15,000 however the most relevant is that relating to the RESTORE study as it is this which will likely inform the product license application. In this case patients received a mean of seven doses in the first year, costing the equivalent of £10,500 per patient. Laser therapy demonstrated less variance in mean resource use, typically two or three treatments per annum, resulting in costs ranging from about £1,000 to £2,000 per patient. Estimates of cost-effectiveness are also displayed in table 2 for a range of commonly reported outcomes.

Table 2. Cost-effectiveness of different outcomes for first year of treatments for diabetic macular oedema

	Bevacizumab 1.25 mg			Ranibizumab 500 micrograms				Laser therapy		
	BOLT	PACORES	Kook	DRCR.net (prompt)	DRCR.net (deferred)	RESOLVE*	RESTORE	BOLT	DRCR.net	RESTORE
n (eyes)	42	48	59	187	188	102	115	38	293	110
Mean [median] treatments per patient	[9]	2.35	2.7	[8] + 2.2	[9] + 0.4	10.15	7	[3]	2.66	2.1
Cost based on mean utilisation	£6,264	£1,636	£1,879	£13,332	£13,772	£15,266	£10,528	£1,773	£1,572	£1,241
≥ 15 letter gain	11.9%			30%	28%	22.6%		5.3%	15%	8.2%
Cost for one eye to achieve ≥ 15 letter gain	£52,639			£44,440	£49,186	£67,547		£33,453	£10,480	£15,135
≥ 10 letter gain	31%	58.3%		50%	47%	[redacted]	[redacted]	7.9%	28%	15.5%
Cost for one eye to achieve ≥ 10 letter gain	£20,206	£2,805		£26,664	£29,302	[redacted]	[redacted]	£22,443	£5,615	£8,007
Mean change (letters)	5.6		5	9	9	10.3	6.8	-4.6	3	0.9
Cost per letter gained	£1,119		£376	£1,481	£1,530	£1,482	£1,548	(£385)**	£524	£1,379

* : The RESOLVE [15] study used two different doses of ranibizumab (300 and 500 micrograms) and [redacted] patients received a permitted doubling of dose. [redacted] patients also received at least one laser treatment. Pooled results are presented.

** : The value in parentheses relating to the cost per letter gained with laser therapy in the BOLT study means that it would actually cost this much per letter lost as opposed to gained.

The PACORES [27] and Kook [20] studies are non-comparative studies.

Table 3. Annual incidence of new cases of clinically significant DMO resulting in visual impairment, and associated predicted costs for the first year of treatment with aVEGF therapies.

Primary Care Cluster	Primary Care Trust	NHS North East population [33]	New cases per annum*	Bevacizumab		Ranibizumab [16]
				Lower estimate [27]	Upper estimate [11]	
Durham and Darlington	County Durham	20.0%	[redacted]	[redacted]	[redacted]	[redacted]
	Darlington	3.8%				
North of Tyne	Newcastle	10.2%	[redacted]	[redacted]	[redacted]	[redacted]
	North Tyneside	8.0%				
	Northumberland	12.1%				
South of Tyne	Gateshead	7.5%	[redacted]	[redacted]	[redacted]	[redacted]
	South Tyneside	5.9%				
	Sunderland	10.7%				
Tees	Hartlepool	3.6%	[redacted]	[redacted]	[redacted]	[redacted]
	Middlesbrough	5.6%				
	North Tees	7.4%				
	Redcar & Cleveland	5.2%				
NHS North East		100%	[redacted]	[redacted]	[redacted]	[redacted]

Totals may not sum to expected values due to rounding

* : Using an incidence of [redacted] of all diabetic patients [15] and assuming that one-third of patients have bilateral disease. [31]

The cost estimates in table 2 should only be applied to the cost of the first year of therapy. There is little evidence to guide expected health care utilisation in subsequent years for aVEGF therapies. The two-year results of the PACORES study indicate that a mean of 4.4 bevacizumab 1.25 mg injections are required over two years [19] and patients in the DRCR.net study continued to receive additional ranibizumab and laser therapy in the second year. [18] In the READ-2 study the mean number of injections over two years in the ranibizumab monotherapy group was 9.3 which included an initial load of four, monthly, injections. Where ranibizumab was combined with laser therapy drug use was lower. [22] On balance it is likely that repeated injections of aVEGF would be required in order to maintain the desired therapeutic effect although at a decreasing frequency. It is also likely that laser therapy would be ceased beyond a specific level due to progressive macular destruction and limits on the expected benefits of laser.

There are an estimated 114,500 patients with diabetes within NHS North East, about 4.46% of the population. [28,29] The estimated prevalence of DMO of any severity is 7.05% (8,000 patients). [30,31] However the prevalence of clinically significant DMO causing visual impairment is estimated at 2.64% of all diabetic patients (3,000 patients). Of these, it is estimated that two-thirds will have unilateral disease (2,000 patients) and one-third bilateral disease (1,000 patients). [31] Therefore it is estimated there is a total of 4,000 eyes that are visually impaired due to DMO and this represents the potential treatment pool for NHS North East.

In clinical studies of ranibizumab the proportion of patients with bilateral disease was less than one-third, at about 20 to 25%. [16,18] However the higher figure will be used as this is from a UK-based epidemiology study.

Based on these figures the current cost of treating all eligible eyes with laser therapy is estimated at £5.9 million based on a mean of 2.5 treatments per annum.

Based on the results in table 2, the first-year cost of treating all eyes with bevacizumab ranges from £6.5 to £25 million. Based on the results of the RESTORE study, the first-year cost of treating all eyes with ranibizumab is £42 million.

However, of greater relevance is the annual incidence of clinically significant DMO resulting in visual impairment as once the initial pool of patients has been treated this will represent a large proportion of the expected ongoing annual patient volume. No independent source for the incidence of clinically significant DMO resulting in visual impairment was identified. Literature produced by Novartis Pharmaceuticals (UK) reports a rate of [redacted]% per annum of all diabetic patients. [15] Transposing this to NHS North East yields [redacted] patients, or [redacted] cases if it is assumed that one-third of patients will present with bilateral disease.

[redacted]

Total accumulated costs would be greater still as a proportion of patients are expected to enter second and subsequent treatment years although with reduced healthcare utilisation.

Novartis Pharmaceuticals has provided a 'budget impact model' based on NHS North East data. [redacted]. [16]

Novartis Pharmaceuticals currently provides a 'ranibizumab reimbursement scheme', more commonly known as a risk-sharing or patient access scheme, for Lucentis® in the treatment of age-related macular degeneration. It is not known if such a scheme would also be available where Lucentis® is used for the treatment of DMO however if a similar scheme was available then expected mean patient treatment costs would be reduced.

Not withstanding any differences in administration frequency or dose regimens, or discount schemes, bevacizumab will always be less costly than ranibizumab based on an equal number of doses due to the large difference in the cost of bevacizumab 1.25 mg vs. ranibizumab 500 micrograms. Similarly, the *prn* dose regimen appears likely to always be less costly than a loading-dose regimen as in the longer term there is no evidence that the frequency of maintenance doses differs. Therefore the least costly aVEGF treatment option is bevacizumab using a *prn* regimen and the most costly is ranibizumab using a loading-dose regimen.

Points to consider

Currently neither bevacizumab nor ranibizumab are licensed for the treatment of DMO however it is anticipated that ranibizumab will receive such a relevant licensed indication in the first quarter of 2011. No such license application will be made for bevacizumab. NICE is currently conducting a single technology appraisal of ranibizumab for DMO which is expected to be published before the end of 2011. [32] Development of ranibizumab in DMO will continue to be supported in a number of prospective studies by Novartis Pharmaceuticals. An equivalent development programme is not in place with bevacizumab.

The strongest evidence for the use of bevacizumab comes from the BOLT study, [11] however this recruited patients who had received at least one prior laser treatment and is therefore not directly relevant to the intended population. Evidence for the use of ranibizumab also included a large proportion of patients who had received at least one prior laser treatment.

The evidence for aVEGF therapies over current standard treatment with laser therapy is compelling. Use of aVEGF therapies consistently demonstrates significantly better visual acuity even with longer term indirect comparisons. Intravitreal use of aVEGF therapies also appears to present an acceptable balance between risks and benefits compared with laser therapy. Most studies only recruited patients with centre-involving disease and therefore the evidence may not necessarily be applicable to peripheral disease. This corresponds to current treatment practice.

Laser therapy is a relatively low cost therapy to administer, incurring only the cost of admission and requiring relatively few treatment sessions (two or three in the first year). By comparison, use of bevacizumab may represent a reduction in costs primarily due to a reduced administration frequency where it is provided on a *prn* basis. However both aVEGF therapies represent an increase in costs if they are administered using a loading dose regimen followed by *prn* dosing. If all aVEGF regimens are assumed to be of equal effectiveness then the most cost-effective treatment option is bevacizumab using a *prn* regimen.

The aim of treatment with laser therapy, the current standard of care, is prevention of any further loss of visual acuity as the evidence demonstrates that it does not restore vision. The results obtained from studies of aVEGF therapy potentially present a shift in treatment aim as clinically significant mean changes in visual acuity do occur, with significant proportions of patients achieving even greater gains such as at 10 or 15 letter gains (table 2).

No new or unexpected safety concerns emerged during studies of aVEGF therapies in DMO. The adverse effect profiles were similar to those observed in studies of age-related macular degeneration and the treatments present an acceptable risk.

On crude estimates of cost per letter gained, treatment with bevacizumab is about as cost-effective as laser treatment but yields overall greater gains. Ranibizumab is the most costly and the most effective but the least cost-effective.

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Author's declaration of interests

The author has participated in several advisory boards and similar, and non-promotional educational meetings, for Novartis Pharmaceuticals, including some specifically regarding Lucentis® although none regarding use in diabetic macular oedema.