North East Treatment Advisory Group

Anti-vascular endothelial growth factor therapies (bevacizumab and ranibizumab) in the management of macular oedema secondary to retinal vein occlusions

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Summary

- Macular oedema as a result of a retinal vein occlusion is a common cause of visual loss. Current treatment relies on laser therapy for patients with a branch occlusion, or possibly a dexamethasone steroid eye implant for patients with a more severe central occlusion.

- A large volume of evidence for the anti-vascular growth factor therapies bevacizumab and ranibizumab indicate a substantial improvement in efficacy in indirect comparisons with existing treatment options. The aVEGF treatments have not been compared with each other for this indication. The evidence indicates that they are about as effective as each other with improvements of about three lines on a sight chart.

- The safety of intravitreal aVEGF is well established across a number of indications. Studies of aVEGF in RVO did not raise any new or unexpected safety issues. Intravitreal aVEGF is considered to present a favourable risk-benefit trade-off in other indications which deliver similar improvements in visual acuity.

- aVEGF are costly therapies to deliver, not only due to drug costs but also due to the cost of specialist care required for administration. Bevacizumab is substantially cheaper than ranibizumab at about £105 vs. £900 per dose. The cost per dose including administration is estimated at £700 and £1,500 respectively.

- The evidence base for bevacizumab indicates that a PRN regimen for bevacizumab is as effective as loading-dose regimen. The first-year cost of bevacizumab per patient is estimated at £2,500. The evidence for ranibizumab focuses principally on a loading-dose regimen and therefore the mean cost per patient for the first-year of therapy is expected to be much greater at about £12,800.

- Clinicians have indicated that aVEGF could replace existing treatment options for a large number of patients although adjunctive use of laser therapy may be required, and some patients may prefer the reduced dose regimen of dexamethasone implants.

- Significant off-set costs will be generated, with each episode of laser treatment estimated to cost £600 and the annual cost of dexamethasone implant estimated at £3,000 per patient per annum.

Introduction

Bevacizumab (Avastin®, Roche) and ranibizumab (Lucentis®, Novartis) are recombinant anti-vascular endothelial growth factor (aVEGF) proteins with the same cellular targets and mode of action. [1,2] 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. [1-3] Bevacizumab is licensed only for a number of neoplasms but has been extensively investigated for several ophthalmic indications. [1] Ranibizumab is licensed for intravitreal administration and requires preparation immediately prior to administration with the drug extracted from a single-use vial. [2] Bevacizumab is only licensed for intravenous administration but is often compounded in pre-filled syringes for intravitreal administration with multiple doses extracted from a single vial.

Neither bevacizumab or ranibizumab are currently licensed in Europe for the treatment of macular oedema secondary to retinal vein occlusion. Ranibizumab (Lucentis®) is licensed for the treatment of macular oedema (MO) following retinal vein occlusion (RVO) in the USA and is expected to gain a similar license for European markets in mid-2011. [4,5] The National Institute for Health and Clinical Evidence is expected to publish a single technology appraisal for ranibizumab in the treatment of MO secondary to RVO in late 2011. [6]

Retinal vein occlusion is a common vascular abnormality associated with conditions such as hypertension, diabetes, glaucoma and other vascular and haematological disorders. One of the consequences of occluded veins in the retina is impaired haemostatic clearance leading to increased pressure in the retinal vasculature. This is turn can damage the retinal microvasculature causing the vessels to leak or haemorrhage. The leakage will affect the macular and lead to macular oedema, a common cause of loss of visual acuity and blindness in patients with retinal vein occlusions. The macula is the central part of the retina responsible for colour vision and perception of fine detail (i.e. visual acuity). Other complications of retinal vein occlusion include vitreous haemorrhage, ischaemia and neovascularisation, all of which can cause or compound loss of vision. [6-8]

The condition is sub-divided into two main classifications; either central or branch retinal vein occlusion depending on the site of vascular occlusion. This distinction is important with respect to the prognosis and treatment parameters. CRVO is usually caused by a thrombus in the central vein as it exits the optic nerve head whereas BRVO will typically occur at a single arterio-venous crossing within the retinal vasculature. More than one BRVO may exist, and BRVO may also exist in conjunction with CRVO. Usually only one eye is symptomatic although bilateral retinal vein occlusions are relatively common. Symptomatic BRVO is about twice as common as CRVO. Generally, CRVO will result in greater visual impairment than BRVO and is more difficult to treat. [6-8]

RVO is further divided into two sub-categories: ischaemic and non-ischaemic, the former being the more severe. Non-ischaemic RVO may resolve completely without any complications or may progress to the ischaemic type. BRVO presents with a variable degree of visual loss; approximately 50 to 60% of untreated eyes with BRVO retain adequate visual acuity after one year, whilst 25% will have more severe vision loss. The impact of vision loss associated with RVO can have a profound effect on vision-related quality of life. Patients may struggle with daily tasks, lose confidence and become increasingly dependent on family and carers. [6,9]

In BRVO laser therapy is used to restore visual acuity where visual loss is not severe. Restoring visual acuity in patients with macular oedema secondary to CRVO is more difficult. Laser therapy is not used as studies have demonstrated no improvement. Off-license use of intravitreous triamcinolone is sometimes used and is supported by a volume of poor quality data. However, despite initially good responses, the effects of intravitreous triamcinolone tend to diminish, requiring additional and more frequent injections. [7-10]

Dexamethasone intravitreal implant (Ozurdex®) has recently been made available in the UK and was recommended by the North East Treatment Advisory Group for non-ischaemic CRVO only, in October 2010. [11]

Due to an emerging evidence base there is increasing interest in the use of aVEGF therapies such as bevacizumab and ranibizumab, both for C- and B-RVO. [6-9] Consequently the North East Treatment Advisory Group has been requested by the North East Retinal Group to conduct an appraisal of, and issue a recommendation for, the management of macular oedema (MO) secondary to retinal vein occlusion (RVO) using the aVEGF therapies bevacizumab or ranibizumab.

Incidence and prevalence

No prevalence or incidence data for RVO or macular oedema secondary to RVO has been identified for England and Wales. An appraisal of Ozurdex® published by the Scottish Medicines Consortium in December 2010 states that the prevalence of BRVO is 0.6% to 1.1% and for CRVO is 0.1% to 0.4%. This corresponds to between 600 and 1,100, and between 100 and 400 per 100,000 population respectively. [12]

A recent US study reported a 15 year incidence of 500 new cases per 100,000 population for CRVO and 1,800 cases per 100,000 population for BRVO in patients aged 43 to 84 years. [13] This corresponds to an annual incidence of about 15 and 52 cases per 100,000 within NHS North East respectively, or a combined annual incidence of 67 cases per 100,000 for RVO. However, only 60% of BRVO cases are estimated to progress to macular oedema, of which about 26% are estimated resolve spontaneously.[14,15] No similar data relating to the development of macular oedema in CRVO exist although there are more reliable estimates of the proportion of cases of macular oedema secondary to CRVO that spontaneously resolve. [8] This indicates a resolution rate of about 30% in non-ischaemic CRVO and between 0 and 73% (mean 50%) in ischaemic CRVO. [8] Although this data is derived from a small patient population it is approximately the same as that observed in BRVO. [14,15] Therefore it will be assumed that the same diagnostic and prognostic parameters for BRVO apply to CRVO. Taking these figures yields estimates for the annual incidence of BRVO and CRVO secondary to macular oedema and which does not spontaneously resolve of 24 and 7 per 100,000 respectively. Transposing these to NHS North East gives an annual estimate of about 620 patients with BRVO and 180 patients with CRVO. This population (n = 800) therefore represents the estimated annual number of cases that may require treatment for macular oedema secondary to RVO within NHS North East.

Interim guidelines published by the Royal College of Ophthalmologists indicate that the number of cases of RVO that require treatment is only 200 to 260 per million, [7] equating to 520 to 676 within NHS North East.

Clinical evidence

A comprehensive literature search was used to retrieve articles relating to the use of bevacizumab and ranibizumab in the management of any type of retinal vein occlusion. Data is summarised in table 1 relating to all studies in English that recruited at least 10 patients to at least one active aVEGF arm (specifically bevacizumab or ranibizumab) and where the minimum follow-up is at least 12 weeks or three months (an exception is made for a small study that investigated two different doses of ranibizumab where the combined aVEGF patient population was ≥ 10). [47]

There is a greater number of studies published relating to use of bevacizumab [16-46] than ranibizumab [47-54] for MO secondary to RVO however the cumulative number of patients is about the same at about 1,000 each. It is possible that some of these patients have been reported in more than one study, particularly with bevacizumab studies, despite efforts to identify this where possible. In general, the majority of evidence for bevacizumab is from retrospective uncontrolled studies. There is only one small randomised study that involved bevacizumab, [46] whereas four out of eight ranibizumab studies were randomised comparisons and accounted for almost all of the exposed patients. [51-54]

The overall quality of bevacizumab evidence is lower than that for ranibizumab, with most studies being relatively small and without a control group. Few were prospectively conducted. Another confounding factor is that a range of different doses and regimens have been investigated in bevacizumab studies. The most common dose of bevacizumab used appears to be 1.25 mg and there is little indication that the actual dose, within the range 1.0 to 2.5 mg, has an impact on outcomes. With respect to ranibizumab, the number of different doses investigated demonstrates less variance utilising either 300 or 500 micrograms per dose but whereas the majority of bevacizumab patients received a particular dose (1.25 mg), about half of ranibizumab patients received the 300 microgram dose. In common with other indications for ranibizumab, and given that no important clinical differences emerged in the studies, it is likely that 500 micrograms will be the licensed dose.

With respect to the regimen for bevacizumab, the most commonly utilised has been a '*pro re nata*' (PRN) or 'when required' regimen with an initial dose followed by subsequent doses only if clinically indicated. The precise parameters used to determine re-injection also varied between studies but were broadly similar and relied on macular thickness and changes in visual acuity.

There are some subtle but potentially crucial differences in the nature of the patients recruited to the studies. Many of the patients recruited to bevacizumab studies were treatment-refractory and had received prior treatment with other therapies such as intravitreal steroids and laser therapy. However the majority of patients treated with ranibizumab were accounted for by the BRAVO [53] and CRUISE [54] studies which specifically excluded patients with such recent treatment histories. The BRAVO [53] and CRUISE [54] studies also only recruited patients with their first vein occlusion in the affected eye.

More than half of patients in both the BRAVO [53] and CRUISE [54] studies had been diagnosed with RVO in the affected eye for less than three months. The time from diagnosis of RVO to treatment was an average of about three to four months in the ranibizumab studies, whereas, often due to the use of prior therapies, there tended to be a greater lag time in studies of bevacizumab.

Another potentially crucial difference is that the BRAVO [53] study specifically permitted the use of rescue laser therapy according to standard treatment criteria which included a minimum three month observation period. The rate of use of rescue laser therapy in the first six months was greater in sham-treated patients compared with either ranibizumab group (55% vs. about 19%). [SENTENCE REMOVED DUE TO DATA CONFIDENTIALITY]. [53]

The only studies that are known to have reported changes in patient quality of life following the use of aVEGF therapy for MO secondary to RVO are the BRAVO [53] and CRUISE [54] studies. These studies specifically investigated the effects on visual function at six months by assessing a variety of activities that rely on near, distance and peripheral vision, and driving, colour, eye pain, general and mental health, independence and social functioning. [55] The results demonstrated improvements in all groups relative to baseline with significantly greater improvements in ranibizumab-treated patients compared with sham. In patients treated with ranibizumab 500 micrograms the improvements were 10.4 points in BRVO and 6.2 in CRVO patients (range 0 to 100, baseline scores not reported).

There were no obvious differences in the age and sex profiles of patients recruited to, or reported in, the studies with mean ages typically being in the 60 to 70 years decade and a slight male gender bias. Baseline BCVA values tended to be around 50 letters with some notable exceptions in some of the bevacizumab studies, in which some patients had substantially worse baseline BCVA.

If reliably reported in the original reference, the non-ischaemic status of the RVO diagnosis is also reported in table 1. However this information was not consistently or reliably reported in all references and therefore some results that may appear to relate to either sub-type of RVO may actually originate from a single sub-type. Some studies also included patients with hemi-retinal RVO, which is a more extensive form of BRVO and has therefore been listed simply as BRVO in table 1.

The results reported for the BRAVO [53] and CRUISE [54] studies are those relating to an intention-to-treat analysis using the last-observation-carried-forward method. Similar differential reporting was often absent in case series reports and non-randomised studies and this could introduce a degree of bias particularly affecting the apparent results from bevacizumab studies (i.e. reported results may be biased and enhance the apparent effect of bevacizumab due to a survivor bias).

Most demonstrated substantial, and often significant, changes in macular thickness following use of an aVEGF. This physiological change supports the observed changes in visual acuity and the two outcomes are clearly correlated.

Table 1. Efficacy outcomes of studies of aVEGF (bevacizumab or ranibizumab) in the treatment of MO secondary to RVO

Ref	RVO	n eyes (outcome)	Intervention	Duration (outcome)	BCVA Gain letters, mean or median	p vs. control or baseline
BEVACIZUMAB STUDIES (continued on next page)						
16	N-I CRVO	25	1.50 mg 6w x 3	6m	10.5	0.015
17	N-I BRVO	21	1.50 mg 6w x 3	6m	13.0	0.002
18	BRVO	16	1.25 mg 4w x 2	16w	30.0	
	CRVO	15	1.25 mg 4w x 3	16w	0.0	
19	BRVO	34	1.25 mg 4w x 2, then PRN (mean 2.9)	6m	15.3	< 0.001
20a	CRVO	8	1.00 mg 4w x 3, then PRN (mean 4.8)	6m	12.0	> 0.05
	BRVO	21	1.00 mg 4w x 3, then PRN (mean 5.5)	6m	15.0	< 0.001
	Combined	29	1.00 mg 4w x 3, then PRN (mean 5.3)	6m	15.0	< 0.01
20b	CRVO	6	1.00 mg 4w x 3, then PRN (mean 8)	12m	7.0	> 0.05
	BRVO	18	1.00 mg 4w x 3, then PRN (mean 8)	12m	18.0	< 0.001
	Combined	24	1.00 mg 4w x 3, then PRN (mean 8)	12m	16.0	< 0.001
21	CRVO	18	1.25 mg PRN (mean 4.6)	6m	15.0	0.005
	BRVO	28	1.25 mg PRN (mean 3.7)	6m	18.0	< 0.001
22	N-I BRVO	42	Dose and frequency not specified	mean 12m (> 5.5m)	10.5	< 0.04
23	BRVO	9	1.25 mg PRN (min 6w - mean 2.0)	6m	1.0	0.18
	BRVO	16	Triamcinolone 4.0 mg PRN (min 3m - mean 1.0)	6m	13.5	
	BRVO	6	1.25 mg PRN (min 6w - mean 3.83)	12m	7.0	0.14
	BRVO	11	Triamcinolone 4.0 mg PRN (min 3m - mean 1.20)	12m	16.5	
24	N-I CRVO	10	1.25 mg (single dose?)	3m	8.5	
25	CRVO	10	1.25 mg PRN (mean 5.0)	2yr	8.0	
26	BRVO	13	1.25 mg PRN (mean 1.7)	> 6m	32.0	0.083
	BRVO	16	Triamcinolone 4.0 mg PRN (mean 1.2)	> 6m	19.0	
27	BRVO	23	1.25 mg PRN (min 6w - mean 3.4)	48w	15.0	< 0.001
28	CRVO	27	2.50 mg PRN (min 6w - mean 4.1)	mean 60w (> 25w)	9.0	< 0.01
	BRVO	34	2.50 mg PRN (min 6w - mean 4.9)		9.0	< 0.001
29	BRVO	47	1.25 mg PRN (mean 2.44)	mean 17.1m, > 12m	23.0	0.892
	BRVO	87	Triamcinolone 4.0 mg PRN (mean 1.09)	mean 23.2m, > 12m	19.0	
30	N-I CRVO	21	1.25 mg PRN (mean 3.7)	12m	0.0	0.771
31	CRVO	13	2.5 mg PRN (mean 2)	mean 6.5m (5.5 to 12)	22.5	< 0.01
	BRVO	12			20.0	< 0.05

Ref	RVO	n eyes (outcome)	Intervention	Duration (outcome)	BCVA Gain letters, mean or median	p vs. control or baseline
BEVACIZUMAB STUDIES (continued from previous page)						
32	BRVO	22	1.25 mg single injection	12w	18.0	< 0.05
	BRVO	28	Triamcinolone 4.0 mg single injection	12w	6.0	
	BRVO	22	1.25 mg single injection	24w	5.0	> 0.05
	BRVO	28	Triamcinolone 4.0 mg single injection	24w	1.5	
33	BRVO	39	Dose and frequency not specified	mean 8.8m	8.0	0.011
34	N-I CRVO	30	1.25 mg PRN	3m	10.0	0.79
	N-I CRVO	42	Triamcinolone 4.0 mg PRN	3m	11.0	
35	BRVO	10	1.50 mg PRN (mean 1.4)	mean 13m	14.0	0.18
	BRVO	10	Triamcinolone 8.0 mg PRN (mean 1.6)	mean 15m	3.0	> 0.05
36	BRVO	12	1.25 mg PRN (mean 1.6)	6m	25.0	0.01
	BRVO	15	Triamcinolone 4.0 mg PRN (mean 1.4)	6m	7.0	0.12
	BRVO	10	1.25 mg + Triamcinolone 2.0 mg PRN (mean 1.4)	6m	10.0	0.48
37	BRVO	32	2.5 mg PRN (range 1 to 3)	mean 4.7m (3 to 8)	15.0	< 0.01
38	BRVO	27	1.25 mg PRN (mean 2)	mean 5.3m (3 to 8)	15.0	< 0.001
39	CRVO	46	1.25 mg 4w x 2, then PRN (mean 3.0)	6m	13.9	< 0.001
40	CRVO	11	1.25 mg (mean 2.6)	4m	10.0	0.03
41a	BRVO	24	1.25 mg PRN (mean 1.5)	6m	6.0	< 0.005
	BRVO	21	2.5 mg PRN (mean 2)	6m	24.0	0.05
41b	BRVO	38	1.25 mg PRN (mean 3.6)	24m	19.0	< 0.0001
	BRVO	25	2.5 mg PRN (mean 4.3)	24m	32.0	< 0.0001
42	CRVO	44	1.25 mg PRN (mean 7.2)	24m	17.5	< 0.0001
	CRVO	42	2.5 mg PRN (mean 8.1)	24m	13.5	< 0.0001
43	CRVO	30	1.25 mg PRN (mean 2.7)	6m	9.0	0.001
	CRVO	17	1.25 mg PRN (mean 3.2)	12m	9.0	0.004
44	BRVO	42	1.25 mg PRN (mean 2.7)	6m	13.0	< 0.001
	BRVO	17	1.25 mg PRN (mean 3.3)	12m	15.0	0.015
45	BRVO	50	1.25 mg PRN (mean 2.0)	12m	13.5	< 0.0001
46*	N-I BRVO	15	1.25 mg PRN (mean 2.5)	12m	15.5	< 0.05
	N-I BRVO	15	Laser therapy (mean 2.3 treatments)	12m	10.0	

Ref	RVO	n eyes (outcome)	Intervention	Duration (outcome)	BCVA Gain letters, mean or median	p vs. control or baseline
RANIBIZUMAB STUDIES						
47	N-I CRVO	5	300 mcg 4w x 3, then PRN (mean 4.5)	9m	1.4	0.859
	N-I CRVO	5	500 mcg 4w x 3, then PRN (mean 4.5)	9m	1.4	
48	CRVO	12	PRN min 4w (dose not specified, mean 7.4)	12m	17.5	0.006
49	N-I BRVO	28	500 mcg PRN (mean 6)	9m	14.3	< 0.001
50	CRVO	20	500 mcg 4w x 3, then PRN (mean 8.5)	12m	18.5	< 0.001
51*	CRVO	15	500 mcg 4w x 3, then PRN (mean 4.3)	6m	12.0	0.067
	CRVO	14	Sham (placebo) 4w x 3, then PRN (mean 5.5)	6m	-1.0	
52*	BRVO	10	300 mcg 4w x 3	4m	10.0	
	BRVO	10	500 mcg 4w x 3	4m	18.0	
	CRVO	10	300 mcg 4w x 3	4m	17.0	
	CRVO	10	500 mcg 4w x 3	4m	14.0	
53a*	BRVO	131	500 mcg 4w x 6 (mean 5.7)	6m	18.3	< 0.0001
	BRVO	134	300 mcg 4w x 6 (mean 5.7)	6m	16.6	< 0.0001
	BRVO	132	Sham (placebo) 4w x 6 (mean 5.7)	6m	7.3	
53b*	BRVO	DATA REMOVED DUE TO CONFIDENTIALITY				
	BRVO					
	BRVO					
54a*	CRVO	130	500 mcg 4w x 6 (mean 5.6)	6m	14.9	< 0.0001
	CRVO	132	300 mcg 4w x 6 (mean 5.8)	6m	12.7	< 0.0001
	CRVO	130	Sham (placebo) 4w x 6 (mean 5.5)	6m	0.8	
54b*	CRVO	DATA REMOVED DUE TO CONFIDENTIALITY				
	CRVO					
	CRVO					

Shading indicates changes in study population as some populations have been reported in more than one study.
w : weeks. m : months. * : Randomised study. N-I : Non-ischaemic
References 53b and 54b relate to unpublished data.
Results are reported to the same degree of accuracy as reported in the original reference. The visual acuity outcome in all studies of ranibizumab was reported as the number of letters on a standard sight chart. However, only a few bevacizumab studies reported visual acuity in these units, with most reporting as the logarithm of the minimum angle of resolution (LogMAR). Other units included decimal fraction, Snellen units, and the number of lines. All results have been converted to the same units (number of letters) using a standard algorithm and therefore a small degree of error cannot be ruled out. (www.precision-vision.com/index.cfm/feature/9/a--visual-acuity.cfm)

Summary of the clinical evidence

On balance, and despite the pros and cons of the available evidence, the two treatments appear to be about as effective as each other in the management of MO secondary to B- or C- RVO. Ranibizumab has been more rigorously evaluated by virtue of undergoing large prospective randomised studies although by their very nature these studies are somewhat constrained in the clinical characteristics of the patients. This, coupled with the studies being placebo-controlled, may limit the relevance of the data to clinical practice where laser therapy is commonly used for BRVO. In addition, published results are only available with up to six-month's follow-up although data with up to 12 months follow-up has been provided and is reported in table 1.

Safety

The safety of intravitreal injections of either bevacizumab or ranibizumab has been established across a multitude of studies in various indications, particularly in the management of age-related macular degeneration, some with extensive follow-up and most relating to multiple repeat dosing.

The effects can be distinguished between those relating to the drug, which are often limited due to the localised nature of administration and very small doses, 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 MO secondary to RVO, ranibizumab is licensed for the treatment of other ophthalmic conditions and was developed and is 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.

None of the studies referred to in table 1 identified any unexpected adverse effects, or any known adverse effects at a greater than expected frequency. In general, the most common adverse effects were those relating to the mode of administration producing effects such as minor conjunctival haemorrhage, irritation, and transient eye pain and discomfort. More serious but rare effects relate to infective and inflammatory complications and inadvertent physical damage.

A recent report described vascular and cardiac outcomes in nearly 40,000 patients treated with intravitreal bevacizumab and 19,000 patients treated with intravitreal ranibizumab for age-related macular degeneration. Some patients were counted in more than one group as therapies were switched during the course of the observation period. The overall rates of serious vascular and cardiac sequelae were low but were slightly higher in bevacizumab- compared with ranibizumab-treated patients. However numerous other factors could rationally have caused this apparent small increased risk and this does not provide conclusive evidence that bevacizumab presents a greater safety risk than ranibizumab in ophthalmology. [56]

Cost analysis

The cost analysis will be based on an assumption that the BRAVO [53] and CRUISE [54] trial data will be the pivotal studies supporting the license application for Lucentis® for the treatment of MO secondary to RVO. This assumption is supported by the licensing of Lucentis® in other markets. [4] This also has the advantage that evidence underpinning estimates of resource use is taken from the largest and highest quality sources of data for any aVEGF treatment in MO secondary to RVO.

In the absence of evidence to the contrary it is assumed that the dose of bevacizumab used is 1.25 mg, and the regimen is a PRN regimen with a minimum four-weekly dose interval.

The treatment of any ischaemic disease will not be considered at all as the local clinical network has indicated they would not seek to treat ischaemic disease based on the evidence currently available.

Therefore, there are two distinct groups of patients, those with non-ischaemic BRVO and those with non-ischaemic CRVO. However, it has not been possible to accurately identify the proportion of patients with ischaemic disease relative to non-ischaemic disease at any point in time. Non-ischaemic disease will often progress to ischaemic disease at a variable rate in the absence of treatment. At any point in time the majority of patients with RVO are believed to have non-ischaemic disease. [8,9]

The cost of treatment is essentially a component of the cost of the drug plus the cost of a hospital admission for the drug to be administered. The cost of a single dose of intravitreal bevacizumab 1.25 mg in a pre-filled syringe is estimated at £105. [57] The cost of a single vial of ranibizumab from which a 500 microgram dose is extracted is £913. [58] The cost of admission for an intravitreal drug injection, assumed to be covered by the department of health tariff for 'vitreous retinal procedures – category 1' (BZ23Z) is £591. [59] Therefore the cost per dose of bevacizumab or ranibizumab is about £700 and £1,500 respectively, the difference being only the difference in cost between the two drugs. Note that the admission cost does not include the market forces uplift factor, which is typically between 2% and 3.5% for hospital trusts within NHS North East.

The mean cost per patient per period of time will depend on the number of doses administered in any given period. The evidence detailed in table 1 indicates that the mean number of doses during the first year of treatment with bevacizumab at a dose of 1.25 mg and using a PRN regimen is about 3.5 regardless of whether the underlying pathology is B- or C- RVO. However there is a considerable about of uncertainty regarding this level of use due in part to the overall small number of patients to which this data pertains and the quality of the evidence sources. With respect to an equivalent mean resource use for ranibizumab, the evidence from the BRAVO [53] study indicates a rate of X injections for BRVO patients, and evidence from the CRUISE [54] study indicates X injections for CRVO patients. There is less uncertainty with this data compared with bevacizumab. The estimated mean cost per patient per indication is detailed in table 2.

Table 2. Estimated mean cost per patient per annum (year 1) to treat MO secondary to RVO with aVEGF therapy (bevacizumab or ranibizumab)

Diagnosis sub-type (all non-ischaemic)	**Bevacizumab**	**Ranibizumab**
BRVO	£2,436	£12,637
CRVO	£2,436	£13,390
Overall mean*	£2,436	£12,807

* Assumed ratio of non-ischaemic BRVO to CRVO of 24:7

As can be seen in table 2, there is a striking difference in the estimated mean cost per patient depending on whether that patient is treated with bevacizumab or ranibizumab. This is due to two factors – the first being the difference in cost per dose estimated at over £800. The second, and more significant, factor is the difference in year 1 dose frequency, with ranibizumab estimated at about X doses and bevacizumab estimated at only about 3.5 doses. These large differentials per patient become even more pronounced when scaled up to represent the total number of patients per annum (table 3).

The costs displayed in table 3 represent the use of aVEGF in all cases of RVO, including ischemic RVO which are not assumed to have spontaneously resolved after a period of at least three months. They are not adjusted to account for non-treatment of ischaemic RVO or for non-treatment of cases considered too severe or too mild to warrant treatment with aVEGF and therefore represent the likely maximum annual incidence. The figures in table 3 should therefore be considered as the maximum likely costs of treatment per annual cohort of patients for year 1 only. There is too little data to estimate the rate of continuation of therapy beyond year 1. It is highly likely that a large proportion of patients will require continued treatment with aVEGF therapy beyond year 1 although at a reduced frequency. The estimated treatment volume and hence costs in table 3 do not take into account an accumulation of patients as would likely occur within a short space of time, nor potential offset costs from treatments not used, for example laser therapy in BRVO or Ozurdex® in CRVO. The data in table 3 also assume that the treatment population consists of new incident cases only and not any of the prevalent cases that exist and may therefore underestimate treatment numbers in the first few years.

Significant off-set cost savings will be generated where aVEGF is used in preference to, or with a reduction in, other therapies. For example, each episode of laser therapy is estimated at £600 per patient and Ozurdex® dexamethasone implant is estimated at £3,000 per patient per annum. Substitution of bevacizumab for Ozurdex®, which is currently recommended for non-ischaemic CRVO only, is estimated to reduce net costs.

Table 3. Cost of first-year of treatment with aVEGF (bevacizumab or ranibizumab) for MO secondary to RVO

Primary Care Cluster	Primary Care Trust	NHS North East population [60]	Annual number of new RVO cases requiring treatment*	First-year cost of treatment*	
				Bevacizumab	Ranibizumab
Durham & Darlington	County Durham	20.0%	190	£462,840	£2,433,359
	Darlington	3.8%			
North of Tyne	Newcastle	10.2%	242	£589,512	£3,099,331
	North Tyneside	8.0%			
	Northumberland	12.1%			
South of Tyne	Gateshead	7.5%	193	£470,148	£2,471,780
	South Tyneside	5.9%			
	Sunderland	10.7%			
Tees	Hartlepool	3.6%	174	£423,864	£2,228,44
	Middlesbrough	5.6%			
	North Tees	7.4%			
	Redcar & Cleveland	5.2%			
NHS North East		100%	799	£1,946,364	£10,232,915

* New incident cases only; all cases of RVO (including some ischaemic) which have not resolved spontaneously after three months.
Totals may not sum to expected values due to rounding

Points to consider

- Current treatment for MO secondary to RVO consists of laser therapy for BRVO and possibly Ozurdex® dexamethasone implant for non-ischaemic CRVO. Based on the results described in this report, the use of aVEGF therapies in RVO appear to provide the most effective treatment for this indication by delivering substantial gains in visual acuity above that seen with other treatment options.

- The evidence for aVEGF therapies indicates that bevacizumab and ranibizumab can produce similar results in terms of improvements in visual acuity. Although the cumulative numbers of patients from which this evidence is derived are about equal with either treatment, the quality of the evidence differs. Fewer studies of higher quality support ranibizumab. A larger number of studies of generally poor or lower quality, utilising greater variation in dose regimens, support bevacizumab. Bevacizumab has longer-term outcomes available, extending up to two years and has more often been compared against active comparator groups. However, the largest single cohort of patients treated with bevacizumab for MO secondary to RVO is only 50, compared with 134 for ranibizumab.

- Many of the BRVO patients in studies of either therapy and regardless of treatment group were also treated with adjunctive laser therapy.

- The manufacturer of ranibizumab is committed to developing its evidence base for a number of ophthalmic indications including MO secondary to RVO. It is not known if any higher quality studies of bevacizumab are planned.

- The safety of intravitreal aVEGF therapies is well established. In studies of bevacizumab and ranibizumab in RVO no new safety issues emerged and the treatments presented a low safety risk overall. Minor, transient and self-limiting complications related to the mode of administration were relatively common. Serious complications were rare. Ranibizumab is supported by regulatory post-marketing safety evaluations which are absent for bevacizumab in ophthalmology.

Points to consider (continued from page 15)

- aVEGF are costly treatments to deliver, in part due to the requirement for, and associated cost of, specialist care for repeat administration. Bevacizumab is less costly than ranibizumab and the evidence base indicates that a PRN regimen, resulting in fewer overall doses being administered, is about as effective as a regular regimen of either bevacizumab or ranibizumab. Ranibizumab has only been investigated with a 'loading' regimen followed by PRN dosing and consequently the mean cost per patient per annum is expected to be substantially greater than with bevacizumab (£2,500 vs. £12,800). Some off-set costs will be expected, with a likely mean reduction in use of laser therapy per patient, and in for non-ischaemic CRVO the potential for complete substitution of dexamethasone implants.

- The manufacturer of ranibizumab currently provides a price-capped patient access scheme for the only indication approved by NICE. It is possible that a similar or identical scheme may also be offered for other NICE-approved indications. A similar scheme will not be created for bevacizumab.

- Currently neither aVEGF therapy is licensed for MO secondary to RVO. Ranibizumab (Lucentis®) is expected to be licensed within Europe for this indication in mid-2011 with corresponding NICE guidance via a single technology appraisal expected before the end of 2011.

- Interim guidelines from the Royal College of Ophthalmologists [7] recommend that ranibizumab is considered as a treatment option for non-ischaemic BRVO and CRVO, and that bevacizumab is considered as an option only in specific circumstances in ischaemic B- and C- RVO. These guidelines do not consider cost-effectiveness. The guidelines lay down specific criteria for initiating, continuing and ceasing therapy which appear to be in-line with other ophthalmic indications and are broadly related to the available evidence base.

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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. This includes some specifically regarding Lucentis® although none regarding use in macular oedema secondary to retinal vein occlusion.