North East Treatment Advisory Group

Bevacizumab (Avastin®) and Ranibizumab (Lucentis®) in the management of non-AMD choroidal neovascular disease

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Summary

- Choroidal neovascularisation can be due to numerous causes other than age-related macular degeneration although these represent a minority of overall cases compared with those due to AMD.

- Within NHS North East about 30 patients annually receive treatment for non-AMD CNV with photodynamic therapy. PDT is licensed for myopic CNV, the most common form of non-AMD CNV, and is supported by evidence from randomised studies.

- Anti-vascular endothelial growth factor agents (specifically bevacizumab and ranibizumab) are an effective first-line treatment for AMD. There is a growing evidence base for their use in non-AMD CNV, especially myopic CNV, although the majority of the evidence is from case series reports without comparator or control groups.

- The evidence is consistently in favour of a benefit for aVEGF therapy demonstrating results that alter patient outcomes compared to the natural course of the disease, and which appear to produce outcomes that are at least as good as those observed with PDT. Only one study reports follow-up beyond one year. Most of the evidence relates to use of intravitreal bevacizumab 1.25 mg.

- Safety of aVEGF therapies in non-AMD CNV is poorly reported. However the risk profile of intravitreal aVEGF therapies has been well established from wide clinical use and randomised studies in the case of ranibizumab, and from large observational reports and limited clinical use in the case of bevacizumab. The safety of intravitreal ranibizumab and bevacizumab is considered acceptable with rare systemic effects, and few local complications or effects.

- Only one treatment centre within NHS North East is able to provide PDT, whereas there are four that are able to provide intravitreal injections. It has been assumed that aVEGF will be used as a substitute for PDT with the same requirements for dose frequency and duration of treatment.

- aVEGF therapies are less costly than PDT with respect to drug and admission costs. The cost per treatment episode is £578 with bevacizumab, £1,362 with ranibizumab, and £1,846 for PDT. On the assumption that two treatments are required per year for two years only, the total cost to NHS North East is £69,360 with bevacizumab, £163,440 with ranibizumab and £221,520 for PDT.

Introduction and background

An application has been received from the ophthalmology team at the Royal Victoria Infirmary for NETAG to consider intravitreal bevacizumab (Avastin®) or ranibizumab (Lucentis®) for the treatment of choroidal neovascularisation (CNV) secondary to causes other than age-related macular degeneration (AMD).

The purpose of this appraisal is to consider the clinical effectiveness, safety, financial implications, and other practical considerations of using bevacizumab or ranibizumab for the treatment of non-AMD choroidal neovascular conditions.

CNV has numerous potential causes the most common of which is AMD. However there is still a significant burden of disease due to other causes of CNV with the principal ones being myopic CNV, punctate inner choroidopathy (PIC), and idiopathic CNV. The evidence for each type is considered separately in a following section with a brief description of the underlying aetiology.

Both bevacizumab and ranibizumab are semi-synthetic anti-vascular endothelial growth factor (aVEGF) antibodies which inhibit the growth of new blood vessels and can potentially cause regression of existing vessels. [1]

Bevacizumab has been available in the UK since March 2005 and is currently licensed for colon, rectal, breast, lung and renal cancers, typically at doses between 250 and 1000 mg administered intravenously. [2] There is a substantial published evidence base concerning the use of intravitreal bevacizumab for various choroidal neovascular conditions, although predominantly AMD, at doses between 1.0 and 2.5 mg. It is not licensed for this indication.

Ranibizumab (Lucentis®, Novartis) has been available in the UK since February 2007. It is only licensed for the treatment of neovascular (wet) AMD. The licensed dose schedule for ranibizumab is 0.5 mg by intravitreal injection monthly for three months followed by monthly check-ups and further intravitreal injections if clinically indicated. [2]

Despite both molecules having the same mode of action there are distinct and potentially important differences between them. Ranibizumab was specifically developed for ocular use and intravitreal administration whereas bevacizumab was developed for intravenous administration. Bevacizumab is a full-length antibody derived from the same murine monoclonal antibody precursor as ranibizumab, a humanised antibody fragment. Consequently ranibizumab has a molecular mass of 48 kilo-Daltons (kD) and bevacizumab has a larger mass of 149 kD. [1,3]

Both molecules are produced by recombinant processes, ranibizumab via a bacterial vector and bevacizumab via mammalian cells. This results in glycosylation of the bevacizumab molecule but not ranibizumab. [1]

These differences in molecular mass and glycosylation are believed to be the main factors influencing differences in half-life between the two drugs. [1] Ranibizumab has a vitreous half-life of about nine days and a serum half-life also of nine days. [2,4,5] The vitreous half-life of bevacizumab has been estimated at 7 to 10 days, a finding that contradicts earlier speculation that it may remain in the eye for longer than ranibizumab due to its larger mass. [1,6,7] Its serum half-life is about 20 days, more than twice that of ranibizumab, and this has led to speculation that it may present a greater risk of systemic adverse effects. [1,2] Serum concentrations of both drugs following intravitreal administration are extremely low. [3-5]

The principal current treatment option for patients with non-AMD CNV is photodynamic therapy (PDT) which consists of infusion of a photosensitive drug, verteporfin (Visudyne®, Novartis), followed by laser therapy directed at the affected eye(s). Patients are frequently monitored and may receive up to four treatments per annum. Visudyne® is specifically licensed for myopic CNV as well as neovascular AMD. [2] Other treatment options include photocoagulation which relies upon the thermal energy of powerful lasers to destroy problem blood vessels. This treatment is seldom used as it is considered to present greater risks than PDT.

The application states that the indication for treatment and re-treatment is the presence of useful vision with a reasonable probability of preservation or improvement if treated with aVEGF therapy. This will be determined by assessing whether there are signs of an active CNV lesion, as indicated by the presence of fluid on tomography or vascular leakage on fluorescein angiogram, in eyes with only a small degree of non-reversible damage. Currently, treatment of non-AMD CNV with PDT can proceed if this is determined to be clinically appropriate, however if treatment with aVEGF is required then an individual funding request is submitted to the patient's primary care trust. This can result in temporal delays during which a patient's sight may deteriorate. If such a request is unsuccessful then a patient does have the option of seeking privately-funded treatment.

There is only one treatment centre within NHS North East that is able to provide PDT and this is based at the Royal Victoria Infirmary in Newcastle. Data provided by the centre shows that in the 40 months from June 2004 to September 2007 a total of 95 patients have received PDT for non-AMD CNV indications. Specifically; 47 were for myopic CNV, 21 were for PIC, 5 were for angioid streaks, 9 were classed as idiopathic (unknown cause) and the remaining 13 were for other miscellaneous causes.

However, since the availability of anti-VEGF therapy and its approved use in the treatment of neovascular AMD there has been growing interest in using aVEGF drugs for non-AMD CNV.

Clinical Evidence

Myopic CNV

Myopic CNV is the second most common cause of CNV following AMD and the most common cause in younger patients (aged < 50 years). Myopia (short sightedness) is itself associated with various structural changes within the eye, and within this group of changes macular CNV is the most common vision-threatening complication, particularly with high myopia (also known as pathological or degenerative myopia and defined as refractive error > -6 dioptres). [8] PDT with verteporfin (Visudyne®) is licensed for the treatment of myopic CNV and is currently the principal treatment used in its management. [2]

The evidence in table 1 shows a significant number of cases in which successful treatment outcomes have been achieved following use of aVEGF drugs, with few serious complications or adverse effects. [9-20] In the majority of cases bevacizumab was used, [9-17] usually at a dose of 1.25 mg, with only three reports using ranibizumab. [18-20] There is an absence of comparisons, randomised or otherwise, with either an alternative treatment or no treatment. Therefore the sum total of the evidence amounts to a large collection of individual cases and it is not possible to estimate what the outcomes may have been with an alternative, or nil, treatment. The absence of randomised treatment allocation means there is a large risk of selection bias.

The natural course of untreated severe myopic CNV is variable and reports yield conflicting information with some demonstrating high rates of visual stabilisation or spontaneous improvement, and others reporting similarly high rates of worsening visual acuity. [8]

The NETAG application was for the use of intravitreal aVEGF as an alternative to PDT: One- and two-year results are available from a randomized placebo-controlled study of verteporfin and PDT in 81 patients (placebo n = 39) with myopic CNV. The one-year results demonstrated that 72% of PDT patients compared with 44% of placebo-treated patients lost ≤ 8 letters ($p < 0.01$) including 32% vs. 15% improving ≥ 5 letters. Although the two-year results continued to demonstrate a benefit for treatment with PDT the difference with placebo was no longer statistically significant (36% of PDT patients compared with 51% of placebo-treated patients lost ≥ 8 letters [$p = 0.11$]. Improvement of visual acuity ≥ 5 letters was obtained in 40% of PDT cases vs. 13% of placebo treated cases, and improvement ≥ 15 letters was observed in 12% of PDT cases vs. 0% of placebo-treated cases) leading some commentators to conclude that PDT is not a reliable long-term treatment option for myopic CNV. [21-22]

Recently a case-series report of 36 patients (39 eyes) has been published describing the four-year outcomes following verteporfin PDT in myopic CNV. The mean baseline BCVA ETDRS score was 9.0 lines and increased to 10.4 at one year, 9.7 at two years, and 9.6 at three and four years. Better outcomes were observed for patients with higher baseline BCVA score, larger lesions and younger age. The authors state that alternative treatment options may be especially useful for older patients with low BCVA. [23]

Outcomes for patients with myopic CNV treated with PDT appear to be about as good as those seen with intravitreal aVEGF up to one year, and durable up to four years. However there are some concerns with the use of PDT: A high rate of subretinal fibrosis (45%) in myopic CNV (n = 33) following PDT (follow-up 14 to 24 months) has been observed although this did not appear to affect visual acuity. [24]

Angioid streaks

Angioid streaks are tiny breaks in the elastin-filled tissue found in the back of the eye. They often occur as part of the natural history of a condition called pseudo-xanthoma elasticum (PXE), a rare disorder of degeneration of elastic fibres resulting in calcification of the skin, retina and blood vessels. In many cases of angioid streaks no obvious cause is identified. If left untreated, angioid streaks of any aetiology will usually result in macular degeneration and progress to blindness. [25-26]

The evidence base relating to the treatment of angioid streaks with aVEGF drugs is sparse, equating to five case-series reports with a sum total of 36 patients and maximum follow-up of 28 months. All were treated with intravitreal bevacizumab at a dose of 1.25 mg, with a mean of about 2 doses administered per annum. All report overall positive or stable visual acuity outcomes with no reports of adverse effects. [27-31] Reports on the use of conventional PDT for angioid streaks amount to 78 patients but have yielded disappointing results, with progressive loss of visual acuity in the longer term and no alteration of the progressive nature of the underlying disease. [32-36]

Table 1. Summary evidence from key studies of use of aVEGF in cases of non-AMD CNV

Ref	Population	Intervention	Prior treatment	Visual acuity outcome	Safety
Myopic CNV ***(all with refractive error > -6 dioptres)***					
9	Non-randomised sequential case series in a Japanese population: No treatment (control) n = 71 (74 eyes) PDT n = 42 (44 eyes) IVB n = 43	IVB 1.25 mg with subsequent doses only if clinically indicated. Mean 1.6 doses per patient. Mean 1.4 sessions of PDT per patient.	Of IVB patients, four had received prior steroid therapy, nine had received PDT, and one had received PDT and steroids. Of PDT patients eight had received prior steroid therapy	At one-year follow-up mean LogMAR BCVA improved from 0.68 to 0.45 with IVB, from 0.61 to 0.54 with PDT and deteriorated from 0.57 to 0.86 in the control group.	None observed following treatment with IVB
10	n = 63 (48 female) Japanese patients Mean age 58 yrs (range 24 to 83)	IVB 1.0 mg with subsequent doses only if clinically indicated. Mean 2.4 doses per patient (range 1 to 6)	Five had received steroid therapy	At one-year follow-up mean LogMAR BCVA improved from 0.57 to 0.33.	Two patients developed oedema and swelling in the eye one day post IVB. One case of retinal detachment two months post IVB.
11	n = 29 Chinese patients Mean age 49 yrs (range 26 to 76)	IVB 1.25 mg monthly for three consecutive months with subsequent doses only if clinically indicated. Mean number of doses 3.6 per patient (range 3 to 12)	16 had received previous PDT at least 6 months prior to IVB.	At one-year follow-up mean LogMAR BCVA improved from 0.62 to 0.38. Better outcomes observed for treatment naïve patients.	Two serious complications observed, although not causally related to IVB due to natural disease processes
12	n = 28 (29 eyes) (23 female) Spanish patients Mean age 50 yrs (range 29 to 82) Two patients lost to follow-up and not included in results	IVB 1.25 mg monthly for three consecutive months with no apparent subsequent doses permitted.	13 had received previous PDT at least 3 months prior to IVB.	At one-year follow-up mean LogMAR BCVA improved from 0.55 to 0.38 ($p = 0.007$). Better outcomes observed for younger (age < 50 yrs) and treatment naïve patients.	None observed
13	n = 20 (11 female) Italian patients Mean age 53 yrs (range 33 to 77)	IVB 1.25 mg monthly for three consecutive months with subsequent doses only if clinically indicated. Mean number doses 4 (range 3 to 7).	Two had received previous treatment with PDT, nine had undergone refractive or cataract surgery	At one-year follow-up mean BCVA ETDRS had improved from 25 to 43 letters with no patients experiencing deterioration in acuity. Mean improvement was 18 letters (range 0 to 37, $p < 0.001$). Better outcomes for younger patients (< 50 years) with fewer mean doses.	None observed

Ref	Population	Intervention	Prior treatment	Visual acuity outcome	Safety
Myopic CNV ***(all with refractive error > -6 dioptres)*** **cont.**					
14	n = 17 (16 female) Spanish patients. Mean age 55 yrs (range 37 to 75)	IVB 1.25 mg with subsequent doses only if clinically indicated. Mean number of doses 1.1 per patient (range 1 to 3)	Nine had received previous PDT	At six-months follow-up mean BCVA ETDRS had improved from 42.7 to 51.1 letters (p = 0.04). Better outcomes observed for younger (age < 50 yrs) and treatment naïve patients.	One case of retinal epithelium pigment tear. No other effects observed.
15	n = 21 (22 eyes) (16 female) Japanese patients Mean age 67 years (range 48 to 81)	IVB 1.25 mg with subsequent doses only if clinically indicated. Two patients subsequently received an additional dose.	Four patients had received previous PDT	At six months follow-up mean LogMAR BCVA improved from 0.67 to 0.34.	Not reported
16	n = 22 Mean age 46 yrs (range 26 to 76)	IVB 1.25 mg monthly for three consecutive months. Three additional monthly doses administered if persistent CNV leakage. Two eyes required 6 injections.	Eleven patients had received previous PDT	Mean baseline LogMAR BCVA was 0.60 and had improved to 0.35 at six months (p < 0.001). 21 eyes demonstrated visual improvement and one demonstrated severe loss despite six doses of IVB.	None observed
17	n = 11 (12 eyes) (7 female), Asian Indian patients. Mean age 47 yrs (range 21 to 67)	IVB 1.25 mg with subsequent doses only if clinically indicated. Mean 1.6 injections per eye after mean of 7 months' follow-up.	Not stated.	Mean baseline LogMAR BCVA was 1.30 and had improved to 0.78 at six months (p = 0.005). Eight eyes improved, three remained stable or improved little, and one worsened.	No serious complications. One case of 'floaters' in the visual field and one case of mild inflammation.
18	n = 23 Spanish patients (17 female) Mean age 51 yrs (range 17 to 77)	Intravitreal ranibizumab with subsequent doses only if clinically indicated. Mean 1.5 injections over 12 months. Actual dose(s) not specified.	Six eyes had received previous PDT plus IVB, four had been treated with IVB only, and four had been treated with PDT only.	After one year: baseline visual acuity score was 53.0 and had improved to 62.6. Better results observed for patients who had not been pre-treated, and younger age (< 50 yrs).	One case of partial corneal desepithelisation.
19	n = 14 Swiss patients	Intravitreal ranibizumab 0.5 mg with subsequent doses only if clinically indicated. Mean 2.7 doses per patient.	Seven had received previous PDT at least 6 months prior to ranibizumab.	For patients with > 6 months follow-up (n = 11) mean LogMAR BCVA improved from 0.71 to 0.32 (p = 0.001)	None observed
20	n = 26 (20 women) Spanish patients Mean age 53 yrs (range 20 to 84)	Intravitreal ranibizumab 0.5 mg with subsequent doses only if clinically indicated. After three months the mean number of treatments was 1.9 (range 1 to 3).	Eleven had received previous PDT	At 3 months mean BCVA ETDRS score was 60.1 compared with 50.4 at baseline (p < 0.001)	None observed

Ref	Population	Intervention	Prior treatment	Visual acuity outcome	Safety
Angioid streaks					
27	n = 6 (9 eyes) (2 PXE, 4 idiopathic) Four male Mean follow-up 19m (range 10 to 28) Mean age 71 yrs (range 53 to 86)	IVB 1.25 mg with subsequent doses only if clinically indicated. Mean 4.5 injections per eye.	None	Relative to baseline: ≥ 3 lines: 4 eyes 0 to 2 lines: 4 eyes ≥ -3 lines: 1 eye	None observed
28	n = 11 (6 female) Mean follow-up 24m (range 20 to 29) Mean age 47 yrs (range 33 to 58)	IVB 1.25 mg with subsequent doses only if clinically indicated. Mean 3.5 doses per patients (range 2 to 6) Mean dose interval 4m	None	Mean BCVA improved from 0.28 at baseline to 0.56 at 20 months ($p < 0.0001$)	Not reported
29	n = 5 (6 eyes) (4 PXE) Three male Mean follow-up 10m (range 7 to 14) Age range 46 to 79 yrs	IVB 1.25 mg with subsequent doses only if clinically indicated. Repeat doses administered every 1.8 to 4 months. 3 patients received concomitant PDT.	All had history of PDT or photocoagulation	BCVA improved in five out of six eyes from baseline to end of follow-up period	Not reported
30	n = 9 (all PXE) Mean follow-up 6m (range 4 to 8) Mean age 54 yrs (range 41 to 66)	IVB 1.25 mg with subsequent doses only if clinically indicated. Patients received a mean of 1.8 doses (range 1 to 3)	Six had received steroid therapy plus PDT	BCVA improved or remained stable for all patients compared with baseline ($p = 0.056$)	None observed
31	n = 5 (4 male) (all with PXE) Mean age 54 yrs (range 47 to 60) Follow-up 3 to 9 months	IVB 1.25 mg with subsequent doses only if clinically indicated. Two patients received 2 doses with a six week interval, and three received 1 dose.	Two had received PDT	BCVA improved for all patients compared with baseline	Not reported
Punctate inner choroidopathy					
37	n = 4 (2 male) Age range 21 to 37 yrs	IVB 1.25 mg monthly for three consecutive months	One patient had received PDT	After 6 months all patients demonstrated improved visual acuity ranging from 1 to 5 additional lines on a standard sight chart. The greatest improvements were in patients with the worst baseline acuity	None observed
38	n = 1 25 yr old female	3 doses of IVB 1.5 mg at six-weekly intervals	None	VA had improved from 0.5 at baseline to 0.8 at 10 weeks post last dose	None reported

Ref	Population	Intervention	Prior treatment	Visual acuity outcome	Safety
Idiopathic CNV					
40	n = 32 (23 male) Asian Indian patients. Mean age 36 yrs (range 18 to 50).	IVB 1.25 mg with subsequent doses only if clinically indicated. Mean 1.7 injections per eye (range 1 to 4).	Three patients had received previous PDT	At 12-week follow-up: Mean LogMAR BCVA improved from 1.02 to 0.49 ($p < 0.01$). 19 patients experienced visual improvement, 11 were stable, and 2 moderate visual loss.	One case of mild inflammation treated with steroids. No other effects observed.
41	n = 10 (5 male) Japanese patients. (range 16 to 41)	IVB 1.0 mg with subsequent doses only if clinically indicated.	All had received prior steroid therapy for at least three months.	At 3 month follow-up: Mean BCVA had improved from 0.46 at baseline to 0.69 ($p = 0.003$)	Mild swelling in one eye
37	n = 9 (6 female). Age range 20 to 48 years.	IVB 1.25 mg monthly for three consecutive months	Six patients had received previous PDT	At 6 months all demonstrated improved visual acuity ranging from 1 to 5 additional lines on a standard sight chart.	None observed
Other non-AMD CNV					
37	n = 2 patients with central serous chorioretinopathy, both male aged 49 and 56 yrs.	IVB 1.25 mg monthly for three consecutive months	None	At 6 months both demonstrated improved visual acuity of 5 and 6 additional lines on a standard sight chart respectively	None observed
42	Active peripapillary choroidal neovascular membranes: n = 5 (6 eyes) 3 were considered secondary to AMD, 1 secondary to angioid streaks and 1 was idiopathic	IVB 1.25 mg monthly for three consecutive months with subsequent doses only if clinically indicated. Five eyes received 3 doses, one eye received 6 but was still without response.	Two patients had previous surgical intervention	Mean follow-up 13m (range 6 to 16): Mean visual acuity improvement in 5 eyes was 4 lines (range 2 to 10). It deteriorated in one eye, which also failed to respond to treatment.	Not reported
43	n = 1 24 yr old Chinese male with choroidal osteoma in one eye	IVB 1.25 mg, two doses with a 10 week interval.	PDT 16 months prior to IVB	Marked visual improvement which was stabilised with about 8 months follow-up.	None reported
39	Inflammatory neovascular conditions including PIC (23 eyes) and idiopathic (12 eyes) causes: n = 96 (99 eyes) (63 female) Mean age 39 yrs	33 eyes received IVB 2.5 mg and 66 eyes received IVB 1.25 mg with subsequent doses only if clinically indicated. Mean number of IVB doses: 12m: 2.3 18m: 3.0 24m: 3.6	Not reported	Mean LogMAR BCVA Baseline: 0.65 (99 eyes) 12m: 0.39 (95 eyes) 18m: 0.40 (46 eyes) 24m: 0.34 (27 eyes) $p < 0.05$ at all points compared with baseline.	One case of mild ocular hypertension, one case of haemorrhage, and four cases of fibrosis. No other complications observed.

One eye per patient unless otherwise indicated. **Key:** AMD – age-related macular degeneration; BCVA – best corrected visual acuity; CNV – choroidal neovascularisation; ETDRS – early treatment diabetic retinopathy study; IVB – intravitreal bevacizumab; LogMAR – logarithmic conversion of the minimum angle of resolution; PDT – photodynamic therapy (plus verteporfin); PIC – punctuate inner choroidopathy; PXE – pseudo-xanthoma elasticum; VA – visual acuity.

Punctate Inner Choroidopathy

PIC is an inflammatory disorder of the choroid which occurs predominantly in female patients with moderate myopia between the ages of 10 and 40. Although rare, CNV due to PIC is problematic due to the young age of patients at the onset of vision loss. [25-26] Current treatment consists of oral steroids with or without PDT. However oral steroid therapy is often unpopular with young female patients due to adverse effects such as weight gain.

Evidence relating specifically to the treatment of PIC with aVEGF is poor [37-39] with the majority of evidence originating from a single report of CNV due to mixed aetiologies which included 23 cases of PIC. [39] This probably reflects the comparative rarity of the condition although 20% of non-AMD CNV cases treated within NHS North East were for PIC. However, the evidence that is available is consistent in demonstrating benefits of treatment with IVB 1.25 mg at a mean of 2 to 3 doses in the first year and 3 to 4 doses by two years. [39]

Idiopathic CNV

Where a definitive cause of CNV cannot be identified, whether primary or secondary, the condition is known as idiopathic CNV. Evidence relating to the treatment of idiopathic CNV with aVEGF amounts to 63 cases, most with only three months' follow-up but some extending to two years. Again, the evidence is consistently in favour of a benefit of treatment with IVB, usually at a dose of 1.25 mg, with few adverse effects. [37,40,41] There have only been nine cases of idiopathic CNV out of 95 non-AMD CNV cases within NHS North East since June 2004.

Miscellaneous causes

There are numerous other known causes of CNV including inherited disorders, acquired inflammatory causes, and neoplasms. These have been collectively assessed in only a handful of non-comparative studies but all demonstrated an overall benefit of treatment with IVB. [37,39,42,43]

Summary of the clinical evidence

The bulk of the evidence amounts to a series of case reports without a control or comparator group, and where such groups are included allocation is not random leading to allocation and selection bias. This is an important weakness in the evidence base. The published evidence goes back as far as 2005 indicating that some treatment centres will have at least five years experience of treating non-AMD CNV with aVEGF therapies. The majority of the evidence relates to treatment of myopic CNV and this is not surprising given that it is the most common cause of non-AMD CNV. This is welcome given that half of relevant cases arising within NHS North East have also been myopic CNV. Evidence for the use of aVEGF therapy in the treatment of other types of non-AMD CNV is

particularly poor, for example in angioid streaks there are only five small case series reports.

With an absence of longer-term follow-up (> 1 year) it is difficult to assess the likely duration or steady-state frequency of treatment. The mean number of doses administered in the studies overall is about 3 per annum but this figure is skewed by those studies that employed a loading regimen. If these are excluded the mean number of doses is about 2 per annum.

A significant number of patients had received prior treatment with PDT or other therapies. This may have an impact on the potential success of subsequent aVEGF therapy. On balance it is likely that these patients represent more severe or advanced cases than would be expected if they had received aVEGF as first-line therapy, not least due to the temporal delay but also because failure to respond to PDT may indicate severe disease. Therefore it is reasonable to expect the outcome from first-line use of aVEGF therapy in practice to be at least as good as the outcomes reported in table 1.

No independently published guidelines applicable to UK practice, including guidance or advice from the Royal College of Ophthalmologists, concerning the use of aVEGF drugs for the treatment of non-AMD CNV was identified.

Safety

The safety aspects of use of aVEGF therapies for non-AMD CNV are not well reported in the relevant studies (see table 1). However the data that is available do not indicate any undue risk. There is extensive experience of the use of intravitreal aVEGF therapies in the treatment of AMD, including evidence from randomised controlled studies for ranibizumab [44-46] and large observational datasets for bevacizumab. [47-49]

Adverse effects of intravitreal aVEGF can stem from the method of administration, or systemic or local effects of the drugs. The safety of intravitreal bevacizumab has been described in a recent NETAG appraisal report. [50]

In summary, the safety of intravitreal ranibizumab and bevacizumab is considered acceptable with rare systemic effects, and few local complications or effects.

Audit and follow-up

The application states that the following will apply:

Treatment outcome will be monitored by assessment of visual acuity, tomography and, if required, angiography.

Adverse effects will be monitored by assessment of visual acuity, tomography, angiography, and via patient interview.

The following data will be routinely collected for audit purposes:

- The number of patients treated, and disease sub-type
- The number of intravitreal injections administered
- LogMAR visual change
- Mean change in vision (letters), monitored at 3, 6 and 12 months following the initial treatment
- Number of patients with vision improvement (gain ≥ 15 letters), stability (change < ±15 letters), or worsening (loss ≥ 15 letters)
- Any potential or actual complications

Practical Implications

Administration of intravitreal aVEGF for the treatment of non-AMD CNV is no different to administration in cases of AMD. Regional ophthalmology teams now have considerable experience in the treatment of AMD with ranibizumab therefore no additional training, staff, equipment or facilities are anticipated in order to accommodate cases of non-AMD CNV requiring intravitreal aVEGF.

The application states that if patients with non-AMD CNV are to be treated with an aVEGF drug they will be fully informed and counselled concerning the off-license nature of the treatment, and this will be documented. It may, however, still be necessary to provide them with the opportunity to pursue a licensed treatment option (i.e. PDT) if deemed appropriate.

If bevacizumab is to be used then hospital pharmacy departments will need to ensure they have made the necessary arrangements to purchase pre-filled syringes of the correct dose, that they are stored correctly, and that ordering is done in a timely manner to ensure there are no delays or waste. Bevacizumab syringes from a key supplier only have a two-week shelf-life from the date of manufacture. Other suitable suppliers may also be available. Ophthalmology teams will need to maintain communication with their pharmacy departments to ensure supplies are available when they are required.

Impact on patients

There is no evidence relating to the impact of intravitreal aVEGF vs. PDT from the patient perspective. Both treatments involve relatively minor ophthalmological procedures carried out on a day-case basis, assumed to be at a similar frequency and in that respect the impact on time (e.g. with respect to employment or on families) will remain the same. PDT involves the administration of an intravenous drug which is not required with intravitreal aVEGF therapy. Currently the only treatment centre within NHS North East that is able to deliver PDT is based in Newcastle, whereas centres at Newcastle, Sunderland, Teesside, and Darlington are all able to provide intravitreal aVEGF therapy. This means that patients will have a greater choice of treatment centre and may reduce the distance, duration, and cost of journeys. Both procedures result in some minor pain and discomfort for patients. Following intravitreal injections patients are required to use antibiotic eye drops for a short period. Importantly for patients there is a suggestion that longer-term outcomes (e.g. visual acuity) following aVEGF therapy are better than those achieved with PDT. This may be particularly important given that non-AMD CNV patients tend to be younger than AMD patients and are often in employment or have responsibility for children.

Pharmacoeconomic analysis

The use of aVEGF therapy for non-AMD CNV is assumed to represent a substitution for existing therapy, specifically verteporfin (Visudyne®) plus PDT. It is assumed that aVEGF therapy will be considered the first-line treatment option for cases of non-AMD CNV and that use of PDT for these patients will reduce to nil. In practice it is possible that some patients may not be suitable for aVEGF and will therefore still receive PDT and some other patients may fail to adequately respond to aVEGF and may therefore receive PDT as a second-line treatment option. Both of these scenarios will have an impact on overall cost of treatment per patient. There may also be some cases that would never have been considered for PDT but could now be treated with aVEGF. These would represent an additional healthcare burden and consequently additional costs.

The treatment regimen for aVEGF is assumed to be provided as a single initial dose followed by monitoring and subsequent doses only if clinically indicated based on visual acuity. An alternative is for three once-monthly injections followed by monitoring and additional doses as indicated. However there is no evidence that this more intensive, and more expensive, regimen provides better outcomes than the less intensive regimen for non-AMD CNV. The clinical criteria for repeat treatment with aVEGF are not explicitly defined and instead need is inferred from the mean number of doses administered.

It will be assumed that the mean number of treatment courses of PDT per eye is two per annum. This is based on a mean of 5.1 over two years as was observed in the VIP study [22] and a mean of 3.3 over four years in the case series reported by Ruiz-Moreno et al. [23] The VIP study results may represent excessive levels of treatment compared with actual practice because patients were intensively monitored within the controlled study. [22] Consequently, the more conservative treatment intensity realised by Ruiz-Moreno et al [23] is perhaps a more realistic scenario.

It will be assumed that the mean number of aVEGF treatments required is also two per annum per eye. The mean number of doses administered in the relevant studies is about three per annum, although this is skewed by studies that used a monthly loading dose regimen. When these studies are excluded the mean is reduced to about two per annum. There is little evidence concerning the longer term requirements, for example the study with the longest follow-up regarding the use of aVEGF (specifically IVB) reports a mean of 3.6 doses after two years. [39] Studies of ranibizumab indicate a similar dose frequency. [18-20] A treatment duration of two years is also the same as that currently anticipated for the treatment of AMD with aVEGF.

It will be assumed that treatment will only continue for two years after which either the condition has progressed such that no treatment option is suitable, or the patient has achieved a sustained recovery. Therefore, at any one time, there will be two annual patient cohorts receiving treatment at a mean of two doses per annum (i.e. four treatments in two years per eye).

VAT is applied to all relevant costs at 17.5% although the actual rate is currently 15% until 31st December 2009. Market forces factor rates are not applied to treatment costs as these vary depending on the provider trust. Current rates applicable to the relevant providers within NHS North East vary between 2.2 and 3.4%.

Following an earlier appraisal report concerning the potential use of intravitreal bevacizumab the group stated that the appropriate presentation of bevacizumab for future appraisals is single-use pre-filled syringes prepared by a third-party under a special manufacturing license. Such syringes are available from a range of suppliers; in this analysis it is assumed that they are purchased from Moorfields Pharmaceuticals. Potential risks of using bevacizumab from a third-party provider are continuity of supply and exposure to unexpected price fluctuations. In such situations a trust may find it is necessary or desirable to aseptically compound preparations itself however this will impact upon capacity of existing facilities and is likely to result in increased costs.

Drug costs: verteporfin (Visudyne®) is £999 per dose, bevacizumab pre-filled syringes are £100 each (excl delivery charges; currently £10 for between 1 and 4 items), and ranibizumab (Lucentis®) is £894 per dose. Antibiotic eye drops are usually indicated for a period following intravitreal drug administration. Such preparations are generally low cost (typically < £5 per episode) and have not been included in further calculations. The appropriate current tariff prices for treatment visits are £468 for intravitreal drug administration and £847 for PDT.

The cost per treatment episode (admission plus drug) is: £1,846 for PDT, £578 with bevacizumab, and £1,362 with ranibizumab. Estimated annual cost per patient (eye) is: £3,692 for PDT, £1,156 with bevacizumab, and £2,724 with ranibizumab. Cost per patient (eye) until treatment ceases after two years is estimated at: £7,384 for PDT, £2,312 with bevacizumab, and £5,448 with ranibizumab.

Currently the only centre within NHS North East than has facilities to provide PDT is based at Newcastle Hospitals NHS Trust. Therefore it is assumed that all NHS North East non-AMD CNV patients requiring treatment have been treated by this centre. The centre has provided data that indicates treatment of 95 patients over 40 months, corresponding to about 30 patients per annum. Assuming that this treatment rate remains stable and patients receive a mean of two treatments per annum for four years, the respective cumulative annual treatment costs (at current prices) are: £221,520 for PDT, £69,360 with bevacizumab, and £163,440 with ranibizumab.

Regardless of the assumptions based on the number of doses or duration of treatment, using the single assumption that the number of treatments of PDT and aVEGF are equal, compared with PDT, treatment with either ranibizumab or bevacizumab represents a substantial reduction in cost (about 26% and 69% respectively). Even if treatment with bevacizumab is required twice as often as treatment with PDT it will still represent substantially less cost than PDT.

Points to consider

A licensed treatment, Visudyne®, is available for the most common of non-AMD CNV cases (i.e. myopic CNV) which has proven efficacy in a randomised clinical trial. However the treatment is costly, the longer-term outcomes are not impressive, and it is considered to present greater safety risks compared to intravitreal aVEGF. No other drug treatments are licensed for any type of non-AMD CNV.

There is a growing evidence base for the use of aVEGF therapies, almost exclusively bevacizumab, in the treatment of non-AMD CNV. None of these studies are adequately randomised; most consist of case series reports with follow-up of between six and 12 months. However, follow-up does extend to 2 years. [39] The evidence is consistently in favour of clinically significant improvements for aVEGF at least as good as that expected with PDT, despite a large proportion of patients having previously been treated with PDT.

The safety profile of intravitreal aVEGF therapies for non-AMD CNV conditions is not well reported in the relevant studies but indicates a favourable risk:benefit profile. There is a substantial evidence base concerning the safety of intravitreal bevacizumab and ranibizumab, principally in AMD, from numerous studies. This demonstrates an acceptable safety profile with rare systemic effects and few local effects.

Use of either bevacizumab or ranibizumab will result in substantial cost reductions compared with existing treatment (i.e. PDT). Bevacizumab is substantially less costly than ranibizumab. Ranibizumab has been specifically formulated for intravitreal administration whereas bevacizumab has been formulated for intravenous administration.

No additional training, infrastructure, or hardware is considered necessary in case of a switch of treatment from PDT to aVEGF. Patients will be able to choose from a greater number of providers of aVEGF compared with PDT.

As the bulk of the evidence relates to myopic CNV can a recommendation be extended to cover all other non-AMD CNV cases, or should any recommendation be restricted only to those cases for which sufficient evidence is available or can non-AMD CNV be considered homogenously.

Drug and dose: The majority of studies used bevacizumab 1.25 mg.

Frequency: The majority of studies utilised a statim dose proceeded by monitoring and additional doses only as indicated. An alternative regimen is for monthly doses for three months followed by monitoring and additional doses only as indicated. There is no evidence of differences in efficacy or safety between the regimens.

Protocol: The appraisal is based on substitution of PDT with aVEGF only.

Guidelines: The criteria for treatment or re-treatment have not been explicitly defined. A suitable evidence-based guideline detailing such explicit criteria could be made a condition of a positive treatment recommendation.

Author's declaration

The author has participated in several non-promotional educational presentations sponsored by Novartis and has participated in two advisory boards specifically regarding ranibizumab (Lucentis®) in AMD.

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Appendix 1. Notes on visual acuity [26]

Visual acuity is a clinical measure of a patient's minimum angle of resolution, or sharpness of vision. Measurement is usually performed under conditions of high contrast using black alphabetic letters on an illuminated background ('lightbox'). Commonly used arrangements include the Snellen pattern and the Early Treatment Diabetic Retinopathy Study chart. Results of visual acuity can be presented in a number of ways. The familiar 20/20 refers to being able to read a piece of standard text at a distance of 20 feet. The metric equivalent is 6/6 vision representing six metres. These are equivalent to being able to resolve the difference between two pieces of text (characters) separated by about 1.6 mm at 6 metres distance. Visual acuity of 20/40 can be interpreted as the ability to see the same detail from 20 feet away as a person with 'normal' eyesight would see from 40 feet (i.e. poorer vision than normal). It is possible, and indeed common, to have vision superior to 20/20.

In the decimal system a value of 1.0 is equal to 20/20. The logarithm of the minimum angle of resolution (LogMAR) is another scale which has the advantage of converting the geometric sequence of a traditional chart to a linear scale. It is a measure of visual acuity loss with greater values representing worsening acuity. It is not often used clinically but is reported because it provides a statistically neater equivalent for the traditional statements of 'lines lost' or 'lines gained', which are valid only when all steps between lines are equal, which is not usually the case. Where available, LogMAR results are preferentially reported in table 1.

Visual acuity scales

Imperial (feet)	Metric (metres)	Decimal	LogMAR
20/200	6/60	0.10	1.00
20/160	6/48	0.13	0.90
20/120	6/36	0.17	0.78
20/100	6/30	0.20	0.70
20/80	6/24	0.25	0.60
20/60	6/18	0.33	0.48
20/50	6/15	0.40	0.40
20/40	6/12	0.50	0.30
20/30	6/9	0.63	0.18
20/20	6/6	1.00	0.00