North East Treatment Advisory Group

Bevacizumab (Avastin®) for neovascular glaucoma secondary to ischaemic central retinal vein occlusion

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Summary

- Neovascular glaucoma is an acutely painful condition that presents a severe threat to vision. It is often, but not exclusively, secondary to central retinal vein occlusion. It is currently treated with, sometimes multiple, treatment sessions of laser therapy with separate use of anti-glaucoma medication.

- Bevacizumab is an anti-vascular endothelial growth factor agent which is considered to provide several advantages over, and combined with, existing treatment options for NVG. It is not licensed for ophthalmic use.

- Bevacizumab in NVG has been reported in a large and increasing number of studies. However these are generally of low quality with small patient numbers, no randomisation and no control group. None have been specifically performed in NVG secondary to CRVO although the evidence indicates that outcomes are not different compared with other NVG cohorts. Relief of glaucoma and pain is often rapid. A benefit in terms of reduced need for, or facilitation of, laser therapy or other established therapies has not been demonstrated. Effects on visual acuity, whilst not the primary aim of treatment, are inconsistent.

- The safety of intravitreal bevacizumab has been established in many thousands of patients, although few specifically with NVG. The studies of bevacizumab in NVG did not realise any new or unexpected safety concerns.

- Intravitreal bevacizumab is a costly treatment at about £720 per dose with the majority of costs due to the cost of admission. It is not clear how many doses will be required per patient. An accompanying treatment algorithm specifies that after two doses subsequent doses should only be administered after individual application.

- The cost-effectiveness of bevacizumab for NVG has not been demonstrated. Clinical evidence indicates that it provides a useful new therapeutic option compared with existing treatments.

Introduction

Neovascular glaucoma (NVG) occurs when new fibrovascular tissue grows and blocks the route aqueous humour drainage. This obstruction leads to increased pressure within the eye known as glaucoma. The primary causes of NVG are many but principally involve diabetes, ocular ischaemic syndrome or central retinal vein occlusion (CRVO). In these diseases NVG is accompanied by low oxygen in the retina which stimulates the formation of new vessels. Where NVG is secondary to CRVO the onset is usually rapid with the majority occurring within six months of CRVO. [1,2]

Glaucoma itself can be acutely painful and presents a severe threat to vision. NVG generally has a poor prognosis with visual loss common, especially if there has been a delay to treatment. [1]

The prevention of growth of new blood vessels carries obvious appeal in treating NVG. [3] Currently NVG secondary to ischaemic CRVO is treated with laser therapy to obliterate the ability of new blood vessels to grow. This is highly effective but the laser must be directed accurately to the area(s) where new blood vessel growth is occurring. In addition, laser therapy is not useful for reducing the established vascular growths preventing the aqueous humour from flowing out of the eye and therefore has no effect on the glaucoma aspect of the disease. Often multiple laser treatment episodes are required. Laser treatment is difficult and sometimes impossible where the view of the damage is obscured, for example by intravitreal haemorrhage or cataracts. Inhibiting new vessel growth is an attractive option as it will target an upstream mechanism of the glaucoma itself which could help resolve the raised intraocular pressure (IOP) of glaucoma with attendant relief of pain and discomfort that is not possible with laser treatment. [1-3]

Bevacizumab (Avastin®, Roche) is a recombinant full-length antibody with activity against vascular endothelial growth factor. [4] It is licensed only for a number of neoplasms but has been extensively investigated and is widely used in several ophthalmic indications. It 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.

An application has been made for the use of intravitreal bevacizumab in neovascular glaucoma secondary to central retinal vein occlusion. The specific aims of treatment are to induce regression of neovascular growth, allow regression of haemorrhage and subsequently permit the use of standard retinal laser treatment to control pressure and reduce pain. Therefore the use of intravitreal bevacizumab in this indication can be considered as an adjunctive or facilitative treatment to laser therapy without an expectation of direct therapeutic benefit from the drug itself.

Clinical Evidence

A large amount of evidence, generally of low quality due to small sample sizes and non-comparative treatment allocations, exists for the use of bevacizumab in NVG. Table 1 describes in more detail the studies that are of greatest relevance to the treatment application.

In addition to the case series reported in table 1, a relevant systematic review of the use of bevacizumab in the treatment of NVG included indexed articles up to August 2008. [19] Of the studies in table 1, only three are included in the review. [8,17,19] The review does not specifically focus on NVG secondary to CRVO but instead considers evidence for NVG stemming from a wide range of primary causes. Meta-analysis was not performed on any outcome due to heterogeneity in important variables such as reported outcomes, disease characteristics and follow-up. A narrative analysis states: [20]

- The majority of studies (80%) consist of six or fewer patients
- There is a lack of medium and long term studies
- There is a suggestion that success of treatment [of IOP] improves visual acuity but this is difficult to demonstrate with the available evidence
- The relapse rate is about 20% with average follow-up of 4.2 months
- Safety problems are rare at less than 1%

Table 1. Key studies on the use of bevacizumab in neovascular glaucoma

Ref	Study design	Patients (n / eyes)	Intervention	Outcomes (CRVO only)	Outcomes (All)	Safety
6	Retrospective case series vs. control case series	NVG due to retinal ischaemia. Bev plus laser: 12 / 14 vs. Laser alone: 11 / 15 CRVO Bev plus laser: 5 Laser: 4	Bev 1.25 mg followed by single or multiple laser therapy sessions commenced within one week vs. laser alone	Not reported separately	Visual acuity: No changes in either group. No durable or reliable significant differences in changes of other parameters.	Not reported
7	Prospective case series	NVG with majority refractory to conventional treatments, most commonly laser therapy All: 50 / 52 CRVO: Not stated / 20	Bev 1.25 mg. Repeat injections for three patients, and two additional injections for one patient.	Not reported separately	Follow-up six months. 29 eyes with usable sight at baseline demonstrated significant improvement in VA with mean change from 1.8 to 1.5 (LogMAR) ($p = 0.03$). Of remaining 14 eyes, seven demonstrated no change, four worsened and three with no usable sight improved significantly.	Extensive use of multiple additional care to manage IOP (e.g. drainage devices) and other conditions (e.g. cataract removal)
8	Case series	NVG All: 6 / 6 CRVO: 4 / 4	Bev 1.25 mg with laser therapy about one month after each Bev dose. Two patients received repeat injections	Follow-up range 3 to 19 months (median 11). Visual acuity deteriorated in two patients, no change in one and improvement in one (although vision remained very poor).		Not reported.

Key: Bev – intravitreal bevacizumab; CRVO – central retinal vein occlusion; IOP – intraocular pressure; NVG – neovascular glaucoma

Ref	Study design	Patients (n / eyes)	Intervention	Outcomes (CRVO only)	Outcomes (All)	Safety
9	Prospective case series	NVG All: 23 / not stated CRVO: 7 /	3 x Bev 1.25 mg with four-week intervals	Follow-up 12 months. Improved vision in six patients, slight deterioration in one. Including drastic visual improvement in some patients.		Two CRVO patients required additional surgical intervention to control IOP
10	Retrospective case series	NVG, many despite previous treatments. All: 52 / 56 CRVO: not stated / 16	Bev 1.25 mg. Most patients also received post-Bev laser therapy as well as other treatments. More than half of eyes received a repeat Bev dose.		Median follow-up six months (range 0 to 18): Change in median visual acuity does not appear to be clinically significant with no gains in light perception and only small improvements in acuity.	
11	Prospective case series	NVG All: 12 / 14 CRVO: not stated / 4	Laser therapy followed immediately by a single dose of Bev 1.25 mg		Follow-up six months: VA had deteriorated in three, unchanged in eight, and improved in three eyes. All patients reported early onset of pain relief and showed substantial and significant reductions in IOP.	Twelve eyes demonstrated substantial regression of neovascularisation although by 10 months four eyes recurrence.
12	Retrospective case series	NVG All: 18 / 18 CRVO: 2 / 2	In the whole cohort, patients received one or two doses of Bev 1.25 mg and most also received laser therapy afterwards		Mean follow-up 1 year: BCVA improved by 0.31 LogMAR (p = 0.5)	Extensive use of a range of additional therapies. Adverse effects not reported.
13	Case series	NVG All: 18 / 20 CRVO: 6 / 6	CRVO patients only: Three intravitreal Bev 1.25 mg Two intracameral Bev 1.25 mg One 21 x intravitreal Bev 1.25 mg	Not reported separately	Mean follow-up 68 weeks (range 50 to 93): No significant changes in mean visual acuity at any time point. Mean IOP almost halved at 12 month follow-up.	Extensive use of a range of additional therapies. No treatment related complications occurred.
14	Case series (abstract only as article not in English)	NVG All: 20 / not stated CRVO: 8 / not stated	Bev 2.50 mg followed by laser therapy (interval unknown)		Follow-up 4.5 months: Extensive control of IOP, dependent on severity of NVG with more severe cases being more difficult to control.	

Ref	Study design	Patients (n / eyes)	Intervention	Outcomes (CRVO only)	Outcomes (All)	Safety
15	Case series (abstract only as article not in English)	NVG All: 12 / 13 CRVO: 2 / not stated	Bev 1.25 mg plus other therapy, particularly laser therapy.		Mean follow-up six months: Marked regression of neovascularisation and rapid relief of symptoms. IOP decreased substantially in eight eyes. Four required additional therapy.	One case of retinal detachment one month after Bev. Causality not established. No side effects observed.
16	Randomised trial	NVG All: 26 / 26 CRVO: 9 / 9	3 x Bev 2.5 mg at four week intervals (n = 14) vs. sham injections (n = 12)	Not reported separately	Mean follow-up 5.9 months: No significant change in visual acuity in either group at any time point. IOP and neovascularisation significantly decreased in bevacizumab patients, no change or increase in control patients.	Extensive use of additional treatments for the underlying condition for most patients. Four patients in the Bev group had mild transient hyphema. No serious adverse events in either group.
17	Case series	NVG secondary to ischaemia: 32 / 29 Also 9 / 7 with iris neovascularisation without glaucoma	Bev 1.0 mg. Repeat injection for 18 eyes, mean number of injections 1.6 per eye.	1 patient, not reported separately.	Mean follow-up 13 months (range 6 to 22): No changes in mean VA. VA increased ≥ 3 lines in 34%, no change in 46% and worsened ≥ 3 lines in 19%.Significant decreases in IOP, although many still required glaucoma specific treatments.	No treatment related adverse effects observed.
18	Retrospective case series	Iris neovascularisation and secondary angle-closure glaucoma: 14 / 14	Bev 1.5 mg. Repeat doses at 6 week intervals. Mean 1.8 doses per patient (range 1 to 3).		With follow-up > 4 months: Mean visual acuity not significantly different to baseline. Mean IOP decreased up to 9 months follow-up.	
19	Retrospective comparative case series	NVG not otherwise specified: 23 / 23.	Bev 1.25 mg and photocoagulation on same day (n = 11). Photocoagulation only (= 12)		Mean follow-up 143 and 118 days respectively: No significant differences in visual acuity but all trends in favour of combination therapy. No significant differences in parameters relating to IOP although most trends in favour of combination therapy.	Other than additional treatments for glaucoma, none reported.

Summary of the clinical evidence

There is a large and increasing volume of evidence for the use of bevacizumab in NVG. However, much of the current evidence is of low quality with only one small randomised study. Most originates from case series reports, either prospective or retrospective. In addition, it is difficult to isolate the effect of bevacizumab specifically in NVG secondary to CRVO from all other primary causes of NVG. The differential evidence that is available in CRVO does not indicate that outcomes differ compared with those for all NVG considered together and so this may not be crucial. The evidence base is also confounded by a large degree of heterogeneity across several variables. The dose, and to a lesser extent the regimen, of bevacizumab is perhaps one area where there is good agreement, with a single dose of 1.25 mg being the most commonly applied. This is the dose sought in the application to NETAG. The extent and nature of use of prior and post-bevacizumab therapies varies considerably and might reasonably be expected to have some bearing on outcomes. The desired application of bevacizumab in NVG secondary to CRVO is to facilitate laser photocoagulation. This was seldom stated as the aim of treatment in the studies but despite this laser photocoagulation was a commonly administered treatment in patients treated with bevacizumab.

The results of bevacizumab in NVG are consistent with most patients experiencing either an improvement or stabilisation of visual acuity. In addition, IOP usually demonstrates often drastic reductions to normal levels within a short period of time, and which persist in the long term. Measurement of IOP is somewhat confounded by the use of specific anti-glaucoma therapies. As most of the evidence is from non-comparative studies the confirmation and identification of the magnitude of any therapeutic effect is difficult. The few comparative studies indicate that outcomes are only marginally affected and that bevacizumab may be adding little benefit to patients.

The results summarised in table 1 have focused principally on outcomes of visual acuity as this is assumed to be the ultimate aim of treatment for non-life threatening eye conditions. However it should be noted that use of bevacizumab in NVG is consistently associated with other important outcomes such as reduced and stabilised IOP and pain. Ascertaining an isolated effect on IOP is confounded by extensive use of anti-glaucoma therapies and pain is typically secondary to IOP.

There is little evidence relating to the longer term effects on the use of bevacizumab for NVG regardless of the primary cause.

Safety

Intravitreal bevacizumab has been used in many thousands of patients for a multitude of indications. Appraisal of this evidence indicates that it does not present an increased risk compared with other intravitreal aVEGF therapies that have been specifically designed and formulated for ocular use. However, the use of an intravitreal injection in glaucoma might reasonably be expected to present additional safety concerns compared with use of intravitreal injections in other conditions. This is because intravitreal injection requires penetration of an eye which is already under increased hydrostatic pressure, into which an additional aqueous volume is being injected. Despite these potential risks the evidence from the available studies does not indicate an obvious increased risk of treatment. Indeed, intravitreal bevacizumab is frequently accompanied by rapid control of IOP although often other therapies are used at the same time. The overall number of patients from which this evidence is derived is small and in many of the reports adverse effects or other safety sequalae are poorly reported. Therefore considerable uncertainty remains over the true safety profile of intravitreal bevacizumab in glaucoma, or more specifically NVG secondary to CRVO. Isolated reports exist within the case series reports, or have been published as separate case reports of problems. For example, one case of central retinal arterial occlusion is reported believed to be caused by the increased aqueous volume following intravitreal bevacizumab injection. It is reported to have resolved rapidly following surgical alleviation of the raised IOP. [7] In other reports, IOP fails to resolve, even with bevacizumab, and surgical interventions are required although there is no causality assumed. The systematic review concludes that 'In 24 different studies (127 eyes) a very favourable benefit/risk to intravitreal bevacizumab on treating NVG was found'.

Cost analysis

Where applicable, costs include VAT at 20% unless otherwise indicated.

Bevacizumab is available in 100 mg vials for intravenous infusion, costing £291 each. [21] The preparation of syringes for intravitreal administration will require prior compounding. This can be done onsite, for example in pharmacy aseptic facilities, or pre-filled syringes can be purchased from third parties such as Moorfields Pharmaceuticals. NETAG has previously specified that the appropriate comparator for analyses is pre-filled syringes purchased from a third party provider. For that purpose, Moorfields Pharmaceuticals are able to supply pre-filled syringes containing bevacizumab 1.25 mg for about £85 each plus VAT and a delivery charge. [22] Thus each syringe is estimated to cost about £110. As well as the cost of a syringe an admission will be required. This is assumed to incur the payment-by-results tariff code BZ23Z 'vitreous retinal procedures – category 1'. This attracts a fee of £591 per admission, which combined with the market forces factor (typically between 2 and 3.5% for NHS North East provider trusts) [23] means that the total cost per dose of bevacizumab is about £720.

The use of bevacizumab in this indication represents additional health care use as it is intended as an adjunct to facilitate standard treatment with laser photocoagulation. Currently in complicated cases of NVG multiple laser treatment sessions may be required because the intended site for laser application is not always clear. Therefore the prior use of bevacizumab could increase the number of cases which receive only a single laser treatment session thus reducing the mean admission rate per patient. Each admission for laser photocoagulation is expected to incur a cost of £450 (based on laser treatment being carried out under payment-by-results tariff code BZ24C, 'non-surgical ophthalmology with length of stay 1 day or less and age 19 years and over'. [23] However as there is currently no evidence to support this assumption an additional admission per bevacizumab injection will be assumed.

If intravitreal bevacizumab is to be administered within the same appointment session as that which is scheduled for laser photocoagulation, as was reported in some studies, then an additional admission would not be required. A treatment algorithm (flow-chart) included as part of the application indicates that this would not be the intended practice (see appendix 1).

Estimating the number of patients within NHS North East is complicated by the highly specific nature of the indication. No relevant epidemiological data was identified. The application for use within a single trust estimates 10 patients per annum although the epidemiological data to support this estimate is not known. If it is assumed that this estimate is correct, then on the basis of ratios of treatment of age-related macular degeneration across NHS North East ophthalmological units, it is estimated that there will be 25 patients per annum within the region. If all patients receive a single dose the cost of bevacizumab alone is estimated at about £2,750 per annum. Evidence from the largest cohort of NVG patients (not specifically secondary to CRVO) for which the appropriate data is available indicates that repeat injections are not often required, with a mean of 1.1 injections per patient. [7] Thus the estimated cost for bevacizumab only for NHS North East is about £3,000. The overall cost is substantially increased when admission costs are included with an additional £15,000.

Table 1. Annual cost per PCO for bevacizumab for NVG secondary to CRVO based on estimate of 25 patients within NHS North East per annum.

	Estimated number of patients	Estimated cost of bevacizumab	Estimated cost with admission
NHS Durham & Darlington	6	£725	£4,325
NHS North of Tyne	8	£970	£5,770
NHS South of Tyne & Wear	6	£725	£4,325
NHS Tees	5	£605	£3,605
NHS North East	25	£3,025	£18,025

Points to consider

Bevacizumab is not licensed for any ophthalmic indications although it has been extensively studied for numerous indications and has previously been recommended by NETAG for other indications.

The application for use of bevacizumab as an adjunct to standard treatment (usually laser photocoagulation) in NVG secondary to CRVO is highly specific. No studies specifically for this indication have been reported however a large number of generally low quality studies have been reported for bevacizumab in NVG due to numerous causes. A significant proportion of the patients in these reports have NVG secondary to CRVO although reporting of results for this sub-group is poor. Where results are reported separately they demonstrate little or no difference to that seen in the overall group. Generally, visual acuity is modestly improved or at least stabilised. IOP is drastically reduced in a short space of time and pain is usually reduced. Numerous confounders, such as non-comparative data and use of additional treatments, mean that results should be interpreted with cautiously.

The safety of intravitreal injections, and intravitreal bevacizumab specifically, has been established in large cohorts of patients for numerous indications. The incidence of serious adverse effects is low. In the reported studies in NVG [6-19] no new, unexpected, or increased incidence of adverse effects was observed. The use of additional treatments, in particular laser photocoagulation and anti-glaucoma treatments, was extensive but expected within this population. Indeed, the application for use of bevacizumab in NVG secondary to CRVO is as an adjunctive treatment to facilitate targeted laser photocoagulation.

Although each dose of bevacizumab is not itself particularly expensive, overall treatment costs are high due to the cost of admission. There are potential offset costs if subsequent admissions for, for example, additional laser treatments, can be avoided although there is no evidence to support this. Estimated patient numbers are low, at 25 within the region per annum, although these have not been independently verified.

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Declaration of interests: The author has no relevant interests to declare.

Appendix 1. Proposed treatment pathway for NVG secondary to CRVO