North East Treatment Advisory Group

Pre-operative use of anti-vascular endothelial growth factor agents prior to vitrectomy for patients with diabetic retinopathy

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Summary

- Vitrectomy is a significant ophthalmic surgical procedure that is used to restore vision in diabetic patients who have suffered vitreal haemorrhage due to diabetic retinopathy.

- Vitrectomy is a delicate procedure that can be complicated by vascular adhesion and further damage to fragile vessels.

- Anti-vascular endothelial growth factor agents specifically, bevacizumab (Avastin®) and ranibizumab (Lucentis®), inhibit, and potentially cause the regression of, neovascular growth.

- There is limited evidence that when administered intravitreally prior to vitrectomy they reduce the complexity of surgery (use of fewer instruments, reduced need for techniques such as diathermy, and shorter duration) and intra- and post-operative complications such as haemorrhage.

- Use of aVEGF therapies in this scenario will present an additional treatment risk with respect to drug exposure and the technique of intravitreal administration. However the risk of local or systemic effects from aVEGF drugs appears to be small and ophthalmologists are experienced in the intravitreal administration of drugs. These risks should be considered against changes in the risk of events during and following vitrectomy.

- All of the published evidence relates to the use of bevacizumab, although the doses used vary from 1.0 mg to 2.5 mg, with most patients having received 1.25 mg. The preferred option stated in the treatment application is bevacizumab 1.25 mg.

- There is considerable variation in the length of period between drug administration and surgery, ranging from two to 30 days. There is also some uncertainty as to the optimal period with some recommending no more than, and others no less than, seven days. The treatment application states between two and ten days with a target of three to seven days.

- Use of intravitreal aVEGF therapy in this scenario represents an additional treatment burden with associated impact on patients and costs. The estimated cost to NHS North East based on 40 patients per annum is £23,000 with bevacizumab and £54,500 with ranibizumab. Non-drug costs represent a substantial part of the overall cost of treatment.

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 use prior to surgical vitrectomy for patients with advanced proliferative diabetic retinopathy. The application has the support of ophthalmologists within NHS North East.

The application states that patients will be admitted to a specialist ophthalmic centre, on an outpatient basis, two to ten days (target three to seven days) prior to their planned date for surgery. An intravitreal dose of an anti vascular endothelial growth factor (aVEGF) drug will be administered during this appointment. The application indicates that bevacizumab at a dose of 1.25 mg is the preferred option although ranibizumab at a dose of 0.5 mg is included as an alternative.

Both drugs are semi-synthetic aVEGF molecules that inhibit the growth of new blood vessels and 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 ophthalmic conditions, although predominantly age-related macular degeneration (AMD). It is not licensed for any ophthalmic indications.

Ranibizumab (Lucentis®, Novartis) has been available in the UK since February 2007. It is only licensed for the treatment of neovascular (wet) AMD at a dose of 0.5 mg, with multiple doses required. [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. At equimolar concentrations within vitreous humour ranibizumab has greater affinity than bevacizumab for VEGF although the clinical significance of this difference is not clear. [1,3] 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]

Proliferative diabetic retinopathy is a condition in which small new blood vessels form on the retina and optic disc of the eye in response to retinal ischaemia due to microvascular occlusion, a common complication of diabetes. [8-10]

The vitreous cavity is a space of about 4.5 cm^3 volume located behind the lens and extending to the retina. The space is occupied by vitreous humour, a transparent jelly-like material that seems only to provide volume and mass. [8,9]

If an eye with proliferative retinopathy is not treated the fragile new vessels will bleed into the vitreous cavity resulting in a vitreous haemorrhage. This can result in impaired vision or blindness due to the loss of translucency of the humour. [8-10]

Vitrectomy is a surgical procedure involving removal of the vitreous humour via aspiration through small holes made in the white of the eye. Once the humour has been removed any leaking blood vessels can be sealed. The procedure can vary in complexity and can take up to three hours. Patients will usually require a short hospital stay. Eventually the vitreous humour is replaced by aqueous humour and normal vision is restored. [8,9]

The rationale for using aVEGF therapies prior to surgery is principally to reduce intraoperative complications resulting from excessive haemorrhage of sensitive membranes which are already complicated by additional neovascular growth. Additional benefits may also be realised from fewer and less serious post-operative haemorrhagic complications, faster and improved recovery, and improved outcomes relating to visual acuity and vision. [11] The application to NETAG only cites a reduction in intraoperative complications as the indication for use.

Clinical evidence

A number of studies have been identified that describe quantitative and narrative experiences of surgery following pre-operative use of aVEGF drugs from the perspective of the surgical operators.

Oshima et al report the largest group of patients to have received pre-operative intravitreal bevacizumab as an adjunct to vitrectomy for diabetic eye disease, specifically diabetic retinal detachment. Their data is from a sequential case series report of 26 patients (33 eyes) treated without the use of bevacizumab and, following a change in practice, outcomes of 33 patients (38 eyes) treated with intravitreal bevacizumab (IVB) 1.0 mg administered between two and 30 days before surgery (mean 8 days). Mean follow-up was 18 months in the surgery-only group and 12 months in the IVB plus surgery group. The results show that mean operating time was significantly reduced (123 minutes vs. 85 minutes) and significantly fewer instruments were required during surgery. Additionally, six-month post-operative BCVA LogMAR was better in the IVB group than the surgery-only group (mean change -0.81 vs. -0.47, $p = 0.18$). The primary and ultimate retinal reattachment rates were high and did not differ significantly between groups. Adverse events and other sequelae are extensively reported. Post-operative haemorrhage developed in 13% and 27% of eyes respectively with repeated vitrectomy required in five eyes in total. Neovascular growth occurred in 40% and 67% of eyes and recurrent retinal detachment in 5% and 9% respectively. [12]

Rizzo et al report intra- and post-operative results of a small randomised study in patients with proliferative diabetic retinopathy. Twenty-two patients (mean age 52 years, range 24 to 63) underwent vitrectomy with 11 randomised to receive IVB 1.25 mg five to seven days before surgery. Patients were assessed pre-operatively with respect to disease complexity, and the groups were well balanced in this respect and the underlying indications for surgery. The mean surgical time was 57 minutes in the IVB group and 83 in the control group. The mean number of tool exchanges was 27 in the IVB group compared with 53 in the control group. There were 3 vs. 7 cases of mild intra-operative bleeding, 2 vs. 9 cases of severe intra-operative bleeding, and 2 vs. 9 instances of diathermy during surgery in the IVB and control groups respectively. Pre-operative visual acuity (BCVA LogMAR) was 1.87 and 2.04, and at six months post-operation had changed to 0.88 and 2.01 in the IVB and control groups respectively. No adverse effects due to IVB were observed. [13]

The IBeTra study was a semi-randomised open study designed to compare the rate of intraoperative bleeding in diabetic patients undergoing vitrectomy with and without preoperative IVB. Twenty patients were recruited (age range 42 to 66 years, 10 male). Treatment allocation was performed by random selection with the next patient automatically receiving the alternative treatment. This resulted in ten patients in each treatment group, which were well balanced with respect to several parameters. The majority (15) had received prior photocoagulation therapy. Patients allocated to IVB received 1.5 mg two weeks prior to surgery.

The main outcome measure was the erythrocyte count of the fluid retrieved from the vitrectomy instruments, with higher counts taken to represent a greater degree of intraoperative haemorrhage. The mean count was 14,865 x 10^3 for patients in the IVB group and 176,240 x 10^3 for patients without IVB ($p < 0.0001$). [14]

Romano et al report the results of a prospective pilot study of preoperative IVB in 31 patients (32 eyes) with proliferative diabetic retinopathy due to undergo vitrectomy. Patients (19 male) had a mean age of 46 years (range 34 to 68) and received IVB 2.5 mg between four to seven days prior to surgery. Patients received a further IVB 2.5 mg dose at the end of surgery. The authors report a narrative of their experience of the intraoperative period

> *"Preoperative IVB injection proved to be helpful in minimizing the intraoperative bleeding … . Less bleeding facilitates surgery and, in theory, makes it safer by reducing the need to raise intra-ocular pressure for haemostasis in these patients, who already have impaired retinovascular perfusion. Very little intraoperative bleeding was noted when cutting fibrovascular tissue that showed the presence of neovessels at ophthalmoscopy before the injection of bevacizumab."*

At six months post-operation there were no vitreous haemorrhages in 29 eyes, moderate haemorrhage in one eye, and severe hemorrhage in 2 eyes compared with 15 severe and 17 moderate haemorrhages prior to surgery. Visual acuity (mean BCVA LogMAR) had improved from 1.6 to 0.4 in 29 eyes and remained stable in three. A number of adverse events were reported but none were causally associated with IVB. [15]

Yeoh et al report a prospective case series from 16 patients involving 18 eyes (mean age 46 years, range 28 to 61) who were due to undergo vitrectomy for complications arising from severe proliferative diabetic retinopathy. These patients were selected due to certain risk factors and received IVB 1.25 mg a mean of 9 days (range 6 to 14) prior to surgery. At six months post-surgery 14 eyes had improved acuity, one was unchanged and three were worse. These results are not collectively quantified. At the same time point, seven eyes had re-bled with a mean lag time of 44 days (range 7 to 81). No adverse events were observed other than those related to the disease or the procedure. The authors report their experiences of the intraoperative period: [16]

> *"At the time of surgery, we observed that eyes treated with Avastin had significant regression of the vascular component ….. This made surgery technically easier, as the fibrovascular complex was readily separated from the retina with less intraoperative bleeding, which in turn provided better visualization. … the observation was made by all the consultants on the vitreoretinal unit, experienced in diabetic vitrectomies, that the fibrovascular membranes were not as adherent to the retina as would have been expected without preoperative Avastin, and they certainly did not bleed as much. In our series, we needed intraoperative diathermy in only six cases, but would have expected to use it in the majority of similar diabetic cases."*

Liu et al report the use of pre-operative bevacizumab in 13 patients (15 eyes) with diabetic retinopathy. IVB 1.25 mg was administered 3 to 14 days prior to vitrectomy which included the intraoperative administration of triamcinolone. They report that bleeding occurred in the one eye that received IVB only three days before surgery, and the remaining 14 eyes had little haemorrhage. No adverse effects occurred. They conclude that IVB 7 to 14 days prior to vitrectomy with triamcinolone can reduce the risk of haemorrhage and facilitate surgery. [17]

Ishikawa et al report their experience of using IVB preoperatively in six patients (eight eyes) undergoing vitrectomy due to severe proliferative diabetic retinopathy. The principal aim of the study was to ascertain the optimal time for preoperative administration of IVB. Patients were aged between 33 and 64 years. IVB 1.25 mg was administered using the following pre-operation intervals: 3 days for two eyes, 5 days for one eye, 7 days for three eyes, 8 days for one eye and 30 days for one eye. Summary quantitative results are not presented however the authors report generally positive experiences which they attribute to the use of IVB and suggest that a shorter pre-surgery interval is suitable and possibly preferable to intervals ≥ 7 days. No adverse effects related to IVB are reported. [18]

Summary of the clinical evidence

The evidence base for the pre-operative use of aVEGF therapies prior to vitrectomy for patients with proliferative diabetic retinopathy is generally poor. Some of the evidence is not directly applicable to the application due to, for example, use of bevacizumab doses other than 1.25 mg, administration earlier than 10 days prior to surgery, co-administration of steroids, or additional intra-operative administration of bevacizumab. All of the evidence relates to the use of bevacizumab although no consistent dose is used, with most using 1.25 mg and others 1.0, 1.5 or 2.5 mg. It is also not clear as to the optimum time for drug administration prior to surgery with some authors recommending no more than seven days, and others stating that it should be no less than seven days. Within the studies the period ranges from two to 30 days. Evidence is largely from several case report series without a control group. The one adequately randomised study has only small patient numbers and no firm conclusions can be drawn from this, a point that the authors make themselves. [13] The other randomised study also used few patients, a higher dose of bevacizumab (1.5 mg), and reported a surrogate outcome of unknown clinical significance. [14] The largest case series report relates to a specific complication of diabetic retinopathy (tractional retinal detachment) and utilised a lower dose (1.0 mg). [12] Quantitative results are infrequently and inconsistently reported but all show the same effect with IVB: shorter duration and less complex surgery, and fewer immediate post-operative complications. However some of the surgical parameters that are reported may be subject to high levels of variation regardless of the use of IVB, with potential causative factors relating to the patient, surgical team, common practice or guidelines, or the local health infrastructure. Narrative descriptions of surgery support the quantitative data but are clearly subject to several sources of bias.

Of particular interest is the suggestion that medium-term visual acuity is better in patients who have received bevacizumab although this is provided by only one small study [13] and is by itself a weak signal.

Other strategies have also been studied to assess their effect at reducing the risk of surgical complications during vitrectomy although none have been successfully incorporated into practice. For example sodium hyaluronate was compared with saline placebo in 26 patients and produced significantly less media opacity. However the benefit was no longer detectable after two weeks suggesting only short term effects. Another study investigated the use of thrombin in 28 patients and reported significantly reduced bleeding time (12 vs. 111 seconds) although at the expense of greater risk of intraocular inflammation. [19]

Safety

None of the reports previously referred to investigated adverse effects of pre-operative bevacizumab as a primary aim. [12-18] In general adverse effects are poorly reported. It must be remembered that a high frequency of adverse events or complications could be expected in this patient group given the nature of the procedure and the fragile state of the eye(s) being operated on. Most reports focused on the intra- and post-operative period with little or no reference to the pre-operative administration of bevacizumab. In this respect, the use of bevacizumab would be expected to present an additional risk with regards to the process of intravitreal administration and exposure to bevacizumab itself. This has to be balanced against an apparent reduction in the risk of intra- and post-operative complications, e.g. consistently reported reduced incidence of haemorrhage. One report identifies the rapid progression of pre-existing retinal detachment is 18% of eyes treated with IVB. [12]

A case report highlighting a complication from using pre-operative IVB makes an association with the presence of a macular hole (cyst) in previously unaffected tissue. The hole was 'managed conventionally' and the patient made an otherwise uneventful recovery. The authors recommend investigation of lower doses of IVB in this setting. [20]

One other case report describes the emergence of newly developed multiple extensive retinal haemorrhages in an elderly female patient. The patient had received prior treatment for diabetic retinopathy but had subsequently suffered vitreous haemorrhage and faintly visible multiple retinal haemorrhages. She had then been treated with vitrectomy, phacoemulsification with lens implant, photocoagulation and IVB 1.25 mg immediately post-surgery. The authors conclude that IVB may require more cautious use as an adjunct to surgery in patients with diabetic retinopathy. [21]

There is extensive experience of the use of intravitreal aVEGF therapies in the treatment of AMD, including evidence from randomised controlled studies for ranibizumab [22-24] and large observational datasets for bevacizumab. [25-27]

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. [28] So far no significant risk of local or systemic adverse effects has been confirmed.

Impact on patients

There is no direct evidence relating to the impact on patients. Patients will require at least one additional hospital visit for a relatively minor ophthalmic procedure (intravitreal injection) which entails some limited pain and discomfort as well as use of antibiotic eye drops for a period following the procedure. As many patients with diabetic retinopathy are of working age this may have an impact on employment for some patients or their families. However there may also be benefits from reduced duration of surgery (vitrectomy) and fewer intra- and post-operative complications. Additionally, there is some limited evidence for the benefit of aVEGF drugs in diabetic retinopathy, even without vitrectomy, with resultant effects on visual acuity.[29] Patients may therefore utilise less healthcare in the future.

Practical considerations

Regional ophthalmology teams have considerable experience in the treatment of AMD with intravitreal ranibizumab therefore no additional training, staff, equipment or facilities are anticipated to support the use of intravitreal aVEGF pre-vitrectomy.

If a pre-vitrectomy aVEGF drug is deemed appropriate it is recommended that patients are fully informed of the off-license nature of the treatment that is being offered, and counseled concerning the expected risks and benefits. This aspect of the consultation should be documented.

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.

Pharmacoeconomic analysis

The use of pre-operative aVEGF drugs prior to vitrectomy represents an additional use of healthcare resources without substitution. The application refers to use of either bevacizumab 1.25 mg or ranibizumab 0.05 mg. There is no published evidence relating to ranibizumab in this situation although its mode of action is the same as bevacizumab and ophthalmologists in the region have extensive experience of using the drug. Following an earlier appraisal report concerning the potential use of intravitreal bevacizumab the group decided that the appropriate presentation of bevacizumab for future appraisals should be 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.

The shelf life of pre-filled bevacizumab syringes from Moorfields Pharmaceuticals is two weeks from date of manufacture.

VAT is included, where appropriate, at a rate of 17.5% although the current rate of VAT is 15% until 31st December 2009.

It is assumed that no additional pre-operation check-up visits or appointments are required other than a single day-case admission for administration of intravitreal aVEGF therapy. The current indicative price for such an appointment is £468 per episode per patient, excluding the market forces factor (currently between 2.2 and 3.4% for relevant trusts). Costs are displayed in table 1.

Table 1. Drug and treatment costs of intravitreal aVEGF

	Drug cost (incl VAT at 17.5%)	Cost including administration
Bevacizumab (pre-filled syringes from Moorfields Pharmaceuticals, including delivery charge)	£110	£578
Ranibizumab	£894	£1,362

Prices correct for year 2009-10

The application estimates that about 40 patients per year will be treated with pre-vitrectomy aVEGF. On this basis the total annual cost to NHS North East is estimated at £23,000 with bevacizumab and £54,500 with ranibizumab. The total cost will be particularly sensitive to the number of patients requiring treatment. No independent verification of the estimated number of patients has been possible. Costs per PCT based on 40 patients per annum in NHS North East are displayed in table 2.

Table 2. Estimated cost per drug per PCT and PCO

PCO	PCT	% NHS North East population	Adjusted estimated no. patients	Bevacizumab	Ranibizumab
Durham	Co. Durham	19.9%	8	£4,624	£10,896
	Darlington	3.8%	2	£1,156	£2,724
	Total	23.7%	10	£5,780	£13,620
South of Tyne	Gateshead	7.6%	4	£2,312	£5,448
	South Tyneside	5.9%	3	£1,734	£4,086
	Sunderland Teaching	10.7%	5	£2,890	£6,810
	Total	24.2%	12	£6,936	£16,344
Tees	Hartlepool	3.6%	2	£1,156	£2,724
	Middlesbrough	5.6%	3	£1,734	£4,086
	North Tees	7.4%	3	£1,734	£4,086
	Redcar and Cleveland	5.2%	3	£1,734	£4,086
	Total	21.7%	11	£6,358	£14,982
North of Tyne	Newcastle	10.2%	5	£2,890	£6,810
	North Tyneside	8.0%	4	£2,312	£5,448
	Northumberland Care	12.2%	5	£2,890	£6,810
	Total	30.3%	14	£8,092	£19,068
Total			47	£27,166	£64,014

Note: The total number of cases, and consequently costs, is greater than that estimated in the application (47 vs. 40) due to rounding up of non-integer values.

Other costs that may fall on healthcare budgets and that have not been included in this analysis include:

- Patient transport costs, although these are often not borne by healthcare budgets and represent relatively small values.
- Costs arising from complications of intravitreal drug administration (e.g. infection). However ophthalmologists are experienced in intravitreal drug administration and complications are rare. Prophylactic ocular antibiotics are routinely used and infective complications are uncommon.
- Unforeseen delays to surgery (vitrectomy) resulting in requirement for re-administration of aVEGF. No data is available concerning the frequency or duration of such delays.
- Greater number of patients. The incidence of diabetes is increasing year on year and it is likely that in the future greater numbers of patients will require ophthalmic surgery for diabetic retinopathy.

It may be possible to offset certain costs against the cost of aVEGF. It has not been possible to quantify or estimate any of these costs. Those that will be of benefit to the healthcare providers include:

- Reduced duration of surgery.
- Reduced complexity of surgery, resulting in use of fewer instruments and other ancillary equipment.
- Reduced complications of surgery resulting in shorter duration, more predictable and quicker recovery, and earlier discharge.
- Reduced post-operative complications.

Potential offset costs that may benefit healthcare purchasers include:

- Reduced post-operative complications resulting in fewer discharge delays (shorter hospital stay) or re-admissions.
- Improved outcomes resulting in reduced future healthcare use.

Audit and follow-up

The applicants have indicated a willingness to perform regular audits of cases where aVEGF is used pre-vitrectomy at annual intervals for at least the first three years after use is approved and commenced.

Patients with diabetic retinopathy who are treated with vitrectomy are regularly followed up typically at 1 day, 1 to 2 weeks, and 1, 3, 6 and 12 months. No additional post-operative healthcare use due to the use of pre-operative aVEGF is anticipated.

Points to consider

- Are the potential benefits of pre-operative use of aVEGF balanced by the cost, safety, and impact on patients. What level of confidence can be put on the results of the studies and are they applicable to NHS North East.
- Is it necessary to specify a preferred drug, is bevacizumab or ranibizumab preferred. All of the published evidence relates to bevacizumab. Ranibizumab is used extensively within NHS North East and was designed for intravitreal administration. Ranibizumab is substantially more costly than bevacizumab.
- Is a limit required on the annual number of patients who can receive this treatment so as to minimise exposure and contain costs within those projected in the analysis.
- Are the proposed audit and follow-up processes sufficient to ensure appropriate and safe use.

Authors 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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