Northern (NHS) Treatment Advisory Group

Sequential pharmacological therapies in the management of macular oedema secondary to retinal vein occlusion

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Introduction

Retinal vein occlusion is a common vascular abnormality associated with conditions such as hypertension, diabetes, glaucoma and other vascular and haematological disorders. One of the consequences of occluded veins in the retina is impaired haemostatic clearance leading to increased pressure in the retinal vasculature. This is turn can damage the retinal microvasculature causing the vessels to leak or haemorrhage. The leakage will affect the macular and lead to macular oedema, a common cause of loss of visual acuity and blindness in patients with retinal vein occlusions. The macula is the central part of the retina responsible for colour vision and perception of fine detail (i.e. visual acuity). Other complications of retinal vein occlusion include vitreous haemorrhage, ischaemia and neovascularisation, all of which can cause or compound loss of vision. [1-3]

The condition is sub-divided into two main classifications; either central (CRVO) or branch retinal vein occlusion (BRVO) depending on the site of vascular occlusion. This distinction is important with respect to the prognosis and treatment parameters. Generally, CRVO will result in greater visual impairment than BRVO and is more difficult to treat. More than one BRVO may exist, and BRVO may also exist in conjunction with CRVO. Usually only one eye is symptomatic although bilateral retinal vein occlusions are relatively common. Symptomatic BRVO is about twice as common as CRVO. [1-3]

The annual incidence of RVO has been estimated based on a 15-year study which reported 500 new cases of CRVO and 1,800 cases of BRVO per 100,000 people aged 43 to 84 years. [4,5] The National Institute for Health & Care Excellence (NICE) has estimated that 22 patients per 100,000 of the population would require pharmacological treatment for RVO. [6] It is not known what proportion of these patients may require sequential pharmacological treatment.

In BRVO laser therapy is used to restore visual acuity where visual loss is not severe. Restoring visual acuity in patients with macular oedema secondary to CRVO is more difficult and laser therapy is not used as studies have demonstrated no improvement [1,7]

NICE has recommended two pharmacological treatments for macular oedema secondary to RVO (box 1), differentiated according to whether the occlusion is central or branch. [1,6]

Box 1. NICE recommendations for pharmacological treatment of RVO

Dexamethasone intravitreal implant (Ozurdex®)

Dexamethasone intravitreal implant is recommended as an option for the treatment of macular oedema following BRVO when treatment with laser photocoagulation has not been beneficial or is not considered suitable because of the extent of macular haemorrhage. [1]

Dexamethasone intravitreal implant is recommended as an option for the treatment of macular oedema following CRVO. [1]

Ranibizumab (Lucentis®)

Ranibizumab is recommended as an option for treating visual impairment caused by macular oedema following BRVO when treatment with laser photocoagulation has not been beneficial or is not considered suitable because of the extent of macular haemorrhage. [6]

Ranibizumab is recommended as an option for treating visual impairment caused by macular oedema following CRVO. [6]

Ozurdex® (Allergan Pharmaceuticals) is a biodegradable ocular implant that contains dexamethasone and is licensed for the treatment of macular oedema secondary to branch or central retinal vein occlusion. It is available in a complete drug delivery system for intraviteal injection directly through the white (sclera) of the eye. The implant contains 700 micrograms of dexamethasone which is slowly and inconsistently released over a period of six months. Its principal mode of action in macular oedema is believed to be via inhibition of vascular endothelial growth factor (VEGF), thus inhibiting the growth of new blood vessels which are often leaky and which can themselves obscure vision. [8-11] The target frequency for administration of Ozurdex®, based on experience in clinical studies, is six-monthly and it is not recommended that two eyes are treated concurrently. [8,12-14]

Ranibizumab (Lucentis®, Novartis) belongs to a class of drugs that specifically block the action of VEGF. In RVO vision is reduced as a result of retinal vascular disease. Thromboses in the retinal veins can increase retinal capillary pressure, resulting in increased capillary permeability and the discharge of blood and plasma into the retina. This leads to macular oedema and varying levels of ischaemia through reduced perfusion of capillaries. These changes trigger an increase in VEGF, which increases vascular permeability and new vessel proliferation. [6] By inhibiting the action of VEGF ranibizumab can reduce oedema and limit visual loss or improve vision. Hence the basis for inhibiting VEGF in RVO. [6] Bevacizumab (Avastin®, Roche) is a distinctly different molecule to ranibizumab although its pharmacological activity is identical. Despite not being licensed for ophthalmic use it is used in various ophthalmic indications including RVO outside of its product license.[15]

Ranibizumab and bevacizumab are typically administered via intravitreal injection at monthly intervals initially and then as required depending on response. [15]

The Northern (NHS) Treatment Advisory Group (N-TAG) has been requested to conduct an appraisal of, and issue a subsequent recommendation in relation to, the sequential pharmacological treatment of macular oedema secondary to retinal vein occlusion with Ozurdex® after ranibizumab or bevacizumab, or with ranibizumab or bevacizumab after Ozurdex®.

The scope of this appraisal will relate principally to pharmacological treatments for RVO which have been recommended by NICE. [1,6] In addition, due to the biological commonalities between ranibizumab and bevacizumab, the latter drug, although not licensed for RVO, will also be considered within the scope of this appraisal.

Clinical evidence

Only one directly relevant source of evidence for the sequential use of treatments within the scope of this appraisal was identified. [16]

This involved the use of Ozurdex® after a lack of response with bevacizumab. This small retrospective review of records (n = 18) found modest but clinically significant benefits from a switch in therapy to Ozurdex®. [16]

Other useful evidence of less relevance includes a non-comparative prospective study of dual therapy with bevacizumab and Ozurdex®. [17] Patients (n_{eyes} = 34) received intravitreal bevacizumab followed two weeks later with an Ozurdex® implant. Overall results in terms of visual acuity and macular thickness were positive, and the authors reported a lower than expected re-treatment rate after six months. [17]

In a similar study patients were treated with three monthly loading doses of bevacizumab followed by an Ozurdex® implant (n_{eyes} = 26) compared with Ozurdex® alone (n_{eyes} = 38). Results at six months did not support the use of combination therapy compared with Ozurdex® monotherapy. [18]

The key studies which supported the license for ranibizumab in RVO (CRUISE and BRAVO) specifically excluded patients with recent prior treatment of any nature. [19,20] The key study of Ozurdex® in RVO (GENEVA) was conducted before ranibizumab was commercially available for RVO and is unlikely to have been a common prior treatment. [21]

Safety

In the limited evidence relating to sequential treatment safety outcomes were poorly reported. No new or unexpected adverse effects or other safety sequalae were reported. [16]

Both Ozurdex® and ranibizumab have been in use for a number of years for various indications and have established an acceptable risk:benefit ratio.

There are differences in the treatments which could lead to theoretical differences in safety profiles. For example, Ozurdex® is administered less frequently with one implant per eye once every four to six months, [12] whereas ranibizumab and bevacizumab may be administered as frequently as monthly, with regular monthly check-ups in the interim. [15] The Ozurdex® needle is slightly larger than those usually used for intravitreal injections. [12] No direct comparative evidence was identified to show that needle size or injection frequency affect adverse effect rates.

Both treatment modalities are associated with raised intra-ocular pressure (IOP). Although not in direct comparison, Ozurdex® does appear to be associated with a greater frequency and severity of raised IOP than intravitreal bevacizumab or ranibizumab. In the pivotal GENEVA study [21] and evidence from practice [22], about 1 in 4 or 1 in 5 Ozurdex® patients experience raised IOP which required at least one medication to control the IOP. Medication used to manage IOP is usually in the form of a topical eye drop. However, raised IOP associated with ranibizumab is usually transient persisting for less than one day, and is believed to be related to an intraocular volume increase.

Cost analysis

Costs include VAT at 20% unless otherwise indicated.

Separately, both ranibizumab and Ozurdex® have been determined as cost effective for the NHS, [1,6] with a substantial mandatory discount conditional on the use of ranibizumab. [6] However no evidence was identified concerning the cost-effectiveness of a treatment switch from one treatment strategy to another. Bevacizumab is substantially less costly than ranibizumab [15] but is not widely used in RVO due to a lack of robust evidence and product license.

The NICE costing template which accompanied the ranibizumab for RVO technology appraisal estimated a mature RVO treatment cohort of about 2,000 patients per annum for the North East & Cumbria of whom only about 625 would require pharmacological treatment. [6] An unknown, but likely to be minority, proportion of these patients may be considered suitable for or otherwise require a switch in treatment strategy.

The NICE cost template for ranibizumab (Lucentis®) in RVO does not model prior or subsequent treatment with Ozurdex®. [6]

Each Ozurdex® implant costs £1,044 each. [23] Ranibizumab (Lucentis®) is available at a substantial discount to the NHS and costs £534 per dose. [24] Bevacizumab intravitreal syringes can be purchased from licensed compounding facilities typically at less than £100 per dose. [15]

Administration costs will be the same per episode at about £400 regardless of treatment modality. However bevacizumab and ranibizumab will require more frequent administration (estimated 7 to 9 injections in the first year) and patients will require monthly monitoring. [6,15]

Points to consider

Given the absence of good quality clinical evidence to support any switching or sequential pharmacological RVO treatment strategy, any decision to change between one therapeutic modality to another should be based upon non-clinical or safety factors.

A draft treatment protocol from the North East Retinal Group has indicated the following points for switching therapy:

- Nil, or diminished, or suboptimal clinical response
- Raised and uncontrolled IOP with Ozurdex®
- Allergy, hypersensitivity, anaphylaxis or other toxic response or other disabling side effects to first therapy

None of these points is specifically supported by any direct clinical evidence. Some of points, whilst appearing to be rationale, are not further qualified with specific criteria. For example no threshold for IOP has been specified and neither has 'uncontrolled' been defined. With respect to other adverse effects, clarification has not been provided concerning 'other disabling side effects' or 'other toxic response'.

It is not clear to what extent patient choice can or should be accommodated should a patient, for any reason, wish to change their treatment modality at any point in the course of their condition.

The second point relating to intra-ocular pressure may be a rational option given that the incidence of raised IOP is recognised as being a significant adverse effect associated with Ozurdex® in particular, although it does occur with ranibizumab too. In the GENEVA study 24% of patients required medication to help manage IOP. An unknown proportion of these may experience uncontrolled raised IOP even with the use of medications. Raised IOP is listed as a 'very common' (i.e. incidence > 10%) adverse effect associated with ranibizumab. It is not known whether the incidence of raised IOP with one treatment would be independent of the risk with the other treatment.

The treatments are by no means similar in their administration and dosing. For example Ozurdex® is only indicated once every six months at the most frequent, whereas ranibizumab is licensed for monthly administration initially. Ozurdex® requires injection with a larger bore needle at an oblique angle into the sclera (white) of the eye whereas intravitreal injections of ranibizumab are administered using a finer needle through a more direct path.

Although not specifically precluded by NICE guidance, a switch from one treatment strategy to another would not have been considered by NICE as this was not a feature of the supporting evidence. Whether a treatment decision can be taken in isolation of prior RVO treatment modalities for the same indication is not entirely clear from current NICE recommendations. NICE guidance does refer to prior use of laser photocoagulation in the treatment of BRVO for both treatments but only as a pre-condition or consideration before using either ranibizumab *or* Ozurdex®.

The commissioning liabilities for managing access based on prior RVO treatments therefore remains untested. It may be desirable or preferable to allow any adverse sequalae leading to a therapeutic switch to completely resolve before a new treatment strategy is initiated.

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