

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Ranibizumab for the treatment of macular oedema caused by retinal vein occlusion (RVO)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Retinal Vein Occlusion (RVO) is presently managed differently dependent on whether the vascular occlusion involves the central retinal vein (CRVO), or a branch of the retinal venous system (BRVO). In addition, there are differences in management strategies dependent on whether the goal is to control neovascularisation and prevent vitreous haemorrhage and/ or rubeotic glaucoma, or in preventing / reversing visual loss due to macular oedema. These management strategies have been based on the CVOS (for central retinal vein occlusion study) and BVOS (for branch retinal vein occlusion study).

For the purposes of this appraisal I will restrict my comments to the management of macular oedema due to RVO.

In general terms, patients with significant retinal ischaemia (as evidenced by relative afferent pupil defect, significant non-perfusion on fundus fluorescein angiography - FFA or other ancillary tests) or significant ischaemia affecting the fovea (often referred to as macular ischaemia diagnosed on FFA) have not been shown to benefit from management of the macular oedema with any treatment modality. In these ischaemic patients the majority of ophthalmologists do not treat the macular oedema and in the BRAVO and CRUISE studies of ranibizumab in BRVO and CRVO respectively, clinical evidence of retinal ischaemia was an exclusion criterion. The RCOphth interim guideline on management of RVO (December 2010) does not advocate treatment of macular oedema in the presence of significant retinal ischaemia.

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Macular oedema due to non-ischaemic BRVO has traditionally been managed with a period of observation. This provided time for blood to clear from the macular region allowing correct interpretation of FFA necessary to plan and deliver laser photocoagulation treatment effectively. (The presence of blood in the retina interferes with laser placement and absorption, and treatment outcomes). The period of observation also allowed the clinician to identify any cases that spontaneously improved. If at 3 months macular oedema was still reducing acuity to a level between 6/12 and 6/60, in the absence of significant foveal ischaemia, then macular grid laser photocoagulation has been proven in a large randomised controlled trial (RCT) to be an effective treatment in up to 30% of cases and is widely practiced. This approach is still supported by the recent RCOphth interim guideline on management of RVO, particularly if patients present after the 3 month timeline, especially in the absence of any other proven treatments. However, over the past decade many ophthalmologists have been increasingly using off label agents such as intravitreal triamcinolone (IVTA) or more recently in a few units anti-VEGF agents (primarily bevacizumab) either as monotherapy or in combination with grid laser.

The recent licensing of the dexamethasone implant Oxurdex is supported by the RCOphth interim guideline for both non-ischaemic BRVO and CRVO but uptake throughout the NHS has been slow due probably due to geographical variations in funding prior to NICE final appraisal and inexperience with using the implant device.

Macular oedema due to non-ischaemic CRVO fails to respond to grid laser (although there is a trend to treatment benefit in younger patients) and is therefore rarely used and not advocated in the RCOphth interim guidelines. As with the management of macular oedema secondary to BRVO there has been a move towards off label use of IVTA and anti-VEGF agents (primarily bevacizumab). However, this is not in routine NHS use, as such use is subject to local PCT or Hospital Trust funding which is generally not available particularly for bevacizumab.

As outlined above, intravitreal steroid injections have been used widely over the past decade in an attempt to treat macular oedema due to both BRVO and CRVO in the absence of any other useful treatment. The most commonly used formulation is intravitreal triamcinolone acetonide (IVTA). This is in the form of off label use of Kenalog (Squibb) which is unlicensed for this indication. Although 4mg IVTA has been commonly used there is much variation in practice in terms of dosage (1mg – 20mg), timing (early versus delayed use in laser resistant cases) and frequency (3 monthly/ 6monthly etc). The short-lived benefit of this form of IVTA along with the significant risks of raised intraocular pressure (secondary glaucoma) requiring treatment, cataract formation and sterile inflammatory endophthalmitis have led to a fall in its use of the past 2-3 years. However, there is some renewed interest in its potential use in CRVO following publication of the SCORE–CRVO trial (SCORE study report 5. Arch Ophthalmol 2009; 127:1101-14). In this RCT a specially prepared preservative-free formulation of IVTA was used (TRIVARIS, Allergan) and did show some sustained benefit with an acceptable safety profile for the 1mg dose of triamcinolone. Unfortunately, this preparation is commercially unavailable and

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differences between it and Kenalog in terms of preservatives, particle size and pH limit any direct comparison between Kenalog and the SCORE data.

More recently, anti-vascular endothelial growth factor (anti-VEGF) intravitreal injections have been used increasingly to treat macular oedema due to both BRVO and CRVO. Most commonly, this has been with the use of off-label use of intravitreal bevacizumab (Avastin). This practice varies from unit to unit dependent on local pharmacy approvals and funding. There is also significant variation in dosage and dosing schedules, and no universally agreed treatment protocols. Although some case series have shown benefit in treatment of macula oedema in RVO there is a lack of RCT evidence of efficacy, or safety, and long-term data.

The RCOphth interim guidelines reminds ophthalmologists of the GMC's Good Medical Practice guidelines which specifically states that "When prescribing a medicine for use outside the terms of its license then you must a) be satisfied that it better serves the patient's needs than an appropriately licensed alternative".

Alternative therapies such as radial optic neurotomy, arteriovenous sheathotomy and laser induced chorio-retinal anastomosis have all been tried with varying reports of success but are infrequently used in the UK. These are only experimental at the present, and not recommended by the RCOphth.

The technology under appraisal ranibizumab 0.5mg (LUCENTIS, Novartis) has received regulatory approval for use in RVO in the US with EU approval expected mid 2011. There is wide experience throughout UK NHS with ranibizumab for management of wet AMD but only very limited experience with its use for RVO, mainly in the independent sector at present. The reported significant visual gains in treating macular oedema secondary to both non-ischaemic BRVO and CRVO is extremely encouraging with a significant unmet need at present throughout the NHS. Its use is supported by RCOphth interim guidelines. The results from the CRUISE and BRAVO trials indicate that visual outcomes in treated eyes are better in those treated early compared to delayed treatment. Unlike in the laser treated eyes, there is no reason to await the clearance of macular haemorrhages in order to determine appropriateness of laser photocoagulation.

The technology is unsuitable for use in primary care settings and should be delivered by an ophthalmologist experienced in medical retinal disorders. It is likely to be delivered in an outpatients' clean room setting similar to its use for AMD.

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The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The introduction of ranibizumab, once licensed, will be a significant step forward in the management of patients with RVO in the NHS. The management of macular oedema throughout the UK varies significantly. Although grid laser therapy for non- ischaemic BRVO (but not CRVO) is widely available the alternative/adjutant use of other therapies for both BRVO and CRVO is dependent on experience and funded/approved availability of off-label use of IVTA and bevacizumab (Avastin).

Although these patients are already attending ophthalmic units for monitoring of their condition there will be a significant increase in frequency of visits. It is likely that patients will have to attend monthly at least for the first 12 months, supplemented with extended intervals after that period for selected patients. Optical Coherence Tomography (OCT) assessment is likely for each of these visits. It is anticipated that the delivery of a service to manage macular oedema in RVO will be similar to service

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provision for managing exudative AMD with ranibizumab. In essence, this will be repeated out-patients sessions with intermittent PRN injections given in a dedicated outpatient clean room. Many units throughout the UK have ophthalmologists trained in the assessment and management of medical retinal disorders such as RVO and will be experienced in managing macular oedema with repeated intravitreal injections. However, service provision will be need to meet the minimum requirements outlined in the RCOphth interim guidelines for RVO and include clerical and support services similar to AMD services as proposed in the RCOphth Document “Commissioning Contemporary AMD Services: A guide for commissioners and clinicians July 2007”.

Particular advantages of ranibizumab over IVTA and to a lesser extent Ozurdex include the reduced incidence of raised intraocular pressure, need for IOP pressure treatment and glaucoma surgery. In contrast to bevacizumab (Avastin), there is good RCT data on efficacy and safety to support the use of ranibizumab and it is likely to succeed with EU licensing for its use in RVO. Although intravitreal bevacizumab (Avastin) is used widely throughout the world and many ophthalmologists support its use for good health economic reasons, there still remains doubt over its long term safety particularly in arteriopathies. The recent paper by Curtis et al (Arch Ophthalmol 2010; 128:1273-1279) looking at 146, 942 Medicare beneficiaries over the age of 65 needs further critical appraisal to assess the relative systemic safety of bevacizumab versus ranibizumab. In that paper, a total of 19, 026 patients received ranibizumab and 21, 815 received bevacizumab as first-line therapy for wet AMD. There was a statistically significant 22% reduction in the 1 year incident of stroke in the ranibizumab group compared to the bevacizumab group (1.8% versus 2.2% HR 0.78 95%CI 0.64 - 0.96). However, the authors undertook a secondary analysis on a subgroup of patients and found that when comparing exclusive providers of ranibizumab or bevacizumab that the reduction in incident stroke was no longer statistically significant. The subgroup of course had less patients included, by definition. The committee must consider which of these 2 analyses is the most valid when comparing systemic safety data for the use of bevacizumab as a comparator in the present STA.

A recent paper comparing safety of bevacizumab versus ranibizumab in management of wet AMD showed, at 1 year, the proportion of patients with serious systemic adverse events (primarily hospitalizations) was higher with bevacizumab than with ranibizumab (24.1% vs. 19.0%; risk ratio, 1.29; 95% confidence interval, 1.01 to 1.66) (Ranibizumab and Bevacizumab for neovascular age-related macular degeneratin. The CATT Research Group. NEJM April 28th 2011 epub ahead of print). An oral presentation of the 2 year interim data of adverse events from this study was given at the Association for Research in Vision and Ophthalmology (ARVO – 2nd May 2011) and did not show any differences in serious systemic adverse events. This 2 year safety data has not been published and the study was seriously underpowered for such infrequent serious adverse events. Another oral presentation by Gower et al at ARVO 2011, on an analysis of records of patients who have received ranibizumab or bevacizumab showed that there was a higher incidence of haemorrhagic stroke and gastrointestinal bleeding in bevacizumab treated patients compared to ranibizumab.

Certain subgroups of patients with significant retinal and / or macular ischaemia are unlikely to improve acuity and not recommended for treatment with ranibizumab. Patients with macular oedema of greater duration than 12 months were excluded from

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the BRAVO and CRUISE trials and thus it is debatable whether they will benefit from the technology.

Recommended treatment algorithms are available in the RCOphth interim RVO guidelines and are summarised here for the use of ranibizumab.

In the case of non-ischaemic BRVO macular oedema, ranibizumab (or alternatively Ozurdex) should be considered as first line treatment for patients presenting within 3 months of onset. For patients presenting after 3 months then macular grid laser should be considered as an alternative to ranibizumab or Ozurdex. The follow up schedule for ranibizumab treatment should be monthly for the first 6 months then considered on a PRN basis for subsequent visits. Discontinuation of the ranibizumab treatment should be considered if there has been no therapeutic benefit in terms of visual acuity deteriorating at 2 consecutive visits or if new MI or CVA raises concerns over the risk to benefit ratio for a particular patient.

In the case of non-ischaemic CRVO macular oedema, ranibizumab (or alternatively Ozurdex) should be considered as first line treatment for patients presenting with VA of 6/12 or worse + OCT central foveal thickness ≥ 250 microns. The follow up and discontinuation criteria are the same as for BRVO outlined above.

The trial design of both BRAVO and CRUISE reflects well the typical patient presenting with RVO in the UK. The primary outcome used in the trials was mean change in visual acuity from baseline and is a useful and tangible outcome measure. The percentage of patients gaining 15 letters or more improvement in LogMAR acuity from baseline and the percentage of patients improving to commonly predefined thresholds such as 6/12 (driving equivalence) or 6/60 (partial sight registration) are all well presented in the trials.

The safety profile presented is very favourable and consistent with ranibizumab use in AMD with minimal significant local or systemic concerns. The long term outcomes for vision and complications are unknown.

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Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

NONE

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

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If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

The patient group that may benefit from the ranibizumab technology are already attending ophthalmic units for monitoring and treatment. However, there will be an increase in frequency of visits. It is likely that patients will have to attend monthly at least for the first 12 months, and subsequently with extended intervals after that period for selected patients. Optical Coherence Tomography (OCT) assessment is likely for each of these visits. It is anticipated that the delivery of a service to manage macular oedema in RVO will be similar to service provision for managing exudative AMD with ranibizumab. In essence, this will be repeated out-patients sessions with intermittent PRN injections given in a dedicated outpatient clean room. With appropriate funding this should be achievable.

There will be an immediate impact on service provision and in many cases initially may be dovetailed in to an already overstretched AMD service provision. The expertise among ophthalmologists with interest in treating RVOs exists already. However, staff and facilities to fulfil the general nature of the guidance may require some expansion, which should be available within the proposed 3 months.

A variation to the 3 month mandatory implementation of guidance and funding directive on this technology will be unwelcome.

It is imperative that the provision and funding of service reflects the standard outlined in the RCOphth interim RVO guidelines.

Equality

Are there any issues that require special attention in light of the NICE's duties to have due regard to the need to eliminate unlawful discrimination and promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others?

NONE