NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

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

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Sobha Sivaprasad

Name of your organisation King's College Hospital NHS Foundation Trust

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? *Yes*
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? *Yes –part of the RCOphth guidelines writing committee*
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? *No*
- other? (please specify)*No*

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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?

Retinal Vein Occlusion (RVO) is managed differently depending upon whether the occlusion of the retinal venous system involves the central or branch retinal vein, and also whether there exists, or is risk of development of, neovascularisation, rubeotic glaucoma and/or macular oedema.

Macular oedema caused by a branch RVO (BRVO) is currently treated with a grid pattern of laser photocoagulation if visual acuity is between 6/12 and 6/60. This is the standard treatment throughout the NHS, but is not appropriate for patients with macular haemorrhage. Standard practice is to wait at least 3 months following the initial BRVO until the majority of haemorrhage has been absorbed. This also allow for observation to assess for spontaneous improvement. However, during this time vision may deteriorate. Laser has limited benefit for patients with a large degree of macular ischaemia.

Laser is also generally unsuitable for patients with macular oedema due to a central RVO (CRVO) and is not recommended due to the CVOS study which looked at laser in CRVO patients with macular oedema and found no clinical benefit. Usually these patients are monitored, in particular for development of neovascular complications although there are opportunities to use newly licensed products including ranibizumab and dexamethasone in some cases.

The Retinal Vein Occlusion Guidelines produced by the Royal College of Ophthalmologists in 2010 were unable to recommend bevacizumab for CRVO or BRVO. The evidence in CRVO is limited to case series (without controls). There is some short-term data to suggest that bevacizumab may be helpful for BRVO patients where laser has failed to improve macular oedema. However, further data from randomised controlled trials is required to assess long-term safety and efficacy and to establish the appropriate dosing regimen. I understand that the lack of data for bevacizumab was also noted during the appraisal of dexamethasone and I agree that it is difficult to make comparisons at this time based on the evidence available. Although there is some limited use of bevacizumab in the NHS, this is quite restricted at most units by local pharmacy approvals. In light of the recently licensed pharmacotherapies, it is difficult to justify the need to use bevacizumab which is unlicensed for intraocular use. The SmPC for bevacizumab was recently altered to include cases of severe intraocular inflammation following intravitreal administration of the drug. Any use of this unlicensed product must therefore be considered in light of GMC guidelines on 'Good Medical Practice' and the manufacturer's advice.

Triamcinolone is very rarely used in RVO now and is also contraindicated for intraocular use by its manufacturer.

Dexamethasone intravitreal implant has recently received marketing approval and is recommended for some BRVO patients and for CRVO. However, experience with the drug and the drug delivery system is limited at present.

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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?

The duration of symptoms will generally predict the level of benefit achieved. Patients with a longer duration of macular oedema may respond less well to treatment, as the longer the duration of oedema the more the fovea is damaged. As noted above, the degree of macular ischeamia and macular haemorrhage will guide use of laser in BRVO. There is a particular need for an effective treatment for ischaemic patients.

Some patients with BRVO will experience spontaneous improvement of symptoms, but there is no way in which to identify these patients at presentation. Because of the importance of duration of treatment on outcomes, it is preferable to treat early rather than to risk progression to a chronic state in which prognosis is poor.

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)?

Ranibizumab should be used in the existing retinal clinics, under the supervision of an ophthalmologist experienced in medical retinal disorders.

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?

N/A

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.

As noted the Guidelines for the Management of Retinal Vein Occlusion produced by the Royal College of Ophthalmologists (RCOphth) have been available since 2010. I am a member of the 2010 guidelines development group. The guidelines development group of ophthalmologists supported a team at NHS Evidence to search the published literature systematically. Relevant literature was graded according to strength of evidence. All UK consultant ophthalmologists were consulted on a draft of the guideline, as well as 2 non-UK experts and comments incorporated accordingly. I therefore consider that the methodology used is robust.

The availability and strength of evidence for each recommendation varies as demonstrated in the full report. For some areas of recommendations, the evidence was graded D (i.e. evidence available only from non-analytic studies). With respect to the use of ranibizumab for RVO, the guidelines development group concluded that there was grade A evidence based on the BRAVO and CRUISE trials.

The RCOphth guidelines provide treatment algorithms for RVO. The guidelines for the use of ranibizumab (written prior to EU marketing approval) recommend its use as a first line treatment for macular oedema due to BRVO or CRVO if visual acuity (VA) is 6/12 or worse and central retinal thickness (CRT) on OCT 250 microns or more. Based on the BRAVO and CRUISE studies, a monthly injection schedule for 6-12 months is suggested with a subsequent PRN re-treatment regimen based on the retreatment criteria in the studies.

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It is noted that the posology in the SmPC (issued since the guidelines were developed) suggests monthly treatment until VA is stable for three consecutive monthly assessments whilst on treatment. Thus, particularly so for BRVO, injections for each of the first 6 months may not be required, and as a result the number of injections required in the first year may be lower than seen in the BRAVO trial.

Frequency of follow up in the first 6 months will be dependent upon VA, OCT and FFA findings and guided by the SmPC. From month 6 to 18, monitoring may decrease to 3 monthly depending on individual patient characteristics and their response to treatment.

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?

Compared to the treatments used now, ranibizumab will improve patients' vision dramatically. Despite statistical significance, in the BVO Study the benefit of the grid laser treatment was relatively modest with average improvement in visual acuity slightly more than one line in a small group of eyes at three years. In some BRVO patients laser therapy is associated with safety issues such as worsening of the visual field. The BRAVO study (investigating macular oedema due to BRVO) demonstrated significant benefits at 6 months for ranibizumab, with a mean gain of +18.3 letters from baseline (0.5 mg dose), compared to only +7.3 letters in the sham group. At 12 months, benefits were maintained in the 0.5 mg group (+18.3 letter gain versus baseline; the sham group gained a mean of +12.1 (having received 6 months prn ranibizumab). The speed of these improvements in vision will allow this young group of patients to return to normal functioning much sooner than those receiving laser.

The results of the CRUISE study are even more impressive. CRUISE reported a gain in BCVA score from baseline of +14.9 and +0.8 letters in the 0.5 mg ranibizumab and sham injection treatment groups respectively.

Ranibizumab will require patients to attend the clinic more often for monitoring and more frequent treatment than is needed for laser. Most patients are willing to have an intravitreal injection if there is a chance their vision can be improved. All clinics in the UK are familiar with ranibizumab through use in wet AMD and there will not be any difficulties in using it.

Ranibizumab has an advantage over dexamethasone in that there is a decreased risk of increased intraocular pressure and cataracts. Retreatment with dexamethasone is less frequent than ranibizumab, although perhaps not as infrequent as suggested in the dexamethasone GENEVA studies due to the efficacy peaking at 60 days, and wearing off rapidly thereafter, meaning re-treatment may be required as early as 4 months after initial injection. The larger gauge delivery system of dexamethasone means that it is more complex to delivery compared to anti-VEGF intravitreal injections. Initial use of dexamethasone is therefore expected to be undertaken in the day theatre, whereas ranibizumab will be used in the dedicated injection rooms already used for wet AMD clinics.

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.

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If patients do not show any improvement or stabilisation in vision after an initial treatment period of 3 months, cessation of treatment would be considered. Where patients continue to show improvement, it is important to continue treatment as the ranibizumab studies show that further gains can be achieved. The clinical trials of ranibizumab and dexamethasone and earlier smaller observational studies show that early treatment is preferable, rather than to wait as is currently necessary before using laser photocoagulation. Most clinicians would be reluctant to wait for spontaneous resolution before initiating ranibizumab treatment for this reason. For CRVO patients in particular, there is a risk that delayed treatment will not achieve the same improvements in visual acuity. This is also demonstrated in the CRUISE study.

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?

The trial populations reflect the patients that present in the UK. The trials did not include patients with clinically significant ischaemia.

The BRAVO and CRUISE trials used monthly follow-up and injections as required, which is the way in which ranibizumab is used currently. The use of laser after 3 months for patients with BRVO, and not at all for CRVO, fits with current practice.

The most important outcomes were measured (BCVA and CRT), and also quality of life and visual function (NEI-VFQ25 questionnaire). It is important to measure the impact of visual impairment on patient's ability to function and undertake their daily activities. Unlike the wet AMD population, patients with RVO are younger and likely to be working and driving. The sudden nature of an RVO means that vision loss is often sudden. This is obviously distressing, whether bilateral or unilateral. It can have a profound impact on patients and studies have demonstrated that a decrease in the VFQ-25 score is related to the visual acuity in the involved eye.

Even the loss of vision in one eye is detrimental to function as peripheral field, contrast sensitivity and depth perception can be affected. It is therefore important to treat the vision loss, even if the fellow eye has good vision. This patient population is at risk of glaucoma and diabetic eye disease; there is evidence to suggest an association of glaucoma and diabetes mellitus in patients with an RVO. Around 10% of patients may develop an RVO in the fellow eye. This increases the need to treat the affected eye on clinical presentation, in order to prevent bilateral visual impairment in the future due to other conditions.

The use of proportion of patients with a 15 letter improvement or deterioration in BCVA is the gold standard outcome for clinical trials. However, a smaller change in BCVA is still clinically meaningful for patients, and can mean the difference between ability to drive or eligibility for visual impairment registration. It will be important to understand the proportion of patients reaching these outcomes, and also the proportions of patients with 10 letters change in BCVA. 10 letter changes are accepted as clinically meaningful and a standard outcome in diabetic macular oedema.

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?

There is a risk of endophthalmitis and haemorrhage from intravitreal injection. Endophthalmitis in clinical practice is very infrequent and most adverse effects can be managed in the retinal clinic.

The cumulative effect of repeated steroid use over time is a concern, as long term evidence is not available. The risk of increased intraocular pressure (IOP) will require additional monitoring to initiate IOP lowering treatment and to assess the response to these treatments, especially given the expected higher rate of retreatment with dexamethasone than used in the GENEVA studies. Raised IOP is not a concern with ranibizumab injections, and there is more long term experience with ranibizumab through its use in wet AMD since 2008.

An additional benefit that should be considered is the potential that ranibizumab may prevent neovascular complications such as iris and retinal neovascularisation which can require significant degree of intervention to prevent visual deterioration and severe intractable glaucoma.

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.

NHS Evidence conducted a review of annual evidence update of cardiovascular morbidity and mortality associated with RVO. Current evidence suggests no increased cardiovascular risk in this patient population, although this has been debated given that some studies in non-UK populations suggest there may be an increased risk.

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.

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

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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)?

RVO patients would continue to be seen and treated in the retinal clinic. At Kings, around 50 patients per year are seen. This is approximately 30 BRVO and 20 CRVO cases. Only the BRVO cases where the macula is threatened are treated. These numbers are manageable within the existing clinics. Our staff is fully trained to deliver a ranibizumab service to RVO patients. It will be important to have immediate provision to initiate ranibizumab for RVO patients, to ensure that early treatment and optimal outcomes can be achieved. A variation to the 3 month mandatory implementation of guidance on this technology will be unwelcome.