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Single Technology Appraisal (STA)

Dexamethasone intravitreal implant for treating diabetic macular oedema [ID653]

Thank you for agreeing to give us a statement on your 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: Moorfields Eye Hospital

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**
- 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?

Diabetic macular oedema is a serious ophthalmic condition which generally leads to deterioration of vision and moderate visual loss in many cases if left untreated. Historically the objective of treatment was to limit the deterioration in vision, however with the availability of anti-VEGF treatment (ranibizumab) the goal of therapy has become improvement in vision.

DMO with visual impairment is currently treated with an anti-VEGF (ranibizumab). As this is supported by NICE guidance, this practice is universal in England and Wales. Ranibizumab is generally used as per the manufacturer's recommendations:
- initially a minimum of 3 injections on a monthly basis
- followed by as needed treatment
- visual acuity and OCT assessment are done monthly
- PRN treatment is dependent on OCT and VA changes

The clinical trials have demonstrated the optimal VA gains are achieved with ongoing monthly treatment however trials of the PRN regimen have shown significant (though lower) VA gains with 7 injections in the first year.

The majority of patients respond to some degree with this intensive regimen, however with limited alternatives there has been a tendency to persevere with ranibizumab treatment even when the benefits were modest.

The alternatives to ranibizumab treatment are as follows:

Observation
Careful monitoring without active treatment, beyond optimisation of modifiable risk factors (eg glucose control, blood pressure control), is often implemented when continuation with ranibizumab treatment is not practical or little benefit has been seen.

Macular laser treatment
The use of laser to treat the macula was established in the 1980s to treat the clinical diagnosis of DMO (Clinically significant macular oedema, CSMO) when slowing in deterioration in VA was shown. With the introduction of ranibizumab, the goal of therapy has become VA gain and thus the use of laser has reduced dramatically. The use of laser is also limited by the patients it can be used with in practice. Laser treatment leads to burns/scarring of the retina. This cannot be applied to the centre of the macular and thus for many patients with DMO it is not appropriate.

Bevacizumab
Bevacizumab is not a licenced product and therefore with the widespread availability of ranibizumab use of bevacizumab is not justifiable from a patient safety perspective.

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Fluocinolone implant (Iluvien)
This treatment is available for pseudophakic patients considered insufficiently responsive to other therapies and who have had chronic oedema for a significant period of time. The efficacy has been demonstrated in clinical trials in patients with oedema present for >3 years. In practice the use of the fluocinolone also has been limited by the clinical implications of an implant which delivers fluocinolone for 3 years and which is only removable surgically.

Patient variation: there is a very significant variation in how patients present and their response to available treatments. It is for this reason that the treatment has to be individualised and that the 'average' results from the formal clinical trials only inform individual response to a degree.

Clinical setting: this technology will only be used in specialist clinics by experienced ophthalmologists.

Ozurdex is available in the UK and NICE guidance has supported use in the treatment of Retinal Vein Occlusion (RVO) and Uveitis. Ozurdex was the first intravitreal treatment to be approved for RVO and since then considerable, widespread experience has been established using this therapy. My understanding is that there has been some off label use of this product for DMO in the UK but this has been limited predominantly by funding.

I foresee the place of Ozurdex in current practice will be consistent with the indications described in the label.
- It will be used in patients for whom anti-VEGF (ranibizumab) therapy is not appropriate. This includes a wide range of patients, the most significant of which would be patients who cannot attend the ophthalmology clinic on a monthly basis. For patients to experience the proven benefits of ranibizumab seen in the clinical trials this schedule needs to be maintained. If it is not then the visual acuity suffers. It could also include patients who are of child bearing age, those with a history of recent cardiovascular events or patients who had had a vitrectomy.
- Ozurdex will also be used in patients when the response experienced with ranibizumab has been low. Low response has not been consistently defined however with the availability of this effective alternative to ranibizumab, it will be important to define this. It would make sense for a combination of VA and OCT readings of retinal thickness to contribute to this definition.

Ozurdex will also be considered in patients who are pseudophakic as these patients do not have the potential to develop cataract which is often accelerated in phakic patients on intravitreal steroid treatment.

Important definition: The reduction in vision associated with DMO generally presents with 'Centre-involving' oedema of the retina defined as increased thickness of the retina on OCT scan of the exquisitely sensitive centre of the macular (fovea).

The most relevant guidelines available in the UK are the 'Diabetic Retinopathy Guidelines' developed by Scientific Department of the Royal College of Ophthalmologists (published December 2012).

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The guidelines were developed by a working group of 16 UK based experts and an external US based reviewer. Medline was used to access the relevant information. Evidence was classified depending on the sources (eg randomised controlled trial, case series, expert opinion.)

The treatment of DMO is considered in a dedicated section 'Management of diabetic maculopathy'. The summary of the management recommendations are as follows:

Patients with non centre-involving CSMO
- Laser photocoagulation

Comment: This is based on level strong RCT evidence. It should be noted this is a small proportion of DMO patients as the reduction in VA is usually due to involvement of the centre of the macula.

Patients with centre-involving macular oedema with reduced vision
- anti-VEGF (ranibizumab)

- anti-VEGF (bevacizumab) has been used but unlicenced
- steroid (preservative free) + laser could be considered
- steroid implant (fluocinolone) consider if unresponsive to other treatments while considering the side effect profile

Comment:
The ranibizumab data is the most compelling and comes from RCT evidence.
The bevacizumab data is limited and the product is unlicenced.
The evidence for preservative free steroid + laser is limited. Also there is no preservative free steroid licenced for use in the eye.
The fluocinolone data is from an RCT however the patients involved were not unresponsive to other treatments and thus not directly relevant evidence.

Patients unwilling or unsuitable for intravitreal injections
- macular laser may be offered, if thought appropriate by the ophthalmologist

Comment: Laser therapy will be rarely appropriate due to the high proportion of patients with centre of the macula involvement. It should also be noted the Guidelines comment that most of the laser data was established with the diagnosis of Clinically Significant Macular Oedema (CSME) prior to the assessment with OCT scanning and thus the extrapolation to the patients diagnosed with this modern technology should be made with caution.

The advantages and disadvantages of the technology

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The large, 3 year Ozurdex registration studies in DME clearly demonstrated that Ozurdex produced significant visual acuity benefits compared to sham treatment. This was achieved with 4.1 injections over the 3 years of the study. This improvement in vision associated with a low treatment burden is a distinct advantage for patients especially if they are having to travel significant distances, maintain employment and attend additional clinics for other complications of diabetes.

The practicalities of using Ozurdex in clinical practice for DMO will be routine as there is already extensive clinical experience of Ozurdex use for the treatment of RVO. Recently the needle used to introduce the implant was modified and this has resulted in easier delivery. Follow up of patients after injection is required on a regular basis to assess both efficacy and safety. With respect to efficacy many clinicians assess patients with VA and OCT from 4 months post injection to gauge if/when an subsequent treatment is needed. With respect to potential rises in intra-ocular pressure (IOP), a common approach to monitoring involves IOP measurement at 2 months post treatment.

The retreatment following an initial Ozurdex injection should be based on detecting a worsening of VA or retinal thickness based on OCT. If a patient has gained limited benefit, or the benefit is maintained then retreatment is not given.

In the registration trials for Ozurdex, the minimum retreatment interval was 6 months and thus the evidence base of both efficacy and safety is based on this approach. Retreating at a 6 month interval is feasible from a logistical perspective and certainly significantly less intensive than the monthly injections (at least 4 of the first 6 months) required with ranibizumab. Clinical experience suggests that the optimum separation of treatments will depend on the individual patient and that some patients appear to benefit from earlier than 6 month retreatment based on detecting a reduction in VA or increase in retinal thickness.

The 2 side effects that need to be considered are rise in IOP and acceleration of cataract formation. The MEAD studies produced safety data for 350 patients receiving Ozurdex for 3 years, thus there are very robust data available on both of these elements.

The rises in IOP were generally modest and where present were controlled with topical IOP treatment. This was required in approximately a third of patients. The rise in IOP very much followed the pharmacokinetics of the treatment and thus this peaked 2 months after injection and had returned to baseline by 6 months. Less than 1% of patients required surgical intervention to control the pressure.

Patients with diabetes are known to be at increased risk of cataract formation. Of the patients in the MEAD studies 85% had lens opacity observed at baseline. During the 3 years of the study cataract surgery was performed in 59% of the patients in the Ozurdex arm compared to 7% in the sham group. This exacerbation of cataract formation is well established for intravitreal steroids and in line with expectations. Interestingly, when cataract surgery is performed in patients with DMO typically the macular oedema deteriorates, however in the Ozurdex group this was not shown, implying a protective, stabilising effect of the dexamethasone at time of surgery.

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Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

No issues identified.

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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 identified.

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 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)?

As Ozurdex is already used for the treatment of other conditions I would not envisage that additional education, training or resources would be required. Indeed there is potential for there to be benefits for both the delivery of the care and receipt of the care, via the reduction in treatment burden.

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