NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Rituximab in combination with corticosteroids for treating anti-neutrophil cytoplasmic antibody-associated vasculitis

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: [redacted]

Name of your organisation UKIVAS

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 No
- 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)

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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?

ANCA vasculitis treatment is divided into 3 phases – induction of remission, maintenance of remission and tapering of therapy during follow up. Induction of remission is usually achieved using glucocorticoids combined with cyclophosphamide. Cyclophosphamide is usually given intravenously but can be given as low dose continuous oral therapy. The aim of induction is to achieve remission and this is usually achieved with between 3 and 6 months of therapy. At this time cyclophosphamide is conventionally replaced with azathioprine. Cyclophosphamide is too toxic for long term use (bladder cancer, infertility, bone marrow suppression and infection being the main risks) and therefore modern practice is to try and minimise exposure to cyclophosphamide. Relapse is usually treated with an increase of immunosuppression or a further course of cyclophosphamide. This approach has been endorsed by both the British Society for Rheumatology (BSR) Guidelines (Lapraik CJ, et al Rheumatology 2007; 46: 1615-16), and the European League Against Rheumatism Guidelines (Muhkytar et al, Ann Rheum Dis 2009; 68:310-7) and is accepted in the UK as the standard of care.

Thus the main alternative to the technology is to continue with the use of cyclophosphamide as the major induction agent.

There are no geographical variations in the management of AAV, although preference for IV or PO cyclophosphamide depends on access to infusion facilities.

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 typical patient with AAV presents *de novo* with a generalised multisystem disease which is potentially life or organ threatening. Current practice is to treat patients initially according to disease severity. Patients with severe disease (creatinine >500umol/l +/- pulmonary haemorrhage) receive high dose glucocorticoids, cyclophophamide and plasma exchange; patients with generalised organ threatening disease but creatinine < 500umol/ receive high dose glucocorticoids, and cyclophophamide. Only in those with the mildest disease defined as no evidence of organ or life threatening disease is consideration given to alternative to cyclophosphamide such as methotrexate. All patients with ANCA vasculitis have a tendency to relapse – those with PR3 antibodies being at higher risk of relapse than those with MPO antibodies. Short term prognosis is determined primarily by age and renal function at presentation. The long term mortality is determined by infection, malignancy and cardiovascular disease.

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The patient who has a major relapse requires further immunosuppression and the same assessment applies as to severity.

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)?

The technology will only be used in secondary/tertiary care with input from specialist clinics.

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?

The technology is already available. Other licensed indications for rituximab include lymphoma and rheumatoid arthritis. There is variation in the use of rituximab to treat AAV depending on whether any individual PCT or CCG is willing to fund it. This use is outside the current license.

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.

The British Society for Rheumatology (BSR) and European League Against Rheumatism have both produced guidelines (Lapraik CJ, et al Rheumatology 2007; 46: 1615-16), Muhkytar et al, Ann Rheum Dis 2009; 68:310-7) The BSR guidelines on management of ANCA vasculitis are currently being revised, the methodology used in their development has been approved by NHS evidence. It is hoped that they will be published in Summer 2013.

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?

Rituximab will be easier to use than IV cyclophosphamide because treatment protocols will involve only 4 IV infusions over a period of 4 weeks compared with 9-12 infusions over 6 months. This will reduce demand on infusion facilities. Rituximab is generally better tolerated than cyclophosphamide and therefore requirements for anti-emetics will be reduced.

Cyclophosphamide is associated with significant risk of infertility in women and men. Pre treatment egg or sperm preservation is often not practicable because of the need for urgent therapy. The risk is related to cumulative dose of cyclophosphamide. Whilst most patients with AAV are postmenopausal there are a significant number

below the age of 50. Rituximab is not considered to be associated with infertility and would therefore be an advantageous option in this group of patients.

Infection is also a risk from cyclophosphamide therapy, rituximab is not associated with a similar risk of infection and therefore would be an advantageous therapy in those at high risk of infection.

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.

Use of rituximab for maintenance of remission is less clear cut than its use to induce remission. A strategy of repeated treatment every 4-6 months for 2 years appears to be more effective than a wait and see approach of waiting until relapse occurs. (Jones et al, Arthritis Rheumatism 2012; 64: 3760).

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 trials reflect the clinical situations where rituximab would be used in the UK – induction of remission in a patient presenting *de novo* or induction of remission in a patient with relapsing disease.

Outcome was determined in the RAVE and RITUXVAS trials using the Birmingham Vasculitis Activity Score (BVAS). This is an appropriate and validated score for this purpose. The RAVE study combined BVAS score with a withdrawal glucocorticoid therapy as the definition of remission. BVAS at presentation predicts long term outcome. However both clinical trials had relatively short primary endpoints (RAVE 6 months and RITUXVAS 12 months), long term follow up data is awaited.

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?

Side effects from Rituximab are relatively infrequent. There is a risk of anaphylaxis but this is very uncommon. Hypogammaglobulinaemia is a risk with repeated infusions the exact risk is still to be quantified and this may be permanent and pose a risk of infection. Late onset neutropaenia is usually transient and occurs in around 3% of infusion cycles. It occurs several weeks after an infusion and lasts for 2-4 weeks. Progressive multifocal leucoencephalopathy is a very side effect.

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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

I do not believe that there are diversity or equality issues that need to be considered

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.

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)?

Rituximab is given intravenously therefore facilities for IV infusions will need to be in place. Most acute hospitals have such facilities either as a clinical investigation unit,

or oncology suite or a day unit experienced in the administration for biologic agents (e.g. rheumatology units). Many rheumatology units have experience in the administration of rituximab for rheumatoid arthritis and oncology units in the management of lymphoma. Although the numbers are likely to be small facilities would need to be established. However demand for 2 or 3 weekly infusions of cyclophosphamide should be reduced by the introduction of this technology.