Appendix G -Professional organisation statement template

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: [redacted]
British Society of Paediatric and Adolescent Rheumatology (BSPAR)
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)? MEMBER OF BSPAR [redacted] and CONVENOR of BSPAR [redacted]
- other? (please specify) GLOBAL CHIEF INVESTIGATOR OF A ROCHE SPONSORED INTERNATIONAL TRIAL OF RITUXIMAB IN ANCA VASCULITIS IN CHILDREN

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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?

The pathogenesis of ANCA vasculitis in children is identical to the pathogenesis in adults. The standard care for induction of remission of severe ANCA associated vasculitis (AAV) in children is corticosteroids plus intravenous cyclophosphamide. Prior to the publication of the RAVE and RITUXVAS trials in the New England Journal of Medicine, we reserved rituximab for patients who had progressive disease before remission using cyclophosphamide; for those who had frequently relapsing disease. Two publications describing this experience, and recommendations for the place of rituximab in paediatric ANCA vasculitis from our group are:

1. Guerry MJ, Brogan P, Bruce IN, D'Cruz DP, Harper L, Luqmani R, Pusey CD, Salama AD, Scott DG, Savage CO, Watts RA, Jayne DR. Recommendations for the use of rituximab in anti-neutrophil cytoplasm antibody-associated vasculitis. Rheumatology (Oxford). 2011. [Epub ahead of print].

2. Eleftheriou, D., Melo, M., Marks, S. D., Tullus, K., Sills, J., Cleary, G., Dolezalova, P., Ozen, S., Pilkington, C., Woo, P., Klein, N., Dillon, M. J., Brogan, P. A. (2009). Biologic therapy in primary systemic vasculitis of the young. Rheumatology 48(8), 978-986.

Since the publication of the two pivotal clinical trials, we believe that rituximab can be used for unselected children with ANCA vasculitis in place of cyclophosphamide as first-line induction therapy, with corticosteroids.

<u>Areas of controversy in relation to the use of rituximab in ANCA vasculitis in children</u>
1. Whether or not cyclophosphamide should be given with rituximab
2. Whether or not another DMARD (such as azathioprine or mycophenolate mofetil) should be given as maintenance therapy post rituximab
3. Dosing of rituximab: two currently use dosing regimens are in routine use: 750 mg/m² (maximum 1 g) for two doses given two weeks apart; or 375 mg/m² given for four doses one week apart. We do not know if these are equally efficacious or not.
4. The use of rituximab to maintain remission in ANCA vasculitis is beginning to be described in adults. We have not yet adopted this approach in paediatrics, but would look to do so in the future if the adult trials suggest benefit.

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?
Both pivotal clinical trials in adult AAV demonstrated similar efficacy for rituximab and cyclophosphamide in unselected patients.
However:

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1. The RAVE trial taught us that rituximab may be particularly effective for those with disease resistant to cyclophosphamide. Our experience in children would support that finding in the real-world setting.
2. As a general statement, patients with severe ANCA vasculitis as defined using major items on the Birmingham vasculitis activity score (or its paediatric equivalent, the paediatric vasculitis activity score, PVAS; for example those with rapidly progressive glomerulonephritis, alveolar haemorrhage, major CNS involvement, severe vasculitis of the gut, sight threatening vasculitis such as scleritis, and other severe vasculitic manifestations) have a worse prognosis than those with limited forms of AAV, and will benefit from rituximab. This is true for adults and children. However, it is increasingly recognised that apparently limited forms of ANCA vasculitis in children can have a poor prognosis, for example those with orbital involvement. We are increasingly of the view that these paediatric patients will also benefit from rituximab.
3. We are increasingly concerned about late complications of cyclophosphamide in children since children have many years of life ahead of them. Late sequelae such as infertility, bladder cancer, and other cancers are of major concern. Replacement of cyclophosphamide with rituximab is therefore particularly important in children with AAV.
4. Paediatric patients who are intolerant of cyclophosphamide (for example due to severe intractable vomiting), or have MESNA hypersensitivity (MESNA always given with intravenous cyclophosphamide in paediatrics) particularly benefit from rituximab.
5. Our experience has taught us that adolescent patients may particularly benefit from rituximab for several reasons:
a. Two intravenous infusions may be enough to gain control of the disease; thus if adolescents forget to take other medicines (such as corticosteroids, MMF, azathioprine etc- all required to be taken daily) they are still protected from the disease since they are under the influence of B cell depletion.
b. Post pubertal adolescents are at high risk of infertility from cyclophosphamide; hence our overwhelming experience is that the adolescents welcome the opportunity to have their vasculitis treated using a cyclophosphamide-free protocol. Rituximab provides that for them.

Risk
From our experience of using rituximab in ANCA vasculitis (from 2005 at GOSH) we have not identified any subgroups who are particularly at harm from rituximab. Our overwhelming experience is that these patients who have received rituximab, have been spared repeated courses of cyclophosphamide; thus the burden of disease in children in the short, medium, and probably long-term is reduced by rituximab. We have observed hypogammaglobulinaemia, but this seems no worse than the hypogammaglobulinaemia associated with cyclophosphamide. Some children therefore require IVIG replacement if they have low levels of IgG and recurrent infections.

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)?
Rituximab would only be given to children with ANCA vasculitis in secondary/specialist clinics/hospital settings. Typically in the UK this will be either paediatric rheumatology; paediatric nephrology; paediatric immunology centres of excellence.

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?
Rituximab has been in use within the NHS in paediatric rheumatology since 2005. The major unlicensed indications are:
1. Children with ANCA vasculitis
2. Children with SLE
3. Children with other forms of vasculitis including polyarteritis nodosa, that is recalcitrant to more conventional treatment such as cyclophosphamide.
4. Children with chronic active EBV infection.

In paediatric rheumatology, the main licensed indication for rituximab is rheumatoid factor positive JIA, (probably indistinguishable from typical rheumatoid arthritis).

*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.*
Published clinical guidelines for the use of rituximab in children with ANCA vasculitis are:
1. Guerry MJ, Brogan P, Bruce IN, D'Cruz DP, Harper L, Luqmani R, Pusey CD, Salama AD, Scott DG, Savage CO, Watts RA, Jayne DR.
Recommendations for the use of rituximab in anti-neutrophil cytoplasm antibody-associated vasculitis. Rheumatology (Oxford). 2011. [Epub ahead of print].
2. Brogan PA; The standard treatment of childhood vasculitis; in: the Oxford Handbook of paediatric rheumatology, first edition, 2013: 174-178. Eds: Foster H and Brogan PA; Oxford University Press, Oxford UK.

The incorporation of rituximab for children with ANCA vasculitis is based on our experience (as per the references mentioned in section 1; other case reports exist but not listed here); and two major clinical trials in adults (RAVE and RITUXVAS).

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 undoubtedly reduces the burden of disease associated with ANCA vasculitis and its treatment in childhood. In unselected patients, it is equally effective

in the short term as cyclophosphamide for the induction of remission, and with comparable short term toxicity (data based on the RAVE and RITUXVAS trials). However, its spares children from the late sequelae of cyclophosphamide toxicity: infertility, bladder cancer and other malignancies.

It is easier to give than IV cyclophosphamide since only 2 to 4 infusions are required depending on which protocol is used), as opposed to 7 to 10 infusions of monthly IV cyclophosphamide; if paediatric patients are non-compliant with other medications, they are still protected from the disease because they are under the influence of B cell depletion. These are important practical considerations in the paediatric/adolescent population, where non-adherence to medication for chronic illness is very common.

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.

Starting rituximab
1. Any child with ANCA vasculitis that the treating physician would consider severe enough to receive cyclophosphamide.
2. Any child with ANCA vasculitis who has failed cyclophosphamide (either because of progressive disease before remission with cyclophosphamide; frequently relapsing disease; or cyclophosphamide intolerance).

Stopping rituximab
1. Hypersensitivity reactions to rituximab
2. Development of progressive multifocal encephalopathy
3. Severe intractable hypogammaglobulinaemia (although usually IVIG replacement is effective)
4. Those with prolonged B cell depletion (requires monitoring of CD19 counts using flow cytometric assays). Clinicians may be more cautious about retreating such patients with rituximab if the remaining B cell deplete prior to the retreatment.

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?
I am familiar with the evidence base for rituximab in ANCA vasculitis. The obvious difference relevant to paediatric practice is that children were not included in the two pivotal RCTs. We emphasise again that the pathogenesis of ANCA vasculitis in children is identical to that of the adult disease. I (Dr Paul Brogan) am global chief investigator for an open-label, Roche sponsored clinical trial of rituximab in children with ANCA vasculitis that has recently received R&D approval at GOSH (see below). This is an important part of the paediatric investigation plan for this drug in ANCA

vasculitis. The primary endpoint for the two pivotal trials was remission within or at six months from start of treatment. Remission was defined using standard disease activity measures (BVAS3, or BVASWG); this is entirely appropriate. The paediatric version of this tool, PVAS, is now developed, published, in routine clinical use in centres of excellence, and also been used in pivotal paediatric trials including the aforementioned Roche trial. One of the most important clinical factors defining long-term outcome is renal survival; demonstrated improvement in renal function; we can therefore extrapolate that long-term survival is improved. Long-term outcome studies for both RAVE and RITUXVAS are ongoing and will provide specific data in relation to the issue. This will also apply to the planned paediatric trial.

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?

In the short term, adverse reactions such as infection, and neutropenia, are the same for rituximab and cyclophosphamide. Clinical trials do not address, however, the potential for long-term harm in relation to either drug. We know that cyclophosphamide is associated with late complications such as infertility and malignancy. No such signals have been identified yet for rituximab. So we think that in children in the longer term rituximab is a safer option and cyclophosphamide.

One important concern in relation to rituximab is the development of progressive multifocal leukoencephalopathy caused by JC virus. This has been described in adults with autoimmune disease (including ANCA vasculitis) who have received rituximab. However these patients had previously received other major immunosuppressants therefore it is impossible to attribute this complication solely to rituximab. That said, this important late signal will be carefully monitored in children who have received rituximab.

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.

The aforementioned open-label international clinical trial of rituximab in children with ANCA vasculitis, sponsored by Roche (trial WA25615). This trial is due to begin recruiting imminently (R&D approved in some centres now including GOSH).

Implementation issues

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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)?

At the moment rituximab is given in centres fully trained to do so. Since the requirements for delivery of the drug are no more than that required for cyclophosphamide (and arguably less resources are required for rituximab) we do not believe that any additional resources will be required to give rituximab. We would predict that there will be significant cost saving in the longer term from rituximab, due to better disease control and the fact that patients only have to attend hospital 2-4 times to receive rituximab, as opposed to 7-10 times for IV cyclophosphamide.

Equality

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.

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I cannot think of any examples where this would be a concern. As a general point there is inequality in terms of access to biologic therapies in the devolved nations. This has recently come to light for canakinumab. I would hope that this would not be observed in relation to rituximab for ANCA vasculitis.