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: Dr Peter Lanyon

Name of your organisation: British Society for Rheumatology
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)?

- 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)? **I am not an employee of BSR, but am a member of BSR Council and BSR Clinical Affairs Committee.**

- other? (please specify). **I have recently been appointed as chair of the NHS Commissioning Board Clinical Reference Group for Specialised Rheumatology; ANCA Vasculitis is a condition that is within the Specialised Service definitions.**

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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?

Response

Management involves three phases; remission induction, remission maintenance, and treatment of relapse. At regular intervals it is important to formally assess and define disease activity and damage status using validated instruments (e.g. BVAS, VDI), so that accurate ascertainment of remission, refractory disease or relapse can be documented in every patient.

Remission Induction

Cyclophosphamide is currently the standard remission induction agent, and is usually given for 3-6 months, adjusted for age, body weight and renal function. The majority of people treated with Cyclophosphamide will attain remission. However, 15% will not, and will continue to have active or progressive disease that is refractory to conventional treatment.

Methotrexate is an alternative comparator drug for remission induction in some situations where there is localised disease only, although it is associated with a higher risk of relapse than Cyclophosphamide.

Mycophenolate Mofetil is also an alternative agent; the final results of the MYCYC trial comparing this with Cyclophosphamide are awaited.

Current trial evidence does not appear to provide evidence of superiority of Rituximab compared to Cyclophosphamide as a remission agent. However, Cyclophosphamide has significant side effects including gonadal toxicity, bone marrow depression, haemorrhagic cystitis and an increased risk of future development of bladder cancer. There are therefore specific situations where the ability to use another agent and avoid the use of Cyclophosphamide would be very beneficial e.g.

- Women who have not completed a family and who are at risk of infertility due to a Cyclophosphamide induced premature menopause.
- Any previous uroepithelial malignancy.
- Any intolerance of Cyclophosphamide, either due to side effects or cytopenia.

Rituximab is currently likely to be used as a first-line remission induction agent in these situations. At the moment, it has not replaced Cyclophosphamide as the first line agent of choice for all patients needing initial remission induction as no clear benefit over Cyclophosphamide has yet been established and the long term optimal treatment strategy i.e. timing and duration of retreatment, and long term safety have yet to be determined.

Rituximab is also currently used as a remission induction agent for refractory disease i.e which has remained active despite an adequate trial of Cyclophosphamide and

steroids. This (and frequently relapsing disease) is a clinical situation which comprises many of the individual case series of Rituximab use. The comparators in this situation are likely to include Plasma Exchange, continued higher dose Cyclophosphamide or progression to renal replacement therapy.

Relapse

Rituximab is currently used as a remission induction agent at time of first relapse. There is evidence from the RAVE trial that Rituximab is more effective than Cyclophosphamide (the main comparator in this setting) and also avoids the cumulative risk of further Cyclophosphamide exposure.

Remission maintenance.

Clinicians currently used Rituximab if it has been required to induce remission and the disease has been characterised by previous relapses on alternative maintenance agents, or where the risk of relapse also includes (known from previous relapses) a risk of threatened organ damage, or where alternative remission maintenance agents have not been tolerated due to toxicity. The most likely used comparators in this setting would be Azathioprine, Methotrexate (if no renal disease) and Mycophenolate Mofetil.

As a general comment, there may be some geographic variation in practice; access to use of Rituximab for specific (e.g. refractory or relapsing) situations outlined above is likely to vary currently according to whether the patient is treated in specialist centre where clinicians have expertise in the treatment of vasculitis and whether there are local agreements with individual PCTs to fund. It is anticipated that the advent of specialised commissioning and a single NHS CB commissioning policy for Rituximab (currently in draft form until April 2013) will be a lever for improving the standards of care regardless of a patient's geography.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient?

Response

Yes, patients with vasculitis who have significant renal disease at diagnosis, older age, and co morbidities are likely to have a worse prognosis. However, in some cases the disease is "limited" to a single area (typically the head and neck) and, paradoxically, this type of disease can be less responsive to conventional treatment than systemic disease.

Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?.

Response

To my knowledge this has not been clearly defined, but it is likely that subgroups with both systemic and local (granulomatous) disease will benefit (and this has also been my personal experience).

In terms of risk, the long-term safety of repeated courses of Rituximab in a younger person (i.e. the cumulative risks of long term ongoing B cell depletion on normal immune function) are not known. There may also be a higher risk of adverse effects

of B cell depletion in those patients who already have a compromised immune system due to previous extensive immunosuppression.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics?

Response
Exclusively secondary care. This is a rare disease, and all patients should ideally be managed in collaboration with a multidisciplinary team comprising expertise in Rheumatology, Nephrology, ENT and Respiratory Medicine at a centre commissioned to provide Specialised care.

Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

Response
Rituximab is in widespread use in most Rheumatology units already under a NICE Rheumatoid Arthritis TAG. There may be additional capacity issues within day case units, offset potential by less Cyclophosphamide use.

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?

Response
Rituximab is already in use in many specialist vasculitis centres broadly in line with the off-licence situations outlined above. However, what is not known is how much variation there is in clinical practice in the care of patients who are not attending specialised centres; there has been a lack of any uniform commissioning policy in this situation. The extent of variation is not known i.e. to date there have been no national audits of the management and outcome of this condition, nor any systematic data collection on a national level of the outcome of individual Rituximab IFR requests that have supported this use (and this might potentially be a useful exercise).

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.

Response
BSR guidelines on the management of vasculitis are expected shortly, as is the NHS CB Policy document, which is currently in draft version.

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?

Response
Rituximab will potentially be easier to use logistically than an equivalent course of IV Cyclophosphamide. It will also require less concomitant drug treatment i.e. it will not require Mesna or anti-emetics.
Rituximab has not shown superiority to Cyclophosphamide for all patients, however there are specific situations as detailed above and in guidelines where it would be preferred.

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.

Response
These situations are probably adequately addressed in current guidelines, but in general it is essential that accurate decisions are made about the *disease states* that would drive any decisions rules i.e. formal documentation and MDT assessment to determine whether disease is active, in remission or relapsing.

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?

Response
I would consider the UK/Europe and USA-based trials to be representative of the UK population and practice, other than the potential that by including significant renal disease, that the trials may have been less representative of the group of patients who have ENT-limited disease. Apart from this caveat, it is likely that the results can be extrapolated.

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?

Response
Outcomes should include disease activity including remission rates, time to remission, number and severity of relapses, time to relapse i.e. disease-free interval, adverse effects of treatment (infection, leucopenia etc), cumulative steroid dose and organ damage. Patient –related outcomes should also be included

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?

Response
One main difference between Rituximab and Cyclophosphamide is the much longer half-life /duration of action. Whereas any immediate short term toxicity with Cyclophosphamide, particularly cytopenia is likely to be transient and reversible, any side effects directly related to B cell depletion with Rituximab are unlikely to recover in the short term.
This particularly relates to risks of hypogammaglobulinaemia, and it might be helpful to attempt to ascertain the exact risk of this from amongst patients who have received Rituximab in clinical practice outside of clinical trials; as this is the majority of use in the UK to date, particularly long-term retreatment. This observational data will not have been captured by clinical trials The effect of significant hypogammaglobulinaemia when this occurs is likely to result by need to take preventative antibiotics and/or IVIG replacement.
Late onset neutropenia is also another potential adverse event that is probably not adequately captured in clinical trials.

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.

Response
I am not aware of additional information

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)?

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Response
It depends on the exact guidance!. If the guidance does not recommend Rituximab, this would have a major adverse effect on those groups of patients who already have access to treatment in many centres in the UK according to the consensus within existing guidance.
It would be essential to mandate formal assessment of diagnosis, disease activity and damage by multidisciplinary teams trained and experienced in the managements of these conditions including outcome tools, aligned to the goals of Specialised Commissioning.

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.

Response
I do not think this is likely to be the case.

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