Response to NICE Single Technology Appraisal (STA) Consultation Document 2

Rituximab in combination with glucocorticoids for treating anti-neutrophil cytoplasm antibody associated vasculitis [ID567]

This is a response on behalf of representatives of a consortium of professional organisations and vasculitis experts (Appendix). It includes comments on the NICE appraisal (referenced by section number).

Summary

- The introduction of rituximab has been 'scene changing' in the management of ANCA associated vasculitis, of major benefit to patients, and it is re-shaping approaches to AAV therapy. Rituximab is currently indicated for relapsing or refractory disease and when cyclophosphamide is contra-indicated and has been routinely used for these indications in expert centres since 2005.

- There is a high level of consensus among vasculitis physicians concerning patient subgrouping, the treatment pathway and the current indications for rituximab, reflected by the 2013 BSR management guidelines for AAV and the 2013 NHS England Clinical Commissioning Policy.

- Improving AAV patient outcomes by cyclophosphamide avoidance has been a focus of AAV clinical researchers for two decades. Rituximab achieves both of these goals.

- This response represents the views of a consortium of six professional organisations and the majority of expert vasculitis physicians within the UK.

- The provisional recommendation is not sound, would change current best practice, and is not a suitable guidance for the NHS.

Introduction

Expert clinical opinion is pleased to note that there has been a change in the preliminary recommendations for the use of rituximab in ANCA-associated vasculitis (AAV) following consultation. However, NICE now recommend use of rituximab for patients with AAV once the maximum cumulative cyclophosphamide dose is exceeded and for those patient currently receiving cyclophosphamide, who are intolerant of cyclophosphamide or resistant to therapy, may continue to receive it. NICE has decided not to support the use of rituximab as primary therapy for those patients where cyclophosphamide should be avoided. These recommendations as stated differ from expert use of rituximab in current NHS practice.

Rituximab was originally introduced for the treatment of patients with refractory AAV or those patients where cyclophosphamide should be avoided, with the first case report of use published in 2001. Since then use has increased with over 160 publications in the literature and 700 patients treated. Data, collected from experts in the treatment of AAV in the UK, suggests that approximately 20% of patients have received rituximab, such that it is now

part of routine practice in restricted circumstances as recommended by the 2011 UK consensus statement for use of rituximab in AAV.

This has been recognised by NHS England (the commissioner of care for these patients), as reflected in Clinical Commissioning Policy (A13/p/a) which indicates that Rituximab is commissioned for us in AAV for 1) those patients with relapsing disease, 2) with primary treatment failure or with 3) adverse reactions or contra-indications to cyclophosphamide, which reflects the consensus statement on use of rituximab in AAV published in 2011 (Guerry 2011 Rheum). As outlined in the Policy, NHS England considered the place of rituximab in current clinical practice, whether research supported benefit for patients and whether its use represented best use of NHS resources, for the small numbers of patients (estimated in the policy as only 20-25 patients in each region per annum) who will require treatment with rituximab. The BSR guidelines for treatment of AAV have adopted a similar position. BSR guidelines recommend use of RTX for remission induction of AAV in *de novo* patients for whom CYC is indicated but its avoidance is desirable where:

(1) Fertility preservation required
    (a) There is no time for egg harvesting due to the fulminant nature of vasculitis
    (b) Male fertility is also affected by cyclophosphamide
(2) Severe infection, including infection requiring hospitalization, and chronic infections, such as, tuberculosis, bronchiectasis; and opportunistic infection
(3) Uro-epithelial malignancy or dysplasia
(4) Cytopaenia/bone marrow insufficiency
(5) CYC allergy/intolerance

Expert clinical opinion urges NICE to recommend use of rituximab that is in line with both current clinical consensus, national Specialist Society guidelines [1](BSR 2013) and current NHS England Commissioning Policy.

Key conclusion

1. The NICE recommendation is for rituximab only to be used in those patients who have exceeded the maximum recommended dose of cyclophosphamide and that a treatment sequence of 2 courses of cyclophosphamide should be received before use of rituximab (1.1, 4-17-4.19). This was based on the most plausible ICER of £12,100 per QALY gained provided by the comparison of 2 courses of cyclophosphamide followed by 1 course of rituximab with 2 courses of cyclophosphamide.

Despite the BSR guidelines stating that cyclophosphamide use should not exceed 25g, there is no evidence for 25g of cyclophosphamide as a safe limit. It is acknowledged there is a continuum of toxicity associated with cyclophosphamide usage with no evidence for a safe minimum dose. The BSR guideline of a lifetime exposure to cyclophosphamide of 25g is based on level C evidence[1]. Recent publications support the view of no minimum safe limit. Malignancy rates in patients recruited to the European Vasculitis Study Group clinical trials, where the median dose of cyclophosphamide was <20g and reflects current CYC usage, are increased with a standardised incidence ratio of 1.6 at five years[2]. This study had a median follow up of 5 years and is likely to have under-estimated the risk of malignancy, especially bladder cancer that has reported latency periods of up to 15-19 years

following cyclophosphamide treatment. A further study based on 467 patients with detailed information on cumulative cyclophosphamide dosing suggested a significant increased risk of bladder cancer for every 10g incremental dose of cyclophosphamide, contributing to the argument that 25g cyclophosphamide is not a safe and that further reductions in exposure below current 'maximum' levels are desirable. Further arguments to reduce current cyclophosphamide exposure are provided by evidence that there may also be an increased risk of malignancy *per se* in patients with Granulomatosis with polyangiitis[3, 4]. Expert clinical opinion is agreed that one course of cyclophosphamide (maximum 10 pulses over 6 months at 15mg/kg dependent on age and renal function) would be the treatment sequence and best reflects current routine practice.

2. The Committee have concluded that there is no evidence to support the use of rituximab in the small group of patients that should avoid cyclophosphamide as primary therapy (4.2, 4.8, 4.21).

Clinical experts note that although the small group of patients that should avoid cyclophosphamide have been excluded from clinical trials, there is substantial evidence from case series that rituximab is as effective in those individuals where cyclophosphamide should be avoided (e.g. [5]) (4.8). Clinical experts would support development of a database to report the outcome of rituximab use in AAV patients.

Expert clinical opinion considers that the model proposed comparing use of methotrexate or mycophenolate as alternative induction agents for those that cannot have cyclophosphamide is not appropriate. The BSR guidelines suggest these agents should only be used for induction therapy where there is no organ threatening disease. Within current practice rituximab has replaced the use of other alternative immunosuppressant agents for those where cyclophosphamide should be avoided and is welcomed by patients and clinicians[1] (4.1-4.3).

The technology

The committee have concluded that there was limited evidence showing rituximab did not affect fertility and that it did not consider rituximab to be a step change in managing AAV (2.1, 4.22, 4.9).

Clinical experts disagree with this conclusion. The introduction of rituximab has been scene changing in the management of AAV and the most significant advance in patient care since the introduction of cyclophosphamide in the 1970s. It has proved a reliable treatment for those failing standard of care, an alternative to those in whom cyclophosphamide avoidance is desirable and is reshaping approaches to disease management. There is data on long-term safety and efficacy of RTX from several studies in a wide range of patients with connective tissue disease, idiopathic thrombocytopenia and lymphoma. The malignancy risk has been examined in rheumatoid arthritis, an inflammatory autoimmune disease with similarities to AAV, and is low[6, 7]. There is emerging data on rituximab use in and before pregnancy from rheumatoid arthritis, SLE and AAV[8, 9]. The rituximab global drug safety database reports 231 pregnancies associated with maternal rituximab exposure, of those pregnancies with known outcomes no safety signal was identified[8]. The long-term

infective risk of rituximab appears low in rheumatoid arthritis, and it has been preferred to cyclophosphamide in AAV in the presence of severe infection[6, 10, 11].

Evidence for clinical effectiveness

Evidence from the RAVE trial suggests that at 6 months patients who have a relapsing course are more likely to benefit from rituximab as induction therapy compared with cyclophosphamide. RAVE is an induction remission trial and its aim was to investigate short-term outcomes not long term maintenance of remission. None of the patients in the rituximab limb received maintenance therapy. The analysis at 18 months was a secondary end-point and should be viewed as hypothesis generating (4.7). Routine practice within the UK currently utilises rituximab for patients who relapse their disease and where cyclophosphamide avoidance is preferred.

Clinical experts agree there are substantial uncertainties within the economic modelling. The model used to generate the ICER is questioned by clinical experts. There is concern about the plausibility of the utility values placed on the remission and non-remission health states. The costs for the long-term toxicities of cyclophosphamide are not included. Short-term costs acquired from University Hospitals Birmingham and Addenbrookes Hospital have estimated that a cycle of 2g rituximab compared with a course of cyclophosphamide (10 pulses) is equivalent. The ICER quote a cycle of cyclophosphamide, which includes 10 infusions, as £1802. This significantly underestimates NHS treatment costs.

Appendix

Professional organisations

- Arthritis Research UK
- British Association of Paediatric Nephrology
- British Society for Paediatric and Adolescent Rheumatology
- British Society of Rheumatology
- NHS England Specialised Rheumatology Clinical Reference Group
- Rare disease consortium/UKIVAS
- Renal Association
- British Renal Society
- Royal College of Nursing

Nominated Representatives

- Professor Lorraine Harper
  Invited Clinical Specialist at Appraisal Committee Meeting. Nominated by the Renal Association
- [redacted] Arthritis Research UK, Autoimmune Rheumatic Disease Group
- Dr Peter Lanyon

Invited Clinical Specialist at Appraisal Committee. Chair, Specialised Rheumatology, Clinical Reference Group

- [redacted]
  Royal College of Nursing
- [redacted] British Association of Paediatric Nephrology
- [redacted] British Renal Society
- [redacted] British Society of Rheumatology, 2013 AAV management guidelines, [redacted] Rare Disease Consortium/UKIVAS

Clinical Experts in managing patients with vasculitis

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