Response to NICE Single Technology Appraisal (STA) Consultation Document

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

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.

- Review of evidence has not taken account of extensive experience outside the two randomised controlled trials, or follow-up data available from these trials. This data addresses most of the areas of uncertainty.

- 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.

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

- The 'label' rituximab dose is higher than that routinely used in the UK.

- This response represents the views of a consortium of six professional organisations.

- The provisional recommendation is <u>not</u> sound and <u>not</u> a suitable guidance for the NHS.

1) Introduction

a) This is a response on behalf of a consortium of professional organisations (Appendix). It includes comments on the NICE appraisal (referenced by section number) and the evidence reference group (ERG) report (referenced by page number). It focuses on the evidence base, patient subgrouping and the patient treatment pathway.

b) UK clinical research groups have played a leading role in anti-neutrophil cytoplasm antibody associated vasculitis (AAV) for several decades. The clinical experts advising both the NICE appraisal and the ERG have longstanding clinical and research experience in AAV.

c) Expert clinical opinion is summarised in a 2011 UK consensus statement on the use of rituximab (RTX) in AAV treatment, the 2013 NHS England Clinical Commissioning Policy: Rituximab for AAV (reference NHSCB/ A13/P/a) and the 2013 British Society of Rheumatology (BSR) guidelines for the treatment of AAV(1).

d) 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 (CYC) in the 1970s. It has proved a reliable treatment for those failing standard of care, an alternative to those in whom CYC avoidance is desirable and is reshaping approaches to disease management. It entered routine use in specialist centres around 2005 and now plays a key role in the treatment pathway.

2) The evidence base

a) As a rare disease there is a scarcity of RCTs in AAV. The clinical use of RTX in AAV has developed from prospective open label studies, retrospective studies and reviews(2-5). These studies are largely ignored in the ERG review (Section 3.1) yet data relevant to the ERG statements: Page 5, "there is limited evidence that those failing or only partially responding to RTX may respond to a repeat course. " and Page 7 (Section 4.6) "Uncertainty exists as to maintenance therapy.". Of note are :

   i) The high response rates to RTX of 'uncontrolled' or refractory disease in those who have already received CYC, the area with the biggest unmet need.

   ii) The duration of remission after RTX for relapsing or refractory disease, typically 12-18 months and requirement for relapse prevention strategies.

   iii) The efficacy of repeated RTX for relapse after previous RTX.

iv) An analysis of the reasons for apparent RTX failure, infection, under dosing, slowly responding granulomatous disease, and the efficacy of repeated RTX in some of those with a poor RTX response.

v) Discussion of the options for relapse prevention after RTX, and experience of fixed interval RTX or RTX dosing guided by biomarkers (see (8))

b) Rituximab is effective in patients with life-threatening disease. ERG Page 8, "RTX is not proven in very severe, life-threatening vasculitis". The RITUXVAS RCT studied patients with severe renal disease and had a mortality rate reflecting the life-threatening nature of vasculitis(6). Patients with severe alveolar haemorrhage have been included in observational cohorts.

c) Extended follow up of the RAVE and RITUXVAS trials (Section 4.3).

i) The 18 month data from RAVE shows no difference between treatment groups indicating the ability of a single course of rituximab and glucocorticoids to induce lasting remission comparable to cyclophosphamide followed by azathioprine. (7)
ii) At 24 months in RITUXVAS there was no difference in relapse rates between RTX or CYC groups with both groups having glucocorticoids tapered after 12 months and the CYC group continuing on azathioprine. There were also no differences in mortality, end stage renal disease or severe adverse event rates between groups in the follow-up studies (Jones, unpublished).

3) Patient subgrouping (Section 1.2)

a) There have been several systems of patient subgrouping by disease severity and extent in AAV, in part driven by a desire to reduce CYC exposure. A concept developed in the 1990s by both EUVAS and US groups was to divide into those definitely requiring CYC (termed generalised or severe) and those in whom alternatives, such as MTX, could be considered (early systemic or non-severe).

b) Nephritis is the most frequent major disease manifestation and occurs in 70% of AAV patients, so the majority fall within the generalised/severe subgroup.

c) The RAVE trial recruited 'severe' AAV. This was an operational definition of a clinical scenario where the treating physician would normally use CYC and required either a major item of disease activity on BVAS/WG or upgrading of a minor disease item to major by the physician. In contrast all patients in RITUXVAS had at least one major item, nephritis(8).

d) ANCA subtype itself (PR3 or MPO-ANCA) does not influence choice of induction agent.

4) The patient pathway (Figure 1)

a) Patients present with active disease *de novo* or at relapse. They receive induction therapy for 3-6 months and then enter one of three states: remission (on drug), refractory disease or a low disease activity state. Those on drug remission or low disease activity receive relapse prevention 'maintenance' therapy, while refractory patients have an alternative induction therapy. Subsequent changes in disease activity move a patient between states.

b) Induction therapy for most *de novo* patients is CYC and glucocorticoids. Some non-severe patients will receive methotrexate or mycophenolate mofetil in place of CYC, often because CYC avoidance is desirable. Although remission rates with MTX and MMF for *de novo* patients are the same as for CYC at six months, relapse rates following either are higher than after CYC, and long term follow-up after methotrexate induction has revealed much higher glucocorticoid requirement and higher total CYC requirement (NORAM and MYCYC trials) (9).

c) The current use of RTX, as outlined in the 2013 updated British Society of Rheumatology guidelines(1), for remission induction of AAV is:

   i) Relapsing or refractory disease after 'standard of care' therapy with CYC (or MTX or MMF for non-severe disease) and high dose glucocorticoids
   ii) *De novo* patients for whom CYC is indicated but its avoidance is desirable
      (1) Fertility preservation
         (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

d) CYC induction for relapse after primary CYC induction is less desirable than RTX because it is less effective (RAVE relapse subgroup), because CYC intolerance and toxicity is higher with a second course, and because further CYC contributes to the malignancy risk.
   i) Malignancy rates with current CYC usage are increased with a standardised incidence ratio of 1.6 at five years. (10) There is a dose dependent relation between CYC and malignancy risk and further reductions in exposure below current 'maximum' levels are desirable.

e) The only rationale for the use of CYC after RTX is in rare patients for whom RTX is ineffective or further RTX is contra-indicated

f) The goal of therapy is 'complete', off drug remission. There is a cost and patient benefit of 'off drug' as compared to 'on drug' remission.

g) We recommend all patients receiving RTX for AAV are registered with the UKIVAS registry, in line with the 2013 BSR guidelines.

5) Relapse (Figure 2)

a) Relapsing disease, the recurrence of vasculitic activity after on drug or off drug remission, occurs in 25-30% by 2 years and 40-50% by five years(11). Following one relapse a patient is more likely to relapse again and patients suffer the cumulative effects of recurrent periods of disease activity and high drug exposure. Untreated, relapses result in vital organ failure and death.

b) Relapses were categorised by international trial groups in 1995 and 1999 as major (or severe, at least one new or worse major BVAS item) and minor (or non-severe, at least one new or worse minor BVAS item and no major items) (12, 13). Recommended treatment for major was CYC and high dose glucocorticoids and for minor was optimization of remission immunosuppression and moderate increase in glucocorticoids. Neither of these approaches have been validated.

c) Patients developing a relapse from a state of remission will usually, but not always, develop minor features (especially constitutional disturbance, and ENT disease in GPA) before major features (such as nephritis). Thus a major relapse can be a missed minor relapse and in a specialist service most relapses are minor.

d) Patients with a minor relapses are at high risk of further relapses because, the increased glucocorticoids, only serves to suppress symptoms and does not have a sustained effect on relapse risk when glucocorticoids return to baseline. For this reason a second minor relapse can be regarded as the same as a major relapse in terms of therapy selection. This is in line with the upgrading of a patient with non-severe disease activity to severe as applied to eligibility for RAVE.

6) Rituximab dosing

a) This issue is referred to in the appraisal and ERG report but we emphasise that the dose of RTX 1000mg x 2 is widely used and recommended in the NHS England Clinical Commissioning Policy. The EMA label dose of 375mg/m2 x 4 was selected for the RAVE trial, designed in 2002, when there was no experience with other regimens. It

is more expensive and requires four visits rather than two. The two regimens were compared in a retrospective, multicentre cohort study when no pharmacodynamic or clinical differences between regimens were identified(2). The 1000mg x 2 regimen will benefit the cost effectiveness analysis in favour of RTX.

7) Relapse prevention after RTX

a) Section 3.3.7 is not an adequate reflection of the current approach to relapse prevention after rituximab. Specifically, the only data concerning the use of immunosuppression (AZA/MTX) after RTX is negative(2).

b) There are four options

i) No therapy and treat further relapse with RTX
ii) An immunosuppressive agent (azathioprine or methotrexate)
iii) Fixed interval repeat dose RTX
iv) Repeat dose RTX based on biomarkers

(i) is not desirable because it requires close patient monitoring and places the patient at risk of increased tissue damage and morbidity when relapse occurs. (ii) has been assessed in a retrospective, multi-centre, cohort study and continued immunosuppressive had no effect on time to B cell return or to relapse compared to no therapy(2). (iii) relatively large retrospective data sets exist (Massachusets General, Cambridge UK) on fixed interval repeat dosing, and this is being compared to (ii) in the ongoing RITAZAREM RCT(3, 14). In a retrospective comparison with extended follow-up, RTX exposure did not differ between patients treated with RTX at relapse (i) and those receiving a fixed interval regimen (iii) (3). (iv) has been studied in the Mayo clinic where it appears effective although the total RTX exposure was higher than in the fixed interval repeat dosing experience (iii) (4).

c) The MAINRITSAN trial has reported superiority for fixed interval repeat dose RTX compared to AZA for relapse prevention after CYC in an 80% *de novo* population (Guillevin, unpublished).

8) Safety of rituximab

a) The failure of either RAVE or RITUXVAS to report a safety benefit of CYC avoidance or reduction in the RTX treatment groups is not fully understood but the high glucocorticoid exposure for all patients is likely to be a major factor (Page 42). Two other factors of relevance are the recruitment of patients from only a few experienced sites with high quality CYC management and avoidance of toxicity, unlikely to be the case

in routine practice; and an increased risk of adverse events inherent in this patient group due to the severity of their multi-system disease.

b) There is data on long-term safety and efficacy of RTX from several studies (Sections 2.1, 3.2.2). The malignancy risk has been examined in rheumatoid arthritis and is low(15, 16). There is emerging data on rituximab in and before pregnancy from rheumatoid arthritis, SLE and AAV(17, 18).

c) The infective risk of rituximab appears low in rheumatoid arthritis, and it has been preferred to cyclophosphamide in AAV in the presence of severe infection(15, 19, 20).

9) Future directions

a) Patient pathway. The introduction of rituximab continues a list of key advances in AAV therapy that have had a major impact on patient management, which began with glucocorticoids in 1947. We anticipate rituximab becoming first line treatment and this will lead to a step change in the patient pathway with respect to lowering glucocorticoid exposure, reduced frequency of out-patient visits and changes to relapse prevention therapy. Further reductions in cyclophosphamide and glucocorticoid exposure remain clinical research goals.

b) Patient stratification. As further data emerges we anticipate adjustment of rituximab dosing and frequency according to clinical phenotyping and biomarkers including pharmacogenomics. This may lead to lower rituximab doses (as in MAINRITSAN).

c) Other B cell targeted therapies are or being investigated in AAV, including BLyS blockade, belimumab (BREVAS) (ClinicalTrials.gov identifier NCT01663623).

Appendix

Professional organisations

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

Nominated Representatives

- Professor Lorraine Harper
  Invited Clinical Specialist at Appraisal Committee Meeting. Nominated by the Renal Association

  [redacted]

- Dr Peter Lanyon
  Invited Clinical Specialist at Appraisal Committee. Chair, Specialised Rheumatology, Clinical Reference Group

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Figure 1 The patient pathway

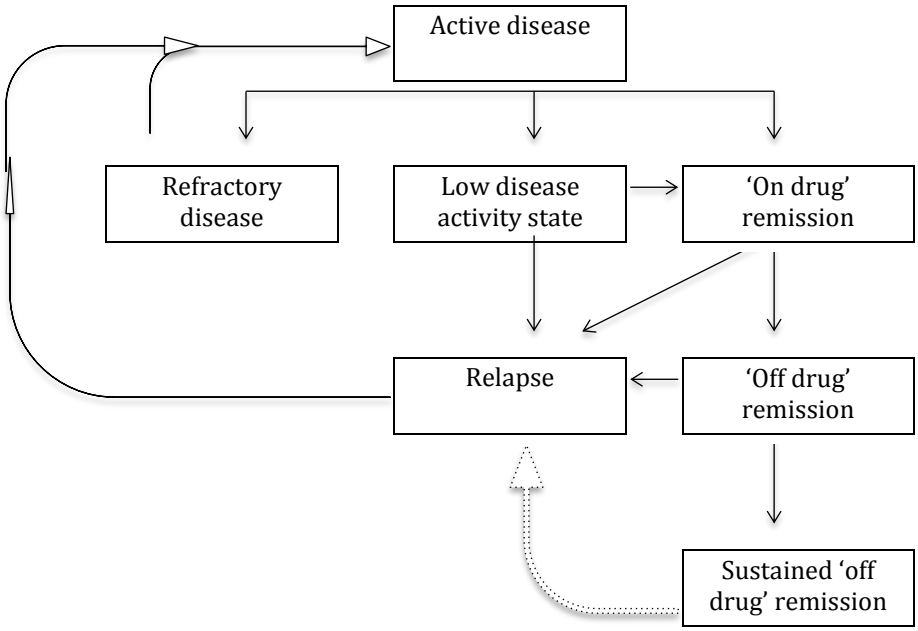
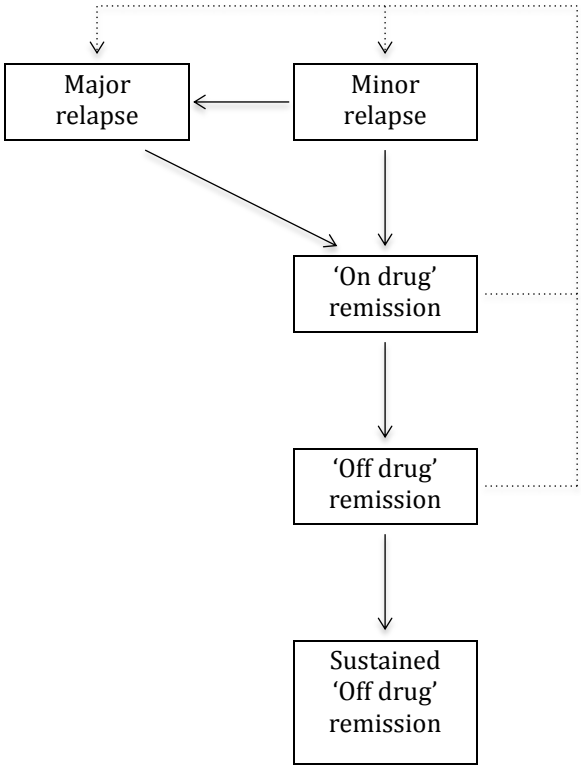


Figure 2 Relapse pathway



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