NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Technology Appraisal Review Proposal paper

Review of TA308; Vasculitis (anti-neutrophil cytoplasmic antibody-associated) – rituximab (with glucocorticoids)

Original publication date:	March 2014
Review date	March 2017
Existing recommendations:	Optimised To see the complete existing recommendations and the original remit for TA308, see Appendix A.

1. Proposal

The guidance should be transferred to the "static guidance list". That we consult on this proposal.

2. Rationale

The existing recommendations are optimised (narrower than the marketing authorisation) because rituximab is only recommended for people who: cannot take cyclophosphamide; people who have already had cyclophosphamide, but whose disease has not responded to it or people who cannot take any more because they would have a cumulative dose outside the limits of the British Society of Rheumatology, or have experienced toxicity because of it.

Rituximab was considered to be of similar clinical effectiveness to cyclophosphamide (shown to be statistically non-inferior in the RAVE trial) but was not recommended as an alternative to cyclophosphamide for the whole population covered by the marketing authorisation. This was because the incremental cost effectiveness ratio (ICER) for rituximab compared with cyclophosphamide was higher than that normally considered a cost effective use of NHS resources. The price of rituximab has not changed since TA308, as such, the ICER for the wider population covered by the marketing authorisation for rituximab (which remains the same as the time of TA308) is unlikely to change. There were other uncertainties in the economic analysis because some disutility values and costs associated with the long term safety benefits of rituximab were not included in the modelling. The systematic searches for this review proposal paper did not identify new data that would address these uncertainties. Overall, there are no new data to suggest that a re-appraisal of rituximab compared with cyclophosphamide would result in a different ICER or recommendation.

The marketing authorisation for rituximab in combination with glucocorticoids is for the induction of remission in adult patients with severely active granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA). The summary of product characteristics states that there were insufficient data available for rituximab maintenance therapy at the time the marketing authorisation was granted. There are currently ongoing clinical trials of rituximab maintenance (after induction of remission) and of rituximab in a population with eosinophilic granulomatosis. NICE can only appraise technologies within their marketing authorisation and would only be able to appraise rituximab for maintenance therapy or for eosinophilic granulomatosis if the company decided to apply for a marketing authorisation to cover these indications. Technology appraisals on the "static guidance list" are reviewed every 5 years, and this time frame will allow a review proposal to be made once the outcome of these trials and the company's intentions regarding applying for an extension to the marketing authorisation are known. Should a marketing authorisation extension be sought sooner than 5 years, it is anticipated that this would be identified and considered through the NICE topic selection process.

It should be noted that NHS England have issued a commissioning guide: "rituximab for the treatment of ANCA- associated vasculitis in adults". This document gives commissioning policy on using an off-label dose of rituximab for granulomatosis polyangiitis and microscopic polyangiitis, rituximab for maintenance therapy once a person's vasculitis is in remission and the off-label use of rituximab for eosinophilic granulomatosis with polyangiitis. It is outside the remit of the technology appraisal process to appraise these off-label uses of rituximab. It is recognised that the treatment pathway for ANCA-associated vasculitis may have changed since TA308 was issued and includes some use of off-label rituximab. It is appropriate that the NICE technology appraisal guidance and NHS England commissioning guide should be used in parallel to inform commissioning decisions for within-label and off-label use of rituximab respectively.

3. Summary of new evidence and implications for review

Clinical data from the RAVE and RITUXVAS trials were considered in TA308. There have been no further clinical trials of rituximab for its licensed indication of the induction of remission in adult patients with severely active granulomatosis with polyangiitis and microscopic polyangiitis.

Has there been any change to the price of the technology(ies) since the guidance was published?
No
Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?
No
Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?

The long term safety benefits of rituximab relative to cyclophosphamide were unclear but there are no new published data to address this.
Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?
See Appendix C for a list of related NICE guidance.

The search strategy from the original ERG report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from January 2013 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix C for further details of ongoing and unpublished studies.

4. Equalities issues

It was noted that cyclophosphamide can affect male and female fertility, as such people who had not completed their family and whose fertility may be affected by cyclophosphamide were identified as a group for whom rituximab should be an alternative to cyclophosphamide.

GE paper sign off: **Meindert Boysen, 16 March 2017**

Contributors to this paper:

Information Specialist: Daniel Tuvey

Technical Analyst: Mary Hughes

Associate Director: Linda Landells

Project Manager: Samantha Shannon

Appendix A – Information from existing guidance

5. Original remit

To appraise the clinical and cost effectiveness of rituximab in combination with corticosteroids within its licensed indication for the treatment of antineutrophil cytoplasmic antibody-associated vasculitis.

6. Current guidance

1.1 Rituximab, in combination with glucocorticoids, is recommended as an option for inducing remission in adults with anti-neutrophil cytoplasmic antibody [ANCA]-associated vasculitis (severely active granulomatosis with polyangiitis [Wegener's] and microscopic polyangiitis), only if:

- further cyclophosphamide treatment would exceed the maximum cumulative cyclophosphamide dose or
- cyclophosphamide is contraindicated or not tolerated or
- the person has not completed their family and treatment with cyclophosphamide may materially affect their fertility or
- the disease has remained active or progressed despite a course of cyclophosphamide lasting 3–6 months or
- the person has had uroepithelial malignancy.

1.2 People currently receiving treatment initiated within the NHS with rituximab that is not recommended for them by NICE in this guidance should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

7. Research recommendations from original guidance

N/A

8. Cost information from original guidance

Rituximab is priced at £174.63 per 10 ml vial and £873.15 per 50 ml vial (excluding VAT; British national formulary [BNF] edition 66). No price change as of January 2017.

Appendix B – Explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	Consequence	Selected – 'Yes/No'
A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the specify STA or MTA process.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred to specify date or trial.	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No

Appendix B

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going clinical guideline[1].	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	Yes
The guidance should be withdrawn	The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS. The guidance will be stood down and any funding direction associated with a positive recommendation will not be preserved.	No

[1] Information on the criteria for NICE allowing a technology appraisal in an ongoing clinical guideline can be found in section 6.20 of the guide to the processes of technology appraisal.

Appendix C – other relevant information

Published

N/A

In progress

N/A

Referred - QSs and CGs

N/A

Suspended/terminated

N/A

Appendix C

1. Details of new products

Drug (company)	Details (phase of development, expected launch date)	In topic selection
N/A		

2. Registered and unpublished trials

Trial name and registration number	Details
Maintenance of ANCA Vasculitis Remission by Intermittent Rituximab Dosing Based on B-cell Reconstitution vs a Serologic ANCA Flare (NCT02749292)	Estimated Enrolment: 200 Estimated Study Completion Date: October 2020 This study is currently recruiting participants
An International, Open Label, Randomised Controlled Trial Comparing Rituximab With Azathioprine as Maintenance Therapy in Relapsing ANCA-associated Vasculitis (NCT01697267)	Estimated Enrolment: 190 Estimated Study Completion Date: December 2018 This study is ongoing, but not recruiting participants.
MAINtenance of Remission Using RITuximab in Systemic ANCA-associated Vasculitis II (NCT01731561)	Enrolment: 166 Estimated Study Completion Date: December 2016 This study is ongoing, but not recruiting participants.
Extended Follow Up of the Mainritsan 2 Study. Comparison Between a Long Term and a Conventional Maintenance Treatment With Rituximab: a Placebo-Controlled Randomized Trial (NCT02433522)	Enrolment: 97 Estimated Study Completion Date: January 2019 This study is ongoing, but not recruiting participants.
Pharmacokinetic Study of Rituximab Induction Regimen in ANCA-associated Vasculitis: a Predictive Factor of Clinical Outcome? (MONITUX) (NCT02474888)	Estimated Enrolment: 50 Estimated Study Completion Date: June 2017 This study is currently recruiting participants

Trial name and registration number	Details
Low-dose Glucocorticoids Plus Rituximab Versus High-dose Glucocorticoids Plus Rituximab for Remission Induction in ANCA-associated Vasculitis; a Multicentre, Open Label, Randomised Control Trial (NCT02198248)	Estimated Enrolment: 140 Estimated Study Completion Date: September 2019 This study is currently recruiting participants
A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Evaluate the Safety and Efficacy of CCX168 (Avacopan) in Patients With ANCA-Associated Vasculitis Treated Concomitantly With Rituximab or Cyclophosphamide/Azathioprine (NCT02994927)	Estimated Enrolment: 300 Estimated Study Completion Date: October 2019 This study is currently recruiting participants
Evaluation of Rituximab-based Regimen Compared to Conventional Therapeutic Strategy For Remission Induction In Patients With Newly-Diagnosed or Relapsing Eosinophilic Granulomatosis With Polyangiitis. Prospective, Randomized, Controlled, Double-blind Study (NCT02807103)	Estimated Enrolment: 108 Estimated Study Completion Date: June 2020 This study is currently recruiting participants
A Study Evaluating the Safety and Efficacy of Rituximab in Combination With Glucocorticoids in Participants With Wegener's Granulomatosis or Microscopic Polyangitis (NCT02115997)	Estimated Enrolment: 30 Estimated Study Completion Date: April 2018 This study is currently recruiting participants

3. Relevant services covered by NHS England specialised commissioning

Clinical Commissioning Policy: Rituximab for the treatment of ANCA-associated vasculitis in adults (Reference: NHS England A13/P/a)

4. Additional information

No change to the indication from the original guidance.