Engagement Report

Topic details

Title of policy or policy statement:	Rituximab for the treatment of nodal/paranodal antibody positive inflammatory/autoimmune neuropathy in adults and post-pubescent children
Programme of Care:	Trauma
Clinical Reference Group:	Neurosciences
URN:	2001

1. Summary

This report summarises the feedback NHS England received from engagement during the development of this policy proposition, and how this feedback has been considered.

2. Background

NHS England does not routinely commission rituximab for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) in accordance with the policy: Clinical Commissioning Policy: Rituximab for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy (MMN), vasculitis of the peripheral nervous system & IgM paraprotein-associated demyelinating neuropathy (adults) (NHS England), NHS England reference code: 170026/P.

Although nodal/paranodal antibody positive inflammatory/autoimmune neuropathy has been considered to come under the umbrella of CIDP, there are a number of reasons to consider nodal/paranodal antibody positive autoimmune neuropathies as distinct disease entities and deserving of their own commissioning policy. The core diagnostic feature of nodal/paranodal antibody positive inflammatory/autoimmune neuropathy which distinguishes it from CIDP is the presence of nodal or paranodal autoantibodies directed against cell adhesion molecules present at the node of Ranvier or surrounding paranode of myelinated nerve fibres. Nodal/paranodal antibody positive inflammatory/autoimmune neuropathy differs from 'seronegative CIDP' in having a more rapid disease onset with more severe disease and a different pattern of treatment responsiveness.

The NHS England policy 'Rituximab for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy (MMN), vasculitis of the peripheral nervous system and IgM paraprotein-associated demyelinating neuropathy (adults)', NHS England Reference code: 170026/P, is for patients who have been diagnosed with CIDP, and does not distinguish or specifically address patients with nodal/paranodal antibodies. NHS England does not routinely commission rituximab for CIDP.

The policy proposition describes the features of nodal/paranodal antibody positive neuropathies which distinguishes the condition from CIDP and considers the evidence for the use of rituximab specifically for treating people who have an immune-mediated neuropathy in association with nodal/paranodal antibodies. It has been recommended

that the policy proposition will be progressed as for routine commissioning, recognising the low evidence base in this rare condition.

3. Engagement

NHS England has a duty under Section 13Q of the NHS Act 2006 (as amended) to 'make arrangements' to involve the public in commissioning. Full guidance is available in the Statement of Arrangements and Guidance on Patient and Public Participation in Commissioning. In addition, NHS England has a legal duty to promote equality under the Equality Act (2010) and reduce health inequalities under the Health and Social Care Act (2012).

The policy proposition was sent for stakeholder testing for 2 weeks from 28th January 2021 to 12th February 2021. The comments have then been shared with the Policy Working Group to enable full consideration of feedback and to support a decision on whether any changes to the proposition might be recommended.

Respondents were asked the following questions:

- Do you support the proposition for rituximab for nodal/paranodal antibody positive inflammatory/autoimmune neuropathy in adults and post-pubescent children to be available through routine commissioning based on the evidence review and within the criteria set out in this document?
- Do you believe that there is any additional information that we should have considered in the evidence review? If so, please give brief details.
- Do you believe that there are any potential positive and/or negative impacts on patient care as a result of making this treatment option available? If so, please give details.
- Do you have any further comments on the proposition? If Yes, please describe below, in no more than 500 words, any further comments on the proposed changes to the document as part of this initial 'sense check'.
- Please declare any conflict of interests relating to this document or service area.
- Do you support the Equality and Health Inequalities Impact Assessment?

A 13Q assessment has been completed following stakeholder testing.

The Programme of Care has agreed that the proposition offers a clear and positive impact on patient treatment, by potentially making a new treatment available which widens the range of treatment options without disrupting current care or limiting patient choice, and therefore further public consultation was not required. This decision has been assured by the Patient and Public Voice Advisory Group.

4. Engagement Results

6 stakeholders responded, of which 5 were hospitals and one was a neuropathy information centre for physicians and scientists. All were in favour of the policy.

In line with the 13Q assessment it was deemed that further public consultation was not required.

5. How has feedback been considered?

Responses to engagement have been reviewed by the Policy Working Group and the Trauma Programme of Care. The following themes were raised during engagement:

Keys themes in feedback	NHS England Response
Relevant Evidence	
Pascual-Goni E, Fehmi J, Lleixa M, Martin-Aguilar L, Devaux J, Delmon E, Doppler K, Sommer C, Radunovic A, Carvajal A, Smyth S, Williams L, Mazanec R, Potockova V, Hinds N, Cassereau J, Viala K, Lefilliatre M, Nicolas G, Foley P, Leypoldt S, Keddie S, Lunn M, Zimprich F, Nunkoo VS, Loscher W, Martinez-Martinez L, Diaz-Manera J, Rojas-Garcia R, Illa I, Rinaldi S, Querol. Antibodies to the Caspr1/contactin-1 complex in chronic inflammatory demyelinating polyneuropathy. Brain, accepted for publication, 2021.	Pascual-Goni et al (accepted for publication 2021). As this paper has not yet been published it does not meet the evidence review criteria. However, also the paper does not expand the range of antibodies currently considered within the policy/evidence review and does not provide a higher quality of evidence than currently within the evidence review. It is a further case series (albeit slightly larger in sample size) that shows a generally good response to rituximab.
Desiree De Simoni, Gerda Ricken, Michael Winklehner, Inga Koneczny, Michael Karenfort, Ulf Hustedt, Ulrich Seidel, Omar Abdel-Mannan, Pinki Munot, Simon Rinaldi, Claudia Steen, Michael Freilinger, Markus Breu, Rainer Seidl, Markus Reindl, Julia Wanschitz, Cinta Lleixà, Günther Bernert, Klaus-Peter Wandinger, Ralf Junker, Luis Querol, Frank Leypoldt, Kevin Rostásy, Romana Höftberger. *Antibodies to nodal/paranodal proteins in paediatric immune-mediated neuropathy.* Neurol Neuroimmunol Neuroinflamm Jul 2020, 7 (4) e763; DOI: 10.1212/NXI.0000000000000763	De Simoni et al, 2020. 54 children with GBS (n = 42) and CIDP (n = 12) and retrospectively screened for antibodies against neurofascin155 (NF155), NF186, NF140, contactin-1 (CNTN1), contactin associated protein1 (CASPR1), and glycine-receptor (GlyR) using cell-based assays2,3; 1 patient was additionally tested with CNTN1-ELISA Five of 12 children, who met the EFNS/PNS criteria for CIDP, had nodal/paranodal antibodies: 2 pan-neurofascin (NF155/NF186/140 triple positive), 1 NF155, and 2 CNTN1-antibodies. Of those 5 patients, 3 received rituximab following unsuccessfully being treated with IVIG and corticosteroids. All are stated to have a made a significant improvement as measure by mRS scores (although the baseline scores aren't included, only the outcome scores). The specific ages of the 3 patients treated with rituximab is not known, but it is known that the 5 CIDP patients that were nodal/paranodal antibody positive had an age range of 3-11 so it can confidently be

	said that all 3 were pre-pubescent and within that age range. No safety data is reported. But it is a small group of prepubescent children treated with rituximab with a reported positive outcome. Any GRADE assessment of the evidence would likely class it as very low quality/certainty. But it is some evidence of use and outcome in this age group and the small numbers of patients are not inconsiderable when compared the small numbers currently reported within the evidence review. This new evidence is helpful in providing some evidence of effectiveness for pre-pubescent children and therefore may allow a wider age range for the policy, but it does not materially change the evidence on effectiveness from the evidence review, it supports it and enhances the age range.
Patient Impact Assessment	
No comments received.	
Current Patient Pathway	
See below under 'Changes/addition to policy'	
Potential impact on equality and health inequalities	
No comments received.	
Changes/addition to policy	
The inclusion criteria (page 10) are slightly ambiguous. It would be clearer to rephrase as: RTX may be given to patients who have both (a) nodal/paranodal antibody positive inflammatory/autoimmune neuropathy AND (b) any of the listed criteria i.e. severe disease (MRS4 or ONLS5) or any of the four bullet points under 'other patient groups' who therefore don't need to have severe disease. As written, it's not clear enough that 'other patient groups' means those with antibodies but without severe disease.	The policy proposition has been amended in accordance with the comment.
The policy says that the multi-disciplinary team (MDT) will make the final decision on who to treat. Can the MDT decide to give RTX to patients	The reference to MDT involvement has been removed from the policy proposition.

who don't meet the listed criteria, because these criteria are only 'proposed' or 'considered'?	

6. Has anything been changed in the policy proposition as a result of the stakeholder testing and consultation?

The following changes based on the engagement responses have been made to the policy proposition:

- The following wording on page 10 under 'Starting Criteria' has been changed: '*The decision to commence treatment with rituximab must be made in conjunction with the patient by the relevant multi-disciplinary committee (MDT)*.'

  The sentence now reads: '*The decision to commence treatment with rituximab must be made by the treating clinician in conjunction with the patient.*'

- The following wording on page 10 under 'Inclusion criteria' has been changed:

  The decision to treat patients with nodal/paranodal antibody positive inflammatory/ autoimmune neuropathy will be made by the multi-disciplinary teams of tertiary neuroscience centres. It is proposed that rituximab would be given to patients with nodal/paranodal antibody positive inflammatory/autoimmune neuropathy who have severe disease (Modified Rankin Scale (MRS) ≥4 and/or Overall Neuropathy Limitations Scale (ONLS) ≥5), as soon as possible after diagnosis, and in preference to IVIg.

  Other patient groups who would be considered for treatment with rituximab are those:

  - *who have already been established on regular IVIg with the aim of reducing or completely ameliorating IVIg,*
  - *who have had a poor response to a trial of corticosteroids (failure to improve after 8 weeks of high-dose treatment, e.g. prednisolone 60mg od, or pulsed dexamethasone (40mg od for 4 days) or methylprednisolone (500-1000mg for 3-5 days monthly),*
  - *who cannot be treated with high dose corticosteroids due to intolerance or toxicity or who have or are at a high risk of steroid-related side effects, or*
  - *who relapse during steroid weaning following ≥6 months of steroid treatment.*

  The paragraph now reads:

  It is proposed that patients who have nodal/paranodal antibody positive inflammatory/autoimmune neuropathy will be considered for treatment with rituximab provided they:

EITHER have severe disease (Modified Rankin Scale (MRS) ≥4 and/or Overall Neuropathy Limitations Scale (ONLS) ≥5). Treatment would take place as soon as possible after diagnosis, and in preference to IVIg.

OR fall into one of the following patient groups:

1. *Those who have already been established on regular IVIg with the aim of reducing or completely ameliorating IVIg,*
2. *Those who have had a poor response to a trial of corticosteroids (failure to improve after 8 weeks of high-dose treatment, e.g. prednisolone 50-60mg a day, pulsed dexamethasone (40mg a day for 4 days every 4 weeks) or methylprednisolone (1-2 g monthly),*
3. *Those who cannot be treated with high dose corticosteroids due to intolerance or toxicity or who have or are at a high risk of steroid-related side effects, or*
4. *Those who relapse during steroid weaning following ≥6 months of steroid treatment.*

7. Are there any remaining concerns outstanding following the consultation that have not been resolved in the final policy proposition?

No.