Engagement Report

Topic details

Title of policy or policy statement:	Rituximab for the treatment of IgM paraproteinaemic demyelinating peripheral neuropathy in adults [NHS England URN: 1910]
Programme of Care:	Trauma
Clinical Reference Group:	Neurosciences
URN:	1910

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

A final decision as to whether rituximab will be routinely commissioned will be made by NHS England following a recommendation from the Clinical Priorities Advisory Group. The proposition is: rituximab is recommended to be available as a routine commissioning treatment option for IgM paraproteinaemic demyelinating peripheral neuropathy in adults within the criteria set out in this document.

NHS England does not routinely commission rituximab for IgM paraproteinaemic demyelinating peripheral neuropathy in accordance with the 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.

Paraproteinaemic demyelinating peripheral neuropathy (PDPN) is associated with a range of pre-cancerous and cancerous blood conditions. Paraproteins are antibodies produced by white blood cells, which bind to the myelin sheath surrounding the body's nerve fibres resulting in neuropathy which manifests as sensory disturbance, imbalance, tremor and weakness of muscles.

Treatments for PDPN involve the suppression of the blood cancer which is the underlying cause of PDPN or attempts at physical removal of IgM antibodies from the blood. In the past treatments have included corticosteroids, plasmapheresis, interferon-2-alpha, cyclophosphamide and chlorambucil. None of these treatments in isolation have been found to be effective and most have significant or serious side effects.

There is limited evidence for the use of intravenous immunoglobulin (IVIg) in the short-term for treating numbness, unsteadiness and weakness associated with PDPN.

Rituximab belongs to a group of drugs known as 'biologics' which are themselves usually monoclonal antibodies. These drugs are also sometimes called 'targeted biological therapies' as they work by targeting specific receptors on the surface of cells relevant to the cause of the disease. Rituximab targets and attaches to CD20 proteins found on the surface of B cells (a type of white blood cell that produce the disease-causing antibodies), leading to their destruction.

NHS England has carefully reviewed the evidence to treat PDPN with rituximab. We have concluded that there is enough evidence to make the treatment available at this time.

This policy proposition has been developed by a Policy Working Group made up of four Neurology Consultants, one of whom was Policy Clinical Lead, a Public Health Lead, a Pharmacy Lead, two National Programme of Care Managers, a representative from the GAIN charity and a Clinical Policy Fellow.

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 02/06/2021 to 16/06/2021. 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 IgM paraproteinaemic demyelinating peripheral neuropathy 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.
- Does the Patient Impact Summary present a true reflection of the patient and carers lived experience of this condition?
- Do you support the Equality and Health Inequalities Impact Assessment?

A 13Q assessment has been completed following stakeholder testing. The Programme of Care has decided 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 Public Voice Advisory Group.

3. Engagement Results

Four stakeholders responded, of which two were hospitals, one was an organisation of physicians and scientists dedicated to improving the management of and research into peripheral nerve disease and one was an association of pharmacy practitioners who work with patients with neurological conditions.

All were in favour of the policy with the exception of one of the hospitals which were unclear as to the purpose of the policy (see section 4).

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

4. 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	
No comments received	
Impact Assessment	
No comments received	
Current Patient Pathway	
1) Based on the NICE evidence review linked, and on prior discussions about treatments (the EFNS guideline is 10y old but also referenced evidence), we feel this commissioning policy is welcomed and it is reasonable to endorse it. On one side, there is evidence - moderate to high certainty - that for patients with IgM PDPN, the addition of rituximab confers a statistically significant improvement in the critical outcomes of disability, global impression of change and haematological response, plus the important outcome (physical subscale) of quality of life. On the other side, access to rituximab would prevent the need for IVIg in some cases of relapse of patients with this condition currently treated with other agents. The cost impact would not be significant, taking into account the low number of these patients, and seem justified in terms of potential positive health cost impact, as the commissioning seems to advise by concluding that there is enough evidence to make the treatment available at this time.	Noted

2) The positive impact from this policy is that : • patients will be able to benefit from rituximab treatment; • fewer patients will be treated with intravenous immunoglobulin which is less efficacious and more expensive.	Noted
a. Generally this new policy is strongly supported. b. Policy only mentions intravenous rituximab, but subcutaneous rituximab is now being used in other diseases and generally has fewer adverse effects (lower risk of infusion reaction). I suggest the policy should allow for either subcut or iv. c. Please ensure that the online prior approval software (mentioned in 'governance arrangements' section) is user-friendly, because the software for some other high cost drugs is sometimes frustrating to use. d. The policy is ambiguous about whether more than two cycles of rituximab can be given if patient is continuing to respond clinically (Dosing criteria text suggests yes, flowchart suggests no). My experience is that some patients do have a good clinical response to four or more repeated cycles of rituximab.	2.a) Noted. 2.b) The evidence on which the policy proposition is based is for intravenous rituximab. Therefore, it will not be possible to include sub-cutaneous rituximab in the policy proposition. 2.c) Noted. 2.d) The flowchart has been amended to show that up to 4 cycles of rituximab can be given and that if a patient has had 4 cycles, then the MDT will discuss giving a further cycle or whether an alternative treatment option would be appropriate.
3)The short timeline of the consultation period on top of the overwhelming workload within the NHS means we did not have sufficient time to review the proposal in depth.	3) Noted.
Comments from two consultant neurologists at our centre are as follows: *"We are already treating some of these patients through our haematology MDT clinic. These patients undergo full haematological investigation and if they are thought to have a neuropathy typical of IgM and a bone marrow showing relevant disease or risk of relevant causative disease then we can already treat. This policy is presumably to treat patients without such consideration and I don't think we would do that - we would always want to know the cause of the IgM. The evidence base for treating these patients with rituximab is contentious anyway but I suppose for the small cohort of patients where I am treating them as CIDP with IVIg, having the option available to reduce IVIg*	No action taken.

usage may be worthwhile. I am really not clear what the purpose of this new policy is." "*We are rather more selective with rituximab in this group of patients than the policy seems to state and consider each case carefully in a joint haematology/neurology clinic/MDT setting. Because this clinic is already well-established and is exactly the set-up required for this group of patients, we should definitely be listed as a centre."*	
As a tertiary neurosciences centre with an appropriate MDT already in place, [our] NHS Foundation trust should be listed as a commissioned centre.	Commissioned centres are outlined in the commissioning plan and are not included in the policy.
The policy only mentions consideration of VZV vaccinations, but should perhaps include a wider statement for consideration of "any relevant vaccinations". In the current COVID-19 pandemic, we would certainly want to ensure that consideration is given to prioritising patients for the full COVID-19 vaccine prior to commencement of Rituximab.	Re vaccinations, the proposition has been amended on page 9 to say: 'Immunisation records should be reviewed and where possible any outstanding vaccines administered prior to initiating treatment with rituximab. The green book recommendations should be followed.'
4)Centres that use IVIG for the indication and have haematology on site should be able to use rituximab rather than just tertiary centres to ensure equitable access to treatment and minimise the impact on infusion service capacity at tertiary centres. Alternatively rituximab infusions could be administered locally following approval from the tertiary centre.	4) The policy proposition has been amended on page 8 to say: 'The infusion would be given in a local hospital following approval by the tertiary centre.'
The policy proposes that in some cases it may be necessary to re -treat with rituximab on return of CD 19 count. It would be helpful to specify the definition of CD 19 repopulation. In neurology practice CD 19 repopulation is defined as CD19% equal to or greater than 1%. (Ref 1. Ellwardt E. et al. Monitoring B-cell repopulation after depletion therapy in neurologic patients. Neurology Neuroimmunology & Neuroinflammation 2018;5:e463)	No action taken. The normal range is 6-24%. The PWG is not in favour of a definition because a small clone of cells could produce enough antibody to once again drive the illness and so you could go from 0.1% to 0.3% with a pathological clone of cells and cause disease but still not be 6% of the total.
Hepatitis B reactivation has been reported in patients on anti CD20 therapies. It is recommended that as a minimum Hepatitis B surface antigen (HBsAg) and Hepatitis core antibodies (HBcAb) should be checked prior to initiating treatment with rituximab. Where patients test positive for hepatitis B serology (either HBsAg or HBcAb, they should be monitored and	No action taken. The 'starting criteria' in the policy proposition already state that 'HIV and hepatitis B/C virus Ab screening should also be performed.'

managed with guidance from hepatologists prevent hepatitis B reactivation. Vaccine response during treatment with rituximab may be attenuated. It is recommended that immunisation records should be reviewed and where possible any outstanding vaccines administered prior to initiating treatment with rituximab. The green book recommendations should be followed.	Re vaccinations, the proposition has been amended on page 9 to say: 'Immunisation records should be reviewed and where possible any relevant outstanding vaccines administered prior to initiating treatment with rituximab. The green book recommendations should be followed.'
Potential impact on equality and health inequalities	
No comments received.	
Changes/addition to policy	
No comments received.	

5. 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 patient pathway flowchart has been amended to show that up to 4 cycles of rituximab can be given and that if a patient has had 4 cycles. After 4 cycles have been administered, the MDT will discuss giving a further cycle or whether an alternative treatment option would be appropriate.

Regarding vaccinations, the proposition has been amended on page 9 to say:

'Immunisation records should be reviewed and where possible any outstanding vaccines administered prior to initiating treatment with rituximab. The green book recommendations should be followed.'

The policy proposition has been amended on page 8 to say: 'The infusion would be given in a local hospital following approval by the tertiary centre.'

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

No.