CLINICAL PRIORITIES ADVISORY GROUP
02 June 2021

Agenda Item No	2.1
National Programme	Trauma
Clinical Reference Group	Neurosciences
URN	2001

Title
Rituximab for the treatment of nodal/paranodal antibody positive inflammatory/autoimmune neuropathy in adults and post-pubescent children

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend its approval as an IYSD

Proposition
The policy proposition is to routinely commission rituximab for the treatment of nodal/paranodal antibody positive inflammatory/autoimmune neuropathy in adults and post-pubescent children. Although nodal/paranodal antibody positive inflammatory/autoimmune neuropathy has been considered to come under the umbrella of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), it is a distinct disease and therefore requires its 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. NHS England has carefully reviewed the evidence to treat nodal/paranodal antibody positive inflammatory/autoimmune neuropathy with rituximab in adults and post-

pubescent children. We have concluded that there is sufficient evidence to make the treatment available at this time.

Clinical Panel recommendation
The Clinical Panel recommended that the policy progress as a routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Head of Acute Programmes confirms the proposition is supported by an: Impact Assessment; Engagement Report; Equality and Health Inequalities Impact Assessment; Clinical Policy Proposition. The relevant National Programme of Care has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Engagement Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality and Health Inequalities Impact Assessment

In patients with nodal/paranodal antibody positive inflammatory/autoimmune neuropathy, what is the clinical effectiveness and safety of rituximab compared with current standard treatment?

Outcome	**Evidence statement**
Clinical Effectiveness	
Critical outcomes	
Improvement in strength measured by a 5-point increase in the Medical Research Council (MRC) muscle power scale (or any other measure)	Improvement in strength is critical to decision making because seropositive nodal/paranodal antibody positive inflammatory/autoimmune neuropathy can result in loss of strength. **No evidence was identified for this outcome.**

Outcome	Evidence statement
Improvement in the Overall Neuropathy Limitations Scale (ONLS) or alternative measure as described in studies. **Certainty of evidence:** Very low	The ONLS measures upper and lower limb function of patients with immune-mediated peripheral neuropathies[1]. Apart from changes between 0 and 1, all other 1-point steps in either the arm or leg scale represent clinically meaningful changes in disability. This is critical to decision making because nodal/paranodal antibody positive inflammatory/ autoimmune neuropathy can severely limit patients' ability to perform activities of daily living. One prospective case series (Querol et al 2015) provided non-comparative evidence for ONLS at a range of timepoints up to 24 months for patients with treatment resistant CIDP and IgG4 CNTN1 or NF155 antibodies who were resistant (ONLS ≥5) to IVIG and corticosteroids and were subsequently treated with rituximab. ONLS scores had to be estimated from graphs for three of the four patients initially treated with rituximab. Results for the fourth patient were not reported as they were removed from the study soon after the first rituximab dose due to an ischaemic stroke, reported to be unrelated to treatment. The improvement in the estimated ONLS scores for each of the three patients represented a clinically meaningful change in disability. The change in the ONLS for patients 1,2 and 3 was from 6 to 0 (at 12 months), 6 to 3 (at 12 and 18 months) and 6 to 5 (at 12, 18 and 24 months) respectively. The authors reported that two patients showed a *'substantial improvement that persisted at one year'* and that the third patient improved *'slightly'*. **(VERY LOW)** **There is very low certainty evidence that compared to baseline, rituximab reduces the ONLS score in patients with treatment resistant CIDP (ONLS ≥5 despite previous treatment with IVIG, plasma exchange and steroids) and antibodies against paranodal proteins. The changes in ONLS scores were clinically meaningful and likely to result in improved ability to perform activities of daily living.**

[1] The total ONLS score is the sum of the Arm scale score and the Leg scale score where 0 is normal and the maximum score of 12 represents the most serious disability. The Arm scale score ranges from 0 (normal) to 5 (disability in both arms preventing all purposeful movements). The Leg scale score ranges from 0 (normal to 7 (restricted to wheelchair or bed most of the day, unable to make any purposeful movements of the legs).

Outcome	Evidence statement
Inflammatory neuropathy Rasch-built Overall Disability Scale (R-ODS or iR-ODS) **Certainty of evidence:** Very low	The inflammatory neuropathy Rasch-built Overall Disability Scale (R-ODS) is a validated and responsive measure of disability in inflammatory neuropathies. There are 24 questions about a task e.g. 'are you able to eat?'. Each question can score 0 (not possible to perform), 1 (possible but with some difficulty) or 2 (possible without any difficulty). The total scale ranges from 0 to 48. A lower score represents greater disability and functional impairment. The minimum clinically important difference has been defined as 6% increase on the centile scale (Vanhoutte et al 2015 cited by NHS England). This is critical to decision making because disability caused by nodal/paranodal antibody positive inflammatory/ autoimmune neuropathy can severely limit patients' ability to perform activities of daily living. One prospective case series (Querol et al 2015) provided non-comparative evidence for R-ODS at a range of timepoints up to 24 months for patients with treatment-resistant CIDP and IgG4 CNTN1 or NF155 antibodies who were resistant (ONLS ≥5) to IVIG and corticosteroids and were subsequently treated with rituximab. R-ODS scores had to be estimated from graphs for three of the four patients initially treated with rituximab. Results for the fourth patient were not reported as they were removed from the study soon after the first rituximab dose due to an ischaemic stroke, reported to be unrelated to treatment. The improvement in the estimated R-ODS scores for each of the three patients represented a clinically meaningful change in disability in 2 of the 3 patients. The change in the R-ODS for patients 1,2 and 3 was from 14 to 48 (at 12 months), 28 to 45 at 12 months (46 at 18 months) and 19 to 24 at 12 months (26 at 24 months) respectively. The authors reported that two patients showed a *'substantial improvement that persisted at one year'* and that the third patient improved *'slightly'*. **(VERY LOW)** **This study provides very low certainty evidence that compared to baseline, rituximab causes a clinically meaningful increase in the R-ODS score in some patients with treatment-resistant CIDP and antibodies against paranodal proteins. A clinically meaningful change in R-ODS score is likely to result in reduction in disability.**

Outcome	Evidence statement
Important outcomes	
Quality of life using a recognised quality of life score for example EQ-VAS.	**This outcome is important to decision making because nodal/paranodal antibody positive inflammatory/ autoimmune neuropathy is a disabling disease which is likely to severely impair quality of life.** **No evidence was identified for this outcome.**
Current disease activity scale (CDAS)	CDAS assesses disease activity and whether on-going treatment is required for disease control.[2] A higher CDAS score (range 1 to 5) is associated with a more severe neuropathy. A score of 4 or less indicates clinical effectiveness. (NHS England). **No evidence was identified for this outcome.**
The number/proportion of patients judged to have responded well, poorly or not at all to various therapies **Certainty of evidence:** Very low	Response to rituximab was defined in the case series by Roux et al 2018 as a patient who fulfilled any of the following three conditions: 1. A five-point increase in the MRC sum score 2. A one-point decrease in the ONLS score compared to the scores at the first rituximab infusion 3. An increase of at least one week in the interval between courses of IVIG and PEx compared to the dependence threshold. The response was considered significant if it was maintained for a least two consecutive visits. The definition of a response to rituximab was not reported in the study by Burnor et al 2018. This outcome is important to decision making because the patients with treatment resistant CIDP (as defined above) and antibodies against paranodal proteins require additional and effective treatment options to IVIG and steroids. Two retrospective case series provided non-comparative evidence relating to response to rituximab for patients with CIDP and antibodies against paranodal proteins who had not responded to treatment with IVIG.

[2] CDAS assesses disease activity and whether on-going treatment is required for disease control. On a five-point scale:
1.Cure: ≥5 years off treatment
2. Remission: <5 years off treatment
3. Stable active disease: ≥1 year, on treatment
4. Improvement: ≥3 months <1 year, on treatment
5. Unstable active disease: abnormal examination with progressive or relapsing course
A treatment may be of benefit if it improves strength or disability (CDAS 4), but it may equally be beneficial if it stabilises the disease (CDAS 3) or negates the requirement for ongoing, regular therapy (CDAS 2 or 1) (NHS England).

Outcome	Evidence statement
	• 1 case series (Burnor et al 2018, n=3) provided non-comparative evidence that one patient showed a *'marked improvement'* two weeks to 19 months after treatment with rituximab. One patient was reported to show a 'marked improvement' (timepoint unknown) and one patient was reported to be 'stabilised with a slight improvement' (timepoint unknown). The criteria for a response to be recorded or to be considered a marked or slight improvement were not described. *(***VERY LOW)** • 1 case series (Roux et al 2018, n=3) provided non-comparative evidence for three patients who were treated with rituximab. Two patients are reported to have responded (as defined above) to treatment with rituximab (one patient at 12 months post first rituximab infusion, the other at 1.6 years post first rituximab infusion). One patient did not respond to rituximab at 12 months after the first rituximab infusion. *(***VERY LOW)** **This study provided no evidence about response to rituximab compared to standard treatment for patients with treatment resistant CIDP and antibodies against paranodal proteins. One of the six patients did not respond to treatment with rituximab.**
The number/proportion of patients for whom the intervention has allowed the withdrawal of existing therapies **Certainty of evidence:** Very low	Cessation of treatment with IVIG or other standard therapies as a result of treatment with rituximab is important as it is an indication that rituximab is an effective alternative treatment. One prospective case series (Querol et al 2015) provided non-comparative evidence that one patient (resistant (defined as ONLS ≥5) to IVIG and corticosteroids) *'improved dramatically after rituximab treatment and was able to be withdrawn from other treatments'*. The treatments withdrawn and the timepoint were not reported. The certainty of the evidence was very low. **This study provided limited evidence about the withdrawal of existing therapies following treatment with rituximab for patients with treatment resistant CIDP and antibodies against paranodal proteins. There is very low certainty evidence that compared to baseline, rituximab resulted in a clinical response**

Outcome	Evidence statement
	sufficient to allow other treatments (not specified) to be withdrawn.
The number of times patients attend hospital to receive the intervention compared to patients in the comparator group	The number of times patients attend hospital is important because repeated hospital visits may impact on patients' quality of life. **No evidence was identified for this outcome.**
Safety	
Safety including but not limited to incidences of infusion-related reactions, serious infections, progressive multifocal leukoencephalopathy. **Certainty of evidence:** Very low	Safety outcomes are relevant to patients because adverse events can affect survival, quality of life, tolerability and overall responses. One patient with treatment resistant CIDP and antibodies against paranodal proteins was removed from the study by Querol et al 2015 because she had an ischaemic stroke soon after the first rituximab dose and was lost to follow up. The authors reported that the stroke was unrelated to treatment with rituximab. Roux et al 2018 reported no flare effect and no worsening CIDP following treatment with rituximab in any patients in the case series. A skin rash during first infusion with rituximab and an episode of vomiting was reported but these events may or may not have been observed in the three patients in scope of this review i.e. treatment resistant CIDP and antibodies against paranodal proteins. Burnor et al 2018 did not report adverse events; it is not clear if none occurred. The certainty of the evidence was very low. (**VERY LOW)** **There is limited evidence about the safety of rituximab for patients with treatment resistant CIDP and antibodies against paranodal proteins.**

Abbreviations: CDAS – Current Disease Activity Scale, CIDP – chronic inflammatory demyelinating polyneuropathy, CNTN1 –contactin-1 paranodal protein, IgG4 – a subclass of immunoglobulin, IVIG – intravenous immunoglobulin, m – month, MRC – Medical Research Council, ONLS - Overall Neuropathy Limitations Scale, NF155 – neurofascin-155 paranodal protein, PEx – plasma exchange, R-ODS - Inflammatory neuropathy Rasch-built Overall Disability Scale.

From the evidence selected, is there any data to suggest that there are particular subgroups of patients that would benefit from treatment with rituximab more than others?

Outcome	Evidence statement
Patient Subgroups Subgroup of patients that would benefit from treatment with rituximab more than others	**None identified.** There is insufficient evidence from the results for the patients with treatment resistant CIDP with antibodies against paranodal proteins included in the three case series to be able to identify clinical or any other characteristics which might be associated with a better response to treatment with rituximab. There was heterogeneity among the nine patients for the type of antibody that they were positive for and for disease duration at the time of treatment with rituximab. At least two of the nine patients received other treatments at the same time as rituximab (plasma exchange, cyclophosphamide) which may have confounded the results. It is not clear if the other patients received concomitant treatments or not.

Abbreviations: CIDP – chronic inflammatory demyelinating polyneuropathy

From the evidence selected, what are the criteria used by the research studies to confirm a diagnosis of nodal/paranodal antibody positive inflammatory/ autoimmune neuropathy?

Outcome	Evidence statement
Patient Selection Criteria	None of the studies in this review described the diagnosis of the patients as 'nodal/paranodal antibody positive inflammatory/ autoimmune neuropathy', although the patients extracted from the three case series could all be described in those terms. They all had a diagnosis of CIDP and antibodies against paranodal proteins (NF155 or CNTN1). Both Querol et al 2015 and Roux et al 2018 selected patients with CIDP using the European Federation of Neurological Societies/Peripheral Nerve Society task force criteria 2010. The three patients in the Burnor et al 2018 case series had severe progressive CIDP but the criteria for the diagnosis was not described further. All the patients had had a poor response to treatment with IVIG and at least one other treatment (plasma exchange, steroids, mycophenolate, cyclophosphamide, azathioprine) before being considered for treatment with rituximab.

Abbreviations: CIDP – chronic inflammatory demyelinating polyneuropathy, CNTN1 –contactin-1 paranodal protein, NF155 – neurofascin-155 paranodal protein

In patients with nodal/paranodal antibody positive inflammatory/autoimmune neuropathy, what is the cost effectiveness of rituximab?

Outcome	Evidence statement
Cost Effectiveness The cost of the rituximab compared to the alternatives.	**No evidence was identified for cost effectiveness**

Patient Impact Summary
The condition has the following impacts on the patient's everyday life: • **mobility**: Patients have severe problems in walking about or are unable to walk about. • **ability to provide self-care**: Patients have severe problems in washing or dressing or are unable to wash or dress. • **undertaking usual activities**: Patients have severe problems in doing their usual activities or are unable to do their daily activities. • **experience of pain/discomfort**: Patients have extreme pain or discomfort. • **experience of anxiety/depression:** Patients are extremely anxious or depressed.
Further details of impact upon patients: The condition primarily affects the patient's mobility, dexterity and quality of life as they progressively lose strength, balance and sensation. Simple day-to-day tasks and occupational roles become difficult or even impossible. Over 50% of patients are unable to walk or care for themselves. The patient may also experience neuropathic pain. Diaphragmatic and intercostal muscle paralysis may mean that patients are admitted to ITU for ventilation. **Further details of impact upon carers**: The impact on carers is significant. Carers may have to spend time assisting the patient with mobility aids and hoists and assist with personal care and activities of daily living. Carers may have to make sacrifices in their own lives to assist with the care and managing the patient's financial affairs and this, together with the burden of caring for the patient, may impact on their physical and mental wellbeing.

Considerations from review by Rare Disease Advisory Group
Not Applicable.

Pharmaceutical considerations
The clinical commissioning policy proposition recommends rituximab for the treatment of nodal/paranodal antibody positive inflammatory/autoimmune neuropathy in adults and post-pubescent children. This is an off-label use of

rituximab including use in patients aged less than 18 years old. It is excluded from tariff.

Considerations from review by National Programme of Care
1) The proposal received the full support of the Trauma PoC on the 30th March 2021