NHS England

Evidence review: Rituximab for the treatment of nodal/paranodal antibody positive inflammatory/autoimmune neuropathy

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Contents

1. Introduction

This review examines the clinical effectiveness, safety and cost effectiveness of rituximab compared to current standard treatment including corticosteroids, intravenous immunoglobulin (IVIG), and plasma exchange (PEx) in patients with nodal/paranodal antibody positive inflammatory/autoimmune neuropathy[1].

In addition, the review scope included the identification of possible subgroups of patients within the included studies who might benefit from treatment with rituximab more than others, as well as the criteria used by the included studies to confirm a diagnosis of nodal/paranodal antibody positive inflammatory/autoimmune neuropathy.

2. Executive summary of the review

Three papers were included in this review (Burnor et al 2018, Querol et al 2015, Roux et al 2018).

The paper by Querol et al (2015) was a multicentre, prospective case series which identified nine patients with treatment-resistant chronic inflammatory demyelinating polyneuropathy (CIDP) and antibodies against contactin-1 (CNTN1) or neurofascin-155 (NF155). Relevant outcomes for the four patients who were treated with rituximab were extracted for inclusion in this review. The other two case series were retrospective. Burnor et al 2018 identified 213 patients with a wide range of neuropathies from two tissue databases; results for the three patients with treatment resistant CIDP with NF155 IgG antibodies who were treated with rituximab were extracted for inclusion in this review. Roux et al 2018 identified 28 patients with treatment resistant CIDP who had been treated with rituximab; results for the three patients who had NF155 antibodies were extracted for inclusion in this review.

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

Critical outcomes. The critical outcomes for decision making were improvement in strength[2], improvement in the Overall Neuropathy Limitations Scale (ONLS) and the inflammatory neuropathy Rasch-built Overall Disability Scale (R-ODS). Certainty in the quality of the evidence for the critical outcomes was very low when assessed using modified GRADE.

Improvement in strength
No evidence was identified for this outcome.

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[1] Typically, the antibodies are of the IgG4, IgG1 and IgG3 subclass in neurofascin-155, contactin-1 and caspr-1 antibody positive individuals. The antibody subclass is usually IgG1 and occasionally IgG3 in pan-neurofascin patients. It may be that IgG4 subclass better predicts poor IVIG response and good rituximab response in neurofascin 155, contactin-1, caspr-1 complex. The pan-neurofascin antibody is usually IgG1 and the associated disease is acute onset and severe (NHS England).
[2] measured by a 5 point increase in the Medical Research Council (MRC) muscle power scale or other measure

Overall Neuropathy Limitations Scale (ONLS)[3]
One prospective case series (Querol et al 2015) provided non-comparative evidence for the ONLS from baseline to 24 months for patients with treatment resistant CIDP and IgG4 CNTN1 or NF155 antibodies 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 by the study authors as the patient was removed from the study soon after receiving rituximab due to an ischaemic stroke. The estimated ONLS scores for each of the three patients improved 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. This study provides very low certainty evidence that compared to baseline, rituximab reduced the ONLS scores in patients with treatment resistant CIDP and antibodies against paranodal proteins. The changes in ONLS scores were clinically meaningful and are likely to result in an improved ability to perform activities of daily living.

Inflammatory neuropathy Rasch-built Overall Disability Scale (R-ODS)[4]
One prospective case series (Querol et al 2015) reported non-comparative evidence for R-ODS from baseline to 24 months for patients with treatment-resistant CIDP and IgG4 CNTN1 or NF155 antibodies treated with rituximab. R-ODS scores had to be estimated from graphs for three of the four patients initially treated with rituximab. The changes in the R-ODS scores of all three patients were clinically important improvements from 14 to 48 (at 12 months), 28 to 46 (at 18 months) and 19 to 26 (at 24 months) respectively. Results for the fourth patient were not reported as they were removed from the study due to an ischaemic stroke. 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.

Important outcomes. The outcomes important to decision making were quality of life, current disease activity scale (CDAS), the number/proportion of patients judged to have responded well, poorly or not at all to various therapies, the number/proportion of patients for whom the intervention has allowed the withdrawal of existing therapies (such as IVIG) and the number of times patients attend hospital to receive the intervention compared to patients in the comparator group. Certainty in the quality of the evidence for the important outcomes was very low when assessed using modified GRADE.

Quality of life
No evidence was identified for this outcome.

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[3] The ONLS measures upper and lower limb function of patients with immune-mediated peripheral neuropathies. 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 (disability in both arms preventing all purposeful movements and restricted to wheelchair or bed most of the day, unable to make any purposeful movements of the legs). 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.
[4] The inflammatory neuropathy R-ODS is a 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).

Current Disease Activity Scale (CDAS)
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
Two retrospective case series reported non-comparative evidence for the response to rituximab for six patients with CIDP and antibodies against paranodal proteins who had not responded to treatment with IVIG (Burnor et al 2018, Roux et al 2018).

Apart from the results for one patient described in detail in Burnor et al 2018, limited information about the response to rituximab was reported i.e. marked or slight improvement (Burnor et al 2018) and yes or no where the response to rituximab was defined as a patient who met any one of three conditions (Roux et al 2018) [5]. Compared to baseline, one patient was reported as showing a '*marked improvement'* (described in detail in appendix E) from two weeks to 19 months after treatment with rituximab, one patient was reported as showing a '*marked improvement'* (not further defined, timepoint unknown) and one patient was reported to be '*stabilised with a slight improvement'* (not further defined, timepoint unknown) (Burnor et al 2018).

In the three patients included in the case series by Roux et al 2018, two patients responded to treatment with rituximab at one year and at 1.6 years post first rituximab infusion (not further defined) and one patient did not respond to treatment 12 months after treatment with rituximab. The certainty of the evidence was very low.

The number/proportion of patients for whom the intervention has allowed the withdrawal of existing therapies (such as IVIG)
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.

The number of times patients attend hospital to receive the intervention compared to patients in the comparator group
No evidence was identified for this outcome.

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

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

[5] 1. A 5-point increase in the MRC sum score or 1-point decrease in the ONLS score. 2. Discontinuation of first-line treatment. 3. An increase of at least one week in the interval between courses of IVIG or PEx compared to the dependence threshold.

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.

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

No evidence was identified on the cost effectiveness of rituximab compared with current standard treatment.

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?

There was insufficient evidence from the results for the patients with CIDP with antibodies against paranodal proteins extracted from 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.

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?

None of the studies in this review described the diagnosis of the patients as 'nodal/paranodal antibody positive inflammatory/autoimmune neuropathy'. However, all the patients extracted from the three case series could be described in those terms as they had a diagnosis of CIDP and antibodies against paranodal proteins (NF155 or CNTN1). All of them had had prior treatment with IVIG and at least one other treatment (plasma exchange, steroids, mycophenolate, cyclophosphamide, azathioprine). Two of the three case series (Querol et al 2015, Roux et al 2018) selected patients with CIDP using the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) criteria (Joint Task Force of the EFNS and the PNS 2010). The three patients in the Burnor et al 2018 case series had severe, progressive CIDP with neurofascin antibodies. The criteria for the diagnosis was not described further.

Limitations. The key limitation to identifying the effectiveness of rituximab compared to standard treatment for patients with nodal/paranodal antibody positive inflammatory/ autoimmune neuropathy is the lack of reliable comparative studies. Very low certainty evidence for a limited number of outcomes was identified for a small number of patients from three case series, two of which were not designed to assess the effectiveness of rituximab for patients with this very rare type of neuropathy. There was heterogeneity between the patients for the type of antibody that they were positive for. Disease duration was reported

for six patients and ranged from less than one year to 16 years. At least two patients had concomitant treatments and their outcomes reported may not be wholly attributable to rituximab.

Conclusion. The very low certainty evidence identified for inclusion in this review is insufficient to draw any conclusions about the clinical effectiveness and safety of rituximab compared to standard treatments in patients with nodal/paranodal antibody positive inflammatory/ autoimmune neuropathy. For patients who have failed to respond to IVIG and at least one other treatment, limited non-comparative evidence suggested clinically meaningful improvements from baseline in disability and function for some patients. No evidence on the cost effectiveness of rituximab compared to current standard treatments was identified.

3. Methodology

Review questions

The review question(s) for this evidence review are:

1. In patients with nodal/paranodal antibody positive inflammatory/autoimmune neuropathy, what is the clinical effectiveness of rituximab compared with current standard treatment?
2. In patients with nodal/paranodal antibody positive inflammatory/autoimmune neuropathy, what is the safety of rituximab compared with current standard treatment?
3. In patients with nodal/paranodal antibody positive inflammatory/autoimmune neuropathy, what is the cost effectiveness of rituximab?
4. 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?
5. 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?

See Appendix A for the full review protocol.

Review process

The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2019).

The searches for evidence were informed by the PICO document and were conducted on 20th April 2020.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO framework. Full text references of potentially relevant evidence were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were quality appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE Profiles.

4. Summary of included studies

Three papers were identified for inclusion (Burnor 2018, Querol et al 2015 and Roux et al 2018 and). Table 1 provides a summary of these included studies and full details are given in Appendix E.

The paper by Querol et al (2015) was a multicentre, prospective case series; the other two case series were retrospective. Outcomes were extracted for patients who had nodal/paranodal antibody positive inflammatory/autoimmune neuropathy who had been treated with rituximab.

No cost effectiveness studies suitable for inclusion in this evidence review were identified.

Table 1 Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported [a]
Burnor et al 2018 Retrospective case series Pennsylvania, USA and London, UK	Patients with CIDP with NF155 IgG antibodies who had a poor response to IVIG The study included tissue analysis of 213 patients with autoimmune, genetic and idiopathic neuropathies. Only data for the 3 patients who were NF155 antibody positive who were treated with rituximab were extracted for inclusion in this review No subgroups reported	**Intervention** Rituximab Patient 1: day 86, first of 3 weekly doses of rituximab (375 mg/m^2) administered Patients 2 and 3: dose, frequency of dosing, route of administration, duration of treatment not reported Concomitant therapies: Patient 1: Cyclophosphamide Patient 2: PEx Patient3: none **Comparison** None	**Critical Outcomes** • None **Important outcomes** • Response to rituximab up to 19 months follow up **Safety** • None reported
Querol et al 2015	Patients with CIDP and IgG4 CNTN1 or NF155 antibodies who were resistant (ONLS ≥5) to IVIG and steroids	**Intervention** Rituximab 375mg/m^2 once weekly for 4 weeks followed by	**Critical outcomes** • Overall Neuropathy Limitations Scale (ONLS) up to 24 months follow up

Multicentre, prospective case series Spain (number of centres not reported)	The study identified 9 patients with CNTN1 or NF155 antibodies. Only data for the 4 patients who received rituximab were extracted for inclusion in this review No subgroups reported	1 dose per month for 2 additional doses. Additional rituximab cycles were administered at 1 year if required Concomitant treatments: not reported **Comparison** None	(estimated from graphs) • Inflammatory neuropathy Rasch-built Overall Disability Scale (R-ODS) up to 24 months follow up (estimated from graphs) **Important to decision making** • Number/proportion of patients for whom the intervention has allowed the withdrawal of existing therapies (such as IVIG) (timepoint unknown) **Safety** • Adverse events were reported
Roux et al 2018 Single centre, retrospective case series Paris, France	Patients with CIDP who were treated with rituximab. The study included 28 patients with CIDP and a range of associated diseases. Data for 3 CIDP patients with NF155 antibodies was extracted for inclusion in this review. All had been previously treated with IVIG. No subgroups reported	**Intervention** Rituximab: D0/D15 infusions (1 g) Concomitant treatments: not reported **Comparison** None	**Critical Outcomes** • None **Important outcomes** • Response to rituximab at 1 year to 1.6 years post treatment **Safety** • Adverse events were reported
Abbreviations: CIDP – chronic inflammatory demyelinating polyneuropathy, CNTN1 –contactin-1 paranodal protein, D0/D15 – day 0 and day 15, g – gram, IgG – immunoglobulin, IgG4 – a subclass of IgG, IVIG – intravenous immunoglobulin, m – metre, MAG Mg – milligram, ONLS - Overall Neuropathy Limitations Scale, NF155 – neurofascin-155 paranodal protein, PEx – plasma exchange			
Footnotes a. The outcomes listed in this table are listed in the way that they are described in each study. In some cases, the heading may differ from the exact outcomes listed in the PICO protocol. These outcomes have been included as they are best approximation to the specified critical or important outcome of interest.			

5. Results

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	

Outcome	Evidence statement
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.**
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[6]. 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.**

[6] 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.**
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.**

Outcome	Evidence statement
Current disease activity scale (CDAS)	CDAS assesses disease activity and whether on-going treatment is required for disease control.[7] 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**.** • 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

[7] 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
	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 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

Outcome	Evidence statement
	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.

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**

6. Discussion

This review considered the evidence for the clinical effectiveness and safety of rituximab compared to standard treatment in patients with nodal/paranodal antibody positive inflammatory/ autoimmune neuropathy. The critical outcomes of interest were improvement in strength, improvement in the Overall Neuropathy Limitations Scale (ONLS) or other measure of activity of daily living, and the inflammatory neuropathy Rasch-built Overall Disability Scale (R-ODS). Important outcomes were quality of life, current disease activity scale (CDAS), the number/proportion of patients judged to have responded well, poorly or not at all to various therapies, the number/proportion of patients for whom the intervention has allowed the withdrawal of existing therapies (such as IVIG) and the number of times patients attend hospital to receive the intervention compared to patients in the comparator group.

No comparative studies which met the inclusion criteria for the population, indication and intervention were retrieved by the search. Limited evidence was available from results for nine patients extracted from three case series, only one of which was designed to assess the effectiveness of rituximab for patients with this very rare type of neuropathy. In patients with treatment-resistant CIDP and antibodies against paranodal proteins, the case series provided limited evidence for critical outcomes (ONLS and R-ODS) and important outcomes (response to rituximab and the number of patients for whom the intervention allowed the withdrawal of existing therapies) following treatment with rituximab. No evidence was available for the other outcomes of interest. The case series were at high risk of bias.

Certainty in the evidence for critical and important outcomes was very low when assessed using modified GRADE.

Querol et al 2015 was a multicentre, prospective case series of nine patients with treatment resistant CIDP (ONLS ≥5 despite previous treatment with IVIG, plasma exchange and steroids) and antibodies against CNTN1 or NF155. Relevant outcomes for four patients who received rituximab were extracted for inclusion in this review. Baseline demographic and clinical characteristics for the patients who received rituximab were not fully reported. One patient was withdrawn soon after receiving the first rituximab dose due to an ischaemic stroke, reported to be unrelated to treatment. We noted that, of the remaining three patients, one patient had CNTN1 antibodies, whereas the other two patients had NF155 antibodies. All three patients had the same rituximab treatment initially, but two had further treatments after one year. It is unclear if any concomitant treatments were allowed. The follow up for the three patients who continued treatment with rituximab ranged from 12 to 24 months. The primary outcomes (ONLS and R-ODS) were presented in graph format only, so scores had to be estimated against the y axis. The reduction in ONLS scores for all three patients was one point or more and indicates a clinically important improvement in function and ability to perform activities of daily living. The increase in R-ODS scores for all three patients exceeded 6% and suggests a clinically important reduction in disability. Apart from an explanation for the removal of one patient from the study, no other adverse events were reported; it is not clear if none occurred.

The other two case series were retrospective case series.

Burnor et al 2018 identified 213 patients with a wide range of neuropathies from two tissue databases; results for the three patients with CIDP and NF155 IgG antibodies who were treated with rituximab and therefore met the criteria for inclusion for this review were extracted. There was variation between the three patients for previous treatments (although all had had a poor response to IVIG), patient 1 had NF186 antibodies as well as NF155 antibodies, the details of the rituximab treatment were not reported for patients 2 and 3, and concomitant treatment varied across all three patients. Only limited results were reported i.e. response to rituximab. This was described in a narrative format only. No formal measures of response were used. Patient 1's response was described in detail as a case study; patient 3 appears to have experienced a more modest improvement compared to patients 1 and 2. Patient 3 had rituximab as monotherapy whereas patients 1 and 2 had concomitant treatment. It is not clear to what extent outcomes can be attributed to rituximab alone. The follow up period for patients 2 and 3 and the timepoints for assessing outcomes were not reported. No adverse events were reported; it is not clear if none occurred.

Roux et al 2018 identified 28 patients with CIDP who had been treated with rituximab; results for the three patients who had NF155 antibodies were extracted for inclusion in this review. Baseline characteristics for this subgroup were reported: we noted that patient 3 had anti-GD1a/GD1b antibodies (not associated with nodal/paranodal antibody positive inflammatory/ autoimmune neuropathy) in addition to anti-NF155 and that patients 2 and 3 received rituximab due to insufficient response to previous treatments, whereas patient 1 was dependent on current treatment. Disease duration varied significantly ranging from two to 16 years. Although all patients received the same rituximab dose it is unclear if any concomitant drugs were allowed which might have confounded the response. The response to rituximab definition was broad and required a response to one of three conditions: strength or

functional ability, discontinuation of treatment, or a greater interval between IVIG or PEx treatments. The binary response (yes or no) did not elaborate on the type of response. Adverse events related to treatment with rituximab were reported by the study authors for the whole study population (n=28). However, it is not possible to know if the adverse events were observed in any of the three patients with treatment-resistant or treatment-dependent CIDP and antibodies against paranodal proteins.

In addition to the non-comparative nature of the case series study design and inclusion of two studies not designed to assess the effectiveness of rituximab for patients with nodal/paranodal antibody positive inflammatory/ autoimmune neuropathy, uncertainty about the results stems from the heterogeneous clinical characteristics of the patients. These included:

- the type of antibody (eight patients were positive for NF155 of whom one was also positive for NF186, and one was positive for GD1a/GD1b; one patient was positive only for CNTN1).
- the number and type of previous treatments that had failed. Eight patients had treatment resistant CIDP (all had failed treatment with IVIG and between one and three additional therapies including steroids, PEx, cyclophosphamide, mycophenelate and azathioprine. (One patient had treatment dependent CIDP).
- the duration of disease prior to treatment with rituximab ranged from less than one year to 16 years. This was reported for six patients only.
- at least two of the nine patients had concomitant treatments (cyclophosphamide and PEx, no further details reported) and their outcomes reported may not be wholly attributable to rituximab. It was not clear if concomitant treatments were permitted in the case series by Querol et al 2015 and Roux et al 2018.

7. Conclusion

The evidence included in this review is insufficient to draw conclusions about the clinical effectiveness and safety of rituximab compared to standard treatments in patients with nodal/paranodal antibody positive inflammatory/autoimmune neuropathy. The key limitation to identifying the effectiveness of rituximab compared to standard treatment is the lack of comparative studies.

Limited evidence was identified for nine patients extracted from three case series, only one of which was designed to assess the effectiveness of rituximab for patients with this very rare type of neuropathy. There was heterogeneity among the patients for the type of antibodies that they were positive for and disease duration. Concomitant treatments given to at least two patients may have confounded the results.

This very low certainty, non-comparative evidence for nine patients with treatment-resistant CIDP (who have already failed to respond to IVIG and at least one other treatment) and antibodies against paranodal proteins suggests clinically meaningful improvements from baseline in disability and function for some patients. No evidence on the cost effectiveness of rituximab compared to current standard treatments was identified.

Appendix A PICO Document

The review questions for this evidence review are:

1. In patients with nodal/paranodal antibody positive inflammatory/autoimmune neuropathy, what is the clinical effectiveness of rituximab compared with current standard treatment?
2. In patients with nodal/paranodal antibody positive inflammatory/autoimmune neuropathy, what is the safety of rituximab compared with current standard treatment?
3. In patients with nodal/paranodal antibody positive inflammatory/autoimmune neuropathy, what is the cost effectiveness of rituximab?
4. 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?
5. 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?

PICO Table

P –Population and Indication Describe the relevant population and indication provided previously including if necessary, disease severity or duration, previous treatment, new or recurrent symptoms, any specific co-morbidities and other population factors (for example, age range).	People of all ages with a diagnosis of nodal/paranodal antibody positive inflammatory/autoimmune neuropathy which may also be referred to as nodal/paranodal positive CIDP in studies. People with this condition have one or more of the following antibodies[8]: Neurofascin-155 antibody, contactin-1 antibody, caspr1 antibody, caspr1: contactin-1 complex antibody and neurofascin 140/186 or pan-neurofascin antibody associated neuropathy. Such patients may have received clinical diagnoses of (and be referred to in the literature as suffering from) chronic inflammatory demyelinating polyneuropathy (CIDP), atypical CIDP, Guillain-Barré syndrome (GBS), GBS-like neuropathy, atypical multifocal motor neuropathy (MMN), or may simply have been defined by their serological results (i.e. as nodal or paranodal antibody positive)
I – Intervention Describe the intervention details provided previously including if necessary, details of treatment, mode of delivery,	Typically, an initial dose of 1g of rituximab by intravenous infusion followed by a second identical dose after 2 weeks. Some studies may have used different regimens (e.g. 375mg/m2 every week for 4 weeks).

[8] Typically, the antibodies are of the IgG4, IgG1 and IgG3 subclass in neurofascin-155, contactin-1 and caspr-1 antibody positive individuals. The antibody subclass is usually IgG1 and occasionally IgG3 in pan -neurofascin patients. It may be that IgG4 subclass better predicts poor IVIG response and good rituximab response in neurofascin 155, contactin-1, caspr-1 complex. The pan-neurofascin antibody is usually IgG1 and the associated disease is acute onset and severe.

size/frequency/duration of dose, position of intervention in treatment pathway (e.g. first/second line/salvage) and any background / concomitant medication. Add details of any subgroups or stratifications of interest	Further cycles may be used between 6 months to 5 years apart depending on the response to treatment. Rituximab has largely been used after inadequate responses to first line (IVIG, steroids, plasma exchange) and sometimes second-line (other immunosuppressants) therapies.
C – Comparator(s) What is/are the main alternative/s to compare with the intervention being considered? This should usually be standard current treatment	The alternative treatments to compare to rituximab are: 1) IVIG – typically initial dose of 2g/kg, repeated every 1-12 weeks at empirically determined doses of between 0.6g/kg and 2g/kg thereafter (Eftimov et al., 2013) 2) Corticosteroids – typically daily or alternate-daily oral prednisolone, pulsed oral dexamethasone, or pulsed IV methylprednisoloine (Hughes and Mehndiratta, 2015) 3) Plasma exchange – 1-5 exchanges per cycle every ~4 weeks (Mehndiratta et al., 2015)
O – Outcomes Outcomes should be patient focussed and relate to those detailed in the PPP and the Research Questions covering clinical effectiveness, safety and cost effectiveness as required.	**Clinical Effectiveness** *Critical to decision-making:* *A number of different measures have been used to assess outcomes following rituximab treatment of nodal/paranodal antibody positive inflammatory/autoimmune neuropathy, including:* • Improvement in strength measured by a 5 point increase in the Medical Research Council (MRC) muscle power scale compared to the scores at the first infusion. Other alternative measures can be used as described in studies. This is critical to decision making because seropositive nodal/paranodal antibody positive inflammatory/autoimmune neuropathy result in loss of strength. • Improvement in the Overall Neuropathy Limitations Scale (ONLS) which is designed to assess the limitations of patients with immune-mediated peripheral neuropathies. An improvement would equate to a one-point decrease in the score compared to the score before treatment. Other alternative measures can be used as described in studies. 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. • Inflammatory neuropathy Rasch-built Overall Disability Scale (R-ODS or iR-ODS). A well validated and responsive measure of disability in inflammatory neuropathies. The minimum clinically important difference has been defined as 6% on the centile scale.(Vanhoutte et al., 2015) *Important to decision making*

	• Quality of life using a recognised quality of life score for example EQ-VAS. Other measures can be used as described in studies. This outcome is important to decision making because seropositive CIDP is a disabling disease which may have a severe impact on quality of life. • Current disease activity scale (CDAS). This assesses disease activity, and whether on-going treatment is required for disease control. , on a five-point scale: o 1.Cure: ≥5 years off treatment o 2. Remission: <5 years off treatment o 3. Stable active disease: ≥1 year, on treatment o 4. Improvement: ≥3 months <1 year, on Treatment o 5. Unstable active disease: abnormal examination with progressive or relapsing course This outcome is important because a higher CDAS score is associated with a more severe neuropathy. A score of 4 or less indicates clinical effectiveness. (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). • The number/proportion of patients judged to have responded well, poorly or not at all to various therapies, • The number/proportion of patients for whom the intervention has allowed the withdrawal of existing therapies (such as IVIG) • The number of times patients attend hospital to receive the intervention compared to patients in the comparator group. This is important because hospital visits may impact on patients' quality of life. **Safety** • Safety including but not limited to incidences of infusion-related reactions, serious infections, progressive multifocal leukoencephalopathy. **Cost effectiveness** • The cost of the rituximab compared to the alternatives. This is important because one of the main reasons that rituximab may be preferable to IVIG is that it is less expensive.
Inclusion criteria	

Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	All ages
Date limits	2010-2020
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials and guidelines
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase, Cochrane Library, TRIPdatabase and NICE Evidence Search were searched limiting the search to papers published in English language from 2010 onwards. . Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, guidelines and case reports were excluded.

Search date: 20 April 2020.

Medline Search

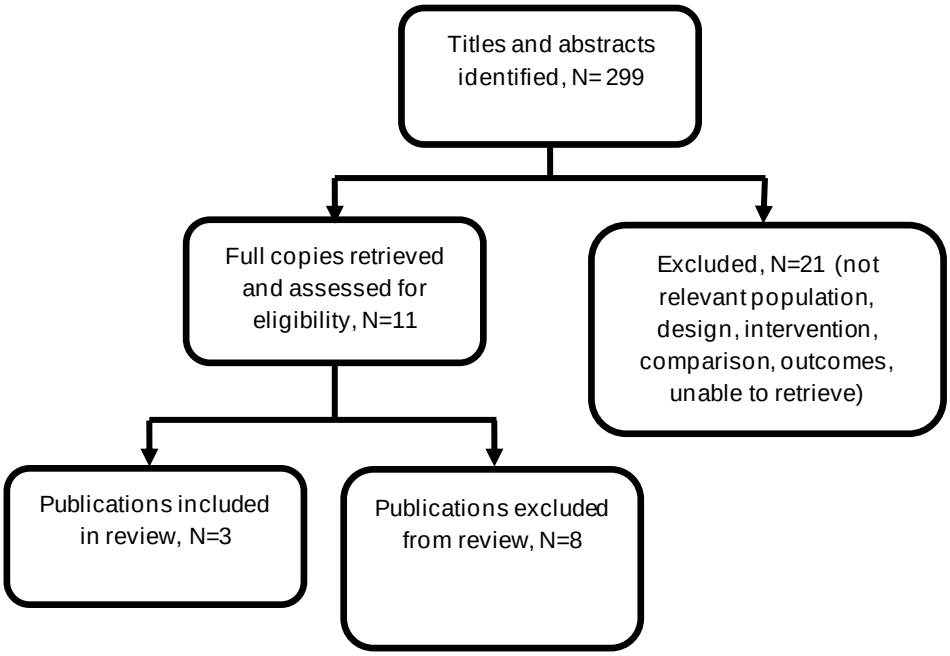
# ▲	Searches
1	exp Polyradiculoneuropathy/
2	((nodal or paranodal or antibody positive or anti-body positive or autoimmun* or auto-immun*) adj3 (neuropath* or polyneuropath* or polyradiculopath*)).ti,ab,kw.
3	((chronic inflamm* demyelinat* adj3 (neuropath* or polyneuropath* or polyradiculopath*)) or cidp).ti,ab,kw.
4	guillain barre.ti,ab,kw.
5	1 or 2 or 3 or 4
6	Rituximab/
7	(rituximab or mabthera).ti,ab,kw.
8	6 or 7
9	5 and 8
10	(letter or comment or editorial).pt. or case report.ti,ab.
11	9 not 10
12	limit 11 to (english language and yr="2010 -Current")

# ▲	Searches
1	Rituximab/
2	(rituximab or mabthera).ti,ab,kw.
3	1 or 2
4	(neurofascin* or contactin* or caspr* or ranvier*).ti,ab,kw.
5	3 and 4

6 (letter or comment or editorial).pt. or case report.ti,ab.
7 5 not 6
8 limit 7 to (english language and yr="2010 -Current")

Appendix C Evidence selection

Figure 1 – Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection decision and rationale if excluded
Querol, L; Devaux, J., Rojas-Garcia R., Illa, I. Autoantibodies in chronic inflammatory neuropathies: diagnostic and therapeutic implications. Neurology 2017. Volume 13: 533-547.	Excluded. Review article. There are no study results for rituximab for patients with nodal/paranodal antibody positive neuropathy
Roux T, Debs R, Maisonobe T, Lenglet T, Delorme C, Louapre C, et al. Rituximab in chronic inflammatory demyelinating polyradiculoneuropathy with associated diseases. J Peripher Nerv Syst. 2018;23(4):235-40.	Included in this review
Cortese A, Lombardi R, Briani C, Callegari I, Benedetti L, Manganelli F, et al. Antibodies to neurofascin, contactin-1, and contactin-associated protein 1 in CIDP: Clinical relevance of IgG isotype. Neurol Neuroimmunol Neuroinflamm. 2020;7(1).	Excluded. This is a prevalence study looking to identify the prevalence and isotopes of nodal/paranodal antibody positive neuropathy among CIDP. There are no results for in scope patients treated with rituximab

Appendix D Excluded studies table

Study reference	Reason for exclusion
Benedetti L, Briani C, Franciotta D, Fazio R, Paolasso I, Comi C, et al. Rituximab in patients with chronic inflammatory demyelinating polyradiculoneuropathy: a report of 13 cases and review of the literature. Journal of Neurology, Neurosurgery & Psychiatry. 2011;82(3):306-8.	Study population does not include any patients diagnosed as having nodal/paranodal antibody positive neuropathy
Chaudhry V, Cornblath DR. An open-label trial of rituximab (Rituxan®) in multifocal motor neuropathy. J Peripher Nerv Syst. 2010;15(3):196-201.	Patients all had MMN and were responders to IVIG. No mention of CIDP or nodal/paranodal antibody positive neuropathy
Cocito D, Grimaldi S, Paolasso I, Falcone Y, Antonini G, Benedetti L, et al. Immunosuppressive treatment in refractory chronic inflammatory demyelinating polyradiculoneuropathy. A nationwide retrospective analysis. European Journal of Neurology. 2011;18(12):1417-21.	Study population does not include any patients diagnosed as having nodal/paranodal antibody positive neuropathy
Desai J, Ramos-Platt L, Mitchell WG. Treatment of pediatric chronic inflammatory demyelinating polyneuropathy: Challenges, controversies and questions. Annals of Indian Academy of Neurology. 2015;18(3):327-30.	N=1 patient received rituximab so out of scope
Doppler K, Sommer C. The New Entity of Paranodopathies: A Target Structure with Therapeutic Consequences. Neurology International Open. 2017;1(1):E56-E60.	No results reported for patients treated with rituximab for nodal/paranodal antibody positive neuropathy
Muley SA, Jacobsen B, Parry G, Usman U, Ortega E, Walk D, et al. Rituximab in refractory chronic inflammatory demyelinating polyneuropathy. Muscle & Nerve. 2020;10:10.	N=1 patient with positive antibodies so out of scope
Savasta S, Foiadelli T, Vegezzi E, Cortese A, Lozza A, Pichiecchio A, et al. Efficacy of rituximab as third-line therapy in combined central and peripheral demyelination. Neurology: Clinical Practice. 2017;7(6):534-7.	No mention of CIDP or nodal/paranodal antibody positive inflammatory/autoimmune neuropathy in the full paper.

Appendix E Evidence Table

Study details	Population	Interventions	Study outcomes Outcomes which are similar to the outcome specified in the PICO protocol have been included	Appraisal and Funding
Burnor E, Yang L, Zhou H, Patterson KR, Quinn C, Reilly MM, et al. Neurofascin antibodies in autoimmune, genetic, and idiopathic neuropathies. Neurology. 2018;90(1):e31-e8. **Study location** Pennsylvania, USA and London, UK **Study type** Retrospective case series **Study aim** 'To measure the frequency, persistence, isoform specificity, and clinical correlates of neurofascin antibodies in patients with peripheral neuropathies' **Study dates** not reported	**Inclusion criteria** Tissue from patients with GBS, CIDP, idiopathic neuropathy or genetic neuropathy (Charcot-Marie Tooth neuropathy) **Exclusion criteria** not stated **Sample size** n=3 The study included tissue from 213 patients. Relevant outcomes for the 3 patients with CIDP with NF155 IgG antibodies who were treated with rituximab was extracted for inclusion in this review. **Baseline characteristics** (n=3) Patient 1: Male, 50 yrs • Symptoms: rapidly progressive weakness/ paraesthesia, evolved into extraocular weakness, ptosis, facial diplegia, dysarthria, • ophthalmoplegia, quadriplegia, oscillating sympathetic hypersensitivity with labile blood pressure. • Previous treatment: IVIG, PEx	**Intervention details (n=3)** Rituximab Patient 1: on day 86, first of 3 x doses of rituximab (375 mg/m^2) at one week intervals Patient 2 and 3: dose, frequency of dosing, route of administration, duration of treatment not reported Concomitant therapies: Patient 1: Cyclophosphamide Patient 2: PEx Patient 3: none **Comparator details** none	**Critical outcomes** • None **Important outcomes** • Response to rituximab Patient 1: yes - *'marked improvement'*. 18 days after the first dose of RTX, *'his ophthalmoparesis began improving, and he was able to move his jaw. Over the course of the next 2 weeks, he was able to open his eyes, stick out his tongue, and nod his head. He was transferred to a long-term ventilator facility. Ten months after his initial presentation, he was transferred to acute rehabilitation, decannulated, and gradually advanced to a normal diet. At the last follow-up 19 months after symptom onset, he was able to ambulate with bilateral ankle-foot orthotics, drive, and grip utensils. There was still severe weakness of all ankle and foot movements, as well as moderate weakness of intrinsic hand muscles.'* Patient 2: yes – *'marked improvement'* (no further details reported) Patient 3: yes - *'stabilised and slight improvement'* (no further details reported) **Safety** No adverse events were reported; it is not clear if none occurred.	This study was appraised using the Joanna Briggs Institute 2017 Critical Appraisal Checklist for Case Series. The appraisal was conducted in relation to the patients within this study who received rituximab. 1. Yes 2. Yes 3. Yes 4. Unclear 5. Unclear 6. Yes 7. Yes 8. No 9. No 10. Not applicable **Other comments:** This was a retrospective case series which identified patients with neuropathy. Only 3 patients met the criteria for inclusion for this review. There was variation between the 3 patients for previous treatments (although all had a '*poor response to IVIG*'), pt 1 had NF186 ab as well as NF155ab, the details of the rituximab treatment

Study details	Population	Interventions	Study outcomes Outcomes which are similar to the outcome specified in the PICO protocol have been included	Appraisal and Funding
	• EMG: diagnostic features of acquired, demyelinating polyneuropathy with evidence of severe axonal loss • CSF protein: 106.1 mg/dL Patient 2: Female, 54 yrs • Symptoms: progressive numbness of all extremities, sensory ataxia, and weakness. Became bedbound with impaired use of the hands Positive for anti-MAG antibodies, initially diagnosed with DADS neuropathy before severe progressive disability. • Previous treatment: prednisone, IVIG • EMG: demyelinating neuropathy with prolongation of all distal latencies (most >130% normal) and diffuse slowing • CSF protein: 180 mg/dL Patient 3: Male, 39 yrs • Symptoms: subacute-onset progressive numbness of the feet/hands, then progressive weakness. Diagnosed with optic neuritis/papilledema,			were not reported for patients 2 and 3, and adjunct treatment varied across all 3 patients. Only limited results were reported i.e. response to rituximab. This was described in a narrative format only. No formal measures of response were used. Patient 1's response was described in detail but patient 3 appears to have experienced a more modest improvement compared to pt 1 and 2. Pt 3 had RTX as monotherapy whereas pts 1 and 2 had concomitant treatment. It is not clear to what extent outcomes can be attributed to rituximab alone. The follow up period for patients 2 and 3 and the timepoints for assessing outcomes were not reported. No adverse events were reported; it is not clear if none occurred. **Source of funding**: Funding declared University of Pennsylvania, Grifols Inc, NIH, Shenghua Yuying Project of Central South

<table>
<tr><th>Study details</th><th>Population</th><th>Interventions</th><th>Study outcomes
Outcomes which are similar to the outcome specified in the PICO protocol have been included</th><th>Appraisal and Funding</th></tr>
<tr><td></td><td>which improved with prednisone treatment.
• Previous treatment: steroids, IVIG, plasmapheresis,
• cyclophosphamide,
• EMG: severe, demyelinating sensory-motor polyneuropathy. Motor conduction velocities 15–29 m/s
• CSF protein: 550 mg/dL</td><td></td><td></td><td>University, Wellcome Trust, Research Council (MRC), National Institutes of Neurological Diseases and Stroke and Office of Rare Diseases</td></tr>
<tr><td>Querol L, Rojas-Garcia R, Diaz-Manera J, Barcena J, Pardo J, Ortega-Moreno A, et al. Rituximab in treatment-resistant CIDP with antibodies against paranodal proteins. Neurology neuroimmunology & neuroinflammation. 2015;2(5):e149.

Study location
Spain (number of centres not reported)

Study type</td><td>Inclusion criteria
Patients with CIDP and IgG4 CNTN1 or NF155 antibodies who were resistant (defined as ONLS ≥5) to IVIG and corticosteroids

Exclusion criteria
previous treatment with rituximab

Sample size
n=4
(The study identified 9 patients with antibodies against CNTN1 or NF155. Relevant outcomes for the 4 patients who received RTX were extracted for inclusion</td><td>Intervention details (n=4)
Rituximab 375mg/m^2 once weekly for 4 weeks followed by 1 dose per month for 2 additional doses.
Additional RTX cycles were administered 1 year after treatment in patients 2 and 3 as they had not achieved full recovery.</td><td>Critical outcomes

Overall Neuropathy Limitations Scale (ONLS)[9]
(estimated from graphs)
<table>
<tr><th>Pt</th><th>0</th><th>3m</th><th>6m</th><th>9m</th><th>12m</th><th>18m</th><th>24m</th></tr>
<tr><td>1: marked improvement</td><td>6</td><td>5</td><td>3</td><td>2</td><td>0</td><td>-</td><td>-</td></tr>
<tr><td>2: marked improvement</td><td>6</td><td>5</td><td>5</td><td>4</td><td>3</td><td>3</td><td>-</td></tr>
<tr><td>3: improved</td><td>6</td><td>6</td><td>-</td><td>-</td><td>5</td><td>5</td><td>5</td></tr>
</table></td><td>This study was appraised using the Joanna Briggs Institute 2017 Critical Appraisal Checklist for Case Series. The appraisal was conducted in relation to the patients within this study who received rituximab.
1. Yes
2. Yes
3. Yes
4. Yes
5. No
6. No
7. No
8. No
9. No
10. Not applicable</td></tr>
</table>

[9] The ONLS measures upper and lower limb function. The total ONLS score is the sum of the arm scale score and the Leg scale score where 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). 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.

<table>
<tr><th>Study details</th><th>Population</th><th>Interventions</th><th>Study outcomes
Outcomes which are similar to the outcome specified in the PICO protocol have been included</th><th>Appraisal and Funding</th></tr>
<tr>
<td>Multicentre, prospective case series

Study aim:
‘To describe the response to rituximab in patients with treatment-resistant chronic inflammatory demyelinating polyneuropathy (CIDP) with antibodies against paranodal proteins and correlate the response with autoantibody titers’.

Study dates
not reported</td>
<td>in this review. 5 patients did not receive rituximab: 2 died, 1 responded to steroids, 1 had previous rituximab for lymphoma and 1 declined).

Baseline characteristics
not fully reported (reported in previous publications)
Patient1
• CNTN1 antibodies
• severely disabled
• non-responder to PEx
• disease duration<1yr at RTX initiation
Patient 2
• anti NF155+
• severely disabled
• non-responder to PEx
• disease duration<1yr at RTX initiation
Patient 3
• anti-NF155+
• disease duration>15 years at RTX initiation
• EMG confirmed axonal degeneration
• PEx: responded to PEx at disease onset, but non-responder to last PEx course
Patient 4
• anti-CNTN1+</td>
<td>Concomitant drugs: none described

Comparator details
None</td>
<td>
<table>
<tr><td>slightly</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
</table>

Inflammatory neuropathy Rasch-built Overall Disability Scale (R-ODS)[10] (estimated from graphs)
<table>
<tr><th>Pt</th><th>0</th><th>3m</th><th>6m</th><th>9m</th><th>12m</th><th>18m</th><th>24m</th></tr>
<tr><td>1: marked improvement</td><td>14</td><td>27</td><td>39</td><td>46</td><td>48</td><td>-</td><td>-</td></tr>
<tr><td>2: marked improvement</td><td>28</td><td>-</td><td>30</td><td>42</td><td>45</td><td>46</td><td>-</td></tr>
<tr><td>3: improved slightly</td><td>19</td><td>20</td><td>-</td><td>-</td><td>24</td><td>25</td><td>26</td></tr>
</table>
Important to decision making
• Number/proportion of patients for whom the intervention has allowed the withdrawal of existing therapies (such as IVIG),
‘Patient 1 improved dramatically after rituximab treatment and was able to be withdrawn from other treatments.’(treatments withdrawn and timepoint not specified)

Safety
Patient 4 had an ischaemic stroke soon after the first rituximab dose and was lost to follow-up. This was</td>
<td>Other comments:
This case series identified 9 patients with antibodies against CNTN1 or NF155; 4 were treated with rituximab. Baseline demographic and clinical characteristics were not fully reported. We noted that pt 1 had anti-CNTN1 ab, whereas pts 2 and 3 had anti-NF155 ab. All 3 patients had the same rituximab treatment initially, but pts 2 and 3 had further treatments after 1 year. It is unclear if concomitant treatments were allowed. The follow up for the 3 patients treated with rituximab ranged from 12 to 24 months. The primary outcomes (ONLS and R-ODS) were presented in graph format only, so scores had to be estimated against the y axis. Pt 1 responded to rituximab sufficiently well for the authors to state that they could be ‘withdrawn from other</td>
</tr>
</table>

[10] The R-ODS is a self-assessment questionnaire about how polyneuropathy affects daily and social activities and to what degree the patient can perform usual activities. 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 function.

Study details	Population	Interventions	Study outcomes Outcomes which are similar to the outcome specified in the PICO protocol have been included	Appraisal and Funding
			reported to be unrelated to treatment. No other adverse events were reported; it is not clear if none occurred.	*treatments'*. It is not clear from the publication what those other treatments were. The patient selection criteria were that they were already resistant (defined as ONLS ≥5) to IVIG and corticosteroids. Adverse events were not reported, apart from an explanation for the removal of patient 4 from the study. **Source of funding** Funding declared. Fondo de Investigaciones Sanitarias—Instituto de Salud Carlos III, European Research Area Network (ACAMIN project), GBS-CIDP Foundation
Roux T, Debs R, Maisonobe T, Lenglet T, Delorme C, Louapre C, et al. Rituximab in chronic inflammatory demyelinating polyradiculoneuropathy with associated diseases. J Peripher Nerv Syst. 2018;23(4):235-40.	**Inclusion criteria** Patients with CIDP according to EFNS-PNS criteria who had been treated with rituximab for either i) an associated haematological or autoimmune disease ii) an insufficient response after the CIDP first-line treatments iii) dependence on the CIDP first-line treatment(s) **Exclusion criteria**	**Intervention details (n=3)** Rituximab: D0/D15 infusions (1 g) Concomitant treatments: none reported **Comparator details** None	**Critical outcomes** • None **Important outcomes** • Response to rituximab (timepoint) Patient 1: No (1 year) Patient 2: Yes (1.6 year) Patient 3: Yes (1 year) Response was defined as a patient who fulfilled any of the following three conditions: 1. a 5-point increase in the MRC sum score 2. a 1-point decrease in the ONLS score compared to the scores at the first rituximab infusion	This study was appraised using the Joanna Briggs Institute 2017 Critical Appraisal Checklist for Case Series. The appraisal was conducted in relation to the patients within this study who received rituximab. 1. Yes 2. Yes 3. Yes 4. Unclear 5. Unclear 6. Yes 7. Yes 8. Yes

Study location Paris, France **Study type** Single centre, retrospective case series **Study aim** 'To analyse the response to rituximab in a cohort of CIDP patients with associated disorders' **Study dates** January 2004 to December 2016	Patients with anti-MAG antibodies **Sample size** n=3 The study included 28 patients. Data for 3 CIDP patients with NF155 antibodies was extracted for inclusion in this review **Baseline characteristics** Patient 1: Female, 66 yrs • anti-NF155 ab • disease duration: 6 years • previous treatments: IVIG/ steroids/ PEx/ mycophenelate Patient 2: Female, 75 yrs • anti-NF155 ab • disease duration: 16 years • previous treatments: IVIG/ PEx Patient 3: Female, 62 yrs • anti-NF155ab/anti-GD1a/GD1b ab • disease duration: 2 years • previous treatments: IVIG/ azathioprine		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 2 consecutive visits. **Safety** Adverse events that were observed for the 28 patients in the case series were reported. No flare effect was observed in any patients and none of the patients had worsening CIDP during follow up. One patient (outside of the scope of this review) developed a CNS lymphoma. A skin rash during first infusion with rituximab and an episode of vomiting was also reported. It is unknown if either of these two adverse events were observed in any of the three patients with CIDP and antibodies against paranodal proteins. .	9. Yes 10. Not applicable **Other comments:** Only 3 patients were suitable for inclusion in this review. The only outcome within scope of the PICO was response to rituximab. Baseline characteristics for these patients are reported: we noted that patient 3 had GD1a/GD1b antibodies in addition to anti-NF155 and that patients 2 and 3 received rituximab due to insufficient response to previous treatments, whereas patient 1 was dependent on current treatment. Disease duration varied significantly ranging from 2 to 16 years Although all patients received the same rituximab dose it is unclear if any concomitant drugs were allowed which might have confounded the response. Adverse events were reported but it is unknown whether these occurred in the patients in scope of this review. **Source of funding** Funding declared

Study details	Population	Interventions	Study outcomes Outcomes which are similar to the outcome specified in the PICO protocol have been included	Appraisal and Funding
				One author declared *'personal fees and non-financial support from Janssen and Gilead'.*

Abbreviations: ab – antibody, CDAS – Current Disease Activity Scale, CIDP – chronic inflammatory demyelinating polyneuropathy, CNTN1 –contactin-1 paranodal protein, CSF – cerebrospinal fluid, D0/D15 – day 0 and day 15, EFNS-PNS – European Federation of Neurological Societies/Peripheral Nerve Society, EMG – electromyography, g – gram, GBS – Guillain-Barre Syndrome, IgG – immunoglobulin, IgG4 – a subclass of IgG, IVIG – intravenous immunoglobulin, m – metre, MAG – myelin associated glycoprotein , Mg – milligram, mg/DL – milligram per decilitre, m/s – metres per second, MRC – Medical Research Council, ONLS - Overall Neuropathy Limitations Scale, NF155 – neurofascin-155 paranodal protein, NF186 – neurofascin-186 paranodal protein, PEx – plasma exchange, Pt(s) – patient(s), R-ODS - Inflammatory neuropathy Rasch-built Overall Disability Scale, RTX – rituximab, UK – United Kingdom, USA – United States of America, yrs - years.

Appendix F Quality appraisal checklists

JBI Critical Appraisal Checklist for Case Series

1. Were there clear criteria for inclusion in the case series?
2. Was the condition measured in a standard, reliable way for all participants included in the case series
3. Were valid methods used for the identification of the condition for all participants included in the case series?
4. Did the case series have consecutive inclusion of participants?
5. Did the case series have complete inclusion of participants?
6. Was there clear reporting of the demographics of the participants in the study?
7. Was there clear reporting of clinical information of the participants?
8. Were the outcomes or follow up results of cases clearly reported?
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?
10. Was statistical analysis appropriate?

Appendix G GRADE Profiles

Table 1: In patients with nodal/paranodal antibody positive inflammatory/autoimmune neuropathy, what is the clinical effectiveness of rituximab compared with current standard treatment?

<table>
<tr><th colspan="5" rowspan="2">QUALITY</th><th colspan="3">Summary of findings</th><th rowspan="2">IMPORTANCE</th><th rowspan="2">CERTAINTY</th></tr>
<tr><th colspan="2">No of patients</th><th>Effect</th></tr>
<tr><th>Study type and number of studies Author year</th><th>Risk of bias</th><th>Indirectness</th><th>Inconsistency</th><th>Imprecision</th><th>Treatment with rituximab</th><th>Treatment with placebo</th><th>Result</th><th></th><th></th></tr>
<tr><td colspan="10">Overall Neuropathy Limitations Scale (ONLS)[11]</td></tr>
<tr><td colspan="10">Overall Neuropathy Limitations Scale (ONLS) up to 24 months follow up (estimated from graphs)[12]</td></tr>
<tr><td>1 multicentre, prospective case series

Querol et al 2015</td><td>Very serious limitation [1]</td><td>Serious indirectness[2]</td><td>Not applicable</td><td>Not calculable[3]</td><td>n=4</td><td>None</td><td>
<table>
<tr><th>Pt</th><th>0</th><th>3m</th><th>6m</th><th>9m</th><th>12m</th><th>18m</th><th>24m</th></tr>
<tr><td>1</td><td>6</td><td>5</td><td>3</td><td>2</td><td>0</td><td>-</td><td>-</td></tr>
<tr><td>2</td><td>6</td><td>5</td><td>5</td><td>4</td><td>3</td><td>3</td><td>-</td></tr>
<tr><td>3</td><td>6</td><td>6</td><td>-</td><td>-</td><td>5</td><td>5</td><td>5</td></tr>
<tr><td>4</td><td colspan="7">Withdrawn from study due to ischaemic cerebral event reported to be unrelated to rituximab. LTFU after 1st dose of RTX.</td></tr>
</table>
</td><td>Critical</td><td>Very Low</td></tr>
</table>

[11] The Overall Neuropathy Limitations Scale (ONLS) measures the limitations of patients with immune-mediated peripheral neuropathies by assessing upper and lower limb function. 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). The total ONLS score is the sum of the arm scale score and the Leg scale score where the maximum score of 12 represent the most serious disability. 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.

[12] Multiple timepoints presented in order to show the change in score over time for each of the three individual patients.

<table>
<tr><td colspan="9">Inflammatory neuropathy Rasch-built Overall Disability Scale (R-ODS)[13]</td></tr>
<tr><td colspan="9">Inflammatory neuropathy Rasch-built Overall Disability Scale (R-ODS) up to 24 months follow up (estimated from graphs)[14]</td></tr>
<tr><td>1 multicentre, prospective case series

Querol et al 2015</td><td>Very serious limitation [1]</td><td>Serious indirectness[2]</td><td>Not applicable</td><td>Not calculable [3]</td><td>n=4</td><td>None</td><td>
<table>
<tr><td>Pt</td><td>0</td><td>3m</td><td>6m</td><td>9m</td><td>12m</td><td>18m</td><td>24m</td></tr>
<tr><td>1</td><td>14</td><td>27</td><td>39</td><td>46</td><td>48</td><td>-</td><td>-</td></tr>
<tr><td>2</td><td>28</td><td>-</td><td>30</td><td>42</td><td>45</td><td>46</td><td>-</td></tr>
<tr><td>3</td><td>19</td><td>20</td><td>-</td><td>-</td><td>24</td><td>25</td><td>26</td></tr>
<tr><td>4</td><td colspan="7">Withdrawn from study due to ischaemic cerebral event reported to be unrelated to rituximab. LTFU after 1st dose of RTX.</td></tr>
</table>
</td><td>Critical</td><td>Very Low</td></tr>
<tr><td colspan="9">The number/proportion of patients judged to have responded well, poorly or not at all to various therapies</td></tr>
<tr><td colspan="9">Response to rituximab</td></tr>
<tr><td>1 case series

Burnor et al 2018</td><td>Very serious limitation [4]</td><td>Serious indirectness[2]</td><td>Not applicable</td><td>Not calculable [5]</td><td>n=3</td><td>None</td><td>Patient 1: Yes. 18 days after the first dose of RTX, ‘his ophthalmoparesis began improving, and he was able to move his jaw. Over the course of the next 2 weeks, he was able to open his eyes, stick out his tongue, and nod his head. He was transferred to a long-term ventilator facility.
Ten months after his initial presentation, he was transferred to acute rehabilitation, decannulated, and gradually advanced to a normal diet. At the last follow-up 19 months after symptom onset, he was able to ambulate with bilateral ankle-foot orthotics, drive, and grip utensils. There was still severe weakness of all ankle and foot movements, as well as moderate weakness of intrinsic hand muscles.’

Patient 2: Yes – ‘marked improvement’ (no timepoint or further details reported)</td><td>Important</td><td>Very Low</td></tr>
</table>

[13] Inflammatory neuropathy Rasch-built Overall Disability Scale (R-ODS) is a self-assessment questionnaire about the relationship between daily activities and the subject’s health. The answers give information about how polyneuropathy affects daily and social activities and to what degree the patient can perform usual activities. There are 24 questions about a task e.g. ‘are you able to eat?’. Each question can score either 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 function.

[14] Multiple timepoints presented in order to show the change in score over time for each of the three individual patients.

							Patient 3: Yes - *'stabilised and slight improvement'* (no timepoint or further details reported)		
1 case series Roux et al 2018	Very serious limitation [4]	Serious indirectness[2]	Not applicable	Not calculable [6]	n=3	None	Patient 1: No (at 1 year follow up) Patient 2: Yes (at 1.6 year follow up) Patient 3: Yes (at 1 year follow up)	Important	Very Low
Number/proportion of patients for whom the intervention has allowed the withdrawal of existing therapies (such as IVIG)									
Number of patients for whom rituximab allowed withdrawal of existing therapies (therapies not specified, no timepoint reported)									
1 multicentre, prospective case series Querol et al 2015	Very serious limitation [1]	Serious indirectness[2]	Not applicable	Not calculable [5]	n=4	None	*'Patient 1 improved dramatically after rituximab treatment and was able to be withdrawn from other treatments.'*	Important	Very Low

Abbreviations: LTFU – lost to follow up, RTX - rituximab

Footnotes

1. *Very serious risk of bias due to the case series study design, requiring extraction of outcomes for 4 of the 9 patients included in the study*
2. *Serious indirectness due to non-comparative case series*
3. *Imprecision not calculable due estimated scores derived from graphs. No analysis of change in scores was possible.*
4. *Very serious risk of bias due to retrospective, case series study design and extraction of outcomes for in scope patients.*
5. *Imprecision not calculable due to narrative results*
6. *Imprecision not calculable due to broad definition of response*

Glossary (content adapted from the NICE Glossary)

Adverse event. Any undesirable event experienced by a person while they are having a drug or any other treatment or intervention, regardless of whether the event is suspected to be related to or caused by the drug, treatment or intervention.

Case series. Reports of several patients with a given condition, usually covering the course of the condition and the response to treatment. There is no comparison (control) group of patients.

Prospective study. A research study in which the health or other characteristic of patients is monitored (or 'followed up') for a period of time, with events recorded as they happen. This contrasts with retrospective studies.

Retrospective study. A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected.

References

Included studies

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- NHS England. PICO Protocol for Rituximab for the treatment of nodal/paranodal antibody positive inflammatory/autoimmune neuropathy (URN 2001)