NHS England

Evidence Review:

Rituximab for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy (MMN), vasculitis of the peripheral nervous system and IgM paraprotein-associated demyelinating neuropathy (Adults)

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Contents

1. Introduction

Peripheral neuropathy (PN) is damage to, or disease affecting, nerves which may impair sensation, movement, gland or organ function, or other aspects of health, depending on the type of nerve affected.

Immune-mediated peripheral neuropathies represent a spectrum of peripheral nerve disorders that can be classified according to time course, predominant involvement of motor/sensory fibres, distribution of deficits and clinically related parameters such as electrophysiology and serum antibodies. They include chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy (MMN), vasculitis of the peripheral nervous system and IgM paraprotein-associated demyelinating neuropathy.

This document considers the evidence for the use of rituximab in the treatment of immune-mediated peripheral neuropathies. Rituximab is a type of biological medication called a monoclonal antibody. It works by attaching to certain blood cells from the immune system (B cells) and destroying them.

2. Summary of results

The evidence review sought to provide a response to three key questions:

Question 1: Is rituximab clinically effective to treat adult patients with immune mediated peripheral neuropathy including chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy (MMN) (with or without block), vasculitis of the peripheral nervous system and IgM paraprotein-associated demyelinating neuropathy (with or without anti-MAG antibodies) who do not respond to steroid therapy?

Two double blinded randomised placebo trials (level 1/-1) evaluating the effectiveness of rituximab in IgM anti-myelin associated glycoprotein antibody demyelinating neuropathy (Dalakas et al, 2009) and (Leger et al, 2013) showed no significance in intention to treat analysis. There is level 3 evidence which has reported improvements in CIDP, MMN and IgM Paraprotein associated demyelinating neuropathy. The majority of these studies have been small case series/case reports providing low level evidence. There have been no recent studies evaluating the role of rituximab in non-systemic vascular neuropathies (NSVN). To date there has been no collective consensus on primary end points, and numerous sensory/motor/functional scores have been adopted across all studies.

i) Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP): There is low level evidence (level 3) showing clinical improvement following use of rituximab in CIDP. Rituximab has been used in patients with CIDP following partial or complete lack of response from conventional therapies (intravenous immunoglobulin, corticosteroids and plasma exchange). Three case series have been identified to date (level 3 evidence), of which two series showed a functional improvement (functional scales utilised MRC, INCAT, ONLS, RODS) following treatment with Rituximab. The medium follow-up was one year in all three case series. Benedetti et al, 2011 reported 13 cases, of which 8 patients had a co-occurring haematological condition, and this small patient cohort were particularly responsive to rituximab, which has also been observed in case reports (Cochrane Review 2013). Side Effects: Gorson et al, 2007 reported two cases that required increased doses of IVIG following treatment with rituximab. No side effects were otherwise reported in the studies.

ii) Multifocal motor neuropathy (MMN): IVIG is widely recognised as first line therapy in MMN, with both corticosteroids and plasma exchange shown not to be beneficial. There are two low level evidence (level 3) studies evaluating the use of rituximab in MMN. Chaudhry et al, 2010 (n=6) showed no reduction in IVIG usage and function (measured using 4 score scales) post rituximab treatment. Steiglbauer et al, 2009 (n=3), showed a clinical improvement following treatment. No side effects were reported in these studies.

iii) Vasculitis of the peripheral nervous system: The Peripheral Nerve Society have extrapolated data from small to medium vessel primary systemic vasculitides for rituximab and recommended that it remains an unproven treatment option. First line therapy in non systemic vasculitic neuropathy (NSVN) is based upon level 3 studies and recommends corticosteroids with tapering over months. In rapid progressive neuropathy cyclophosphamide for short term, bridging with long-term methotrexate or azathioprine has been recommended (level 4, Peripheral Nerve Society).

iv) IgM paraprotein-associated demyelinating neuropathy with or without anti-MAG antibodies: Two recent double blinded randomised trials Dalakas et al, 2009 and Leger et al, 2013 have shown no significant benefit. Dalakas et al, 2009 (n=50) used INCAT disability score, and found with removal of one patient in the rituximab group with a normal score at baseline from analysis, the findings were significant P=0.0036. Leger et al, 2013 (n=54) evaluated the absolute change in the INCAT sensory score (ISS) with no significance. However secondary outcomes included INCAT disability score which showed a significant difference when compared to placebo (P=0.037). The authors note a variability in other motor, sensory and functional scores. Two case series (level 3) have shown an improvement following rituximab therapy. Niermeiger et al, 2009 evaluated 17 patients with disabling IgM MGUS polyneuropathy and found significant improvement in strength and sensory function although this did not translate to overall improvement in disability. Benedetti et al, 2008 studied the long term effects of rituximab in anti-MAG polyneuropathy patients (n=10) and found all patients improved at 12 months (sensory, ataxia and muscle scores), 80% maintained improvement at 24 months and 60% at 36 months. Side Effects: The two case series did not report any significant side effects. The randomised controlled trials reported significant side effects varying from 7-23%, including bronchospasm, erythematous rash with severe itching, anaemia, bradycardia, dyspnoea and diplopia. A recent case series (n=3) of reported patients experienced clinical deterioration following administration of rituximab at the second or third dose. Benedetti et al, 2008 conducted a long term study (up to 36 months) and 4/10 patients had deteriorated further. The effect of rituximab both short and long term requires further evaluation in this cohort of patients.

Dosing Administration: There is no established evidence-based protocol for the administration of rituximab in peripherally demyelinating conditions and variations in dose and interval has been noted. Rituximab administration is commonly given at a dose of 375mg/m2 weekly, for four consecutive weeks, or 1g every 2 weeks for a month, with variable continuation of rituximab following induction therapy.

Question 2: Is rituximab cost effective as a treatment for adult patients with immune mediated peripheral neuropathy including chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy (MMN) (with or without block), vasculitis of the peripheral nervous system and IgM paraprotein-associated demyelinating neuropathy (with or without anti-MAG antibodies) who do not respond to steroid therapy or who do not respond to steroid therapy as an alternative or in addition to treatment with IVIG?

To date there have been no studies evaluating cost effectiveness of rituximab as a treatment for adult patients with immune mediated peripheral neuropathy (CIDP, MMN, vasculitis of the peripheral nervous, IgM paraprotein-associated demyelinating neuropathy with our without anti –MAG antibodies.

Question 3: Should rituximab be used as a second line treatment instead of IVIG or as an adjunct to IVIG?

To date there has been no specific study protocols evaluating the use of rituximab as a second line treatment instead of IVIG or as an adjunct to IVIG specifically. The patient cohort has been variable from severe disease to mild/moderate disease, including patients who have been non-responsive towards conventional treatment.

3. Research questions

- Is rituximab clinically effective to treat adult patients with immune mediated peripheral neuropathy including chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy (MMN) (with or without block), vasculitis of the peripheral nervous system and IgM paraprotein-associated demyelinating neuropathy (with or without anti-MAG antibodies) who do not respond to steroid therapy?

- Is rituximab cost effective as a treatment for adult patients with immune mediated peripheral neuropathy including CIDP, MFMN (with or without block), vasculitis of the peripheral nervous system and IgM paraprotein-associated demyelinating neuropathy (with or without anti-MAG antibodies) who do not respond to steroid therapy or who do not respond to steroid therapy as an alternative or in addition to treatment with intravenous immunoglobulin (IVIG)?

- Should rituximab be used as a second line treatment instead of IVIG or as an adjunct to IVIG?

4. Methodology

A review of published, peer reviewed literature has been undertaken based on the research questions set out in Section 3 and a search strategy agreed with the lead clinician and public health lead for this policy area. This has involved a PubMed search and search of the Cochrane database for systematic reviews, in addition to review of any existing NICE or SIGN guidance. The evidence review has been independently quality assured.

An audit trail has been maintained of papers excluded from the review on the basis of the inclusion and exclusion criteria agreed within the search strategy. The full list has been made available to the clinicians developing the policy where requested.

5. Results

A detailed breakdown of the evidence is included in the Appendix.

Appendix One

Grade	Study design and			Outcomes							Reference	Other		
Lrade of evidence	Study design	Study size	Intervention	Category	Primary Outcome	Primary Result	Secondary Outcome	Secondary Result	Study Endpoint	Study Endpoint Result	Reference	Complications noted	Benefits noted	Comments
3	0	0	Rituximab 375mg/m2 (varies in studies from weekly for 4 consecutive weeks to 7 months)	Clinical effectiveness of the intervention	Clinical benefit following treatment with Rituximab	12/17 patients were reported to have clinical benefit from published case reports (7 patients) and one small case series (10 patients)	-	-	-	-	Mahdi-Rogers, Mohamed; van Doorn, Pieter A.; Hughes, Richard A. C.. Immunomodulatory treatment other than corticosteroids, immunoglobulin and plasma exchange for chronic inflammatory demyelinating polyradiculoneuropathy. Cochrane Database Syst Rev 2013;29(1):43-48.	-	Yes	The studies described in the Cochrane review were all observational studies of patients with CIDP, of which 6 were case reports and one a small case series. The population in three of the studies had concomitant disease (haematological). These were observational studies providing insufficient quality to determine whether Rituximab is a clinically effective alternative to treat to CIDP. To note the case reports are dated between 2004-2012. Two cases associated with Evans and Myasthenia Gravis. One study was a paediatric study.
3	Case series	13 M(8) F(5)	12/13 patients received Rituximab 375mg/m2 weekly for 4 consecutive weeks. 1 patient received 1000mg every 6 months for 2 years	Clinical effectiveness of the intervention	Assessing response of Rituximab. Defined as improvement of 2 points in clinical disability/function score or patients who reduced or discontinued pre-Rituximab therapies, Neurological assessment pre and post intervention - weekly first 6 months and then every 3 months. MRC + INCAT score	9/13 patients (69%) responded to Rituximab. From 8/13 patients with co-occurring haematological conditions, 7 were non-responders pre Rituximab and following treatment 6 responded. Improvement in function although no statistical analysis performed. Rituximab response started median 2mnths (1-6mnths) and response lasted for a median period of 1 year (1-5yrs)	-	-	-	-	Benedetti, L.; Briani, C.; Franciotta, D.; Fazio, R.; Paolasso, I.; Comi, C.; Luigetti, M.; Sabatelli, M.; Giannini, F.; Mancardi, G. L.; Schenone, A.; Nobile-Orazio, E.; Cocito, D.. Rituximab in patients with chronic inflammatory demyelinating polyradiculoneuropathy: a report of 13 cases and review of the literature. J. Neurol. Neurosurg. Psychiatr. 2011;82(2):230-232.	None noted in study	Yes - particularly in patients with co-occurring haematological problems	A small case series, multicentre study, n=13 of patients who had had partial or complete lack of response from conventional therapies. Disability before Rituximab was variable (Medical Research Council scale 36-56 and Inflammatory Neuropathy Case + Treatment Disability Score 3-8). 8 of the 13 patients had a co-occurring haematological condition, of which 7 out of 13 were refractory to conventional therapies. One patient had ITP, 4 had IgM MBSU, 1 had non-Hodgkin lymphoma and 1 had Waldenstrom Macroglobulinaemia. No statistical analysis was performed and there was no control arm. No adverse events were noted. Low level evidence study.

4	Case report	1	Rituximab	-	Symptom improvement	Improvement in muscle weakness, weaning from mechanical ventilation, diminution in myokymia.	-	-	-	-	Sadnicka, Anna; Reilly, Mary M.; Mummery, Cath; Brandner, Sebastian; Hirsch, Nicholas; Lunn, Michael P. T.. Rituximab in the treatment of three coexistent neurological autoimmune diseases: chronic inflammatory demyelinating polyradiculoneuropathy, Morvan syndrome and myasthenia gravis. J. Neurol. Neurosurg. Psychiatr. 2011;2(5):e149.	No side effects reported	Yes	This was a study of patients in ITU with pre-existing diagnosis of myasthenia gravis, who were in ITU for respiratory failure and had a diagnosis or Morvan syndrome with CIDP. Treatment was with IVIG , plasma exchange and high dose steroids. Coexistent of three conditions, possibility causing neuropathy - Morvan, Myasthenia Gravis, resulting further in significant bias. No side effects were reported. Evidence downgraded to level 4.
3	Case series	4 patients (1 patient declined, 4 did not meet criteria)	Patients received Rituximab 375mg/m2 weekly for 4 weeks and two further doses for 2 months. Additional cycles 1 year after treatment	Clinical effectiveness of the intervention	Functional improvement measured by ONLS (Overall Neuropathy Limitation Scale) and R-ODS (Rasch built Overall Disability Scale)	1 patient made a full recovery after 12 months, 1 patient significant improvement in function, 1 patient required further dose of Rituximab and 1 patient developed a MCA infarction (not related to Rituximab)	-	-	-	-	Querol, Luis; Rojas-García, Ricard; Diaz-Manera, Jordi; Barcena, Joseba; Pardo, Julio; Ortega-Moreno, Angel; Sedano, Maria Jose; Seró-Ballesteros, Laia; Carvajal, Alejandra; Ortiz, Nicolau; Gallardo, Eduard; Illa, Isabel. Rituximab in treatment-resistant CIDP with antibodies against paranodal proteins. Neurol Neuroimmunol Neuroinflamm 2015;17(1):42125.	None noted in study	Yes	Small case series of treatment resistant patients with antibodies against node of Raniver patients (a subset of CIDP). Involved patients with a significant disability (ONLS>5) who were resistant to IVIG and steroids. No demographic data provided. No adverse events were recorded. This was a small observational study with significant bias, low level evidence study
3	Case series	110 patients, 18 patients treated with Rituximab	Rituximab 375mg/m2 weekly for 4 weeks or 1g every 2 weeks.	Clinical effectiveness of the intervention	Improvement in Rankin Score, medium ranking score pre treatment is 3+/-0.8	6/18 patients treated with Rituximab responded to treatment P=0.89. Overall all patients that responded had an average Rankin score of 1.9 points	-	-	-	-	Cocito, D.; Grimaldi, S.; Paolasso, I.; Falcone, Y.; Antonini, G.; Benedetti, L.; Briani, C.; Fazio, R.; Jann, S.; Matà, S.; Sabatelli, M.; Nobile-Orazio, E.; Italian Network for CIDP Register. Immunosuppressive treatment in refractory chronic inflammatory demyelinating polyradiculoneuropathy. A nationwide retrospective analysis. Eur. J. Neurol. 2011;18(11):1291-1298.	2/18 patients, one patient had an allergic reaction and one a rise in transaminases	Yes	A study of patients with refractory CIDP to conventional treatment. There was significant bias in the study due to its retrospective nature, different centres may adopt different protocols, and the study was reliant upon medical records. Patients were treated with Rituximab or Azathioprine, Cyclophosphamide, Mycophenolate Mofetil, Cyclosporine, Methotrexate, Interferon alpha and Interferon. Complications were noted in 2 patients - one had an allergic reaction, the other a rise in transaminases. No standardised process implemented due to the nature of the study. Findings also found to be insignificant.

3	Case series	6 patients 4M:2F	Rituximab 1g every 2 weeks for a month	Clinical effectiveness of the intervention	The use of total amount of IVIG during the 12months of the study compared to the prior 12 months. Positive response is <50% reduction in total of IVIG, Pre treatment the average number of IVIG infusions was 2.9 weeks (2-4wks)	Overall no significant changes in total IVIG dose or frequency of use after rituximab administration	Improved MRC score by at least 1 grade in >2 muscle groups. 20% increase in grip strength, >2 point score in disability and Rotterdam Handicap scores. Patients reviewed 2,4,6,8, 10 + 12mnths	Pre intervention MRC score (arm/level) 56(29/27), grip strength (R/L) 74(76/75), disability score (leg/arm) 2(1/3), handicap scores 35. Overall no significant changes in secondary outcome measures. Subjectively 4 patients noted subjective improvement in strength, one patient noted worsening and one remained unchanged	-	-	Chaudhry, Vinay; Cornblath, David R.. An open-label trial of rituximab (Rituxan®) in multifocal motor neuropathy. J. Peripher. Nerv. Syst. 2010;50(9):1422-1433.	None noted	No	Open label study of patients with MMN with asymmetrical limb weakness MRC grade <4 in at least one muscle and in at least 2 peripheral nerve distribution, with duration of disease >12 months. The study showed no reduction in IVIG and no significant change in function (as measured by 4 scoring systems). No complications were noted. Small study and the benefits of Rituximab remain inconclusive. Low level evidence study.
3	Case series	6pt (2pts with CIDP, 2pts with MMN + 1pt with anti myelin associated glycoprotein MAG neuropathy)	Rituximab 375mg/m2 weekly for 4 consecutive weeks	Clinical effectiveness of the intervention	Reduced cumulative IVIG dosage by at least 25% at 1 year after rituximab therapy compared to previous year	1 CIDP patient dose of IVIG remained unchanged and in the other CIDP patient dose of IVIG increased by 51%. 1 MMN 43% reduction in IVIG, and 1 patient inc 22% of IVIG. Patients with MAGAb 20% reduction in IVIG	Improved summed strength score by at least 5 points on the MRC scale, increased sensory score by at least 4 points or improved Rankin disability score by 1 grade	No significant improvement in secondary end points	-	-	Gorson, Kenneth C.; Natarajan, Neela; Ropper, Allan H.; Weinstein, Robert. Rituximab treatment in patients with IVIg-dependent immune polyneuropathy: a prospective pilot trial. Muscle Nerve 2007;7(2):45-55.	None noted	No	Prospective uncontrolled 12 month pilot trial of patients with IVIG dependent relapsing immune polyneuropathy. There were only 2 patients with CIDP, 2 patients with MMN and one patient with anti-myelin associated glycoprotein neuropathy. One MMN and the MAGAb patient showed a reduction in IVIG usage after 12 months. No complications were noted. Significant bias in study, very small study, no control arm. Low level evidence study
0	0	0	0	-	0	0	-	-	-	-	Lunn, Michael P. T.; Nobile-Orazio, Eduardo. Immunotherapy for IgM anti-myelin-associated glycoprotein paraprotein-associated peripheral neuropathies. Cochrane Database Syst Rev 2012;12(1):102-110.	0	0	Cochrane evaluated all current immunotherapy. At the time of the review only one study was included to examine the effects of Rituximab Dalakas 2009, which has been described in detail in the CER review.

1+	RCT	54 patients, 26 patients Rituximab + 28 patients placebo. 38M:16F	Rituximab 375mg/m2 received 4 weekly infusions (tx period weeks 1-4)	Clinical effectiveness of the intervention	Evaluate the absolute change in Inflammatory neuropathy cause and treatment (INCAT) sensory score (ISS) at 12 months. F/U baseline, 3, 6, 9 + 12 months	6 patients withdrew from trial, one from placebo group and 6 from rituximab, 1 patient due to SE, 1 patient due to worsening of clinical condition, 1 pre study and 3 patients lost to F/U due to personal reasons. 47 patients completed F/U. At 12 months no change was observed in INCAT sensory score in Rituximab group 1.0+/-2.7 (range -4;8) and in placebo group 1.0+/0 2.8 (range -5;8), not a significant difference (p=0.92)	1) No of patient showing a 2 point and 4 point improvement in ISS, 2) INCAT disability score, 3) MRC sum score 4) Time taken to walk 10 metres 5) Ataxia score 6) Visual analogue pain score 7) Neurologic impairment score 8) Self evaluation questionnaire (functional score) 9) SF-36 scores subset 10) Biological secondary outcomes changes in number B cells, CD20 subcount and anti MAG antibody titres	1) No change in ISS parameters 2) 4 patients (20%) improved at least 2 points on INCAT disability scale + 0% placebo group (P=0.027), 3) analysis of self evaluation scale 5 patients in tx group (26.35) vs 1 patient in placebo group reported an improvement (p=0.0016). There was no significant difference between the placebo group + Rituximab group for the following parameters; MRC score, mean change in 10metres walk time, mean change in NIS, ataxia, VAS score. Absolute changes in SF-36 scores/subscores were largely non-significant, except for mean changes in physical function and emotional role (p=0.006 +0.02). Biological markers: Significant changes found between placebo group and Rituximab group for mean B-cell subcount (p=0.002), change in IgM anti-MAG titres(p=0.0015) and change in CD20+ B cells subcount (p=0.003)	-	-	Léger, Jean-Marc; Viala, Karine; Nicolas, Guillaume; Créange, Alain; Vallat, Jean-Michel; Pouget, Jean; Clavelou, Pierre; Vial, Christophe; Steck, Andreas; Musset, Lucile; Marin, Benoit; RIMAG Study Group (France and Switzerland). Placebo-controlled trial of rituximab in IgM anti-myelin-associated glycoprotein neuropathy. Neurology 2013;65(3):286-293.	In Rituximab group 12/26 patients reported adverse events, and in placebo 14/28. Serious SE in Rituximab - erythematous rash + itching in 2 patients, bradycardia in 1 patient, diplopia in 1, dyspnoea in 1, fractured tibia in 1, anaemia in 1 patient (related to haemorrhagic polyp in left colon)	No	This study looked at patients with IgM anti-MAG demyelinating neuropathy, with a treatment INCAT sensory score >4, visual analogue pain scale >4, ataxia score >2 and IgM monoclonal antibody peak. The comparator was placebo. The authors report 6 serious adverse effects in the Rituximab group (erythematous rash and itching in 2 patients, bradycardia in 1 patient, diplopia in 1 patient, dyspnoea in 1 patient, fractured tibia in 1 patient, and anaemia in 1 patient, related to a haemorrhagic polyp in the left colon) and two in the placebo group. No obvious consequence of B-cell depletion, no impairment of clinical immunity and no signs of opportunistic infections were noted in the study. Authors recognise the limitation of the study in terms of choice of primary endpoint as currently no consensus has been established. This double blinded randomised control trial has shown that the intention to treat and per protocol analysis does not show any difference in mean change in ISS between Rituximab and placebo group. However there has been significant differences in secondary outcomes such as INCAT disability score and self evaluation questionnaire score. Multi study trial, with limited follow-up of 12 months. High quality study.
1-	RCT	26 patients of which 13 patients treated with Rituximab, 13 patients with placebo	4 weekly infusions of Rituximab 375mg/m2 or placebo. Every 2 months Immunoglobulin levels measured, every 4 months anti-MAG tires and SGPG autoantibodies	Clinical effectiveness of the intervention	Improvement in INCAT disability score of one or more at 8 month follow up. Time to walk to 10 metres	4/13 patients in the treatment group had an improvement in INCAT disability group, compared to 0/13, P=0.096. One of the patients in tx group had an INCAT score of zero and no room for improvement, when this patient was excluded the findings were significant P=0.036. INCAT score in placebo at baseline 1.45+/-0.7 to1.54+/-0.07 and in Rituximab group 1.46+/-1.0 to 1.00+/-0.67. Time to walk to 10m significantly improved in Rituximab group. In placebo 8.3+/-3.2 to 9.3+/-3.9, in Rituximab group 9.5+/-4.2 to 7.4+/-2.5 (P=0.0042)	Improvement in MRC scale and mean sensory scale	There was a non-significant change in mean sensory scores in the Rituximab group. However in the Rituximab group the improved patients had a significant improvement in sensory scores when compared to those patients that did not improve, 10.8+/-1.8 vs 6.0+/-3.2, P=0.02. Authors suggest possibly patients with a more sensory component more likely to respond	-	-	Dalakas, Marinos C.; Rakocevic, Goran; Salajegheh, Mohammad; Dambrosia, James M.; Hahn, Angelika F.; Raju, Raghavan; McElroy, Beverly. Placebo-controlled trial of rituximab in IgM anti-myelin-associated glycoprotein antibody demyelinating neuropathy. Ann. Neurol. 2009;47(5):859-864.	One patient developed bronchospasm during infusion, exited from study. Minor SE: increase in baseline temp, headaches, mild hypotension	No	Study of patients with anti MAG demyelinating polyneuropathy (A-MAG0-DP) against placebo. Intention to treat analysis did not reach significance P=0.096, although removal of patient with normal INCAT score significant improvement in Rituximab group p=0.0036. Authors comment that there may be a possible association with Anti-MAG antibody titres and severe sensory impairment to increase change of response towards Rituximab. One patient developed bronchospasm during infusion and exited from the study. Other minor side effects recorded included increase in baseline temperature, headaches and mild hypotension. Is a double blinded randomized controlled trial, although very small study n<50, therefore downgraded to -1.

0	Case series	3 patients	Planned four weekly rituximab infusions 375mg/m2	Safety of the intervention	Tolerance towards rituximab	Patient A: After 2nd dose developed proximal weakness and severe progression of distal weakness in legs + proximal + distal weakness in arms with painful sensory deficits in arms and leg. After IVIG severity of polyneuropathy returned to levels prior to rituximab. Patient B: After 2nd dose developed rapid deterioration of sensory deficits and progression of distal weakness from mild to severe and additional weakness, Rituximab discontinued. F/U at 2 months showed some slight improvement. Patient C: After 3rd infusion progression of sensory symptoms to proximally. Rituximab stopped and returned to pre-treatment pattern in 2-3 weeks	-	-	-	-	Stork, Abraham C. J.; Notermans, Nicolette C.; Vrancken, Alexander F. J. E.; Cornblath, David R.; van der Pol, W.-Ludo. Rapid worsening of IgM anti-MAG demyelinating polyneuropathy during rituximab treatment. J. Peripher. Nerv. Syst. 2013;19(7):473-475.	Refer to primary outcome box - deterioration of polyneuropathy upon commencing Rituximab	No	All patients had IgM monoclonal gammopathy associated polyneuropathy and anti-MAG antibodies. All patients had sensorimotor neuropathy and 2 pts had MRC grade 4 for weakness of dorsiflexors of foot + toes and one patient Grade 2 . These cases suggested that rituximab can have paradoxical worsening of polyneuropathy, which has been described in other trials. Further larger studies are required to delineate this further. Low grade evidence study.
3	Case series	3 patients	Rituximab 375mg/m2 every 2 weeks for a month + then further dose when B cells reappeared during follow-up. Peripheral B lymphocytes measured every 3 months	Clinical effectiveness of the intervention	Clinical improvement following rituximab. MRC Sum score measured (Medical Research Council) sum score, with max 60 points	Authors report all patients had sustained clinical improvement, MRC score pre and post Rituximab Patient A 43 to 48, patient B 43 to 49 and patient C 48 to 54	-	-	-	-	Stieglbauer, Karl; Topakian, Raffi; Hinterberger, Georg; Aichner, Franz T.. Beneficial effect of rituximab monotherapy in multifocal motor neuropathy. Neuromuscul. Disord. 2009;15(3):176-184.	None noted in study	Yes	MMN patients that have declining efficacy of IVIG. All three patients required further Rituximab doses following induction, patient A=2 doses in 27mnths, B=4 further doses in 39 months and patient C=3 further doses in 30 months. No complications noted. Small case series, significant bias, low level evidence study.

4	0	0	0	-	0	0	-	-	-	-	Collins, Michael P.; Dyck, P. James B.; Gronseth, Gary S.; Guillevin, Loïc; Hadden, Robert D. M.; Heuss, Dieter; Léger, Jean-Marc; Notermans, N. C.; Pollard, John D.; Said, Gérard; Sobue, Gen; Vrancken, A. F. J. E.; Kissel, John T.; Peripheral Nerve Society. Peripheral Nerve Society Guideline on the classification, diagnosis, investigation, and immunosuppressive therapy of non-systemic vasculitic neuropathy: executive summary. J. Peripher. Nerv. Syst. 2010;71(21):1742-1744.	0	No	The Peripheral Nerve Society have made good practice point recommendations (grade U) on immunosuppressive therapy for NSVN (non-systemic vascular neuropathies) on the basis of class III evidence of treatment of NSV and extrapolated evidence for treatments from primary systemic small-medium vessel vasculitis. The recommendation is to treat NSVN patient initially with corticosteroids with tapering over months. If patients present with rapid progressive neuropathy cyclophosphamide (CYC) has been suggested as first line therapy following by long term immunosuppression with methotrexate or azathioprine. Extrapolation from small to medium vessel primary systemic vasculitides, have shown intravenous immunoglobulin, plasma exchange and rituximab to be unproven treatment options. Further studies are required.
3	Case series	10 patients. 7/10 patients were unresponsive to immune or cytostatic therapies	Rituximab 375mg/m2 for consecutive four weeks	Clinical effectiveness of the intervention	Clinical improvement >1 point in at least 2 scales and deterioration <1 point in at least 2 scales. Measures at baseline, 0, 12, 24, 36 months. Measured MRC scale, INCAT disability scale, Sensory sumscore ISS, PCS- Physical composite score and MCS-Mental composite score	All patients improved at 12 months, decreased sensory ataxia in 8 patients, increased muscle strength in 9 pts, improvement in two or more scales. 3 patients improved in upper limbs with improved daily activities. 8/10 patients (80%) maintained clinical improvement at 24 months p=0.02 in both PCS, MCS. 6/10 patients 60% maintained follow-up in last 36 months. 4 patients deteriorating with slowly progressive increase in sensory ataxia.	Anti -MAG titres	Anti MAG titres decreased by 93% at 12 months P=0.005 vs baseline. At 24 months decreased by 80% and at 36 months 60%. 8 patients titres during follow up - up to baseline although in 2 patients two fold increase in the patient	-	-	Benedetti, L.; Briani, C.; Franciotta, D.; Carpo, M.; Padua, L.; Zara, G.; Zambello, R.; Sormani, M. P.; Mancardi, G. L.; Nobile-Orazio, E.; Schenone, A.. Long-term effect of rituximab in anti-mag polyneuropathy. Neurology 2008;80(9):1036-1039.	No significant side effects	Yes	Authors noted the patients maintaining improvement during follow up had baseline titres >1/51,200 P=0.009. Longest prospective study, study number small. Numerous scales used to measure response from sensory/motor/cognitive. Patient cohort was variable, no control group . Low grade evidence.
3	Case series	17 patients, 14M:3F	Rituximab 375mg/m2 once weekly for four weeks	Clinical effectiveness of the intervention	Improvement of one or more point on the overall disability Sum Score (ODSS).	Rituximab improved ODSS in 2/17 patients, remained unchanged in 14/17 and deteriorated in 1/17 patients. Median ODSS changed from 4 to 3 (Non-significant)	1) Improvement of > 1 one point in the Modified Rankin scale (MRS), 2) distal MRC sum score by >5% (distal arms+leg in 8 muscle group, max score of 80 points) or 3) 5% of greater improvement in sensory sum score (max score of 56points). 4) disappearance of CD20 positive B cells in bone marrow biopsy or >50% decrease in M protein concentration. 5) >10% improvement of conduction velocity 6) adverse effects	1) MRS improved in 5/17 patients, median change from 2 to 2 p=0.0025 2) MRC score 9/17 patients showed an improvement, median increase from 90 to 93% p=0.006 3) SSS 9/17 patients improved and deteriorated in 4/17. Group medium changed from 57% to 71% p=0.03. 4) All patients showed CD20 B cell depletion 5) Nerve conduction studies showed >10% improvement of NCV in 4/17 patients	-	-	Niermeijer, J. M. F.; Eurelings, M.; Lokhorst, H. L.; van der Pol, W.-L.; Franssen, H.; Wokke, J. H. J.; Notermans, N. C.. Rituximab for polyneuropathy with IgM monoclonal gammopathy. J. Neurol. Neurosurg. Psychiatr. 2009;.	No significant side effects reported	Yes	Patients with disabling IgM MGUS polyneuropathy. 5 patients previously treated with intermittent cyclophosphamide and prednisolone and 2 patients with fludarabine. Authors comments upon deterioration of patients attributed towards the progressive nature of the polyneuropathy. Significant improvement in strength and sensory function although this did not translate to overall improvement in disability, No significant change in disability as measured by ODSS score. No complications noted.

Appendix Two

Literature search terms

Assumptions / limits applied to search:	
Original search terms:	n/a
Updated search terms - Population	Chronic Inflammatory Demyelinating Polyradiculoneuropathy Chronic Inflammatory Polyradiculoneuropathy CIDP Chronic Inflammatory Polyradiculopathy Multifocal motor neuropathy MMN Vasculitis of the peripheral nervous system Peripheral neuropathy Peripheral vasculitic neuropathy IgM paraprotein-associated demyelinating neuropathy IgM paraprotein-associated demyelinating neuropathies IgM anti-myelin-associated glycoprotein paraprotein-associated peripheral neuropathy IgM anti-myelin-associated glycoprotein paraprotein-associated peripheral neuropathies IgM anti-myelin-associated glycoprotein antibody demyelinating neuropathy IgM anti-myelin-associated glycoprotein neuropathy IgM anti-MAG demyelinating polyneuropathy IgM monoclonal gammopathy of undetermined significance anti-MAG neuropathy IgM MGUS anti-MAG neuropathy
Updated search terms - Intervention	Rituximab CD20 antibody, rituximab GP2013 IDEC-C2B8 IDEC-C2B8 antibody Mabthera Rituxan
Updated search terms - Comparator	Intravenous immunoglobulin IVIG Alphaglobin Endobulin Flebogamma DIF Gamimmune Gamimmune N Gamimune Gamimune N Gammagard Gammonativ Gamunex Globulin-N Immune Globulin Intravenous

	Intravenous immunoglobulins Intraglobin Intraglobin F Intravenous Antibodies IV Immunoglobulins Iveegam Privigen Sandoglobulin Venimmune Venoglobulin Venoglobulin-I
Updated search terms - Outcome	-
Inclusion criteria	**General inclusion criteria**
	In order of decreasing priority, the following are included: 1. All relevant systematic reviews and meta-analysis in the last 5 years and those in 5-10 years period which are still relevant (e.g. no further updated systematic review available) 2. All relevant RCTs and those in the 5-10 years period which are still relevant (e.g. not superseded by a next phase of the trial / the RCT is one of the few or only high quality clinical trials available) >>>> If studies included reach 30, inclusion stops here 3. All relevant case control and cohort studies, that qualify after exclusion criteria >>>> If studies included reach 30, inclusion stops here 4. All relevant non analytical studies (case series/ reports etc) that qualify after exclusion criteria >>>> If studies included reach 30, inclusion stops here 5. Expert opinion
	Specific inclusion criteria
	English language <5 years Title/Abstract 6 additional articles per the suggestion of the clinical evidence reviewer: a. Benedetti, L.; Briani, C.; Franciotta, D.; Carpo, M.; Padua, L.; Zara, G.; Zambello, R.; Sormani, M. P.; Mancardi, G. L.; Nobile-Orazio, E.; Schenone, A.. Long-term effect of rituximab in anti-mag polyneuropathy. Neurology 2008;80(9):1036-1039. b. Collins, Michael P.; Dyck, P. James B.; Gronseth, Gary S.; Guillevin, Loïc; Hadden, Robert D. M.; Heuss, Dieter; Léger, Jean-Marc; Notermans, N. C.; Pollard, John D.; Said, Gérard; Sobue, Gen; Vrancken, A. F. J. E.; Kissel, John T.; Peripheral Nerve Society. Peripheral Nerve Society Guideline on the classification, diagnosis, investigation, and immunosuppressive therapy of non-systemic vasculitic neuropathy: executive summary. J. Peripher. Nerv. Syst. 2010;71(21):1742-1744. c. Gorson, Kenneth C.; Natarajan, Neela; Ropper, Allan H.; Weinstein, Robert. Rituximab treatment in patients with IVIg-dependent immune polyneuropathy: a prospective pilot trial. Muscle Nerve 2007;7(2):45-55. d. Niermeijer, J. M. F.; Eurelings, M.; Lokhorst, H. L.; van der Pol, W.-L.; Franssen, H.; Wokke, J. H. J.; Notermans, N. C.. Rituximab for polyneuropathy with IgM monoclonal gammopathy. J. Neurol. Neurosurg. Psychiatr. 2009;. e. Stieglbauer, Karl; Topakian, Raffi; Hinterberger, Georg; Aichner, Franz T.. Beneficial effect of rituximab monotherapy in multifocal motor neuropathy. Neuromuscul. Disord. 2009;15(3):176-184. f. Stork, Abraham C. J.; Notermans, Nicolette C.; Vrancken, Alexander F. J. E.; Cornblath, David R.; van der Pol, W.-Ludo. Rapid worsening of IgM anti-MAG demyelinating polyneuropathy during rituximab treatment. J. Peripher. Nerv. Syst. 2013;19(7):473-475.

Exclusion criteria	**General exclusion criteria**
	Studies with the following characteristics will be excluded: 1. Do not answer a PICO research question 2. Comparator differs from the PICO 3. < 50 subjects (except where there are fewer than 10 studies overall) 4. No relevant outcomes 5. Incorrect study type 6. Inclusion of outcomes for only one surgeon/doctor or only one clinical site
	Specific exclusion criteria
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