NHS England

Evidence review: Rituximab for IgM Paraproteinaemic Demyelinating Peripheral Neuropathy

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Contents

1. Introduction

This review examines the clinical effectiveness, safety and cost effectiveness of rituximab, with or without conservative management, compared to conservative management alone, medical interventions or placebo in patients with immunoglobulin M (IgM) paraproteinaemic demyelinating peripheral neuropathy (PDPN), with monoclonal gammopathy of undetermined significance (MGUS), lymphoplasmacytic lymphoma (LPL), Waldenstrom's macroglobulinaemia (WM) or low-grade Non-Hodgkin lymphoma.

Rituximab is a monoclonal antibody drug that targets the CD20 protein on the cell surface of B-lymphocytes resulting in their destruction and subsequent reduction in immunoglobulin production. Rituximab was initially developed for the treatment of B-cell lymphoma but is now also used in a variety of B-cell driven autoimmune diseases including rheumatoid arthritis.

Conservative management might include analgesia, physiotherapy or occupational therapy. Medical interventions might include intravenous immunoglobin (IVIG).

2. Executive summary of the review

One paper was included in this review (Lunn and Nobile-Orazio 2016).

The paper by Lunn and Nobile-Orazio 2016 was a systematic review and meta-analysis. The systematic review included eight trials of which two randomised controlled trials (RCT) of rituximab compared to placebo (80 participants; 39 rituximab vs. 41 placebo) were eligible for this rapid evidence review (Léger et al 2013, Dalakas et al 2009). Patients were adults with a diagnosis of MGUS, demyelinating neuropathy and anti-MAG antibodies. Patients were excluded if they had any other possible causes of peripheral neuropathy. No details regarding concomitant conservative management were provided.

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

In patients with IgM paraproteinaemic demyelinating peripheral neuropathy, with MGUS, LPL, WM or low-grade Non-Hodgkin lymphoma, what is the clinical effectiveness of rituximab versus conservative management, medical interventions or placebo?

Critical outcomes. The critical outcomes for decision making are disability, global impression of change and haematological response. Certainty in the quality of the evidence for the critical outcomes was moderate to high when assessed using modified GRADE.

Disability
High to moderate certainty evidence from the systematic review with meta-analysis of two RCTs by Lunn and Nobile-Orazio 2016 showed that rituximab produces a statistically significant improvement in disability as measured on the Inflammatory Neuropathy Cause

and Treatment (INCAT) scale[1]. A significantly higher number of rituximab participants (12/33) improved on INCAT score at 8-12 months compared to placebo (4/40); (risk ratio (RR) 3.51, 95% confidence interval (CI) 1.30 to 9.45, heterogeneity I^2 = 0%, p=0.013, 73 participants). There was also a statistically significantly greater mean improvement in INCAT scores with rituximab at 8-12 months[2] (mean difference (MD) -0.45, 95%CI -0.85 to -0.05, I^2 =0%, p=0.029, 73 participants), but not at 8-9 months MD -0.33 (95%CI -0.73 to 0.07, I^2 = 0%, p=0.11, 70 participants).

Global impression of change

Moderate certainty evidence from the systematic review with meta-analysis of two RCTs by Lunn and Nobile-Orazio 2016 showed that, at 8-12 months, statistically significantly more participants receiving rituximab assessed their condition as being "stable or improved"; (rituximab 27/32 vs. placebo 17/38; RR 1.86, 95%CI 1.27 to 2.71, I^2 =0%, p=0.0014, 70 participants) and "improved" (rituximab 12/32 vs. placebo 1/38; RR 9.67, 95%CI 1.84 to 50.85, I^2 = 0%, p=0.0074, 70 participants) compared to placebo.

Haematological response[3]

There is moderate certainty evidence from the systematic review by Lunn and Nobile-Orazio 2016 that rituximab provides a statistically significantly improved haematological response compared to placebo. This was reported using two measures. Change in serum IgM level at eight months was reported by one of the RCTs included in Lunn and Nobile-Orazio 2016, with a statistically significant decrease for rituximab (mean standard deviation [SD] = -254.4 [55]) compared to placebo (mean [SD] = 32.3 [55]) (MD -286mg/dL, 95%CI -329 to -244, 26 participants. P value was not reported). Change in IgM anti-MAG titre at 8-12 months was reported as meta-analysis of two RCTs in Lunn and Nobile-Orazio 2016, with a statistically significant decrease for rituximab compared to placebo (MD -17.79 units/mL, 95%CI -33.33 to -2.25, I^2 = 0%, p=0.025, 71 participants).

Important outcomes. Outcomes important to decision making are sensory impairment, 10 metre walk test, quality of life and motor impairment. Certainty in the quality of the evidence for the important outcomes was low to high when assessed using modified GRADE.

Sensory impairment

Low certainty evidence from one of the RCTs reported in the systematic review by Lunn and Nobile-Orazio 2016 showed that rituximab did not have a statistically significant impact on sensory impairment as measured by changes in Neuropathy Impairment Score (NIS) score[4] at 12 months. The mean difference in NIS score at 12 months was -0.70, 95%CI -4.03 to 2.63 (mean [SD] = rituximab 1.1 [6] vs. placebo 1.8 [5.1]). P value was not reported.

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[1] The INCAT (Inflammatory Neuropathy Cause and Treatment) disability score is a measure of activity limitation

[2] The follow-up range reflects the time period at which data were reported for the individual RCTs included in the meta-analysis (e.g. 8 months for Dalakas et al 2009 and 12 months for Léger et al 2013)

[3] The PICO states that haematological response as measured by CD-19 count is of interest. However, no studies were identified that reported numerical results for CD-19 count

[4] The NIS is a composite, quantitative measure of both large- and small-fibre dysfunction.

10 metre (m) walk test

The systematic review with meta-analysis of two RCTs by Lunn and Nobile-Orazio 2016 reported moderate certainty evidence that the time to walk 10m did not improve significantly at 8-12 months with rituximab compared to placebo (MD -0.35 seconds, 95%CI, -1.89 to 1.19, I^2 = 0%, p=0.66, 68 participants). There was low certainty evidence that the numbers of participants with improved 10m walk time at six months (reported by one of the RCTs in the systematic review) also did not improve significantly with rituximab (9/13) vs. placebo (5/13) (RR 1.80, 95%CI 0.83 to 3.92, 26 participants, p value was not reported).

Quality of life

Quality of life at 12 months, as measured by the SF-36[5] physical and mental subscale, was reported by one of the RCTs included in the Lunn and Nobile-Orazio 2016 systematic review. This provides high certainty evidence that rituximab statistically significantly improves quality of life as measured by change in physical SF-36 subscores (mean [SD]) rituximab 11.6 [19.6] vs. placebo -3.9 [9.8], MD 15.50, 95%CI 5.24 to 25.76, 37 participants, p value was not reported). However, the effect on change in SF-36 mental subscores was not statistically significant (mean [SD] rituximab 4.5 [9.9] vs. placebo -2.1 [12.8], MD 6.60, 95%CI 0.35 to 13.55, 41 participants, p value was not reported) (moderate certainty).

Motor impairment

One of the RCTs included in the systematic review[6] provided moderate certainty evidence for the median change in muscle strength measurements using the Medical Research Council (MRC) score at 12 months. The RCT (Léger et al 2013) reported no statistically significant difference in the median change in MRC score at 12 months between rituximab 0.0 (95%CI -3 to 0.0) and placebo 0.0 (95%CI -1.5 to 1.5), p=0.17. The second RCT included in the systematic review (Dalakas et al 2009) also reported no significant changes in the MRC score at eight months but no measure of statistical significance was recorded (low certainty).

In patients with IgM paraproteinaemic demyelinating peripheral neuropathy with MGUS, LPL, WM or low-grade Non-Hodgkin lymphoma, what is the safety of rituximab versus conservative management, medical interventions or placebo?

Important Outcomes. Outcomes important to decision making are adverse events.

Adverse Events

The systematic review with meta-analysis of two RCTs by Lunn and Nobile-Orazio 2016 provided low to moderate certainty evidence that there was no statistically significantly difference in the numbers of patients reporting any adverse events (rituximab 26/39 vs. placebo 23/41, RR 1.18, 95%CI 0.84 to1.66, I^2 =0%, p=0.34, 80 participants) (moderate

[5] The SF-36 is scored from 0 to 100 with higher scores indicating better quality of life.
[6] This outcome was not reported in the systematic review. The data were taken from the individual RCT papers

certainty) or severe adverse events (rituximab 2/39 vs. placebo 0/41, RR 3.11, 95%CI 0.34 to 28.54, I^2 =0%, p= 0.32, 80 participants) (low certainty). The timeframe was not provided.

From the evidence selected, are there any subgroups of patients with IgM paraproteinaemic demyelinating peripheral neuropathy who would benefit more from treatment with rituximab?

No evidence was identified regarding any subgroups of patients that would benefit more from treatment with rituximab.

In patients with IgM paraproteinaemic demyelinating peripheral neuropathy with MGUS, LPL, WM or low-grade Non-Hodgkin lymphoma, what is the cost effectiveness of rituximab versus conservative management, medical interventions or placebo?

No evidence was identified on the cost effectiveness of rituximab compared with conservative management, medical interventions or placebo.

Limitations. Although the clinical effectiveness of rituximab in patients with IgM PDPN is supported by evidence from a systematic review of RCTs, the key limitation is the very small number of patients in the studies available to the systematic review. IgM PDPN is a relatively rare condition and this would have affected the number of participants recruited into the studies. As there was no significant heterogeneity among the patients included in the studies it was appropriate to combine the results in meta-analysis. However, the systematic review authors did note significant potential bias in one of the RCTs included in the review. One further limitation is that rituximab was compared to placebo rather than medical interventions such as IVIG.

Conclusion. There is moderate to high certainty evidence that for patients with IgM PDPN, the addition of rituximab confers a statistically significant improvement in the critical outcomes of disability, global impression of change and haematological response and the important outcome of quality of life (physical subscale). Although there is statistically significant improvement in critical outcomes, the clinical benefit and meaningfulness of these improvements is not clear. There was no statistically significant difference between rituximab and placebo on the important outcomes of sensory impairment, 10 metre walk test or motor impairment. There was no statistically significant difference between rituximab and placebo for any adverse events or serious adverse events.

3. Methodology

Review questions

The review questions for this evidence review are:

1. In patients with IgM paraproteinaemic demyelinating peripheral neuropathy, with MGUS, LPL, WM or low-grade Non-Hodgkin lymphoma, what is the clinical effectiveness of rituximab versus conservative management, medical interventions or placebo?

2. In patients with IgM paraproteinaemic demyelinating peripheral neuropathy with MGUS, LPL, WM or low-grade Non-Hodgkin lymphoma, what is the safety of rituximab versus conservative management, medical interventions or placebo?
3. In patients with IgM paraproteinaemic demyelinating peripheral neuropathy with MGUS, LPL, WM or low-grade Non-Hodgkin lymphoma, what is the cost effectiveness of rituximab versus conservative management, medical interventions or placebo?
4. From the evidence selected, are there any subgroups of patients with IgM paraproteinemic demyelinating peripheral neuropathy who would benefit more from treatment with rituximab?

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 4th August 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

One paper was included in this review (Lunn and Nobile-Orazio 2016).

The paper by Lunn and Nobile-Orazio 2016 was a systematic review and meta-analysis. The systematic review included eight trials of which two RCTs of rituximab compared to placebo (80 participants; 39 rituximab vs. 41 placebo) were eligible for this rapid evidence review (Léger et al 2013, Dalakas et al 2009). 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

Lunn and Nobile-Orazio 2016
 	
Systematic review with meta-analysis
 	
RCTs of interest:
• France; Switzerland
• Bethesda, USA
	Two RCTs of rituximab versus placebo (n=80) in patients with IgM PDPN
	
	One RCT included 26 participants (13 rituximab vs. 13 placebo). The second RCT included 54 participants (26 rituximab vs. 28 placebo)
		Intervention
		Rituximab infusions of 375 mg/m^2 weekly for 4 weeks
		
		Comparison
		Identical infusions of placebo
		
		No details of concomitant treatments were reported for either the rituximab or comparator groups
			Critical Outcomes
			• Disability
			  • Number of participants improved on INCAT score at 8-12 months
			  • Mean improvement in INCAT score at 8-12 months
			  • Mean improvement in INCAT score at 8-9 months
			• Global impression of change
			  • Participant subjective impression of change "stable or improved" at 8-12 months
			  • Participant subjective impression of change "improved" at 8-12 months
			• Haematological response
			  • Change in IgM level 8 months after treatment
			  • Change in IgM anti-MAG titre at 8-12 months
			
			Important outcomes
			• Sensory impairment
			  • Mean improvement in NIS at 12 months
			• 10 metre walk test
			  • Improvement in 10 metre walk time at 8-12 months
			  • Number improved in 10 metre walk at 6 months
			• Quality of life
			  • Mean change in SF-36 physical subscores at 12 months
			  • Mean change in SF-36 mental health subscores at 12 months
			• Motor impairment
			  • Change in MRC at 12 months
			  • Change in MRC at 8 months
			• Adverse events
			  • Any adverse event
			  • Severe adverse event

Study	Population	Intervention and comparison	Outcomes reported
Abbreviations: Anti-MAG - anti-myelin-associated glycoprotein; IgM - immunoglobulin M; INCAT – inflammatory Neuropathy Cause and Treatment; ISS – INCAT sensory score; MRC – Medical Research Council; NIS - Neuropathy Impairment Score; PDPN - paraproteinaemic demyelinating peripheral neuropathy; RCT - randomised controlled trial; SF-36 - Short Form 36 Health Survey			

5. Results

In patients with IgM paraproteinaemic demyelinating peripheral neuropathy, with MGUS, LPL, WM or low-grade Non-Hodgkin lymphoma, what is the clinical effectiveness and safety of rituximab versus conservative management, medical interventions or placebo?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Disability **Certainty of evidence:** Moderate to High	Disability is a critical outcome as the symptoms and signs of peripheral neuropathy result in patient disability which impacts of mobility, activities of daily living, independence and wellbeing. 1 systematic review with meta-analysis of two RCTs reported disability, as measured by INCAT score, for rituximab compared to placebo in patients with IgM PDPN (Lunn and Nobile-Orazio 2016): • The number of participants with improved INCAT score at 8-12 months was statistically significantly greater with rituximab (12/33) compared to placebo (4/40) (RR 3.51, 95%CI 1.30 to 9.45, I^2 = 0%, p=0.013, 73 participants). **HIGH** • Mean improvement in INCAT score at 8-12 months was statistically significantly greater with rituximab compared to placebo (MD -0.45, 95%CI -0.85 to -0.05, I^2 =0%; p=0.029, 73 participants). **HIGH** • There was no significant difference in the mean improvement in INCAT scores at 8-9 months (MD -0.33, 95%CI -0.73 to 0.07, I^2 = 0%, p=0.11, 70 participants). **MODERATE** **This study provides high certainty evidence that, in patients with IgM PDPN, at 8 to 12 months, rituximab improves disability, as measured by improvements in INCAT score, compared to placebo. However, there was no difference in mean improvement when assessed at a follow up range of 8-9 months (moderate certainly).**
Global impression of change **Certainty of evidence:** Moderate	Global impression of change is relevant to patients because the major disability of ataxic unsteadiness and tremor are poorly 'measured' in scores. This is a critical outcome/ treatment effect as a holistic measure of treatment, subjectively assessed by the patient and clinician, that will not be captured by individual measures. 1 systematic review with meta-analysis of two RCTs reported global impression of change for rituximab compared to placebo in patients with IgM PDPN (Lunn and Nobile-Orazio 2016): • At 8-12 months rituximab (27/32) statistically significantly improved participant's subjective impression of their condition as "stable or improved" compared to placebo (17/38) (RR 1.86, 95%CI 1.27 to 2.71, I^2 =0%, p=0.0014, 70 participants). **MODERATE** • At 8-12 months rituximab (12/32) statistically significantly improved participant's subjective impression of their condition as "improved" compared to placebo (1/38) (RR 9.67, 95%CI 1.84 to 50.85, I^2 = 0%, p=0.0074, 70 participants). **MODERATE** **This study provides moderate certainty evidence that, in patients with IgM PDPN, rituximab improves patient's subjective impression**

Outcome	Evidence statement
	of change compared to placebo at a follow-up range of 8 to 12 months.
Haematological response **Certainty of evidence:** Moderate	Haematological response is important to patients because these are direct, quantifiable measures of anti-CD20 treatment response and occur prior to clinically detectable change. Sustained reduction in pathological antibodies results in improved outcomes. 1 systematic review with meta-analysis of two RCTs reported haematological response for rituximab compared to placebo in patients with IgM PDPN (Lunn and Nobile-Orazio 2016). Haematological response as measured by change in serum IgM level was reported by one of the RCTs included in the systematic review. Haematological response as measured by IgM anti-MAG titre was reported as meta-analysis of two RCTs: • Eight months after treatment, there was a statistically significant decrease in the level of serum IgM after rituximab compared to placebo (mean [SD] -254.4 [55] vs. 32.3 [55] MD -286mg/dL, 95%CI -329 to -244, 26 participants, p value not reported). **MODERATE** • At 8-12 months, there was a significant decrease in the titre of IgM anti-MAG activity (MD -17.79 units/mL, 95%CI -33.33 to -2.25, I^2 = 0%, p=0.025, 71 participants). **MODERATE** **This study provides moderate certainly evidence that, in patients with IgM PDPN, rituximab significantly improved haematological response compared with placebo, as measured by IgM serum level at eight months and IgM anti-MAG titre at 8-12 months.**
Important outcomes	
Sensory impairment **Certainty of evidence:** Low	Sensory impairment is an important outcome for patients as improvement to sensory impairment can improve independence and function 1 systematic review reported sensory impairment, as measured by changes in NIS, for rituximab compared to placebo in patients with IgM PDPN from 1 RCT (Lunn and Nobile-Orazio 2016): • There was no significant difference in NIS score at 12 months for rituximab (mean [SD] 1.1 [6] compared to placebo (mean [SD] 1.8 [5.1] (MD -0.70, 95%CI -4.03 to 2.63, 45 participants, p value not reported). **LOW** **This study provides low certainty evidence that, in patients with IgM PDPN, rituximab does not significantly improve sensory impairment, as assessed by NIS score, compared to placebo at 12 months.**
10 metre walk test **Certainty of evidence:** Low to Moderate	The 10 metre walk test is relevant to patients because it is an important outcome which crosses between impairment and disability. Imbalance, sensory dysfunction and weakness all contribute to altered walking times which improve after treatment. 1 systematic review with meta-analysis of two RCTs reported 10 metre walk test for rituximab compared to placebo in patients with IgM PDPN (Lunn and Nobile-Orazio 2016). Improvement in 10 metre walk time was reported as meta-analysis of two RCTs. Number of participants who improved in 10 metre walk time was reported by one of the RCTs included in the systematic review: • There was no statistically significant difference in improvement in

Outcome	Evidence statement
	time to walk 10 metres for rituximab compared to placebo at 8-12 months (MD -0.35 seconds, 95%CI -1.89 to 1.19, I^2 = 0%, p=0.66, 68 participants). **MODERATE** • There was no statistically significant difference in the number of participants who improved in 10 metre walk at six months (rituximab 9/13 vs. placebo 5/13 RR 1.80, 95%CI 0.83 to 3.92, 26 participants). No p value was reported. **LOW** **This study provides moderate certainty evidence that, in patients with IgM PDPN, rituximab does not significantly improve 10 metre walk time compared to placebo. It also provides low certainty evidence that, compared to placebo, rituximab does not significantly affect the number of patients with an improved 10m walk time.**
Quality of life **Certainty of evidence:** Moderate to High	Quality of life is an important outcome in these patients as neuropathy impacts on patient's function and activities of daily living. Improvement in quality of life, especially physical functioning, is a marker of successful treatment. 1 systematic review reported quality of life, as measured by mean changes in the physical and mental health subscores of the SF-36, for rituximab compared to placebo in patients with IgM PDPN from 1 RCT (Lunn and Nobile-Orazio 2016): • There was a statistically significant improvement in SF-36 physical subscores (mean [SD] rituximab 11.6 [19.6] vs. placebo -3.9 [9.8], MD 15.50, 95%CI 5.24 to 25.76, 37 participants) for rituximab compared to placebo at 12 months. No p value was reported. **HIGH** • There was no statistically significant difference in SF-36 mental health subscores between rituximab and placebo at 12 months (mean [SD] rituximab 4.5 [9.9] vs. placebo -2.1 [12.8], MD 6.60, 95%CI 0.35 to 13.55, 41 participants). No p value was reported. **MODERATE** **This study provides high certainly evidence that, in patients with IgM PDPN, rituximab significantly improved quality of life on the physical subscale compared with placebo at 12 months. There was no significant difference in the mental health subscale (moderate certainly).**
Motor impairment **Certainty of evidence:** Low to Moderate	Motor impairment occurs late in PDPN probably representing failure to treat early or effectively enough. It contributes greatly to imbalance but is less likely to show a therapeutic effect. It is an important indicator of permanent impairment. The two RCTs included in the systematic review (Lunn and Nobile-Orazio 2016) reported motor impairment, as measured by MRC score. As this outcome was not reported in the systematic review the data were taken from the individual RCT papers: • One RCT (Léger et al 2013) provided evidence for the mean change in MRC score at 12 months. The study reported no significant difference in the median change in MRC score at 12 months between rituximab 0.0 (95%CI -3 to 0.0) and placebo 0.0 (95%CI -1.5 to 1.5) p=0.17. **MODERATE** • The second RCT (Dalakas et al 2009) also reported no significant changes in the MRC score, but no measure of statistical significance was recorded. **LOW**

Outcome	Evidence statement
	This study provides moderate certainty evidence that in patients with IgM PDPN, at 12 months, rituximab does not significantly improve MRC scores compared to placebo.
Safety	
Adverse events **Certainty of evidence:** Low to Moderate	Adverse events are relevant to patients because they may reduce quality of life and require additional treatments. Serious adverse events may negate the expected health improvement associated with treatment. 1 systematic review with meta-analysis of two RCTs reported adverse events for rituximab compared to placebo in patients with IgM PDPN (Lunn and Nobile-Orazio 2016): • At 12 months, there was no statistically significant difference in the occurrence of any adverse event between rituximab (26/39) and placebo (23/41) (RR 1.18, 95%CI 0.84 to1.66, I^2 =0%, p=0.34, 80 participants). **MODERATE** • At 12 months, there was no statistically significant difference in the occurrence of severe adverse events between rituximab (2/39) and placebo (0/41) (RR 3.11, 95%CI 0.34 to 28.54, I^2 =0%, p=0.32, 80 participants). **LOW** **This study provided low to moderate certainty evidence that in patients with IgM PDPN, rituximab does not significantly worsen adverse effects compared with placebo.**
Abbreviations: Anti-MAG - anti-myelin-associated glycoprotein; CI - confidence interval; I^2 - Study heterogeneity (a statistic that indicates the percentage of variance in a meta-analysis that is attributable to study heterogeneity); IgM - immunoglobulin M; INCAT – inflammatory Neuropathy Cause and Treatment; IQR – inter-quartile range; ISS – INCAT sensory score; LPL - lymphoplasmacytic lymphoma; MA - meta-analysis; MAG - myelin-associated glycoprotein; MD - mean difference; MGUS - monoclonal gammopathy of undetermined significance; MRC – Medical Research Council; NIS - Neuropathy Impairment Score; PDPN - paraproteinaemic demyelinating peripheral neuropathy; RCT - randomised controlled trial; RR - risk ratio; SD – standard deviation, SF-36 - Short Form 36 Health Survey; WM - Waldenstrom's macroglobulinemia	

From the evidence selected, are there any subgroups of patients with IgM paraproteinaemic demyelinating peripheral neuropathy who would benefit more from treatment with rituximab?

Outcome	Evidence statement
Subgroups	No evidence was identified regarding any subgroups of patients that would benefit more from treatment with rituximab.

In patients with IgM paraproteinaemic demyelinating peripheral neuropathy with MGUS, LPL, WM or low-grade Non-Hodgkin lymphoma, what is the cost effectiveness of rituximab versus conservative management, medical interventions or placebo?

Outcome	Evidence statement
Cost Effectiveness	No evidence was identified for cost effectiveness.

6. Discussion

This rapid evidence review considered the evidence for the clinical effectiveness and safety of rituximab compared with conservative management, medical interventions or placebo in patients with IgM PDPN, with MGUS, LPL, WM or low-grade Non-Hodgkin lymphoma. The critical outcomes of interest were disability, global impression of change, and haematological response. Other important outcomes included sensory impairment, 10 metre walk test and quality of life, motor impairment and adverse events.

Evidence was available from one systematic review and meta-analysis of RCTs (Lunn and Nobile-Orazio 2016). The systematic review included eight trials (236 participants), of which two RCTs of rituximab versus placebo (80 participants) were eligible for inclusion in this rapid evidence review (Léger et al 2013, Dalakas et al 2009). Dalakas et al 2009 included 26 participants (13 rituximab vs. 13 placebo). Léger et al 2013 included 54 participants (26 rituximab vs. 28 placebo).

Lunn and Nobile-Orazio 2016 was a well carried out systematic review and meta-analysis. The search strategy was comprehensive as the authors made exhaustive attempts to source all relevant studies. No additional statistical tests (such as Egger's test or funnel plots) were used to assess the potential presence of publication bias. However, as only two of the studies included in the systematic review were relevant to this rapid evidence review, this would not have biased the results of the outcomes. The first of the two rituximab vs. placebo RCTs (Dalakas et al 2009) was deemed to have a high risk of bias in two assessed domains (attrition and reporting bias) and unclear risks in two of the six domains assessed (selection bias affecting randomisation and allocation). One of the participants was removed from the analysis who perhaps should not have been randomised. As such, this trial was assessed as very low quality across the outcomes stipulated. The second RCT (Léger et al 2013) was considered less biased and the outcome changes were comparable, in the similar direction and of comparable magnitude to those of Dalakas et al 2009 ($I^2 = 0$ throughout). Where evidence from the systematic review supporting an advantage for rituximab was downgraded, this was generally because of imprecision, probably due to the small size of the studies, or because results were only available from the Dalakas RCT. Evidence favouring rituximab for the critical outcome of global impression of change was downgraded because this involved some degree of indirectness (patient impression of change reported whereas the PICO stated patient and clinician assessment for the definition of global impression of change). The results reported based on this systematic review should therefore be treated with caution.

7. Conclusion

The key limitation to identifying the effectiveness of rituximab compared to placebo is the small number of patients in the studies available to the systematic review. Although it should be noted that IgM PDPN is a relatively rare condition and therefore conducting large, prospective studies may be difficult. One further limitation is that rituximab was only

compared to placebo rather than medical interventions such as IVIG.

Moderate and high certainty evidence from the systematic review by Lunn and Nobile-Orazio 2016 showed that rituximab infusions (375 mg/m^2 rituximab weekly for 4 weeks) produced a statistically significant improvement in disability scores. Compared with placebo, a significantly higher number of rituximab participants improved on INCAT score at 8-12 months. There was also a significantly greater mean improvement in INCAT scores at 8-12 months, but not at 8-9 months. Moderate certainty evidence showed that, at 8-12 months, compared to placebo, rituximab produced a statistically significant improvement in participants' assessment of their condition as "stable or improved" and "improved". There is also moderate certainty evidence that rituximab treatment provides a statistically significantly improved haematological response at 8 months, as demonstrated by a decrease in serum IgM level and in IgM anti-MAG activity titre. Low certainty evidence showed that rituximab did not any impact on sensory impairment as measured by changes in NIS score at 12 months. The time to walk 10 metres and the numbers of participants with improved 10 metre walk time also did not improve significantly (moderate and low certainty respectively). The systematic review also provides high certainly evidence that rituximab statistically significantly improves quality of life as measured by physical SF-36 subscores. However, the effect on SF-36 mental subscores was not significant (moderate certainty). Although the systematic review by Lunn and Nobile-Orazio 2016 showed that there were statistically significant improvements in critical outcomes, the clinical benefit and meaningfulness of these levels of improvements is not clear.

The systematic review by Lunn and Nobile-Orazio 2016 provided low to moderate certainty evidence that there was no statistically significant difference between rituximab and placebo in terms of adverse events and severe adverse events.

No evidence on the cost effectiveness of rituximab compared to current standard treatments was identified. No evidence was identified for any subgroups of patients who might benefit more from treatment with rituximab.

Appendix A PICO Document

The review questions for this evidence review are:

1. In patients with IgM paraproteinaemic demyelinating peripheral neuropathy, with MGUS, LPL, WM or low-grade Non-Hodgkin lymphoma, what is the clinical effectiveness of rituximab versus conservative management, medical interventions or placebo?
2. In patients with IgM paraproteinaemic demyelinating peripheral neuropathy with MGUS, LPL, WM or low-grade Non-Hodgkin lymphoma, what is the safety of rituximab versus conservative management, medical interventions or placebo?
3. In patients with IgM paraproteinaemic demyelinating peripheral neuropathy with MGUS, LPL, WM or low-grade Non-Hodgkin lymphoma, what is the cost effectiveness of rituximab versus conservative management, medical interventions or placebo?
4. From the evidence selected, are there any subgroups of patients with IgM paraproteinemic demyelinating peripheral neuropathy who would benefit more from treatment with rituximab?

PICO Table

P –Population and Indication	Patients of all ages with IgM paraproteinaemic demyelinating peripheral neuropathy with an underlying diagnosis of MGUS, WM, LPL or lymphoma with or without anti-MAG (myelin association glycoprotein)
I – Intervention	Intravenous rituximab with or without conservative management (such as analgesia, physiotherapy, occupational therapy). Rituximab can be given in any dose consistent with use in haematological or rheumatological practice such as 375-750mg/m2 between 2 and 4 times over a month (usual total dose 2000mg total) or low dose usage (e.g. 100mg monthly or 375mg/m2 quarterly).
C – Comparator(s)	1. No treatment/placebo or conservative management alone 2. IVIG with or without conservative management
O – Outcomes	Response to treatment for all measures of clinical effectiveness would be expected at 6-12 months of treatment months unless otherwise stated. *Critical to decision-making:*

	Disability (INCAT (or modified INCAT) score but other scores including modified Rankin score, ONLS score, ODSS, GNDS)[7] or I-RODS score can be considered. MCIDs as below[8] *Disability is a critical outcome as the symptoms and signs of peripheral neuropathy result in patient disability which impacts of mobility, ADLs, independence and wellbeing.* Global impression of change (PGIC/CGIC) *The major disability of ataxic unsteadiness and tremor are poorly 'measured' in score. This is a critical outcome/ treatment effect as a holistic measure of treatment, subjectively assessed by the patient and clinician, that will not be captured by individual measures* Haematological response: as measured by CD-19 count (IgM level and anti-MAG titre may also be reported in studies) *These are direct, quantifiable measures of anti-CD20 treatment response and occur prior to clinically detectable change. Sustained reduction in pathological antibodies results in improved outcomes* <u>*Important to decision-making:*</u> Sensory impairment[9] • Sensory score: INCAT sensory sum score, NIS *This is an important outcome for patients as improvement to sensory impairment can improve independence and function.* 10 metre walk test • *This is an important outcome which crosses between impairment and disability. Imbalance, sensory dysfunction and weakness all contribute to altered walking times which improve after treatment.* Quality of life e.g. SF-36 physical functioning subscale. Other measures can be used as described in studies. *Quality of life is an important outcome in these patients as neuropathy impacts on patient's function and activities of daily living. Improvement in quality of life, especially physical functioning, is a marker of successful treatment.* Motor impairment • Motor score: MRC sum score, Neuropathy Impairment Score (NIS) *Motor impairment occurs late in PDPN probably representing failure to treat early or effectively enough. It contributes greatly to imbalance but is less likely to show a therapeutic effect. It is an important indicator of permanent impairment.* Safety • Adverse events (including but not restricted to: infections, allergy to infusion) Cost effectiveness

[7] Disability is the most useful outcome to measure. Multiple scoring systems for disability have been used in the literature including mRS (modified Rankin scale), i-RODS (inflammatory-Rasch-built overall disability scale), INCAT (Inflammatory Neuropathy Cause and Treatment) disability score, ONLS (Overall Neuropathy Limitations Scale), ODSS (Overall Disability Sum Score) and GNDS (Guy's Neurological Disability Score).

[8] MCID for INCAT, ONLS, ODSS, GNDS, mRS all 1 point. I-RODS – 4 points on 100-point logit scale

[9] Multiple scoring systems have been used to monitor changes in impairment including the MRC (Medical Research Council) sum score, NIS (Neuropathy Impairment Score) and INCAT sensory sum score.

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	2005-2020
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials and guidelines
Study design	Case reports and resource utilisation studies

Appendix B Search strategy

Medline, Embase and Cochrane Library were searched limiting the search to papers published in English Language in the last 10 years. Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials and guidelines, case reports and resource utilisation studies were excluded.

Search dates: 1st January 2005 to 4th August 2020

Embase search

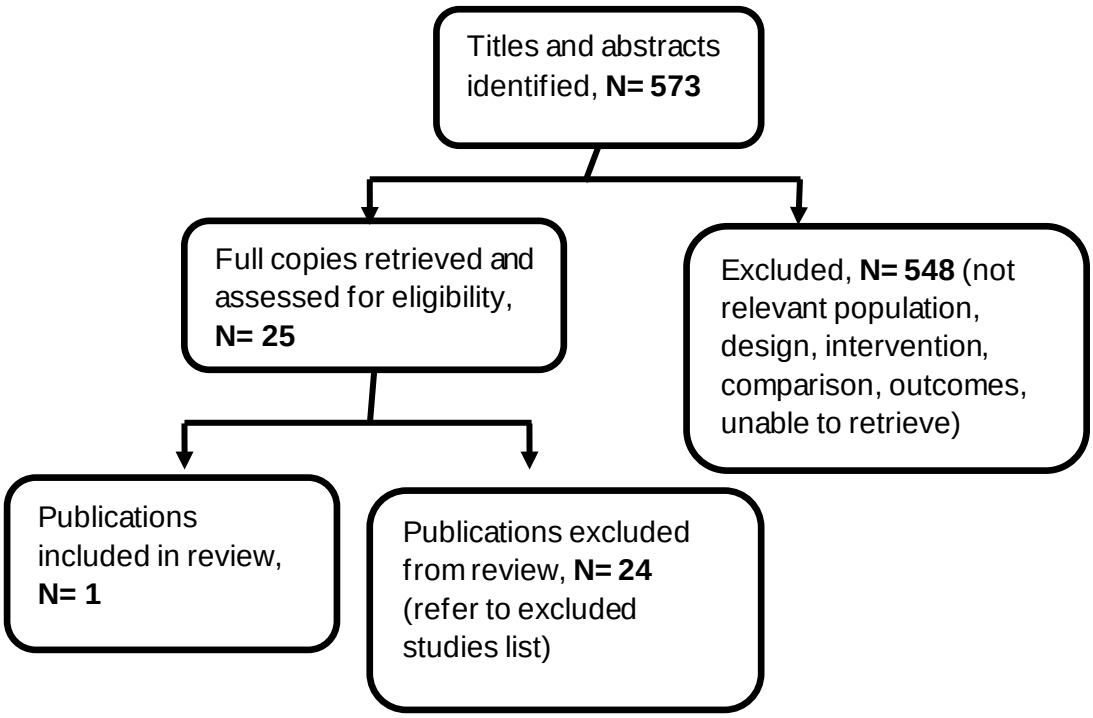
1	peripheral neuropathy/
2	(neuropath* or polyneuropath* or peripheral nerv*).ti,ab,kw.
3	1 or 2
4	Demyelinating Disease/
5	Myelin-Associated Glycoprotein/
6	Paraprotein/ or Paraproteinemia/ or immunoglobulin M/
7	(myelin* or demyelin* or paraprotein* or mag or igm or mgus or gammopath*).ti,ab,kw.
8	4 or 5 or 6 or 7
9	3 and 8
10	Rituximab/
11	(rituximab or mabthera).ti,ab,kw.
12	10 or 11
13	9 and 12
14	(letter or note or editorial or "review" or conference*).pt. or case report.ti,ab.

15	13 not 14
16	limit 13 to "reviews (maximizes specificity)"
17	15 or 16
18	limit 17 to (english language and yr="2005 -Current")

1	peripheral neuropathy/
2	(neuropath* or polyneuropath* or peripheral nerv*).ti,ab,kw.
3	1 or 2
4	Demyelinating Disease/
5	Myelin-Associated Glycoprotein/
6	Paraprotein/ or Paraproteinemia/ or immunoglobulin M/
7	(myelin* or demyelin* or paraprotein* or mag or igm or mgus or gammopath*).ti,ab,kw.
8	4 or 5 or 6 or 7
9	3 and 8
10	immunotherapy/
11	(immunotherap* or therap* or treatment).ti.
12	10 or 11
13	9 and 12
14	limit 13 to "reviews (maximizes specificity)"
15	limit 14 to (english language and yr="2005 -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
Lunn MPT, Nobile-Orazio E. Immunotherapy for IgM anti-myelin-associated glycoprotein paraprotein-associated peripheral neuropathies. Cochrane Database of Systematic Reviews 2016, Issue 10. Art. No.: CD002827. DOI: 10.1002/14651858.CD002827.pub4.	Included
Maurer MA et al. Rituximab induces sustained reduction of pathogenic B cells in patients with peripheral nervous system autoimmunity. Journal of Clinical Investigation. 2012;122(4):1393–1402. DOI: 10.1172/JCI58743.	**Excluded** This was an in vitro Ig gene analysis on samples obtained during a placebo-controlled clinical trial of rituximab in patients with anti-MAG neuropathy. Outcomes of interest from this RCT are already reported within an included systematic review
D'Sa S et al. Investigation and management of IgM and Waldenstrom-associated peripheral neuropathies: recommendations from the IWWM-8 consensus panel. British Journal of Haematology. 2017; 176:728-742.	**Excluded** This is not a study of the clinical effectiveness of rituximab in PDPN. It is a consensus report of the use of clinical outcome measures and recommended models of care for this group of patients

Appendix D Excluded studies table

Study reference	Reason for exclusion
Tang MH, Mathis S, Duffau P, Cazenave P, Sole G, Duval F, et al. Prognostic factor of poor outcome in anti-MAG neuropathy: clinical and electrophysiological analysis of a French Cohort. Journal of Neurology. 2020;267(2):561-71.	Case series and does not report any outcomes which are not already reported in the systematic review of RCTs
Colchester NTH, Allen D, Katifi HA, Burt T, Lown RN, Pinto AA, et al. Chemoimmunotherapy with rituximab, cyclophosphamide and prednisolone in IgM paraproteinaemic neuropathy: evidence of sustained improvement in electrophysiological, serological and functional outcomes. Haematologica. 2020;30:30.	Not the intervention specified in the PICO. (i.e. rituximab with active chemoimmunotherapy (cyclophosphamide plus prednisolone), not conservative treatment)
Campagnolo M, Ruiz M, Falzone YM, Ermani M, Bianco M, Martinelli D, et al. Limitations in daily activities and general perception of quality of life: Long term follow-up in patients with anti-myelin-glycoprotein antibody polyneuropathy. Journal of the Peripheral Nervous System. 2019;24(3):276-82.	Uncontrolled study and does not report any outcomes which are not already reported in the systematic review of RCTs
Benedetti L, Garnero M, Demichelis C, Grandis M, Briani C, Beltramini S, et al. Outcomes after single-cycle rituximab monotherapy in patients with anti-MAG polyneuropathy: A bi-center experience with an average follow-up of 11years. Journal of Neuroimmunology. 2019;337:577081.	Case series and does not report any outcomes which are not already reported in the systematic review of RCTs. Descriptive statement on CD-19 count made but no results data reported
Svahn J, Petiot P, Antoine JC, Vial C, Delmont E, Viala K, et al. Anti-MAG antibodies in 202 patients: clinicopathological and therapeutic features. Journal of Neurology, Neurosurgery & Psychiatry. 2018;89(5):499-505.	Not the population specified in the PICO (i.e. patients recruited based on anti-MAG antibodies level, not based on diagnosis of PDPN)
MacIsaac J, Siddiqui R, Jamula E, Li N, Baker S, Webert KE, et al. Systematic review of rituximab for autoimmune diseases: a potential alternative to intravenous immune globulin. Transfusion. 2018;58(11):2729-35.	Not the population specified in the PICO (i.e. patients with autoimmune diseases included Chronic Idiopathic Peripheral Neuropathy (CIDP), but it was not clear whether other causes of PN were excluded). Also, Criteria for Outcome - 'response' was not defined
Gazzola S, Delmont E, Franques J, Boucraut J, Salort-Campana E, Verschueren A, et al. Predictive factors of efficacy of rituximab in patients with anti-MAG neuropathy. Journal of the Neurological Sciences. 2017;377:144-8.	Case series and does not report any outcomes which are not already reported in the systematic review of RCTs

Galassi G, Tondelli M, Ariatti A, Benuzzi F, Nichelli P, Valzania F. Long-term disability and prognostic factors in polyneuropathy associated with anti-myelin-associated glycoprotein (MAG) antibodies. International Journal of Neuroscience. 2017;127(5):439-47.	Population of patients with different underlying causes and intervention included some patients who had rituximab in combination with other immunosuppressant agents. Results with rituximab not reported separately
Fatehi F, Delmont E, Grapperon AM, Salort-Campana E, Sevy A, Verschueren A, et al. Motor unit number index (MUNIX) in patients with anti-MAG neuropathy. Clinical Neurophysiology. 2017;128(7):1264-9.	This is not a study of the clinical effectiveness of rituximab in PDPN. It is an evaluation of Motor Unit Number Index (MUNIX) as a functional scale in patients with anti-MAG PDPN for evaluating the effects of rituximab therapy
D'Sa S, Kersten MJ, Castillo JJ, Dimopoulos M, Kastritis E, Laane E, et al. Investigation and management of IgM and Waldenstrom-associated peripheral neuropathies: recommendations from the IWWM-8 consensus panel. British Journal of Haematology. 2017;176(5):728-42.	This is not a study of the clinical effectiveness of rituximab in PDPN. It is a consensus report of the use of clinical outcome measures and recommended models of care for this group of patients
Iancu Ferfoglia R, Guimaraes-Costa R, Viala K, Musset L, Neil J, Marin B, Léger J. Long-term efficacy of rituximab in IgM anti-myelin-associated glycoprotein neuropathy: RIMAG follow-up study. Journal of the Peripheral Nervous System. 2016; 21(1):10-4.	Long-term follow up of some RCT participants. Does not report any outcomes which are not already reported in the systematic review of RCTs
Talamo G, Mir MA, Pandey MK, Sivik JK, Raheja D. IgM MGUS associated with anti-MAG neuropathy: a single institution experience. Annals of Hematology. 2015;94(6):1011-6.	Case series and does not report any outcomes which are not already reported in the systematic review of RCTs
Kawagashira Y, Koike H, Ohyama K, Hashimoto R, Iijima M, Adachi H, et al. Axonal loss influences the response to rituximab treatment in neuropathy associated with IgM monoclonal gammopathy with anti-myelin-associated glycoprotein antibody. Journal of the Neurological Sciences. 2015;348(1-2):67-73.	Uncontrolled study and does not report any outcomes which are not already reported in the systematic review of RCTs
Campagnolo M, Ferrari S, Dalla Torre C, Cabrini I, Cacciavillani M, Lucchetta M, et al. Polyneuropathy with anti-sulfatide and anti-MAG antibodies: clinical, neurophysiological, pathological features and response to treatment. Journal of Neuroimmunology. 2015;281:1-4.	Uncontrolled study and does not report any outcomes which are not already reported in the systematic review of RCTs
Léger JM, Viala K, Nicolas G, Creange A, Vallat JM, Pouget J, Clavelou P, Vial C, Steck A, Musset L, Marin B, Group RS. Placebo-controlled trial of rituximab in	RCT included in the systematic review by Lunn et al. Not included separately but data

IgM anti-myelin-associated glycoprotein neuropathy. Neurology 2013; 80**:** 2217-25.	reported as part of the systematic review
Maurer MA, Rakocevic G, Leung CS, Quast I, Luka?išin M, Goebels N, et al. Rituximab induces sustained reduction of pathogenic B cells in patients with peripheral nervous system autoimmunity. J Clin Invest. 2012;122(4):1393-402.	This was an in vitro Ig gene analysis on samples obtained during a placebo-controlled clinical trial of rituximab in patients with anti-MAG neuropathy. Outcomes of interest are already reported within the included systematic review
Léger JM, Viala K, Nicolas G, Creange A, Vallat JM, Pouget J. A randomized placebo-controlled trial of rituximab in IGM anti-myelin-associated glycoprotein antibody demyelinating neuropathy (RIMAG Study). Journal of the peripheral nervous system : JPNS. 2011;16(Suppl 3):S73?4.	This is an early release of an RCT that was later published in full in 2013 and included in the systematic review
Niermeijer JM, Eurelings M, Lokhorst HL, van der Pol WL, Franssen H, Wokke JH, et al. Rituximab for polyneuropathy with IgM monoclonal gammopathy. Journal of Neurology, Neurosurgery & Psychiatry. 2009;80(9):1036-9.	Uncontrolled study and does not report any outcomes which are not already reported in the systematic review of RCTs. Descriptive statement on CD-19 made but no results data were reported
Dalakas MG, Rakocevic G, Salajegheh M, Dambrosia JM, Hahn AF, Raju R. A placebo-controlled trial of rituximab in IgM anti-MAG antibody demyelinating neuropathy. Journal of the peripheral nervous system : JPNS. 2009;14(Suppl 2):38?9.	This is an early release of an RCT that was later published in full and included in the systematic review
Dalakas MC, Rakocevic G, Salajegheh M, Dambrosia JM, Hahn AF, Raju R, Mcelroy B. Placebo-controlled trial of rituximab in IgM anti-myelin-associated glycoprotein antibody demyelinating neuropathy. Ann Neurol. 2009; 65**:** 286-93.	RCT included in systematic review by Lunn et al. Not included separately but data reported as part of the systematic review
Benedetti L, Briani C, Franciotta D, Carpo M, Padua L, Zara G, et al. Long-term effect of rituximab in anti-mag polyneuropathy. Neurology. 2008;71(21):1742-4.	Uncontrolled study (10 patients) and does not report any outcomes which are not already reported in the systematic review of RCTs
Benedetti L, Briani C, Grandis M, Vigo T, Gobbi M, Ghiglione E, et al. Predictors of response to rituximab in patients with neuropathy and anti-myelin associated glycoprotein immunoglobulin M. Journal of the Peripheral Nervous System. 2007;12(2):102-7.	Uncontrolled study and does not report any outcomes which are not already reported in the systematic review of RCTs. Descriptive statement on CD-19 count made but no results data were reported
Renaud S, Fuhr P, Gregor M, Schweikert K, Lorenz D, Daniels C, et al. High-dose rituximab and anti-MAG-	Uncontrolled study and does not report any outcomes which are

associated polyneuropathy. Neurology. 2006;66(5):742-4.	not already reported in the systematic review of RCTs
Kilidireas C, Anagnostopoulos A, Karandreas N, Mouselimi L, Dimopoulos MA. Rituximab therapy in monoclonal IgM-related neuropathies. Leukemia & Lymphoma. 2006;47(5):859-64.	Uncontrolled study (4 patients) and does not report any outcomes of interest

Appendix E Evidence Table

Study details	Population	Interventions	Study outcomes	Appraisal and Funding

Dalakas MC, Rakocevic G, Salajegheh M, Dambrosia JM, Hahn AF, Raju R, Mcelroy B. Placebo-controlled trial of rituximab in IgM anti-myelin-associated glycoprotein antibody demyelinating neuropathy. Ann Neurol. 2009; 65: 286-93.
 	
Study location
USA
 	
Study type
RCT
 	
Study aim
To report the results of a double-blind, placebo-controlled study of rituximab in patients with anti–MAG demyelinating polyneuropathy
 	
Study dates
Not reported
	See Lunn and Nobile-Orazio 2016 for details	See Lunn and Nobile-Orazio 2016 for details	The results for one important outcome were extracted from the RCT paper as the details were not reported in the systematic review
			
			Important outcomes
			
			Motor impairment
			The RCTs authors reported that "no significant changes were noted in the MRC scores in the rituximab group". However, no measure of statistical significance was recorded
			
			Mean ± SD MRC scores were
			• Baseline, 26 participants
			  • Placebo: 131.6 ± 11.2
			  • Rituximab: 134.6 ± 11.9
			• 8 months follow up, 26 participants
			  • Placebo: 133.8 ± 11.5
			  • Rituximab: 137.6 ± 12.9
				See Lunn and Nobile-Orazio 2016 for details of the limitations identified for the Dalakas et al 2009 RCT

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Léger JM, Viala K, Nicolas G, Creange A, Vallat JM, Pouget J, Clavelou P, Vial C, Steck A, Musset L, Marin B, Group RS. Placebo-controlled trial of rituximab in IgM anti-myelin-associated glycoprotein neuropathy. Neurology 2013; 80: 2217-25. **Study location** France, Switzerland **Study type** RCT **Study aim** To determine whether rituximab 375 mg/m^2 was efficacious in patients with IgM anti-MAG antibody demyelinating neuropathy **Study dates** Patients recruited between March 2006 and November 2008	See Lunn and Nobile-Orazio 2016 for details	See Lunn and Nobile-Orazio 2016 for details	The results for one important outcome were extracted from the RCT paper as the details were not reported in the systematic review **Important outcomes** ***Motor impairment*** There was no significant difference in the median change in MRC score at 12 months between rituximab 0.0 (95%CI -3 to 0.0) and placebo 0.0 (95%CI -1.5 to 1.5), p=0.17	See Lunn and Nobile-Orazio 2016 for details of the limitations identified for the Léger et al 2013 RCT
Lunn MP, Nobile-Orazio E. Immunotherapy for IgM anti-myelin-	**Study inclusion criteria** Type of studies: RCTs	**Intervention details** Rituximab infusions of 375 mg/m^2 rituximab weekly for 4 weeks	**Critical outcomes** ***Disability*** A significantly higher number of	This study was appraised using the Joanna Briggs Institute 2017 Critical Appraisal Checklist for systematic review.

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
associated glycoprotein paraprotein-associated peripheral neuropathies. Cochrane Database of Systematic Reviews. 2016;10:CD002827 **Study location** **RCTs of interest:** • France; Switzerland • USA **Study type** Systematic review with meta-analysis **Study aim** To assess the effects of immunotherapy for IgM anti-MAG paraprotein-associated demyelinating peripheral neuropathy **Search dates** January 1966 to January 2016	and quasi-RCTs using any immunotherapy in anti-MAG PDPN. Neuropathy of typical distal symmetrical sensory or sensorimotor and fitting published criteria for slowing of motor nerve conduction in CIDPN The two rituximab RCTs included in this review were double-blind controlled studies Type of participants: any age and diagnosis of MGUS, demyelinating neuropathy and anti-MAG antibodies **Study exclusion criteria** Other possible causes of peripheral neuropathy **Total sample size** Eight trials (236 participants) included in the systematic review. Two trials of rituximab (80 participants) eligible for this review (Dalakas et al 2009, Léger et al 2013)	**Comparator details** Identical infusions of placebo Information relating to concomitant treatments was not reported	rituximab participants improved on INCAT score at 8-12 months; rituximab (12/33) compared to placebo (4/40). RR 3.51, 95%CI 1.30 to 9.45, I^2 = 0%, 73 participants. There was a significantly greater mean improvement in INCAT scores at 8-12 months. MD -0.45, 95%CI -0.85 to -0.05, I^2 =0%, p=0.029, 73 participants. Mean improvement in INCAT score at 8-9 months was not significant. MD -0.33, 95%CI -0.73 to 0.07, I^2 = 0%, p=0.11, 70 participants ***Global impression of change*** The RR for participant subjective impression of change as "stable or improved" at 8-12 months was 1.86 (95%CI 1.27 to 2.71, I^2 =0%, 70 participants) in favour of rituximab For participants subjective impression of change as "improved" only at 8-12 months, the RR was 9.67 (95%CI 1.84 to 50.85, I^2 = 0%, 70 participants) ***Haematological response*** There was a significant decrease in the level of serum IgM at 8 months after rituximab treatment. MD -286mg/dL, 95%CI -329 to -244, 26 participants There was a significant decrease in the titre of IgM anti-MAG activity at 8-12 months MD -17.79 units/mL (95%CI -	1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Yes 7. Yes 8. Yes 9. No 10. Yes 11. Yes **Other comments** This was a well carried out systematic review and meta-analysis. The search strategy was comprehensive as the authors made exhaustive attempts to source all relevant studies. No additional statistical tests (such as Egger's test or funnel plots) were used to assess the potential presence of publication bias. However, as only two of the studies included in the systematic review were relevant to this rapid evidence review, this would not have biased the results of the outcomes. This report was an update of a previous systematic review and included two RCTs of rituximab versus placebo. The first RCT from the previous 2012 update (Dalakas et al 2009) was deemed to have a high risk of bias in two assessed domains (attrition and reporting bias) and unclear risks in two (selection bias affecting randomisation and allocation) of the six domains assessed. One of the participants was removed from the analysis who should perhaps not have been randomised. As such, this trial was assessed as very low quality across the outcomes stipulated. The second

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
	Dalakas et al 2009 included 26 participants (13 rituximab vs. 13 placebo). Léger et al 2013 included 54 participants (26 rituximab vs. 28 placebo) **Baseline characteristics** Baseline characteristics were not significantly different between study groups in Léger 2013. In Dalakas 2009, the groups were very unbalanced with very few men in the rituximab-treated group at randomisation, but the implication of this on the results is not clear. No other differences in baseline characteristics were reported.		33.33 to -2.25, I^2 = 0%, 71 participants) **Important outcomes** ***Sensory impairment*** The mean difference in NIS score at 12 months was not significant. Mean (SD) rituximab 1.1 (6) compared to placebo 1.8 [5.1] (MD -0.70, 95%CI -4.03 to 2.63, 45 participants no p value was reported. ***10 metre walk test*** The time to walk 10m did not improve significantly. MD -0.35 seconds, 95%CI -1.89 to 1.19, I^2 = 0%, 68 participants The number of participants with improved 10m walk time was not significant (RR 1.80, 95%CI 0.83 to 3.92, 26 participants) ***Quality of life*** There was a significant improvement in physical subscores for the Short Form 36 Health Survey (SF-36). MD 15.50, 95%CI 5.24 to 25.76, 37 participants The change in SF-36 mental subscores was not significant. MD 6.60, 95%CI 0.35 to 13.55, 41 participants **Safety** There were not significantly more adverse events of any severity in the rituximab group. RR 1.18, 95%CI 0.84 to 1.66, I^2 =0%, 80 participants	RCT (Léger et al 2013) was considered less biased and the outcome changes were comparable, in the similar direction and of comparable magnitude to those of Dalakas et al 2019 (I^2 = 0 throughout). However, the results should be treated with caution because, even though the results demonstrated no heterogeneity the numbers of participants in individual studies was too small to draw confident conclusions about the efficacy of rituximab in stabilising or improving IgM anti-MAG PDPN. **Source of funding:** This project was supported by the National Institute for Health Research (NIHR) via Cochrane Infrastructure funding to Cochrane Neuromuscular. Cochrane Neuromuscular is also supported by the MRC Centre for Neuromuscular Diseases.

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			Severe adverse events were also not significantly different. RR 3.11, 95%CI 0.34 to 28.54, I^2 =0%, 80 participants	

Anti-MAG - anti-myelin-associated glycoprotein; CI - confidence interval; CIDP – chronic inflammatory demyelinating polyneuropathy; I^2 - Study heterogeneity (a statistic that indicates the percentage of variance in a meta-analysis that is attributable to study heterogeneity); IgM - immunoglobulin M; INCAT – inflammatory Neuropathy Cause and Treatment; IQR – inter-quartile range; ISS – INCAT sensory score; JBI - The Joanna Briggs Institute Critical Appraisal tools for use in Systematic Reviews; MA - meta-analysis; MAG - myelin-associated glycoprotein; MD - mean difference; MGUS - monoclonal gammopathy of undetermined significance; MRC – Medical Research Council; NIS - Neuropathy Impairment Score; PDPN - paraproteinaemic demyelinating peripheral neuropathy; RCT - randomised controlled trial; RR - risk ratio; SD – standard deviation; SF-36 - Short Form 36 Health Survey

Appendix F Quality appraisal checklists

JBI Critical Appraisal Checklist for Systematic Reviews

1. Is the review question clearly and explicitly stated?
2. Were the inclusion criteria appropriate for the review question?
3. Was the search strategy appropriate?
4. Were the sources and resources used to search for studies adequate?
5. Were the criteria for appraising studies appropriate?
6. Was critical appraisal conducted by two or more reviewers independently?
7. Were there methods to minimize errors in data extraction?
8. Were the methods used to combine studies appropriate?
9. Was the likelihood of publication bias assessed?
10. Were recommendations for policy and/or practice supported by the reported data?
11. Were the specific directives for new research appropriate?

Appendix G GRADE Profiles

Table 1: In patients with IgM paraproteinaemic demyelinating peripheral neuropathy, with MGUS, LPL, WM or low-grade Non-Hodgkin lymphoma, what is the clinical effectiveness and safety of rituximab versus conservative management, medical interventions or placebo?

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study type and number of studies Author year	Risk of bias	Indirectness	Inconsistency	Imprecision	Rituximab	Placebo	Result		
Disability									
Number of participants improved on INCAT score at 8 - 12 months									
1 MA of 2 RCTs Lunn and Nobile-Orazio 2016	No serious limitations	No serious indirectness	No serious inconsistency	No serious imprecision	12/33 (36.4%)	4/40 (10.0%)	RR 3.51 (95%CI 1.30 to 9.45, I^2 = 0%) p=0.013	Critical	High
Mean improvement in INCAT score at 8 -12 months (benefit is indicated by lower result)									
1 MA of 2 RCTs Lunn and Nobile-Orazio 2016	No serious limitations	No serious indirectness	No serious inconsistency	No serious imprecision	33	40	MD -0.45 (95%CI -0.85 to -0.05, I^2 =0%) p=0.029	Critical	High
Mean improvement in INCAT score at 8 - 9 months (benefit is indicated by lower result)									
1 MA of 2 RCTs Lunn and Nobile-Orazio 2016	No serious limitations	No serious indirectness	No serious inconsistency	Serious imprecision[1]	31	39	MD -0.33 (95%CI -0.73 to 0.07, I^2 = 0%) p=0.11	Critical	Moderate

Global impression of change									
Participant subjective impression of change "stable or improved" at 8 -12 months									
1 MA of 2 RCTs Lunn and Nobile-Orazio 2016	No serious limitations	Serious indirectness[2]	No serious inconsistency	No serious imprecision	27/32 (84.4%)	17/38 (44.5%)	RR 1.86 (95%CI 1.27 to 2.71, I^2 =0%) p=0.0014	Critical	Moderate
Participant subjective impression of change "improved" at 8 -12 months									
1 MA of 2 RCTs Lunn and Nobile-Orazio 2016	No serious limitations	Serious indirectness[2]	No serious inconsistency	No serious imprecision	12/32 (37.5%)	1/38 (2.6%)	RR 9.67 (95%CI 1.84 to 50.85, I^2 = 0%) p=0.0074	Critical	Moderate
Haematological response									
Change in IgM level 8 months after treatment (benefit is indicated by lower result)									
1 RCT in Lunn and Nobile-Orazio 2016	Very serious limitations[3]	No serious indirectness	Not applicable	No serious imprecision	13	13	MD -286mg/dL (95%CI -329 to -244), p value not reported	Critical	Moderate
Change in IgM anti-MAG titre at 8 - 12 months (benefit is indicated by lower result)									
1 MA of 2 RCTs Lunn and Nobile-Orazio 2016	No serious limitations	No serious indirectness	No serious inconsistency	Serious imprecision[1]	32	39	MD -17.79 units/mL (95%CI -33.33 to -2.25, I^2 = 0%) p=0.025, 71 participants	Critical	Moderate

Sensory impairment									
Mean improvement in NIS at 12 months (benefit is indicated by higher result)									
1 RCT in Lunn and Nobile-Orazio 2016	No serious limitations	No serious indirectness	Not applicable	Very serious imprecision[4]	19	26	Mean [SD] rituximab 1.1 [6] vs. placebo 1.8 [5.1] MD -0.70 (95%CI -4.03 to 2.63) 45 participants; no p value reported	Important	Low
10 metre walk test									
Mean improvement in 10m walk time at 8 -12 months (benefit is indicated by lower result)									
1 MA of 2 RCTs Lunn and Nobile-Orazio 2016	No serious limitations	No serious indirectness	No serious inconsistency	Serious imprecision[1]	31	37	MD -0.35 seconds (95%CI -1.89 to 1.19, I^2 = 0%)	Important	Moderate
Number or participants improved in 10m walk at 6 months									
1 RCT in Lunn and Nobile-Orazio 2016	Very serious limitations[3]	No serious indirectness	Not applicable	Serious imprecision[1]	9/13 (69.2%)	5/13 (38.5%)	RR 1.80 (95%CI 0.83 to 3.92)	Important	Low
Quality of life									
Mean change in SF-36 physical subscores at 12 months (benefit is indicated by higher result)									
1 RCT in Lunn and Nobile-Orazio 2016	No serious limitations	No serious indirectness	Not applicable	No serious imprecision	17	20	MD 15.50 (95%CI 5.24 to 25.76)	Important	High
Mean change in SF-36 mental health subscores at 12 months (benefit is indicated by higher result)									
1 RCT in Lunn and Nobile-Orazio 2016	No serious limitations	No serious indirectness	Not applicable	Serious imprecision[1]	17	24	MD 6.60 (95%CI 0.35 to 13.55)	Important	Moderate

Motor impairment									
Median change in MRC score at 12 months (benefit is indicated by higher result)									
1 RCT Léger et al 2013	No serious limitations	No serious indirectness	Not applicable	Not calculable	20 0.0 (95%CI -3 to 0.0)	27 0.0 (95%CI -1.5 to 1.5)	No significant difference between groups p=0.17	Important	Moderate
Median change in MRC score at 8 months (benefit is indicated by higher result)									
1 RCT Dalakas et al 2009	Very serious limitations[3]	No serious indirectness	Not applicable	Not calculable	13	13	No significant changes in the MRC scores in the rituximab group. No measure of statistical significance was recorded	Important	Low
Adverse events									
Any adverse event (no timeframes were reported)									
1 MA of 2 RCTs Lunn and Nobile-Orazio 2016	No serious limitations	No serious indirectness	No serious inconsistency	Serious imprecision[1]	26/39 (66.7%)	23/41 (56.1%)	RR 1.18 (95%CI 0.84 to1.66, I^2 =0%)	Important	Moderate
Severe adverse event (no timeframes were reported)									
1 MA of 2 RCTs Lunn and Nobile-Orazio 2016	No serious limitations	No serious indirectness	No serious inconsistency	Very serious imprecision[4]	2/39 (5.1%)	0/41 (0%)	RR 3.11 (95%CI 0.34 to 28.54, I^2 =0%)	Important	Low

Abbreviations: anti-MAG - anti-myelin-associated glycoprotein; CI - confidence interval; I^2 - Study heterogeneity (a statistic that indicates the percentage of variance in a meta-analysis that is attributable to study heterogeneity); IgM - immunoglobulin M; INCAT – inflammatory Neuropathy Cause and Treatment; ISS – INCAT sensory score; IQR – inter-quartile range; LPL - lymphoplasmacytic lymphoma; MA - meta-analysis; MAG - myelin-associated glycoprotein; MD - mean difference; MGUS - monoclonal gammopathy of undetermined significance; MRC – Medical Research Council; NIS – neuropathy impairment scores; PDPN - paraproteinaemic demyelinating peripheral neuropathy; RCT - randomised controlled trial; RR - risk ratio; SD – standard deviation; SF-36 - Short Form 36 Health Survey; WM - Waldenstrom's macroglobulinemia

Footnotes

1. Imprecision: Serious imprecision due to wide confidence interval that crosses lower or upper default imprecision threshold
2. Indirectness: Serious indirectness as this outcome reports participant impression of change (the PICO states global impression of change (patient global impression of change (PGIC)/ clinical global impression of change (CGIC) in the definition of this outcome)
3. Risk of bias: Very serious limitations for this outcome only reported by the Dalakas et al 2009 RCT due to selection bias (randomisation and allocation), attrition bias and reporting bias
4. Imprecision: Very serious imprecision due to very wide confidence interval that crosses both lower and upper default imprecision thresholds

Glossary (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 or not the event is suspected to be related to or caused by the drug, treatment or intervention.

Baseline. The set of measurements at the beginning of a study (after any initial 'run-in' period with no intervention), with which subsequent results are compared.

Bias. Systematic (as opposed to random) deviation of the results of a study from the 'true' results, which is caused by the way the study is designed or conducted.

Blinding. A way to prevent researchers, doctors and patients in a clinical trial from knowing which study group each patient is in so they cannot influence the results. The best way to do this is by sorting patients into study groups randomly. The purpose of 'blinding' or 'masking' is to protect against bias.

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.

Clinical importance. A benefit from treatment that relates to an important outcome such as length of life and is large enough to be important to patients and health professionals.

Confidence interval (CI). A way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. A wide confidence interval indicates a lack of certainty about the true effect of the test or treatment - often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example, if a large number of patients have been studied).

Control group. A group of people in a study who do not have the intervention or test being studied. Instead, they may have the standard intervention. The results for the control group are compared with those for a group having the intervention being tested. The aim is to check for any differences. Ideally, the people in the control group should be as similar as possible to those in the intervention group, to make it as easy as possible to detect any effects due to the intervention.

GRADE (Grading of recommendations assessment, development and evaluation). A systematic and explicit approach to grading the quality of evidence and the strength of recommendations.

Meta-analysis. A method often used in systematic reviews to combine results from several studies of the same test, treatment or other intervention to estimate the overall effect of the treatment.

Per-protocol analysis. A comparison of treatment groups in a trial that includes only those patients who completed the treatment they were originally allocated to. If done alone, this analysis leads to bias.

PICO (population, intervention, comparison and outcome) framework. A structured approach for developing review questions that divides each question into 4 components: the population (the population being studied); the interventions (what is being done); the

comparators (other main treatment options); and the outcomes (measures of how effective the interventions have been).

P-value (p). The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that 1 seems to be more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance), it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 0.1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.

Randomised controlled trial (RCT). A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug, treatment or other intervention. One group (the experimental group) has the intervention being tested, the other (the comparison or control group) has an alternative intervention, a dummy intervention (placebo) or no intervention at all. The groups are followed up to see how effective the experimental intervention was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias.

Statistical significance. A statistically significant result is one that is assessed as being due to a true effect rather than random chance.

References

Included studies

- Dalakas MC, Rakocevic G, Salajegheh M, Dambrosia JM, Hahn AF, Raju R, Mcelroy B. Placebo-controlled trial of rituximab in IgM anti-myelin-associated glycoprotein antibody demyelinating neuropathy. Ann Neurol. 2009; 65**:** 286-93.
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- Lunn MP, Nobile-Orazio E. Immunotherapy for IgM anti-myelin-associated glycoprotein paraprotein-associated peripheral neuropathies. Cochrane Database Syst Rev 2016; 10**,** CD002827.