NHS England Evidence Review:

Rituximab for idiopathic membranous nephropathy

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Rituximab for idiopathic membranous nephropathy

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1. Introduction

This evidence review examines the clinical effectiveness, safety and cost effectiveness of rituximab compared with calcineurin inhibitors, alkylating agents or no treatment, with or without supportive therapy, in people with idiopathic membranous nephropathy (IMN).

Rituximab is a chimeric monoclonal antibody that depletes human B Cells and is given as an intravenous infusion. B cells are central in the production of antibodies and therefore rituximab has been widely used for the treatment of autoimmune conditions, where autoantibodies play a key role in the development of disease. Rituximab is currently licensed for the treatment of certain lymphomas or leukaemias and auto-immune conditions such as rheumatoid arthritis and vasculitis, it is not licensed for the treatment of IMN.

The current standard treatment for people with less severe IMN is a period of monitored supportive care. If partial or complete remission is not achieved within 6 months, immunosuppressive therapy is then started with continuation of supportive care. People presenting with severe disease (life-threatening fluid overload, rapidly declining kidney function, or thromboembolic disease) receive supportive care and immediate immunosuppression. Immunosuppressive therapy for IMN involves using alkylating agents (cyclophosphamide or chlorambucil) with corticosteroids, or calcineurin inhibitors (tacrolimus or ciclosporin).

The choice of immunosuppressive therapy is individualised to the patient and takes into consideration pre-existing co-morbidities. If the person is intolerant or has contraindications to both calcineurin inhibitors and alkylating agents, they are offered continued treatment with supportive care.

Calcineurin inhibitors have a high relapse rate of 40% to 50% and are not effective for people with progressive kidney disease. Alkylating agents are effective with dialysis free survival at 10 years being over 90%. However alkylating agents are associated with significant treatment toxicity with 60% of patients experiencing serious adverse events including hospitalisation for infection, cancer, infertility, leucopenia, osteoporosis and diabetes.

In addition, the review scope included the identification of possible subgroups of patients within the included studies who might benefit from treatment with rituximab more than others, as well as the criteria used by the included studies to confirm a diagnosis of IMN.

2. Executive summary of the review

This evidence review examines the clinical effectiveness, safety and cost effectiveness of rituximab compared with calcineurin inhibitors, alkylating agents, or no rituximab treatment, with or without supportive therapy, in patients with idiopathic membranous nephropathy (IMN).

The searches for evidence were conducted on 14 July 2021 and identified 648 references. The titles and abstracts were screened, and 52 full text papers were obtained and assessed for relevance. Three papers were identified for inclusion (Dahan et al. 2017, Fervenza et al. 2019, and Scolari et al. 2021). All 3 were open-label randomised controlled trials (RCTs) in adults. Fervenza et al. 2019 compared rituximab with ciclosporin with a follow-up of 2 years (n=130), Scolari et al. 2021 compared rituximab with a cyclic regimen of cyclophosphamide and corticosteroids with a follow-up of 3 years (n=74), and Dahan et al. 2017 compared rituximab with supportive therapy with a median follow-up of 17 months (n=77). One study was based in France, 1 study was based in Italy and Switzerland, and 1 study was based in North America. Two cost-effectiveness studies which are relevant to the UK were also selected for inclusion (Dai et al 2021, Hamilton et al. 2018).

In terms of clinical effectiveness:

Critical outcomes

- Remission of proteinuria. One RCT provided moderate to high certainty evidence that there was a significant benefit of rituximab compared with ciclosporin in complete or partial remission at 18 and 24 months, but not before 18 months. Two RCTs provided low to moderate certainty evidence that there was no difference between rituximab and cyclic cyclophosphamide and corticosteroids in complete or partial remission or complete remission at any time point up to 36 months, and a significant benefit of rituximab compared with supportive therapy alone in complete or partial remission, complete remission, and protein-to-creatinine ratio at a median of 17 months. However, there was no difference in remission or protein-creatinine ratio between rituximab and supportive therapy up to 6 months.
- Excretory kidney function. Three RCTs provided low to moderate certainty evidence that there was no difference between rituximab and supportive therapy in excretory kidney function. One RCT provided low to moderate certainty evidence on the effects of rituximab compared to ciclosporin. However, no conclusions could be drawn because the confidence intervals were not adjusted for multiple comparisons and could not be used for inference about treatment effects. No statistical analysis was reported for the difference between rituximab and cyclic cyclophosphamide and corticosteroids therefore no conclusions could be drawn.
- End stage renal disease (ESRD). Two RCTs provided moderate to high certainty evidence on the effects of rituximab on ESRD compared with ciclosporin or cyclic cyclophosphamide and corticosteroids. No statistical analysis was provided and there were few events in both groups, therefore no conclusions could be drawn. No evidence was identified that compared rituximab with supportive therapy.

Important outcomes

- Quality of life. One RCT provided low to moderate certainty evidence on the effects of rituximab compared to ciclosporin on quality of life using 5 components of the Kidney Disease Quality of Life Short Form (KDQOL-SF) questionnaire in adults with complete or partial remission. No conclusions could be drawn because the confidence intervals

were not adjusted for multiple comparisons and could not be used for inference about treatment effects. No evidence was identified for rituximab compared with a cyclic regimen of cyclophosphamide and corticosteroids or supportive therapy.

- Anti-phospholipase A2 receptor (Anti-PLA2R) level and positivity. Two RCTs provided moderate certainty evidence that there was no difference between rituximab and a cyclic regimen of cyclophosphamide and corticosteroids in anti-PLA2R levels, but that rituximab decreased anti-PLA2R levels compared supportive therapy. No evidence was identified that compared rituximab with ciclosporin.
- The time interval to maximum reduction of anti-PLA2R antibodies and proteinuria following rituximab administration. No evidence was identified for this outcome.
- Serum albumin. One study provided low to moderate certainty evidence that, compared with supportive therapy, rituximab increased serum albumin at 6 and 17 months but not at 3 months. One study provided moderate certainty evidence on the effects of rituximab compared with a cyclic regimen of cyclophosphamide and corticosteroids; however, no statistical analysis was provided therefore no conclusions could be drawn. No evidence was identified that compared rituximab with ciclosporin.

In terms of safety:

- Serious adverse events. Three RCTs provided moderate to high certainty evidence that there was no difference between rituximab and ciclosporin, a cyclic regimen of cyclophosphamide and corticosteroids, or supportive therapy, in serious adverse events.
- Adverse events. Two RCTs provided moderate to high certainty evidence that there was no difference between rituximab and ciclosporin, or a cyclic regimen of cyclophosphamide and corticosteroids, in adverse events, but rituximab increased infusion-related reactions compared with ciclosporin or cyclic cyclophosphamide and corticosteroids. No evidence was identified for rituximab compared with supportive therapy.

In terms of cost effectiveness:

- Cost effectiveness. Two studies were identified that provided cost-effectiveness estimates for rituximab compared with other treatment options. One study found that rituximab was cheaper over a lifetime but less effective than the modified Ponticelli regimen (cyclophosphamide and corticosteroids). Analysis of the other study found that rituximab was not cost effective compared with tacrolimus, ciclosporin, or cyclophosphamide, but was more cost effective than chlorambucil (ICER above the NICE threshold of £20,000). Because of their limitations, notably the likelihood that the costs used for rituximab are now out of date, no conclusions regarding the cost effectiveness of rituximab could be drawn from these studies. No evidence was identified for rituximab compared with supportive therapy.

In terms of subgroups:

- Age. No evidence was identified for children. Two RCTs found that, compared with ciclosporin or cyclic cyclophosphamide and corticosteroids, remission rates were not significantly different in the pre-specified age subgroups of ≤50 compared with >50 years and <55 compared with ≥55 years, respectively.

- Estimated glomerular filtration rate (eGFR). No evidence was identified that compared outcomes in people with an eGFR greater or less than 60ml/min/1.73m^2.
- Proteinuria at baseline. One RCT found a trend for lower complete remission rates at 12 months in the rituximab arm for adults with more severe proteinuria or lower serum albumin. However, the statistical tests for interaction were nonsignificant.
- Anti-PLA2R level at baseline. Two RCTs found that remission rates were not significantly different in adults with high anti-PLA2R levels compared with adults who had low anti-PLA2R levels at baseline.

Please see the results table (section 5) in the review for further details of outcomes and definitions.

Limitations

The clinical effectiveness studies included in the evidence review had some limitations for determining the efficacy and safety of rituximab compared with calcineurin inhibitors, alkylating agents, or no rituximab treatment, with or without supportive therapy.

While the study by Fervenza et al. 2019 was generally well designed, resulting in some high certainty outcomes, many of the outcomes were downgraded to moderate for imprecision because they were modelled estimates and could not be used to determine the statistical significance of the findings. Most of the outcomes from Scolari et al. 2021 were graded to have low certainty. Outcomes were downgraded for imprecision because the study was not powered to detect a difference in outcomes between the treatment groups. Most of the outcomes from Dahan et al. 2017 were graded to have moderate certainty using modified GRADE. Outcomes were downgraded for risk of bias because the participants were only required to have 3 months without immunosuppressive therapy before randomisation. The observational follow-up outcomes were further downgraded to low certainty because of the possibility of differences in management between the treatment groups in the observational period.

In general, outcomes across the studies were reported poorly with many results reported without point estimates, confidence intervals or p-values meaning interpretation was limited.

Because of the administration and monitoring requirements of the intervention and some of the comparators, all of the studies were open-label. However, because the primary outcome of complete or partial remission was well defined in each of the studies and determined through biochemical assay, bias arising from outcome assessment is unlikely. It is also unlikely that the participant knowledge of their intervention affected adherence to the intervention as rituximab is given as 1 or 2 infusions. While adherence may be better with rituximab, it may be less favourable in terms of infusion-related reactions and intolerance.

All 3 RCTs gave the initial doses of rituximab in 2 separate doses, either at days 1 and 8 or days 1 and 15. However, subsequent dosing of rituximab varied between the studies. Therefore, observed differences in outcomes between the studies cannot solely be attributed to the differences in comparator arms.

While none of the clinical effectiveness studies were conducted in the UK, diagnosis and outcome definitions appeared to follow the Kidney Disease Improving Global Outcomes (KDIGO) guidelines and are therefore likely to be generalisable to UK practice.

The primary outcome of remission of proteinuria is a surrogate outcome and these trials may not have been large enough or for a long enough duration to detect differences in clinical outcomes such as ESRD.

Two studies were identified that provided a cost-effectiveness estimate for rituximab compared with other treatment options. However, the estimates from both studies should be treated with caution. The study by Dai et al. 2021 used clinical effectiveness data from 2 RCTs, one of which was unpublished, and Dahan et al. 2017 which compared rituximab with supportive therapy. Despite this, there was no cost-effectiveness estimate given for rituximab compared with supportive therapy alone. The study by Hamilton et al. 2018 was generally well conducted, however the main limitation was the poorly reported literature search. This resulted in the clinical effectiveness data in the model being derived from 1 RCT which compared the effect of a 6-month course of alternating prednisolone and cyclophosphamide with supportive therapy, and 1 observational study. It is also likely that the costs included in the studies are out of date.

Conclusion

This evidence review found low to high certainty evidence for the efficacy and safety of rituximab for treating IMN compared with calcineurin inhibitors, alkylating agents, and supportive therapy. All 3 clinical effectiveness studies included adults who had a biopsy-confirmed diagnosis of IMN and were at high risk of progressive disease and had not responded to at least 3 months of supportive therapy.

The results of the study by Fervenza et al. 2019 found that there was no difference between rituximab and ciclosporin at inducing complete or partial remission in adults at 12 months, but that rituximab was superior to ciclosporin at inducing complete or partial remission in adults at 24 months.

The results of the study by Scolari et al. 2021 suggest that rituximab was similarly but not more effective at inducing remission of proteinuria compared with a cyclic regimen of cyclophosphamide and corticosteroids. However, this study was not powered to detect a difference in clinical effect.

The results of the observational follow-up by Dahan et al. 2017 found that while there was no statistically significant increase in remission in the randomised phase of the trial at 3 or 6 months, rituximab with supportive therapy was more effective than supportive therapy alone at inducing remission of proteinuria over the longer-term, with most incidences of remission occurring in the observational follow-up period. However, these findings should be interpreted with caution because of the potential bias arising from the short run-in period and because of possible differences in management between treatment groups during the observational follow-up period.

There was no statistically significant difference in adverse events in any of the studies when rituximab was compared with supportive care, ciclosporin or a cyclic regimen of cyclophosphamide and corticosteroids. Alkylating agents, such as cyclophosphamide, are known to be associated with significant side effects including an increased risk of cancer. However, it is unlikely that such adverse events would be observed over the duration of the study by Scolari et al. 2021.

One study found that rituximab was cheaper over a lifetime but less effective than the modified Ponticelli regimen (cyclophosphamide and corticosteroids). Analysis of the other study found that rituximab was not cost effective compared with tacrolimus, ciclosporin, or cyclophosphamide, but was more cost effective than chlorambucil (ICER above the NICE threshold of £20,000). Because of their limitations, notably the likelihood that the costs used for

rituximab are now out of date, no conclusions regarding the cost effectiveness of rituximab could be drawn from these studies. No evidence was identified for rituximab compared with supportive therapy.

None of the included studies were powered to detect differences in clinical outcomes such as ESRD. Furthermore, there was no evidence identified that investigated tacrolimus or chlorambucil as comparators which may be used in UK clinical practice for the treatment of IMN.

There were no subgroups of patients that may benefit more from rituximab than the wider population of interest. No evidence was identified that compared outcomes in people with an eGFR greater or less than 60ml/min/1.73m^2.

The findings of this review are important because people with IMN who do not receive immunosuppressive treatment are more likely to need renal replacement therapy in the form of dialysis or transplant. While there are substantial gaps in the evidence for both the clinical and cost-effectiveness of rituximab compared with these treatment options, this review has shown that rituximab may be non-inferior in terms of efficacy and safety and may be more effective than ciclosporin in inducing remission over the longer-term for adults with a high risk of progressive disease.

3. Methodology

Review questions

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

1. In people with IMN, what is the clinical effectiveness of rituximab compared with current treatment (alkylating agents or calcineurin inhibitors or no rituximab treatment)?
2. In people with IMN, what is the safety of rituximab compared with current treatment (alkylating agents or calcineurin inhibitors or no rituximab treatment)?
3. In IMN, what is the cost effectiveness of rituximab compared with current treatment (alkylating agents or calcineurin inhibitors or no rituximab treatment)?
4. From the evidence selected, are there any subgroups of patients that may benefit from rituximab more than the wider population of interest?
5. From the evidence selected, what are the criteria used by the research studies to define IMN?
6. From the evidence selected how many patients received re-dosing with rituximab and how long after initial treatment with rituximab?

See Appendix A for the full PICO document.

Review process

The methodology to undertake this review is specified by NHS England in its 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO document and were conducted on 14 July 2021.

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 document. Full text of potentially relevant studies 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 critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

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

4. Summary of included studies

Three papers were identified for inclusion (Dahan et al. 2017, Fervenza et al. 2019, and Scolari et al. 2021). Table 1 provides a summary of these included studies and full details are given in Appendix E. All three were randomised controlled trials (RCTs). Dahan et al. 2017 compared rituximab with supportive therapy, Fervenza et al. 2019 compared rituximab with ciclosporin, and Scolari et al. 2021 compared rituximab with a cyclic regimen of cyclophosphamide and corticosteroids. Two cost-effectiveness studies were also selected for inclusion (Dai et al. 2021, Hamilton et al. 2018).

Table 1: Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported
Dahan et al. 2017 RCT France	Adults with IMN confirmed by biopsy <2 years before inclusion (n=77). All participants were treated with the maximum tolerated dose of ACEI and/or ARB, diuretics, and statin, for 6 months before randomisation. Participants were randomised to rituximab and supportive therapy (n=39) or supportive therapy (n=38). There were no notable differences in baseline characteristics.	**Intervention** Intravenous rituximab 375 mg/m^2 on days 1 and 8 after randomisation with supportive therapy (maximum tolerated dose of ACEI and/or ARB, diuretics, and statin) 39 randomised, 37 received treatment **Comparison** Supportive therapy for 6 months 38 randomised, 38 received treatment	**Critical outcomes** • Remission of proteinuria (complete and partial) at 3 and 6 months • Excretory kidney function, including eGFR and serum creatinine at 3 and 6 months **Important Outcomes** • Anti-PLA2R level at 3 and 6 months • Serum albumin at 3 and 6 months **Safety** • Serious adverse events
Dai et al. 2021 Cost-effectiveness analysis Clinical effectiveness data from 75 international RCTs UK costs	Adults with IMN confirmed by biopsy.	**Comparisons** Cyclophosphamide, mycophenolate mofetil, ciclosporin, tacrolimus, leflunomide, chlorambucil, rituximab.	**Cost effectiveness** • ICER
Fervenza et al. 2019 Non-inferiority RCT North America	Adults with IMN confirmed by biopsy (n=130). Participants were randomised to rituximab (n=65) or ciclosporin (n=65). All participants received supportive care that included renin angiotensin system blockers, blood-pressure management targeting a value of less than 130/80 mm Hg, dietary sodium restriction to less than 4 g per day, and dietary protein restriction to 0.8 to 1 g of protein per kilogram of body weight per day during at least the previous 3 months before randomisation. It is unclear whether participants received supportive care throughout the trial. There were more men in the ciclosporin group (82%) compared with the rituximab group (72%); no statistical analyses reported. The authors reported baseline imbalance in the proportion with anti-PLA2R positivity.	**Intervention** Intravenous rituximab 1 g on days 1 and 15; repeated at 6 months in case of partial response. **Comparison** Oral ciclosporin, starting at a dose of 3.5 mg per kilogram of body weight per day. Given in 2 equal doses each day for 12 months.	**Critical outcomes** • Remission of proteinuria (complete and partial) at 6, 12, 18 and 24 months • Excretory kidney function (increased creatinine level) • ESRD **Important Outcomes** • Quality of Life • Anti-PLA2R level **Safety** • Any adverse event • Serious adverse events
Hamilton et al. 2018	Adults with IMN confirmed by biopsy.	**Comparisons**	**Cost effectiveness** • ICER

Cost-effectiveness analysis Clinical effectiveness data from 1 observational study (Italy) and 1 RCT (India) UK costs		Modified Ponticelli regimen (oral cyclophosphamide and intravenous methylprednisolone)	
Scolari et al. 2021 RCT Italy and Switzerland	Adults with IMN confirmed by biopsy (n=74). Participants were randomised to rituximab (n=37) or cyclic regimen of cyclophosphamide and corticosteroids. Three months of ACEI and/or ARB treatment before randomisation. There were no notable differences in baseline characteristics.	**Intervention** Intravenous rituximab 1 g on days 1 and 15 **Comparison** Cyclic regimen of three consecutive cycles (2 months each) where corticosteroids were alternated with cyclophosphamide every other month. The cumulative dose of cyclophosphamide per person was 180 mg/kg.	**Critical outcomes** • Remission of proteinuria (complete and partial) at 12, 18 and 24 months • Excretory kidney function (creatinine clearance) at 24 months • ESRD **Important Outcomes** • Anti-PLA2R level • Serum albumin **Safety** • Any adverse event • Serious adverse events

Abbreviations

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; ICER, incremental cost-effectiveness ratio; PLA2R, phospholipase A2 receptor; RCT, randomised controlled trial

5. Results

In people with IMN, what is the clinical effectiveness of rituximab compared with current treatment (calcineurin inhibitors, alkylating agents, or no rituximab treatment)?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Remission of proteinuria **Certainty of evidence:** Low to high	This outcome is important to patients because a remission of proteinuria is a strong predictor of reduced risk of decline in kidney function. In total 3 RCTs provided evidence relating to remission of proteinuria in adults with IMN, measured at different time points up to 2 years. One study compared rituximab with ciclosporin (a calcineurin inhibitor), 1 study compared rituximab with cyclophosphamide (an alkylating agent) and corticosteroids, and 1 study compared rituximab with supportive therapy (no rituximab treatment). No evidence was identified for children. ***Rituximab compared with ciclosporin*** One RCT (Fervenza et al. 2019, n=130) compared rituximab with ciclosporin. Complete or partial remission at 6 months: • *no statistically significant difference* in complete or partial remission in the rituximab group (23/65, 35%) compared with the ciclosporin group (32/65, 49%) (risk difference −14%, 95% CI −31 to 3%). **(MODERATE)** Complete or partial remission at 12 months: • *no statistically significant difference* in complete or partial remission in the rituximab group (39/65, 60%) compared with the ciclosporin group (34/65, 52%) (risk difference 8%, 95% CI −9 to 25%). **(MODERATE)** Complete or partial remission at 18 months: • *statistically significant increase* in complete or partial remission in the rituximab group (40/65, 62%) compared with the ciclosporin group (15/65, 23%) (risk difference 38%, 95% CI 23 to 54%). **(HIGH)** Complete or partial remission at 24 months: • *statistically significant increase* in complete or partial remission in the rituximab group (39/65, 60%) compared with the ciclosporin group (13/65, 20%) (risk difference 40%, 95% CI 25 to 55%, p<0.001). **(HIGH)** ***Rituximab compared with cyclic cyclophosphamide and corticosteroid*** One RCT (Scolari et al. 2021, n=74) compared rituximab with cyclic cyclophosphamide and corticosteroid. Complete or partial remission at 6 months: • *no statistically significant difference* in complete or partial remission in the rituximab group (19/37, 51%) compared with the cyclic cyclophosphamide and corticosteroid group (24/37, 65%) (OR 0.57, 95% CI 0.22 to 1.45). There was *no statistically significant difference* in complete remission in the rituximab group (3/37,

	8%) compared with the cyclic cyclophosphamide and corticosteroid group (2/37, 5%) (OR 1.54, 95% CI 0.24 to 9.80). **(LOW)** Complete or partial remission at 12 months: • *no statistically significant difference* in complete or partial remission in the rituximab group (23/37, 62%) compared with the cyclic cyclophosphamide and corticosteroid group (27/37, 73%) (OR 0.61, 95% CI 0.23 to 1.63). There was *no statistically significant difference* in complete remission in the rituximab group (6/37, 16%) compared with the cyclic cyclophosphamide and corticosteroid group (12/37, 32%) (OR 0.40, 95% CI 0.13 to 1.23). **(LOW)** Complete or partial remission at 18 months: • *no statistically significant difference* in complete or partial remission in the rituximab group (21/32, 66%) compared with the cyclic cyclophosphamide and corticosteroid group (27/34, 79%) (OR 0.49, 95% CI 0.16 to 1.49). There was *no statistically significant difference* in complete remission in the rituximab group (10/32, 31%) compared with the cyclic cyclophosphamide and corticosteroid group (7/34, 21%) (OR 1.75, 95% CI 0.57 to 5.36). **(LOW)** Complete or partial remission at 24 months: • *no statistically significant difference* in complete or partial remission in the rituximab group (22/26, 85%) compared with the cyclic cyclophosphamide and corticosteroid group (25/31, 81%) (OR 1.32, 95% CI 0.33 to 5.29). There was *no statistically significant difference* in complete remission in the rituximab group (11/26, 42%) compared with the cyclic cyclophosphamide and corticosteroid group (11/31, 35%) (OR 1.33, 95% CI 0.46 to 3.89). **(LOW)** Complete or partial remission at 36 months: • *no statistically significant difference* in complete or partial remission in the rituximab group (17/20, 85%) compared with the cyclic cyclophosphamide and corticosteroid group (16/22, 73%) (OR 2.12, 95% CI 0.45 to 9.96). There was *no statistically significant difference* in complete remission in the rituximab group (6/20, 30%) compared with the cyclic cyclophosphamide and corticosteroid group (7/22, 32%) (OR 0.92, 95% CI 0.25 to 3.41). **(LOW)** ***Rituximab compared with supportive therapy*** One RCT (Dahan et al. 2017, n=75) compared rituximab with supportive therapy. Complete or partial remission at 6 months: • *no statistically significant difference* in complete or partial remission in the rituximab group (13/37, 35.1%) compared with the supportive therapy group (8/38, 21.1%) (OR 2.0, 95% CI 0.7 to 5.7, p=0.21). **(MODERATE)** Complete or partial remission, post-RCT observational follow-up (median 17 months, IQR 12.5 to 24.0 months): • *statistically significant increase* in complete or partial remission in the rituximab group (24/37, 64.9%) compared with the supportive therapy group (13/38, 34.2%) (p<0.01). There was a *statistically significant increase* in complete remission in the rituximab group (7/37) compared with the supportive therapy group (1/38) (p=0.03). **(LOW)** Protein-to-creatinine ratio at 3 months: • *no statistically significant difference* in protein-to-creatinine ratio in the rituximab group (4814.4 mg/g, IQR 3205.5 to 7398.6 mg/g) compared with the

	supportive therapy group (4832.1 mg/g, IQR 2424.9 to 7911.9 mg/g) (p=0.94). **(MODERATE)** Protein-to-creatinine ratio at 6 months: • *no statistically significant difference* in protein-to-creatinine ratio in the rituximab group (3531.2 mg/g, IQR 1796.6 to 6469.4mg/g) compared with the supportive therapy group (5265.8 mg/g, IQR 2500.1 to 7690.7 mg/g) (p=0.18). **(MODERATE)** Protein-to-creatinine ratio, post-RCT observational follow-up (median 17 months, IQR 12.5 to 24.0 months): • *statistically significant increase* in protein-to-creatinine ratio in the rituximab group (2194.8 mg/g, IQR 1309.8 to 5310.0 mg/g) compared with the supportive therapy group (4701.1 mg/g, IQR 2027.8 to 8265.3 mg/g) (p=0.02). **(MODERATE)** **One study provided moderate to high certainty evidence that there was a significant benefit of rituximab compared with ciclosporin in complete or partial remission at 18 and 24 months, but not before 18 months. Two studies provided low to moderate certainty evidence that there was no difference between rituximab and cyclic cyclophosphamide and corticosteroids in complete or partial remission or complete remission at any time point up to 36 months, and a significant benefit of rituximab compared with supportive therapy alone in complete or partial remission, complete remission, and protein-to-creatinine ratio at a median of 17 months. However, there was no difference in remission or protein-creatinine ratio between rituximab and supportive therapy up to 6 months.**
Excretory kidney function **Certainty of evidence:** Low to moderate	This outcome is important to patients because it is a measure of how well a patient's kidneys function. In total 3 RCTs provided evidence relating to excretory kidney function in adults with IMN, measured at different time points up to 3 years. One study compared rituximab with ciclosporin, 1 study compared rituximab with cyclophosphamide and corticosteroids, and 1 study compared rituximab with supportive therapy (no rituximab treatment). No evidence was identified for children. ***Rituximab compared with ciclosporin*** One RCT (Fervenza et al. 2019, n=130) compared rituximab with ciclosporin. Number of adults with ≥50% decrease in creatinine clearance from baseline at 6 months: • number of adults who had ≥50% decrease in creatinine clearance from baseline in the rituximab group (1/65, 1.5%) compared with the ciclosporin group (4/65, 6.2%) (risk difference −4.6%, 95% CI −11.2 to 1.9%). Confidence intervals could not be used to draw conclusions about treatment effects. **(LOW)** Number of adults with ≥50% decrease in creatinine clearance from baseline at 12 months: • number of adults who had ≥50% decrease in creatinine clearance from baseline in the rituximab group (1/65, 1.5%) compared with the ciclosporin group (8/65, 12.3%) (risk difference −10.8%, 95% CI −19.3 to −2.2%). Confidence intervals could not be used to draw conclusions about treatment effects. **(MODERATE)** Number of adults with ≥50% decrease in creatinine clearance from baseline at 18 months:

	• number of adults who had ≥50% decrease in creatinine clearance from baseline in the rituximab group (1/65, 1.5%) compared with the ciclosporin group (8/65, 12.3%) (risk difference −10.8%, 95% CI −19.3 to −2.2%). Confidence intervals could not be used to draw conclusions about treatment effects. **(MODERATE)** Number of adults with ≥50% decrease in creatinine clearance from baseline at 24 months: • number of adults who had ≥50% decrease in creatinine clearance from baseline in the rituximab group (1/65, 1.5%) compared with the ciclosporin group (8/65, 12.3%) (risk difference −10.8%, 95% CI −19.3 to −2.2%). Confidence intervals could not be used to draw conclusions about treatment effects. **(MODERATE)** ***Rituximab compared with cyclic cyclophosphamide and corticosteroid*** One RCT (Scolari et al. 2021, n=74) compared rituximab with cyclic cyclophosphamide and corticosteroid. Serum creatinine at 6 months (n=73): • mean serum creatinine in the rituximab group (1.00 mg/dl, SD 0.25 mg/dl) compared with the cyclic cyclophosphamide and corticosteroid group (0.98 mg/dl, SD 0.47 mg/dl). No statistical analysis reported. **(MODERATE)** Serum creatinine at 12 months (n=72): • mean serum creatinine in the rituximab group (0.98 mg/dl, SD 0.29 mg/dl) compared with the cyclic cyclophosphamide and corticosteroid group (0.98 mg/dl, SD 0.48 mg/dl). No statistical analysis reported. **(MODERATE)** Serum creatinine at 18 months (n=66): • mean serum creatinine in the rituximab group (0.98 mg/dl, SD 0.26 mg/dl) compared with the cyclic cyclophosphamide and corticosteroid group (1.14 mg/dl, SD 0.90 mg/dl). No statistical analysis reported. **(MODERATE)** Serum creatinine at 24 months (n=57): • mean serum creatinine in the rituximab group (0.94 mg/dl, SD 0.20 mg/dl) compared with the cyclic cyclophosphamide and corticosteroid group (1.12 mg/dl, SD 0.77 mg/dl). No statistical analysis reported. **(MODERATE)** Serum creatinine at 36 months (n=42): • mean serum creatinine in the rituximab group (0.97 mg/dl, SD 0.20 mg/dl) compared with the cyclic cyclophosphamide and corticosteroid group (1.22 mg/dl, SD 0.77 mg/dl). No statistical analysis reported. **(MODERATE)** ***Rituximab compared with supportive therapy*** One RCT (Dahan et al. 2017, n=75) compared rituximab with supportive therapy. eGFR at 3 months: • *no statistically significant difference* in eGFR in the rituximab group (66.7 ml/min/1.73m^2, IQR 57.2 to 87.1 ml/min/1.73m^2) compared with the supportive therapy group (68.9 ml/min/1.73m^2, IQR 45.7 to 89.7 ml/min/1.73m^2) (p=0.95). **(MODERATE)** eGFR at 6 months: • *no statistically significant difference* in eGFR in the rituximab group (65.6 ml/min/1.73m^2, IQR 51.0 to 89.0 ml/min/1.73m^2) compared with the supportive

	therapy group (72.5 ml/min/1.73m^2, IQR 52.4 to 89.7 ml/min/1.73m^2) (p=0.75). **(MODERATE)** eGFR at last follow up (median 17 months, IQR 12.5 to 24.0 months): • *no statistically significant difference* in eGFR in the rituximab group (61.1 ml/min/1.73m^2, IQR 48.7 to 83.4 ml/min/1.73m^2) compared with the supportive therapy group (73.1 ml/min/1.73m^2, IQR 50.4 to 90.5 ml/min/1.73m^2) (p=0.48). **(LOW)** Serum creatinine at 3 months: • *no statistically significant difference* in serum creatinine in the rituximab group (94.6 µmol/litre, IQR 78.7 to 114.0 µmol/litre) compared with the supportive therapy group (100.8 µmol/litre, IQR 81.3 to 115.8 µmol/litre) (p=0.88). **(MODERATE)** Serum creatinine at 6 months: • *no statistically significant difference* in serum creatinine in the rituximab group (94.6 µmol/litre, IQR 75.1 to 130.8 µmol/litre) compared with the supportive therapy group (97.2 µmol/litre, 76.0 to 126.4 µmol/litre) (p=0.67). **(MODERATE)** Serum creatinine at last follow up (median 17 months, IQR 12.5 to 24.0 months): • *no statistically significant difference* in serum creatinine in the rituximab group (101 µmol/litre, IQR 87 to 135 µmol/litre) compared with the supportive therapy group (97.2 µmol/litre, 78.5 to 133.5 µmol/litre) (p=0.50). **(LOW)** **These studies provided low to moderate certainty evidence that there was no difference between rituximab and supportive therapy in excretory kidney function. One RCT provided low to moderate certainty evidence on the effects of rituximab compared to ciclosporin. However, no conclusions could be drawn because the confidence intervals were not adjusted for multiple comparisons and could not be used for inference about treatment effects. No statistical analysis was reported for the difference between rituximab and cyclic cyclophosphamide and corticosteroids therefore no conclusions could be drawn.**
End stage renal disease (ESRD) **Certainty of evidence:** Moderate to high	This outcome is important to patients because ESRD is the final, permanent stage of chronic kidney disease, where kidney function has declined to the point that the kidneys can no longer function on their own. In total 2 RCTs provided evidence relating to ESRD in adults with IMN, measured at different time points up to 2 years. One study compared rituximab with ciclosporin and 1 study compared rituximab with cyclic cyclophosphamide and corticosteroids. No evidence was identified for children. ***Rituximab compared with ciclosporin*** • 1 RCT (Fervenza et al 2019) (n=130) reported the number of adults with ESRD in the rituximab group (0/65) and the ciclosporin group (1/65). No statistical analysis was reported. **(LOW)** ***Rituximab compared with cyclic cyclophosphamide and corticosteroid*** • 1 RCT (Scolari et al 2021) (n=74) reported the number of adults with ESRD in the rituximab group (0/37, 0%) and the cyclic cyclophosphamide and corticosteroid group (2/37, 5.4%). No statistical analysis reported. The 2 adults in the cyclic cyclophosphamide and corticosteroid group who developed ESRD had eGFRs at baseline of 69 ml/min/1.73m^2 and 41 ml/min/1.73m^2, respectively. **(LOW)**

	Rituximab compared with supportive therapy No evidence was identified for this comparator. **These studies provided moderate to high certainty evidence on the effects of rituximab on ESRD compared with ciclosporin or cyclic cyclophosphamide and corticosteroids. No statistical analysis was provided and there were few events in both groups, therefore no conclusions could be drawn. No evidence was identified that compared rituximab with supportive therapy.**
Important outcomes	
Quality of life **Certainty of evidence:** Low to moderate	This outcome is important to patients because IMN causes nephrotic syndrome which is associated with increased infections and thrombosis and may have a severe impact on quality of life. In total 1 RCT provided evidence relating to quality of life in adults with IMN, measured at different time points up to 2 years. The study compared rituximab with ciclosporin. ***Rituximab compared with ciclosporin*** 1 RCT (Fervenza et al 2019) (n=130) reported quality of life in adults with complete or partial remission in the rituximab group compared with the ciclosporin group, measured using subscales of the KDQOL-SF. At 6 months: • SF-12 physical health composite subscale (modelled difference in means 2.0, 95% CI −3.5 to 7.5). **(LOW)** • SF-12 mental health composite subscale (modelled difference in means 3.3, 95% CI −1.4 to 7.9). **(LOW)** • Symptom/problem list subscale (modelled difference in means 7.4, 95% CI 0.8 to 14.1). **(MODERATE)** • Effects of kidney disease subscale (modelled difference in means 0.1, 95% CI −7.0 to 7.2). **(LOW)** • Burden of kidney disease subscale (modelled difference in means: 3.3, 95% CI −6.3 to 13.0). **(LOW)** At 12 months: • SF-12 physical health composite subscale (modelled difference in means 0.2, 95% CI −3.8 to 4.2). **(LOW)** • SF-12 mental health composite subscale (modelled difference in means 4.1, 95% CI 0.6 to 7.6). **(MODERATE)** • Symptom/problem list subscale (modelled difference in means 2.3, 95% CI −3.2 to 7.8). **(LOW)** • Effects of kidney disease subscale (modelled difference in means 3.3, 95% CI −4.0 to 10.6). **(LOW)** • Burden of kidney disease subscale (modelled difference in means −4.5, 95% CI −16.1 to 7.1). **(LOW)** At 24 months:

	• SF-12 physical health composite subscale (modelled difference in means 0.2, 95% CI −4.9 to 5.3). **(LOW)** • SF-12 mental health composite subscale (modelled difference in means 0.3, 95% CI −3.7 to 4.3). **(LOW)** • Symptom/problem list subscale (modelled difference in means 2.2, 95% CI −4.3 to 8.8). **(LOW)** • Effects of kidney disease subscale (modelled difference in means 6.9, 95% CI −2.4 to 16.3). **(LOW)** • Burden of kidney disease subscale (modelled difference in means 1.2, 95% CI −12.5 to 14.9). **(LOW)** ***Rituximab compared with cyclic cyclophosphamide and corticosteroid*** No evidence was identified for this comparator. ***Rituximab compared with supportive therapy*** No evidence was identified for this comparator. **One RCT provided low to moderate certainty evidence on the effects of rituximab compared to ciclosporin on quality of life using 5 components of the KDQOL-SF questionnaire in adults with complete or partial remission. No conclusions could be drawn because the confidence intervals were not adjusted for multiple comparisons and could not be used for inference about treatment effects. No evidence was identified for rituximab compared with a cyclic regimen of cyclophosphamide and corticosteroids or supportive therapy.**
Anti-PLA2R level and positivity **Certainty of evidence:** Moderate	This outcome is important to patients because PLA2R autoantibody levels are thought to correlate with disease activity (active disease, partial remission, complete remission) in patients treated with rituximab. In total 2 RCTs provided evidence relating to anti-PLA2R level in adults with IMN, measured at different time points up to 3 years. One study compared rituximab with cyclophosphamide and corticosteroids and 1 study compared rituximab with supportive therapy. No evidence was identified for children. ***Rituximab compared with ciclosporin*** No evidence was identified for this comparator ***Rituximab compared with cyclic cyclophosphamide and corticosteroid*** One RCT (Scolari et al. 2021, n=74) compared rituximab with cyclic cyclophosphamide and corticosteroid. Anti-PLA2R level at 6 months: • *no statistically significant difference* in anti-PLA2R level in the rituximab group (0 RU/ml, IQR 0 to 44 RU/ml) compared with the cyclic cyclophosphamide and corticosteroid group (13 RU/ml, IQR 0 to 86 RU/ml) (p=0.30). **(MODERATE)** Anti-PLA2R level at 12 months: • *no statistically significant difference* in anti-PLA2R level in the rituximab group (2 RU/ml, IQR 0 to 44 RU/ml) compared with the cyclic cyclophosphamide and corticosteroid group (0 RU/ml, IQR 0 to 73 RU/ml) (p=0.83). **(MODERATE)**

	Anti-PLA2R level at 18 months: • *no statistically significant difference* in anti-PLA2R level in the rituximab group (0 RU/ml, IQR 0 to 0 RU/ml) compared with the cyclic cyclophosphamide and corticosteroid group (0 RU/ml, IQR 0 to 57 RU/ml) (p=0.21). **(MODERATE)** Anti-PLA2R level at 24 months: • *no statistically significant difference* in anti-PLA2R level in the rituximab group (0 RU/ml, IQR 0 to 0 RU/ml) compared with the cyclic cyclophosphamide and corticosteroid group (0 RU/ml, IQR 0 to 53 RU/ml) (p=0.26). **(MODERATE)** Anti-PLA2R level at 36 months: • *no statistically significant difference* in anti-PLA2R level in the rituximab group (0 RU/ml, IQR 0 to 18 RU/ml) compared with the cyclic cyclophosphamide and corticosteroid group (0 RU/ml, IQR 0 to 45 RU/ml) (p=0.49). **(MODERATE)** ***Rituximab compared with supportive therapy*** One RCT (Dahan et al. 2017, n=75) compared rituximab with supportive therapy. Anti-PLA2R level at 3 months: • *statistically significant decrease* in anti-PLA2R level in the rituximab group (0.0 RU/ml, IQR 0.0 to 49.1 RU/ml) compared with the supportive therapy group (54.6 RU/ml, IQR 16.5 to 278.4 RU/ml) (p<0.001). **(MODERATE)** Anti-PLA2R level at 6 months: • *statistically significant decrease* in anti-PLA2R level in the rituximab group (0.0 RU/ml, IQR 0.0 to 34.0 RU/ml) compared with the supportive therapy group (45.7 RU/ml, IQR 7.6 to 262.2 RU/ml) (p=0.002). **(MODERATE)** Number of adults PLA2R positive at 3 months: • *statistically significant decrease* in the number of adults who were PLA2R positive in the rituximab group (11/37, 31.4%) compared with the supportive therapy group (25/38, 83.3%) (p<0.001). **(MODERATE)** Number of adults PLA2R positive at 6 months: • *statistically significant decrease* in the number of adults who were PLA2R positive in the rituximab group (13/37, 36.1%) compared with the supportive therapy group (24/38, 75.0%) (p=0.001). **(MODERATE)** **These studies provided moderate certainty evidence that there was no difference between rituximab and a cyclic regimen of cyclophosphamide and corticosteroids in anti-PLA2R levels, but that rituximab decreased anti-PLA2R levels compared supportive therapy. No evidence was identified that compared rituximab with ciclosporin.**
The time interval to maximum reduction of anti-PLA2R antibodies and proteinuria following rituximab administration	This outcome is important to patients because it is thought to correlate with the speed of remission in patients treated with rituximab. No evidence was identified for this outcome.
Serum albumin **Certainty of evidence:** Low to high	This outcome is important to patients because the definition of complete or partial remission may be defined as a composite of proteinuria and serum albumin level. In total 2 RCTs provided evidence relating to serum albumin in adults with IMN, measured at different time points up to 2 years. One study compared rituximab with

	cyclophosphamide and corticosteroids and 1 study compared rituximab with supportive therapy. No evidence was identified for children. ***Rituximab compared with ciclosporin*** No evidence was identified for this comparator. ***Rituximab compared with cyclic cyclophosphamide and corticosteroid*** One RCT (Scolari et al. 2021, n=74) compared rituximab with cyclic cyclophosphamide and corticosteroid. Serum albumin at 6 months: • in the rituximab group (34 g/litre, IQR 28 to 38 g/litre) and the cyclic cyclophosphamide and corticosteroid group (36 g/litre, IQR 28 to 38 g/litre). No statistical analysis reported. **(MODERATE)** Serum albumin at 12 months: • in the rituximab group (37 g/litre, IQR 29 to 42 g/litre) and the cyclic cyclophosphamide and corticosteroid group (37 g/litre, IQR 32 to 40 g/litre). No statistical analysis reported. **(MODERATE)** Serum albumin at 18 months: • in the rituximab group (39 g/litre, IQR 34 to 42 g/litre) and the cyclic cyclophosphamide and corticosteroid group (38 g/litre, IQR 33 to 41 g/litre). No statistical analysis reported. **(MODERATE)** Serum albumin at 24 months: • in the rituximab group (40 g/litre, IQR 35 to 42 g/litre) and the cyclic cyclophosphamide and corticosteroid group (38 g/litre, IQR 34 to 41 g/litre). No statistical analysis reported. **(MODERATE)** Serum albumin at 36 months: • in the rituximab group (38 g/litre, IQR 32 to 41 g/litre) and the cyclic cyclophosphamide and corticosteroid group (39 g/litre, IQR 33 to 43 g/litre). No statistical analysis reported. **(MODERATE)** ***Rituximab compared with supportive therapy*** One RCT (Dahan et al. 2017, n=75) compared rituximab with supportive therapy. Serum albumin at 3 months: • *no statistically significant difference* in serum albumin in the rituximab group (27 g/litre, IQR 21 to 31 g/litre) compared with the supportive therapy group (23 g/litre, IQR 19 to 27 g/litre) (p=0.10). **(MODERATE)** Serum albumin at 6 months: • *statistically significant increase* in serum albumin in the rituximab group (30 g/litre, IQR 26 to 34 g/litre) compared with the supportive therapy group (24 g/litre, IQR 20 to 29 g/litre) (p=0.029). **(MODERATE)** Serum albumin at last follow up (median 17 months, IQR 12.5 to 24.0 months):

	• *statistically significant increase* in serum albumin in the rituximab group (32 g/litre, IQR 26 to 35 g/litre) compared with the supportive therapy group (27 g/litre, IQR 20 to 30 g/litre) (p=0.03). **(LOW)** **One study provided low to moderate certainty evidence that, compared with supportive therapy, rituximab increased serum albumin at 6 and 17 months but not at 3 months. One study provided moderate certainty evidence on the effects of rituximab compared with a cyclic regimen of cyclophosphamide and corticosteroids; however, no statistical analysis was provided therefore no conclusions could be drawn. No evidence was identified that compared rituximab with ciclosporin.**
Safety	
Serious adverse events **Certainty of evidence:** Moderate to high	Drug-related adverse events (side effects) are important to patients because they will impact on their treatment choices and recovery and can sometimes have long-term consequences. No evidence was identified for children. ***Rituximab compared with ciclosporin*** One RCT (Fervenza et al. 2019, n=130) compared rituximab with ciclosporin. • *no statistically significant difference* in the number of adults with serious adverse events in the rituximab group (11/65, 17%) compared with the ciclosporin group (20/65, 31%) (p=0.06). No incidences of cancer or death occurred during the trial. **(HIGH)** ***Rituximab compared with cyclic cyclophosphamide and corticosteroid*** One RCT (Scolari et al. 2021, n=74) compared rituximab with cyclic cyclophosphamide and corticosteroid. • *no statistically significant difference* in the number of adults with serious adverse events in the rituximab group (7/37, 19%) compared with the cyclic cyclophosphamide and corticosteroid group (5/37, 14%) (p=0.75). Three incidences of cancer (2 in the rituximab arm [lung and breast carcinoma] and 1 in the cyclic cyclophosphamide corticosteroid group [prostate carcinoma]). The patient with lung cancer died during follow-up. **(MODERATE)** ***Rituximab compared with supportive therapy*** One RCT (Dahan et al. 2017, n=75) compared rituximab with supportive therapy. • *no statistically significant difference* in serious adverse events in the rituximab group (8 events) compared with the supportive therapy group (8 events) (p=0.87). One incidence of cancer occurred in the supportive therapy group. **(MODERATE)** **These studies provided moderate to high certainty evidence that there was no difference between rituximab and ciclosporin, a cyclic regimen of cyclophosphamide and corticosteroids, or supportive therapy, in serious adverse events.**
Adverse events **Certainty of evidence:** Moderate to high	Drug-related adverse events (side effects) are important to patients because they will impact on their treatment choices and recovery and can sometimes have long-term consequences. No evidence was identified for children. ***Rituximab compared with ciclosporin***

	One RCT (Fervenza et al. 2019, n=130) compared rituximab with ciclosporin. • *no statistically significant difference* in the number of adults with adverse events in the rituximab group (46/65, 71%) compared with the ciclosporin group (51/65, 78%) (p=0.31). **(HIGH)** • *statistically significant increase* in the number of adults with infusion-related reactions in the rituximab group (16/65, 25%) compared with the ciclosporin group (0/65, 0%) (p<0.001). **(MODERATE)** ***Rituximab compared with cyclic cyclophosphamide and corticosteroid*** One RCT (Scolari et al. 2021, n=74) compared rituximab with cyclic cyclophosphamide and corticosteroid. • *no statistically significant difference* in the number of adults with adverse events in the rituximab group (16/37, 43%) compared with the cyclic cyclophosphamide and corticosteroid group (16/37, 43%) (p>0.99). **(MODERATE)** • *statistically significant increase* in the number of adults with drug infusion-related reactions or intolerance in the rituximab group (9/37, 24%) compared with the cyclic cyclophosphamide and corticosteroid group (1/37, 3%) (p=0.01). **(MODERATE)** ***Rituximab compared with supportive therapy*** No evidence was identified for this comparator. **These studies provided moderate to high certainty evidence that there was no difference between rituximab and ciclosporin, or a cyclic regimen of cyclophosphamide and corticosteroids, in adverse events, but rituximab increased infusion-related reactions compared with ciclosporin or cyclic cyclophosphamide and corticosteroids. No evidence was identified for rituximab compared with supportive therapy.**

Abbreviations

KDQOL-SF, Kidney Disease Quality of Life Short Form; PLA2R, phospholipase A2 receptor; RCT, randomised controlled trial

In people with idiopathic membranous nephropathy, what is the cost effectiveness of rituximab compared with current treatment (alkylating agents, calcineurin inhibitors, or no rituximab treatment)?

Outcome	Evidence statement
Cost-effectiveness	Cost effectiveness may not be a priority to individual patients, but it is an important outcome for decision makers. It reflects the incremental clinical effectiveness of rituximab compared with other available treatment options as well as the cost. One network meta-analysis (NMA) (Dai et al 2021) examined the cost effectiveness of different treatment options (rituximab, tacrolimus, chlorambucil, ciclosporin and cyclophosphamide) for IMN based on BNF 2019 prices and the clinical outcome of complete and partial remission rate. The cost-effectiveness compared with rituximab was calculated as: • Tacrolimus: rituximab was dominated • Chlorambucil: £20,351.20 (ICER above the NICE threshold of £20,000) • Ciclosporin: rituximab was dominated

	• Cyclophosphamide: rituximab was dominated The cost effectiveness outcomes modelled in this study should be treated with some degree of caution. The clinical effectiveness data used in the NMA come from 2 RCTs: 1 which is included in the clinical effectiveness section of this evidence review (Dahan et al. 2017) and another RCT (Jinling et al. 2019) which is not in publication. The NMA investigated multiple treatment options for IMN and included 75 RCTs, only 2 of these provided data on the clinical effectiveness of rituximab. The confidence intervals for all the pairwise comparisons of rituximab with other treatment options were very wide, which is likely to lead to a lack of certainty in the resulting cost-effectiveness estimate. Furthermore, the economic model only compares immunosuppressant therapies and it is unclear if other costs (for example supportive therapy) are included in the model. A cost-effectiveness analysis (Hamilton et al. 2018) examined the cost-effectiveness of rituximab compared with the modified Ponticelli regimen (rotating high-dose intravenous corticosteroids and immunosuppression, in this case with methylprednisolone and cyclophosphamide). ICER: • 1 year: rituximab dominates • 5 years: £95 494.13 (primary outcome reported, above the NICE threshold of £20,000) • 10 years: £24 256.91 (above the NICE threshold of £20,000) • Lifetime: £10 246.09 In terms of QALY gains, rituximab has a small benefit over the modified Ponticelli regimen at 1 year but this effect is reversed from 5 years onwards: • 1 year: rituximab 0.954, modified Ponticelli regimen 0.952 • 5 years: rituximab 3.697, modified Ponticelli regimen 3.712 • 10 years: rituximab 6.513, modified Ponticelli regimen 6.603 • Lifetime: rituximab 13.650, modified Ponticelli regimen 14.162 The authors reported that at 5 years after treatment, rituximab is cheaper than the modified Ponticelli regimen and that most of the modelled ICERs were below the £20,000 per QALY threshold set by NICE as the acceptable limit for cost-effectiveness. They reported that rituximab was cheaper over a lifetime but less effective than the modified Ponticelli regimen. Rituximab was associated with a QALY loss of 0.014 at 5 years after treatment. The authors noted that despite its efficacy, the modified Ponticelli regimen is associated with a significant side-effect profile, including an increased risk of infection, osteoporosis, diabetes mellitus, weight gain, hemorrhagic cystitis, infertility, and malignancy. Serious adverse events were included in the model. As with the study by Dai et al. 2021, these findings should be interpreted with caution. Firstly, the clinical effectiveness data are taken from 1 RCT and 1 observational study and may not be representative of the efficacy observed in recent RCTs. Secondly, while the costs for rituximab and the modified Ponticelli regimen included in the model were comprehensive and reflective of UK practice, these are now potentially out of date.

Abbreviations

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNF, British National Formulary; ICER, incremental cost effectiveness ratio; NMA, network meta-analysis; QALY, quality-adjusted life year; RCT, randomised controlled trial

From the evidence selected, are there any subgroups of patients that may benefit from rituximab more than the wider population of interest?

Subgroup	Evidence statement
Adults/ children/ age	No evidence was identified for children. 1 RCT (Fervenza et al 2019) (n=130) found that the treatment effect of rituximab compared with ciclosporin in terms of complete or partial remission, was consistent across the pre-specified age-subgroups of ≤50 and >50 years. Test for interaction p=0.87. 1 RCT (Scolari et al 2021) (n=74) found a trend for lower complete remission rates at 12 months in the rituximab arm for adults <55 years compared with people ≥55 years. However, statistical tests for interaction were nonsignificant.
eGFR greater or less than 60ml/min/1.73m^2 at baseline	No evidence was identified that compared outcomes in people with an eGFR greater or less than 60ml/min/1.73m^2.
Proteinuria at baseline	1 RCT (Scolari et al 2021) (n=74) found a trend for lower complete remission rates at 12 months in the rituximab group for adults with more severe proteinuria or lower serum albumin compared with less severe proteinuria or higher serum albumin. However, statistical tests for interaction were nonsignificant.
Anti-PLA2R level at baseline	1 RCT (Fervenza et al. 2019) (n=130) provided comparative evidence of complete or partial remission by anti-PLA2R level at baseline. In adults with a baseline anti-PLA2R level of ≤40 units/ml, 11/15 adults in the rituximab group were in complete or partial remission at 24 months compared with 7/19 adults in the cyclosporine group (risk difference 36.5%, 95% CI 5.3 to 67.7%). In adults with a baseline anti-PLA2R level of >40 units/ml, 28/50 adults in the rituximab group were in complete or partial remission at 24 months compared with 6/46 adults in the ciclosporin group (risk difference 43.0%, 95% CI 26.1 to 59.8%). Test for interaction p=0.72. 1 RCT (Scolari et al. 2021) (n=74) provided comparative evidence of complete or partial remission in adults who were anti-PLA2R positive at baseline by their baseline anti-PLA2R level. In adults with a baseline anti-PLA2R level >58 units/ml 7/7 (100%) were in complete or partial remission at 24 months in the rituximab group compared with 9/12 (75%) in the cyclic cyclophosphamide and corticosteroid group, p=0.74. In adults with a baseline anti-PLA2R level ≤58 units/ml 6/8 (75%) were in complete remission at 24 months in the rituximab group compared with 5/6 (83%) in the cyclic cyclophosphamide and corticosteroid group, p=1.00.

Abbreviations

PLA2R, phospholipase A2 receptor; RCT, randomised controlled trial

From the evidence selected, what are the criteria used by the research studies to define IMN?

Reference	Criteria
Dahan 2017	Diagnosis: biopsy-proven diagnosis established 2 years before inclusion

	Severity: urinary protein excretion ≥3.5 g/day or a urinary protein-to-creatinine ratio ≥3500 mg/g, and a serum albumin <30 g/litre for at least 6 months.
Fervenza 2019	Diagnosis: biopsy-proven diagnosis Severity: proteinuria of more than 5 g/day on average in two 24-hour urine samples obtained within 14 days, a decline of less than 50% in proteinuria.
Scolari 2021	Diagnosis: biopsy-proven diagnosis within 2 years before inclusion Severity: proteinuria >3.5 g/day on 3 24-hour urine collections (once a week for 3 weeks).

From the evidence selected how many patients received re-dosing with rituximab and how long after initial treatment with rituximab?

Reference	Criteria
Dahan 2017	All participants in the rituximab group received 375 mg/m^2 intravenous rituximab on days 1 and 8. At the end of the 6-month randomized phase, clinicians were free give rituximab (or other treatments) to participants in either group. No detail was provided on the number of adults who received subsequent doses of rituximab.
Fervenza 2019	All participants in the rituximab group received 1 g of intravenous rituximab on days 1 and 15. If proteinuria was reduced from baseline by at least 25% at 6 months but there was not complete remission, a second course of rituximab was given. If complete remission was observed at 6 months, no second course was given. If proteinuria was reduced by less than 25% by 6 months, the person was considered to have treatment failure and no further rituximab was administered. No detail was provided on the number of adults who received subsequent doses of rituximab.
Scolari 2021	All participants in the rituximab group received 1 g of intravenous rituximab on days 1 and 15. No subsequent doses were given throughout the 36-month follow-up period.

6. Discussion

The clinical effectiveness studies included in the evidence review (Dahan et al. 2017, Fervenza et al. 2019, and Scolari et al. 2021) had some limitations for determining the efficacy and safety of rituximab compared with calcineurin inhibitors, alkylating agents, or no treatment, with or without supportive therapy.

Most of the outcomes from Dahan et al. 2017 were graded to have moderate certainty using modified GRADE. Outcomes were downgraded for risk of bias because the participants were only required to have 3 months without immunosuppressive therapy before randomisation. Because the effects of rituximab may be seen 3 months after treatment, it is possible that prior treatment affected the outcomes in the trial and no detail was provided on the type of previous treatment and the number of participants who received treatment 3 months before randomisation. The observational follow-up outcomes were further downgraded to low certainty because of the possibility of differences in management between the treatment groups in the observational period.

While the study by Fervenza et al. 2019 was generally well designed, resulting in some high certainty outcomes, many of the outcomes were downgraded to moderate for imprecision because they were modelled estimates and could not be used to determine the statistical significance of the findings. Some outcomes, such as quality of life, were downgraded further because of wide confidence intervals and low participant follow-up numbers.

Most of the outcomes from Scolari et al. 2021 were graded to have low certainty. Outcomes were downgraded for imprecision because the study was not powered to detect a difference in outcomes between the treatment groups. In general, outcomes across the studies were reported poorly with many results reported without point estimates, confidence intervals or p-values meaning interpretation was limited.

Because of the administration and monitoring requirements of the intervention and some of the comparators, all of the studies were open-label. However, because the primary outcome of complete or partial remission was well defined in each of the studies and determined through biochemical assay, bias arising from outcome assessment is unlikely. It is also unlikely that the participant knowledge of their intervention affected adherence to the intervention as rituximab is given as 1 or 2 infusions. If adherence to the comparator was affected by the open-label design, then this would result in an underestimate of the effect of rituximab. Fervenza et al. 2019 reported that the infrequent intravenous administration of rituximab, compared with twice daily ciclosporin, resulted in better adherence to therapy. However, Scolari et al. 2021 and Fervenza et al. 2021 reported that infusion-related reactions were significantly increased with rituximab compared with ciclosporin or cyclic cyclophosphamide and corticosteroids. Therefore, while adherence may be better with rituximab, it may be less favourable in terms of infusion-related reactions and intolerance.

The doses of rituximab used in the studies were comparable with the recommended doses for other licensed indications such as rheumatoid arthritis. All 3 RCTs gave the initial doses of rituximab in two separate doses, either at days 1 and 8 or days 1 and 15. However, subsequent dosing of rituximab varied between the studies with Dahan et al. 2017 and Fervenza et al. 2019 allowing for subsequent doses of rituximab based on clinical need after a 6-month period, and Scolari et al. 2021 not allowing for subsequent dosing. Therefore, observed differences in outcomes between the studies cannot solely be attributed to the differences in comparator arms.

Only 1 RCT (Fervenza et al. 2019) reported quality of life outcomes, reported as subscales of the KDQOL-SF with no overall quality of life score. These outcomes were only reported for adults who were in complete or partial remission at each time point and who had quality of life data available. Furthermore, the statistical analysis was not adjusted to account for multiple comparisons therefore these data could not be used to determine the effect of rituximab on quality of life.

While none of the clinical effectiveness studies were conducted in the UK, diagnosis and outcome definitions appeared to follow the KDIGO guidelines and are therefore likely to be generalisable to UK practice.

The primary outcome of remission of proteinuria is a surrogate outcome and these trials may not have been large enough or for a long enough duration to detect differences in clinical outcomes such as ESRD. Scolari et al. 2021 reported that the purpose of their study was to gather preliminary data on disease remission to perform a sample size calculation for a larger trial, therefore this study would not be powered to detect differences in treatment effect. From their findings, they estimated that 1,500 people would need to be recruited to detect a 5% difference in remission between the rituximab and cyclic cyclophosphamide and corticosteroid regimen. Fervenza et al. 2019 also performed a power calculation for non-inferiority in which superiority would only be tested if the test for non-inferiority was significant. Dahan et al. 2017 conducted a power calculation for superiority of rituximab. However, this was based on a remission rate of 20% in the supportive therapy group and a 50% rate of remission in the rituximab group. While the observed remission rate in the supportive therapy group was 21%, the remission rate in the rituximab and supportive therapy group was lower than the study was powered to detect (35%).

Two studies (Dai et al. 2021 and Hamilton et al. 2018) were identified that provided a cost-effectiveness estimate for rituximab compared with other treatment options. However, the estimates from both studies should be treated with caution. The study by Dai et al. 2021 used clinical effectiveness data from 2 RCTs, one of which was unpublished, and Dahan et al. 2017 which compared rituximab with supportive therapy. Despite this, there was no cost-effectiveness estimate given for rituximab compared with supportive therapy alone. The study by Hamilton et al. 2018 was generally well conducted, however the main limitation was the poorly reported literature search. This resulted in the clinical effectiveness data in the model being derived from 1 RCT which compared the effect of a 6-month course of alternating prednisolone and cyclophosphamide with supportive therapy, and 1 observational study. It is also likely that the costs included in these studies are out of date.

7. Conclusion

This evidence review found low to high certainty evidence for the efficacy and safety of rituximab for treating IMN compared with calcineurin inhibitors, alkylating agents, and supportive therapy. All 3 clinical effectiveness studies included adults who had a biopsy-confirmed diagnosis of IMN and were at high risk of progressive disease and had not responded to at least 3 months of supportive therapy.

The results of the observational follow-up by Dahan et al. 2017 found that while there was no statistically significant increase in remission in the randomised phase of the trial at 3 or 6 months, rituximab with supportive therapy was more effective than supportive therapy alone at inducing remission of proteinuria over the longer-term, with most incidences of remission occurring in the observational follow-up period. The authors also reported significant decreases in anti-PLA2R levels were seen as early as 3 months, therefore this may serve as an early marker of longer-term response to treatment. However, these findings should be interpreted with caution because of the potential bias arising from the short run-in period and because of possible differences in management between treatment groups during the observational follow-up period.

The results of the study by Fervenza et al. 2019 found that there was no difference between rituximab and ciclosporin at inducing complete or partial remission in adults at 12 months, but that rituximab was superior to ciclosporin at inducing complete or partial remission in adults at 24 months.

The results of the study by Scolari et al. 2021 suggest that rituximab was similarly but not more effective at inducing remission of proteinuria compared with a cyclic regimen of cyclophosphamide and corticosteroids. However, this study was not powered to detect a difference in clinical effect.

There was no statistically significant difference in adverse events in any of the studies when rituximab was compared with supportive care, ciclosporin or a cyclic regimen of cyclophosphamide and corticosteroids. Alkylating agents, such as cyclophosphamide, are known to be associated with significant side effects including an increased risk of cancer. However, it is unlikely that such adverse events would be observed over the duration of the study by Scolari et al. 2021.

One study found that rituximab was cheaper over a lifetime but less effective than the modified Ponticelli regimen (cyclophosphamide and corticosteroids). Analysis of the other study found that rituximab was not cost effective compared with tacrolimus, ciclosporin, or cyclophosphamide, but was more cost effective than chlorambucil (ICER above the NICE threshold of £20,000). Because of their limitations, notably the likelihood that the costs used for rituximab are now out of date, no conclusions regarding the cost effectiveness of rituximab could be drawn from these studies. No evidence was identified for rituximab compared with supportive therapy.

None of the included studies were powered to detect differences in clinical outcomes such as ESRD. To observe differences in these outcomes much larger trials are needed with longer follow-up times, or well conducted meta-analyses which include all of the recent trials, outcomes, and comparators. Furthermore, there was no evidence identified that investigated tacrolimus or chlorambucil as comparators. If tacrolimus and chlorambucil are currently used in UK clinical practice for the treatment of IMN, RCTs may need to be undertaken to assess their effectiveness compared with rituximab.

There were no subgroups of patients that may benefit more from rituximab than the wider population of interest. No evidence was identified that compared outcomes in people with an eGFR greater or less than 60ml/min/1.73m^2.

The findings of this review are important because people with IMN who do not receive immunosuppressive treatment are more likely to need renal replacement therapy in the form of dialysis or transplant. The immunosuppressive treatments currently used are alkylating agents, which are associated with significant side effects including an increased risk of cancer, or calcineurin inhibitors, which are associated with high relapse rates after successful remission. While there are substantial gaps in the evidence for both the clinical and cost-effectiveness of rituximab compared with these treatment options, this review has shown that rituximab may be non-inferior in terms of efficacy and safety and may be more effective than ciclosporin in inducing remission over the longer-term for adults with a high risk of progressive disease.

Appendix A PICO document

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

1. In people with IMN, what is the clinical effectiveness of rituximab compared with current treatment (calcineurin inhibitors, alkylating agents, or no rituximab treatment)?
2. In people with IMN, what is the safety of rituximab compared with current treatment (calcineurin inhibitors, alkylating agents, or no rituximab treatment)?
3. In IMN, what is the cost effectiveness of rituximab compared with current treatment (calcineurin inhibitors, alkylating agents, or no rituximab treatment)?
4. From the evidence selected, are there any subgroups of patients that may benefit from rituximab more than the wider population of interest?
5. From the evidence selected, what are the criteria used by the research studies to define IMN?
6. From the evidence selected how many patients received re-dosing with rituximab and how long after initial treatment with rituximab?

P –Population and Indication	People with a diagnosis of IMN in whom supportive therapy has not achieved partial or complete remission. [Diagnosis may have been made by a combination of antibody tests (anti-PLA2R or anti-THSD7A antibodies) and kidney biopsy.] The following subgroups should be considered: • Adults • Children • People who have an eGFR (Estimated Glomerular Filtration Rate) > or equal to 60ml/min/1.73m^2 • People who have an eGFR less than 60ml/min/1.73m^2 • People grouped by level of proteinuria pre-treatment People grouped by level of anti-PLA2R antibodies pre-treatment.
I – Intervention	Rituximab [Typically, intravenous rituximab at baseline (1g and then 1g after 2 weeks) with the option of a second treatment (1g and then 1g after 2 weeks) at 6 months. Some studies may have used different regimens (e.g. 1000 mg of intravenous medication at baseline and on day 15; 375mg/m^2 rituximab on days 1 and 8) Do not exclude studies using subcutaneous rituximab. Patients may or may not be receiving concurrent best supportive care.]
C – Comparator(s)	There are 3 comparators: 1. Treatment with a calcineurin inhibitor, (either ciclosporin or tacrolimus [Studies may use a variety of dosing regimens] 2. Treatment with an alkylating agent, either (cyclophosphamide or chlorambucil) [(intravenous or oral)

	with or without intravenous or oral corticosteroids. Studies may use a variety of dosing regimens.] 3. No rituximab treatment or placebo] Patients may or may not be receiving concurrent best supportive care
O – Outcomes	**<u>Clinical Effectiveness</u>** There are no known MCIDs for any of these outcomes. <u>Critical to decision-making:</u> • Remission of proteinuria This outcome is important to patients because a remission of proteinuria is a strong predictor of reduced risk of decline in kidney function. [Proteinuria should be measured at periodic intervals, for example at least every 6 months, in grams per 24 hours or as urine protein:creatinine ratio. This outcome may also be presented as an absolute or percentage reduction in these measures. The definition of complete or partial remission varies between studies and may be defined as a composite of proteinuria and serum albumin level.] • Excretory kidney function This outcome is important to patients because it is a measure of how well a patient's kidneys function. [Excretory kidney function is estimated by serum creatinine, creatinine clearance or eGFR, measured at periodic intervals, for example, every 6 months.] • End Stage Renal Disease (ESRD) This outcome is important to patients because ESRD is the final, permanent stage of chronic kidney disease, where kidney function has declined to the point that the kidneys can no longer function on their own. [ESRD is defined as dialysis dependence or eGFR<15 mL/min].] <u>Important to decision-making:</u> • Quality of Life This outcome is important to patients because IMN causes nephrotic syndrome which is associated with increased infections and thrombosis and may have a severe impact on quality of life. [Quality of life can be measured using a recognised quality of life score for example EQ-5D-5L. Other measures can be used as described in studies.] • Anti-PLA2R level. This outcome is important to patients because PLA2R autoantibody levels are thought to correlate with disease activity (active disease, partial remission, complete remission) in patients treated with rituximab. [The level of the autoantibody anti-PLA2R may be measured at periodic intervals, for example, every 3 to 6 months.] • The time interval to maximum reduction of anti-PLA2R antibodies and proteinuria following rituximab administration.

	This outcome is important to patients because it is thought to correlate with the speed of remission in patients treated with rituximab. [The time can be measured in months.] • Serum albumin This outcome is important to patients because the definition of complete or partial may be defined as a composite of proteinuria and serum albumin level. [This outcome is measured at periodic intervals, for example every 3 months and is measured in grams per decilitre; This outcome may also be presented as an increase in serum albumin level in grams per decilitre or as a percentage.] <u>Safety</u> • Safety including but not limited to incidences of infusion-related reactions, serious infections, progressive multifocal leukoencephalopathy, hospitalisations, new onset hyperglycaemia, diabetes, hypertension, decline in renal function as measured by serum creatinine, creatinine clearance or eGFR. <u>Cost effectiveness</u>
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	2011 to 2021
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-publication prints and guidelines
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase, CRD, INAHTA, the Cochrane Library and trials registries were searched limiting the search to papers published in English language.

Search date: 14th July 2021

Database: Medline ALL

Platform: Ovid

Version: Ovid MEDLINE(R) ALL <1946 to July 13, 2021>

Search date: 14th July 2021

Number of results retrieved: 290

Search strategy:

Database: Ovid MEDLINE(R) ALL <1946 to July 13, 2021>

Search Strategy:

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1 Glomerulonephritis, Membranous/ (3365)

2 (((extramembran* or membran*) adj2 (glomerulo* or nephropath*)) or (mn or imn)).tw. (76567)

3 (heymann* adj2 nephri*).tw. (573)

4 1 or 2 or 3 (77481)

5 Rituximab/ (16037)

6 (rituximab* or mabthera* or rituxan* or ruxience* or rixathon* or riximyo* or reditux* or rituxin* or ritumax* or rituzena* or blitzima* or tuxella* or truxima* or ritemvia* or c2b8 or idec102 or "idec 102" or idecc2b8 or 174722-31-74f4x42syq6 or "abp 798" or abp798 or "ct p10" or ctp10 or "gp 2013" or gp2013 or "hlx 01" or hlx01 or "mk 8808" or mk8808 or "pf 05280586" or pf05280586 or "pf 5280586" or pf5280586 or "r 105" or r105 or "rg 105" or rg105 or "ro 452294" or ro452294).af. (26465)

7 5 or 6 (26465)

8 4 and 7 (393)

9 limit 8 to english language (356)

10 animals/ not humans/ (4827634)

11 9 not 10 (356)

12 limit 11 to yr="2011 -Current" (290)

Database: Embase

Platform: Ovid

Version: Embase <1974 to 2021 July 13>

Search date: 14th July 2021

Number of results retrieved: 542

Search strategy:

1 membranous glomerulonephritis/ (8200)

2 (((extramembran* or membran*) adj2 (glomerulo* or nephropath*)) or (mn or imn)).tw. (98517)

3 (heymann* adj2 nephri*).tw. (607)

4 1 or 2 or 3 (100841)

5 rituximab/ (87665)

6 (rituximab* or mabthera* or rituxan* or ruxience* or rixathon* or riximyo* or reditux* or rituxin* or ritumax* or rituzena* or blitzima* or tuxella* or truxima* or ritemvia* or c2b8 or idec102 or "idec 102" or idecc2b8 or 174722-31-74f4x42syq6 or "abp 798" or abp798 or "ct p10" or ctp10 or "gp 2013" or gp2013 or "hlx 01" or hlx01 or "mk 8808" or mk8808 or "pf 05280586" or pf05280586 or "pf 5280586" or pf5280586 or "r 105" or r105 or "rg 105" or rg105 or "ro 452294" or ro452294).af. (92898)

7 5 or 6 (92898)

8 4 and 7 (1164)

9 limit 8 to english language (1110)

10 nonhuman/ not human/ (4820695)

11 9 not 10 (1104)

12 limit 11 to (books or chapter or conference abstract or conference paper or "conference review" or editorial or letter or note) (429)

13 11 not 12 (675)

14 limit 13 to yr="2011 -Current" (542)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); CENTRAL

Platform: Wiley

Version:

CDSR –Issue 7 of 12, July 2021

CENTRAL – Issue 7 of 12, July 2021

Search date: 14th July 2021

Number of results retrieved: CDSR 1; CENTRAL 67.

ID Search Hits

#1 MeSH descriptor: [Glomerulonephritis, Membranous] this term only 117

#2 ((extramembran* or membran*) near/2 (glomerulo* or nephropath*)):ti,ab,kw or (mn or imn):ti,ab,kw 2484

#3 (heymann* near/2 nephri*) 1

#4 #1 or #2 or #3 2485

#5 MeSH descriptor: [Rituximab] this term only 1347

#6 (rituximab* or mabthera* or rituxan* or ruxience* or rixathon* or riximyo* or reditux* or rituxin* or ritumax* or rituzena* or blitzima* or tuxella* or truxima* or ritemvia* or c2b8 or idec102 or "idec 102" or idecc2b8 or "174722-31-74f4x42syq6" or "abp 798" or abp798 or "ct p10" or ctp10 or "gp 2013" or gp2013 or "hlx 01" or hlx01 or "mk 8808" or mk8808

or "pf 05280586" or pf05280586 or "pf 5280586" or pf5280586 or "r 105" or r105 or "rg 105" or rg105 or "ro 452294" or ro452294) 5175

#7 #5 or #6 5175

#8 #4 and #7 68

Database: CRD databases

Platform: CRD databases

Version:

DARE –Up to 2015

NHS EED – Up to 2015

HTA – Up to 2018

Search date: 14th July 2021

Number of results retrieved: NHS EED 1; DARE 1; HTA 0

1 MeSH DESCRIPTOR Glomerulonephritis, Membranous 13 Delete

2 (((extramembran* or membran*) near2 (glomerulo* or nephropath*))) or (mn or imn) 321 Delete

3 ((heymann* near2 nephri*)) 0 Delete

4 #1 OR #2 OR #3 323 Delete

5 MeSH DESCRIPTOR Rituximab 94 Delete

6 ((rituximab* or mabthera* or rituxan* or ruxience* or rixathon* or riximyo* or reditux* or rituxin* or ritumax* or rituzena* or blitzima* or tuxella* or truxima* or ritemvia* or c2b8 or idec102 or "idec 102" or idecc2b8 or "174722-31-74f4x42syq6" or "abp 798" or abp798 or "ct p10" or ctp10 or "gp 2013" or gp2013 or "hlx 01" or hlx01 or "mk 8808" or mk8808 or "pf 05280586" or pf05280586 or "pf 5280586" or pf5280586 or "r 105" or r105 or "rg 105" or rg105 or "ro 452294" or ro452294)) 222 Delete

7 #5 OR #6 222 Delete

8 #4 AND #7 2 Delete

Database: INAHTA database

Platform: INAHTA

Version: Searched 14th July 2021

Search date: 14th July 2021

Number of results retrieved: 0

Search strategy:

Nephropathy and rituximab*

Membranous and rituximab*

Glomerulonephritis and rituximab*

Extramembranous and rituximab*

Trials registry search strategies

Clinicaltrials.gov

Search date: 12th July 2021

Number of results retrieved: 7

Search strategy: membranous nephropathy AND rituximab [Phase III or IV only]

Clinicaltrialsregister.eu

Search date: 13th July 2021

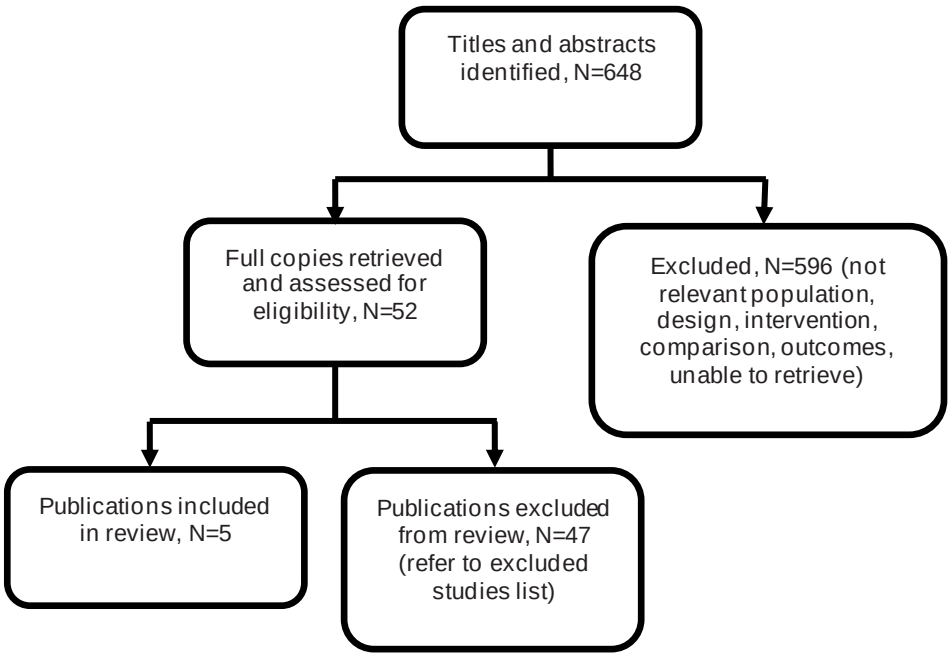
Number of results retrieved: 4

Search strategy: membranous nephropathy AND rituximab [Phase III or IV only]

Appendix C Evidence selection

The literature searches identified 648 references. These were screened using their titles and abstracts and 52 references were obtained in full text and assessed for relevance. Of these, 5 references are included in the evidence summary. The remaining 47 references were excluded and are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection - decision and rationale if excluded
Fervenza FC, Appel GB, Barbour SJ, Rovin BH, Lafayette RA, Aslam N, Jefferson JA, Gipson PE, Rizk DV, Sedor JR, Simon JF, McCarthy ET, Brenchley P, Sethi S, Avila-Casado C, Beanlands H, Lieske JC, Philibert D, Li T, Thomas LF, Green DF, Juncos LA, Beara-Lasic L, Blumenthal SS, Sussman AN, Erickson SB, Hladunewich M, Canetta PA, Hebert LA, Leung N, Radhakrishnan J, Reich HN, Parikh SV, Gipson DS, Lee DK, da Costa BR, Jüni P, Cattran DC; MENTOR Investigators. 2019. Rituximab or Ciclosporin in the Treatment of Membranous Nephropathy. New England Journal of Medicine, 381, 36-46.	Included
Dahan K, Debiec H, Plaisier E, Cachanado M, Rousseau A, Wakselman L, Michel PA, Mihout F, Dussol B, Matignon M, Mousson C, Simon T, Ronco P; GEMRITUX Study Group. 2017. Rituximab for Severe Membranous Nephropathy: A 6-Month Trial with Extended Follow-Up. Journal of the American Society of Nephrology, 28, 348.	Included
Lu W., Gong S., Li J., Luo, H., Wang, Y. Efficacy and safety of rituximab in the treatment of membranous nephropathy. A systematic review and meta-analysis. Medicine 2020. 99:16	Excluded. Not all recent RCTs included. Opted to include all individual RCTs to present results for different comparators separately.

Appendix D Excluded studies table

Study reference	Reason for exclusion
Ales Rigler, Andreja, Jerman, Alexander, Orsag, Alesa et al. (2017) Rituximab for the treatment of membranous nephropathy: a single-center experience. Clinical nephrology 88(13): 27-31	Study design – observational, higher quality evidence available
Bagchi, Soumita, Subbiah, Arun Kumar, Bhowmik, Dipankar et al. (2018) Low-dose Rituximab therapy in resistant idiopathic membranous nephropathy: single-center experience. Clinical kidney journal 11(3): 337-341	Study design – observational, higher quality evidence available
Boyer-Suavet, Sonia, Andreani, Marine, Lateb, Mael et al. (2019) Neutralizing Anti-Rituximab Antibodies and Relapse in Membranous Nephropathy Treated With Rituximab. Frontiers in immunology 10: 3069	Study design – observational, higher quality evidence available
Busch, Martin, Ruster, Christiane, Schinkothe, Claudia et al. (2013) Rituximab for the second- and third-line therapy of idiopathic membranous nephropathy: a prospective single center study using a new treatment strategy. Clinical nephrology 80(2): 105-13	Study design – observational, higher quality evidence available
Cravedi, Paolo, Sghirlanzoni, Maria Chiara, Marasa, Maddalena et al. (2011) Efficacy and safety of rituximab second-line therapy for membranous nephropathy: a prospective, matched-cohort study. American journal of nephrology 33(5): 461-8	Study design – observational, higher quality evidence available
Dahan, K, Johannet, C, Esteve, E et al. (2019) Retreatment with rituximab for membranous nephropathy with persistently elevated titers of anti-phospholipase A2 receptor antibody. Kidney international 95(1): 233-234	Study design – observational, higher quality evidence available
Danes, I, Agusti, A, Vallano, A et al. (2013) Available evidence and outcome of off-label use of rituximab in clinical practice. European journal of clinical pharmacology 69(9): 1689-99	Study design – observational, higher quality evidence available
Delafosse, Marion, Ponlot, Eleonore, Esteve, Emmanuel et al. (2021) Personalized phospholipase A2 receptor antibody-driven rituximab treatment strategy in membranous nephropathy. Kidney international 99(4): 1023-1024	Intervention – tacrolimus and rituximab
Delbarba, E, Santoro, D, Gesualdo, L et al. (2020) Rituximab vs. Cyclophosphamide in the treatment of membranous nephropathy: the RI-CYCLO Trial. Journal of the American Society of Nephrology : JASN 31: B9	Conference abstract
Dogra, L, Sahay, M, Ismal, K et al. (2020) SAT-391 TO STUDY THE RESPONSE TO IMMUNOSUPPRESSION THERAPY IN IDIOPATHIC MEMBRANOUS NEPHROPATHY (IMN): a RANDOMIZED, SINGLE CENTRE STUDY. Kidney international reports 5(3): S164	Conference abstract
Dogra, L, Sahay, M, Ismal, K et al. (2019) Long-term clinical outcomes and response to immunosupression in membranous nephropathy: a prospective, interventional, single-center study. Indian journal of nephrology 29(7): S23	Study design – observational, higher quality evidence available
El-Reshaid, Kamel, Sallam, Hossameldin Tawfik, Hakim, Abbass Ali et al. (2012) Rituximab in treatment of idiopathic glomerulopathy. Saudi journal of kidney diseases and transplantation : an official publication of the Saudi Center for Organ Transplantation, Saudi Arabia 23(5): 973-8	Study design – observational, higher quality evidence available
Fenoglio, R; Sciascia, S; Roccatello, D (2019) Membranous nephropathy: efficacy of low or standard rituximab-based protocols and comparison to the	Study design – observational, higher quality evidence available

ponticelli regimen. Journal of the American Society of Nephrology : JASN 30: 666	
Fenoglio, Roberta, Baldovino, Simone, Sciascia, Savino et al. (2021) Efficacy of low or standard rituximab-based protocols and comparison to Ponticelli's regimen in membranous nephropathy. Journal of nephrology 34(2): 565-571	Study design – observational, higher quality evidence available
Fervenza, FC, Canetta, PA, Barbour, S et al. (2017) A multi-center randomized controlled trial of rituximab versus cyclosporine in the treatment of idiopathic membranous nephropathy (MENTOR). Journal of the American Society of Nephrology : JASN 28: B2	Protocol
Fervenza, FC, Canetta, PA, Barbour, S et al. (2017) A multi-center randomized controlled trial of rituximab versus cyclosporine in the treatment of idiopathic membranous nephropathy (MENTOR). Journal of the American Society of Nephrology : JASN 28: B2	Protocol
Fiorentino, Marco, Tondolo, Francesco, Bruno, Francesca et al. (2016) Treatment with rituximab in idiopathic membranous nephropathy. Clinical kidney journal 9(6): 788-793	Study design – observational, higher quality evidence available
Gao, Shuang, Cui, Zhao, Wang, Xin et al. (2021) Rituximab Therapy for Primary Membranous Nephropathy in a Chinese Cohort. Frontiers in medicine 8: 663680	Study design – observational, higher quality evidence available
Hanset, Nicolas, Esteve, Emmanuel, Plaisier, Emmanuelle et al. (2020) Rituximab in Patients With Phospholipase A2 Receptor-Associated Membranous Nephropathy and Severe CKD. Kidney international reports 5(3): 331-338	Study design – observational, higher quality evidence available
Hasanzadeh, Katayoun, Pour-Reza-Gholi, Fatemeh, Freidoon, Mahboobeh et al. (2019) B lymphocyte subset changes in primary membranous nephropathy. Nephro-Urology Monthly 11(4): e96425	Study design – observational, higher quality evidence available
Huang, Lan, Dong, Qiao-Rong, Zhao, Ya-Juan et al. (2021) Rituximab for the management of idiopathic membranous nephropathy: a meta-analysis. International urology and nephrology 53(1): 111-119	Systematic review and meta-analysis. Not all recent RCTs were included. Opted to include individual RCTs to present results for different comparators separately
Irazabal, Maria V, Eirin, Alfonso, Lieske, John et al. (2013) Low- and high-molecular-weight urinary proteins as predictors of response to rituximab in patients with membranous nephropathy: a prospective study. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 28(1): 137-46	Study design – observational, higher quality evidence available
Kaegi, Celine, Wuest, Benjamin, Schreiner, Jens et al. (2019) Systematic Review of Safety and Efficacy of Rituximab in Treating Immune-Mediated Disorders. Frontiers in immunology 10: 1990	Study design – narrative review
Kong, Wai Yew; Swaminathan, Ramyasuda; Irish, Ashley (2013) Our experience with rituximab therapy for adult-onset primary glomerulonephritis and review of literature. International urology and nephrology 45(3): 795-802	Study design – observational, higher quality evidence available
Lionaki, Sophia, Marinaki, Smaragdi, Nakopoulou, Lydia et al. (2013) Depletion of B lymphocytes in idiopathic membranous glomerulopathy: results from patients with extended follow-up. Nephron extra 3(1): 1-11	Study design – observational, higher quality evidence available
Lu, WanJun, Gong, ShuHao, Li, Juan et al. (2020) Efficacy and safety of rituximab in the treatment of membranous nephropathy: A systematic review and meta-analysis. Medicine 99(16): e19804	Systematic review and meta-analysis. Not all recent RCTs were included. Opted to include individual RCTs to present results for different comparators separately
Michel, Pierre-Antoine, Dahan, Karine, Ancel, Pierre-Yves et al. (2011) Rituximab treatment for membranous	Study design – observational, higher quality evidence available

nephropathy: a French clinical and serological retrospective study of 28 patients. Nephron extra 1(1): 251-61	
Moroni, Gabriella, Depetri, Federica, Del Vecchio, Lucia et al. (2017) Low-dose rituximab is poorly effective in patients with primary membranous nephropathy. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 32(10): 1691-1696	Study design – observational, higher quality evidence available
Munoz-Menjivar, C, Soto Abraham, MV, Jimenez-Hernandez, MA et al. (2020) Second Line treatment of membranous nephropathy: rituximab or tacrolimus. Blood purification 49: 251	Study design – observational, higher quality evidence available
Ramachandran, Raja, Yadav, Ashok K, Kumar, Vinod et al. (2017) CD19 Targeted Low-Dose Rituximab Is Effective in the Management of Refractory Phospholipase A2 Receptor Antibody-Associated Membranous Nephropathy. Kidney international reports 2(1): 89-90	Letter
Roccatello, D; Fenoglio, R; Sciascia, S (2019) Efficacy of low or standard dose rituximab as compared to Ponticelli's regimen in membranous nephropathy. Nephrology dialysis transplantation 34: a123	Study design – observational, higher quality evidence available
Roccatello, D, Sciascia, S, Di Simone, D et al. (2016) New insights into immune mechanisms underlying response to Rituximab in patients with membranous nephropathy: A prospective study and a review of the literature. Autoimmunity reviews 15(6): 529-38	Study design – observational, higher quality evidence available
Ronco, PM, Dahan, K, Debiec, H et al. (2015) A randomized controlled trial of rituximab for severe idiopathic membranous nephropathy (IMN). Journal of the American Society of Nephrology : JASN 26(abstracts): 62a	Conference abstract
Ruggenenti, Piero, Cravedi, Paolo, Chianca, Antonietta et al. (2012) Rituximab in idiopathic membranous nephropathy. Journal of the American Society of Nephrology : JASN 23(8): 1416-25	Study design – observational, higher quality evidence available
Ruggenenti, Piero, Debiec, Hanna, Ruggiero, Barbara et al. (2015) Anti-Phospholipase A2 Receptor Antibody Titer Predicts Post-Rituximab Outcome of Membranous Nephropathy. Journal of the American Society of Nephrology : JASN 26(10): 2545-58	Study design – observational, higher quality evidence available
Seitz-Polski, Barbara, Debiec, Hanna, Rousseau, Alexandra et al. (2018) Phospholipase A2 Receptor 1 Epitope Spreading at Baseline Predicts Reduced Likelihood of Remission of Membranous Nephropathy. Journal of the American Society of Nephrology : JASN 29(2): 401-408	Study design – observational, higher quality evidence available
Siligato, R, Laudani, A, Gembillo, G et al. (2020) The route to individualized therapies in primary membranous nephropathy: BMI and kidney outcomes. Nephrology dialysis transplantation 35(suppl3): iii801	Study design – observational, higher quality evidence available
Sugiura, Hidekazu, Takei, Takashi, Itabashi, Mitsuyo et al. (2011) Effect of single-dose rituximab on primary glomerular diseases. Nephron. Clinical practice 117(2): c98-105	Study design – observational, higher quality evidence available
Suresh, S, Hegde, U, Konnur, A et al. (2021) POS-396 A RANDOMIZED CONTROL TRIAL OF RITUXIMAB VS MODIFIED PONTICELLI REGIMEN IN THE TREATMENT OF PRIMARY MEMBRANOUS NEPHROPATHY – A PILOT STUDY. Kidney international reports 6(4): S170-S171	Conference abstract

Suresh, S, Konnur, A, Gang, S et al. (2021) POS-163 A RANDOMIZED CONTROL TRIAL OF RITUXIMAB VERSUS MODIFIED PONTICELLI REGIMEN IN THE TREATMENT OF PRIMARY MEMBRANOUS NEPHROPATHY – A PILOT STUDY. Kidney international reports 6(4): S66-S67	Conference abstract
van de Logt, Anne-Els; Hofstra, Julia M; Wetzels, Jack F (2016) Pharmacological treatment of primary membranous nephropathy in 2016. Expert review of clinical pharmacology 9(11): 1463-1478	Study design – observational, higher quality evidence available
van den Brand, Jan A J G, Ruggenenti, Piero, Chianca, Antonietta et al. (2017) Safety of Rituximab Compared with Steroids and Cyclophosphamide for Idiopathic Membranous Nephropathy. Journal of the American Society of Nephrology : JASN 28(9): 2729-2737	Study design – narrative review
Wang, Xin, Cui, Zhao, Zhang, Yi-Miao et al. (2018) Rituximab for non-responsive idiopathic membranous nephropathy in a Chinese cohort. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 33(9): 1558-1563	Study design – observational, higher quality evidence available
Zhang, J, Bian, L, Ma, F-Z et al. (2018) Efficacy and safety of rituximab therapy for membranous nephropathy: a meta-analysis. European review for medical and pharmacological sciences 22(22): 8021-8029	Systematic review and meta-analysis. No recent RCTs included.
Zheng, Qiyan, Yang, Huisheng, Liu, Weijing et al. (2019) Comparative efficacy of 13 immunosuppressive agents for idiopathic membranous nephropathy in adults with nephrotic syndrome: a systematic review and network meta-analysis. BMJ open 9(9): e030919	Systematic review and meta-analysis. Not all recent RCTs included.
Zonozi, Reza, Laliberte, Karen, Huizenga, Noah R et al. (2021) Combination of Rituximab, Low-dose Cyclophosphamide, and Prednisone for Primary Membranous Nephropathy: A Case Series With Extended Follow Up. American journal of kidney diseases : the official journal of the National Kidney Foundation	Study design – observational, higher quality evidence available
Zou, Pei-Mei, Li, Hang, Cai, Jian-Fang et al. (2018) Therapy of Rituximab in Idiopathic Membranous Nephropathy with Nephrotic Syndrome: A Systematic Review and Meta-analysis. Chinese medical sciences journal = Chung-kuo i hsueh k'o hsueh tsa chih 33(1): 9-19	Systematic review and meta-analysis. No recent RCTs included.

Appendix E Evidence table

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Full citation Dahan K, Debiec H, Plaisier E et al. (2017) Rituximab for Severe Membranous Nephropathy: A 6-Month Trial with Extended Follow-Up. Journal of the American Society of Nephrology : JASN 28(1): 348-358 **Study location** France (31 centres) **Study type** Open label RCT 6 months randomised with a 24-month (inclusive) observational follow-up **Study aim** 'Because of the lack of randomized, controlled trials (RCTs) using rituximab and the high rate of spontaneous remission, this trial was designed to evaluate the efficacy of rituximab given to all patients at a standard dose (375 mg/m2) in two infusions added to supportive therapy compared with supportive therapy alone in patients with persistent nephrotic syndrome.' **Study dates** 17 January 2012 to 3 July 2014	**Inclusion criteria** Eligible patients were 18 years of age or older, had a biopsy-proven diagnosis established <2 years before inclusion, urinary protein excretion ≥3.5 g/d or a urinary protein-to-creatinine ratio ≥3500 mg/g, and serum albumin <30 g/L for at least 6 months, despite maximal tolerated dose of supportive therapy (angiotensin–converting enzyme inhibitors and/or angiotensin 2 receptor blockers, diuretics, and statin). Proteinuria was measured repeatedly before inclusion to confirm persistence of nephrotic syndrome. The eGFR by MDRD formula had to be >45 ml/min per 1.73 m2 **Exclusion Criteria** Secondary membranous nephropathy, pregnancy, breastfeeding, immunosuppressive treatment in the 3 preceding months, and active infectious disease. Patients with active hepatitis B and those with past hepatitis B infection without anti-Hbs antibodies were excluded **Total sample size** 77 **No. of participants in each treatment group**	**Intervention** Intravenous rituximab 375 mg/m2 on days 1 and 8 after randomisation and supportive therapy **Comparison** Supportive therapy	**Critical outcomes** **Remission of proteinuria** Complete or partial remission where remission was defined as complete if urinary protein excretion <500 mg/d or <500 mg/g creatinine, and partial if urinary protein excretion <3.5 g/d or <3500 mg/g creatinine and ≥500 mg/g creatinine with ≥50% reduction compared with baseline. • At 6 months, 13/37 (35.1%, 95% CI 19.7 to 50.5%) in the rituximab and supportive therapy group achieved complete or partial remission compared with 8/38 (21.1%, 95% CI 8.1 to 34.0%) in the supportive therapy group, (OR 2.0, 95% CI 0.7 to 5.7, p=0.21). Protein-to-creatinine ratio (mg/g) • Baseline: 7680.0 (IQR 4584.3 to 10399.0) in the rituximab and supportive therapy group compared with 7195.1 (IQR 5363.1 to 8965.1) in the supportive therapy group • 3 months: 4814.4 (IQR 3205.5 to 7398.6) in the rituximab and supportive therapy group compared with 4832.1 (IQR 2424.9 to 7911.9) in the supportive therapy group p=0.94 • 6 months: 3531.2 (IQR 1796.6 to 6469.4) in the rituximab and supportive therapy group compared with 5265.8 (IQR 2500.1 to 7690.7) in the supportive therapy group p=0.18 **Excretory kidney function** eGFR (ml/min/1.73 m^2) • Baseline: 66.7 (IQR 55.4 to 82.5) in the rituximab and supportive therapy group	This study was appraised using the Cochrane Risk of Bias tool for randomised control trials Domain 1 1.1. Yes 1.2. Yes 1.3. No information Risk-of-bias judgement Low Domain 2: 2.1. Yes 2.2. Yes 2.3. No information 2.4. N/A 2.5. N/A 2.6. Yes 2.7. N/A Risk-of-bias judgement Some concerns Domain 2: 2.1. Yes 2.2. Yes 2.3. Probably yes 2.4. Probably no 2.5. Probably no 2.6. Yes

	39 adults were randomised to rituximab and supportive therapy (37 received treatment) 38 adults were randomised to supportive therapy (38 received treatment) **Baseline characteristics** There were no notable differences in baseline characteristics.		compared with 72.7 (IQR 58.1 to 88.6) in the supportive therapy group • 3 months: 66.7 (IQR 57.2 to 87.1) in the rituximab and supportive therapy group compared with 68.9 (IQR 45.7 to 89.7) in the supportive therapy group, p=0.95 • 6 months: 65.6 (IQR 51.0 to 89.0) in the rituximab and supportive therapy group compared with 72.5 (IQR 52.4 to 89.7) in the supportive therapy group, p=0.75 Serum creatinine (micromol/litre) • Baseline: 98.1 (IQR 82.2 to 122.9) in the rituximab and supportive therapy group compared with 91.1 (IQR 74.3 to 122.0) in the supportive therapy group • 3 months: 94.6 (IQR 78.7 to 114.0) in the rituximab and supportive therapy group compared with 100.8 (IQR 81.3 to 115.8) in the supportive therapy group, p=0.88 • 6 months: 94.6 (IQR 75.1 to 130.8) in the rituximab and supportive therapy group compared with 97.2 (76.0 to 126.4) in the supportive therapy group, p=0.67 **Important outcomes** **Anti-PLA2R antibody levels** Anti-PLA2R antibody positive • Baseline: 27 (73.0%) in the rituximab and supportive therapy group compared with 28 (73.7%) in the supportive therapy group • 3 months: 11 (31.4%) in the rituximab and supportive therapy group compared with 25 (83.3%) in the supportive therapy group, p<0.001 • 6 months: 13 (36.1%) in the rituximab and supportive therapy group compared with 24 (75.0%) in the supportive therapy group, p=0.001 **Serum albumin** Measured in g/l • Baseline: 22 (IQR 18 to 25) in the rituximab and supportive therapy group compared with 22 (IQR 20 to 26) in the supportive therapy group • 3 months: 27 (IQR 21 to 31)) in the rituximab and supportive therapy group	Risk-of-bias judgement Low Domain 3: Missing outcome data 3.1. No 3.2. Yes 3.3. N/A 3.4. N/A Risk-of-bias judgement Low Domain 4: 4.1. No 4.2. Probably no 4.3. Yes 4.4. Probably no 4.5. N/A Risk-of-bias judgement Low Domain 5: 5.1. Yes 5.2. Probably no 5.3. Probably no Risk-of-bias judgement Low Overall risk-of-bias judgement Some concerns Source of funding: The funder was the French Ministry of health and the sponsor was Assistance Publique –Hôpitaux de Paris. Hoffmann-La Roche provided rituximab for the study. The funders of the study had no role in study design, data analysis, data interpretation or writing the report.

			compared with 23 (IQR 19 to 27) in the supportive therapy group, p=0.10 • 6 months: 30 (IQR 26 to 34) in the rituximab and supportive therapy group compared with 24 (20 to 29) in the supportive therapy group, p=0.029 **Safety** Eight serious adverse events occurred in each group with 3 occurring in the same person within each group, p=0.87.	

eGFR, estimated glomerular filtration rate; IQR, inter-quartile range; MDRD, Modification of Diet in Renal Disease; PLA2R, phospholipase A2 receptor; RCT, randomised controlled trial

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Full citation Fervenza F, Appel GB, Barbour SJ et al. (2019) Rituximab or Ciclosporin in the Treatment of Membranous Nephropathy. The New England journal of medicine 381(1): 36-46 **Study location** North America (22 sites) **Study type** Open label RCT **Study aim** 'To investigate whether rituximab would be non-inferior to cyclosporine in inducing and maintaining remission of proteinuria, regardless of patients' baseline anti-PLA2R status, for up to 24 months in patients with apparent primary membranous nephropathy' **Study dates** March 2012 to September 2015	**Inclusion criteria** Membranous nephropathy confirmed by renal biopsy, 18 to 80 years of age, proteinuria of more than 5 g per 24 hours on average in two 24-hour urine samples obtained within 14 days, a decline of less than 50% in proteinuria despite renin–angiotensin system blockade for at least 3 months before randomization, and a stable quantified 24-hour creatinine clearance of at least 40 ml per minute per 1.73 m2 of body-surface area. **Exclusion Criteria** Adults with presence of active infection or a secondary cause of IMN; type 1 or 2 diabetes mellitus; pregnant or breast feeding; history of resistance to ciclosporin (or other calcineurin inhibitors), rituximab, or alkylating agents. **Total sample size** 130	All participants received supportive care that included renin-angiotensin system blockers, blood-pressure management targeting a value of less than 130/80 mm Hg, dietary sodium restriction to less than 4 g per day, and dietary protein restriction to 0.8 to 1 g of protein per kilogram of body weight per day during at least the previous 3 months before randomisation. Participants who had not received supportive care as part of their routine treatment underwent a 3-month run-in phase. **Intervention** Intravenous rituximab 1 g on days 1 and 15; repeated at 6 months in case of partial response. **Comparison** Oral ciclosporin, starting at a dose of 3.5 mg per kilogram of body weight. Given in two equal doses each day for 12 months.	**Critical outcomes** **Complete or partial remission** The primary outcome was complete or partial remission at 24 months. All time points are presented below. Complete remission was defined as proteinuria of no more than 0.3 g per 24 hours and a serum albumin level of at least 3.5 g per decilitre. Partial remission was defined as a reduction in proteinuria of at least 50% from baseline plus final proteinuria between 0.3 g and 3.5 g per 24 hours regardless of creatinine clearance or serum albumin level. • 6 months: 23 (35%) in the rituximab group compared with 32 (49%) in the ciclosporin group; risk difference −14%, 95% CI −31 to 3% • 12 months: 39 (60%) in the rituximab group compared with 34 (52%) in the ciclosporin group; risk difference 8%, 95% CI −9 to 25% • 18 months: 40 (62%) in the rituximab group compared with 15 (23%) in the ciclosporin group; risk difference 38%, 95% CI 23 to 54% • 24 months: 39 (60%) in the rituximab group compared with 13 (20%) in the	This study was appraised using the Cochrane Risk of Bias tool for randomised control trials Domain 1: Risk of bias arising from the randomization process 1.1. Yes 1.2. Yes 1.3. No Risk-of-bias judgement Low Domain 2: 2.1. Yes 2.2. Yes 2.3. Probably no 2.4. N/A 2.5. N/A 2.6. Yes Risk-of-bias judgement Low Domain 2:

	No. of participants in each treatment group 65 adults were randomised to rituximab 65 adults were randomised to ciclosporin **Baseline characteristics** There were more men in the ciclosporin group (82%) compared with the rituximab group (72%). No statistical analyses reported. The authors reported baseline imbalances in anti-PLA2R levels.		ciclosporin group; risk difference 40%, 95% CI 25 to 55%, p<0.001. **End stage renal disease** Defined as a creatinine clearance of no more than 15 ml per minute, the initiation of dialysis, or renal transplantation. 1 person developed end-stage renal disease in the ciclosporin group. **Important outcomes** **Quality of life** Kidney Disease Quality of Life Short Form (KDQOL-SF) version 1.3 in adults in complete or partial remission: 6 months: • SF-12 physical health composite subscale (modelled difference in means 2.0, 95% CI −3.5 to 7.5). • SF-12 mental health composite subscale (modelled difference in means 3.3, 95% CI −1.4 to 7.9). • Symptom/problem list subscale (modelled difference in means 7.4, 95% CI 0.8 to 14.1). • Effects of kidney disease subscale (modelled difference in means 0.1, 95% CI −7.0 to 7.2). • Burden of kidney disease subscale (modelled difference in means: 3.3, 95% CI −6.3 to 13.0). 12 months: • SF-12 physical health composite subscale (modelled difference in means 0.2, 95% CI −3.8 to 4.2). • SF-12 mental health composite subscale (modelled difference in means 4.1, 95% CI 0.6 to 7.6). • Symptom/problem list subscale (modelled difference in means 2.3, 95% CI −3.2 to 7.8). • Effects of kidney disease subscale (modelled difference in means 3.3, 95% CI −4.0 to 10.6).	2.1. Yes 2.2. Yes 2.3. Probably yes 2.4. Probably no 2.5. Probably no 2.6. Yes Risk-of-bias judgement Low Domain 3: Missing outcome data 3.1. Yes 3.2. N/A 3.3. N/A 3.4. N/A Risk-of-bias judgement Low Domain 4: 4.1. No 4.2. Probably no 4.3. Yes 4.4. Probably no 4.5. N/A Risk-of-bias judgement Low Domain 5: 5.1. Yes 5.2. Probably no 5.3. Probably no Risk-of-bias judgement Low Overall risk-of-bias judgement Low Source of funding: Funded by Genentech and the Fulk Family Foundation

			• Burden of kidney disease subscale (modelled difference in means −4.5, 95% CI −16.1 to 7.1). 24 months: • SF-12 physical health composite subscale (modelled difference in means 0.2, 95% CI −4.9 to 5.3). • SF-12 mental health composite subscale (modelled difference in means 0.3, 95% CI −3.7 to 4.3). • Symptom/problem list subscale (modelled difference in means 2.2, 95% CI −4.3 to 8.8). • Effects of kidney disease subscale (modelled difference in means 6.9, 95% CI −2.4 to 16.3). • Burden of kidney disease subscale (modelled difference in means 1.2, 95% CI −12.5 to 14.9). **Safety** The incidence of adverse events was 46/65 (71%) in the rituximab group and 51/65 (78%) in the ciclosporin group, p=0.31. The incidence of serious adverse events was 11/65 (17%) in the rituximab group and 20/65 (31%) in the ciclosporin group, p=0.06. Increased serum creatinine levels and gastrointestinal events were more common with ciclosporin, whereas pruritus and infusion-related reactions were more frequent with rituximab.	

IMN, idiopathic membranous nephropathy; IQR, inter-quartile range; KDQOL-SF, Kidney Disease Quality of Life Short Form; PLA2R, phospholipase A2 receptor; RCT, randomised controlled trial

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Full citation Scolari F, Delbarba E, Santoro D et al. (2021) Rituximab or Cyclophosphamide in the Treatment of Membranous Nephropathy: The RI-CYCLO Randomized Trial. Journal	**Inclusion criteria** IMN confirmed by renal biopsy, 18 to 80 years of age, proteinuria of more than 5 g per 24 hours on average in two 24-hour urine samples obtained within 14 days, a decline of less than 50% in proteinuria despite	All participants had received treatment with renin-angiotensin system agonists before randomisation. Any medicines not listed in the exclusion criteria were allowed to be given at the discretion of the investigator. No detail reported. **Intervention**	**Critical outcomes** **Remission of proteinuria** The number of adults in complete remission (proteinuria to <0.3 g/d): • at 6 months: 3/37 (8%) in the rituximab group compared with 2/37 (5%) in the	This study was appraised using the Cochrane Risk of Bias tool for randomised control trials Domain 1: Risk of bias arising from the randomization process 1.1. Yes

of the American Society of Nephrology: JASN **Study location** Italy (10 centres) and Switzerland (1 centre) **Study type** Open label RCT **Study aim** 'To obtain estimates of the effects of rituximab relative to the cyclic regimen in people with MN and assess the recruitment potential using a multisite design.' **Study dates** January 2012 to December 2018	renin–angiotensin system blockade for at least 3 months before randomization, and a stable quantified 24-hour creatinine clearance of at least 40 ml per minute per 1.73 m2 of body-surface area. **Exclusion Criteria** Serum creatinine >2.0 mg/dL or estimated GFR <30 mL/min/1.73 m2. Previous treatment with rituximab, corticosteroids, alkylating agents, calcineurin inhibitors, synthetic adrenocorticotropic hormone, mycophenolate mofetil, or azathioprine. Presence of active infection. Secondary cause of MN (eg, hepatitis B and C, systemic lupus erythematosus, medications, malignancies. Type 1 or 2 diabetes mellitus. Pregnancy or breastfeeding. Previous renal vein thrombosis. **Total sample size** 74 **No. of participants in each treatment group** 37 adults were randomised to rituximab 37 adults were randomised to the cyclic regimen of cyclophosphamide and corticosteroids **Baseline characteristics** There were no notable differences in baseline characteristics.	Intravenous rituximab 1 g on days 1 and 15 (Premedication with methylprednisolone, cetirizine, and paracetamol). **Comparison** Cyclic regimen of three consecutive cycles (2 months each) where corticosteroids were alternated with cyclophosphamide every other month: Months 1, 3 and 5: 1 g of intravenous methylprednisolone, repeated daily for three consecutive days followed by oral methylprednisolone (0.4 mg/kg/day) or prednisone (0.5 mg/kg/day) for the remaining days of the month. Months 2, 4 and 6: oral cyclophosphamide (2.0 mg/kg/day) daily. The cumulative dose of cyclophosphamide per person was 180 mg/kg.	cyclic corticosteroid cyclophosphamide group, OR 1.54 (95% CI 0.24 to 9.80). • at 12 months: 6/37 (16%) in the rituximab group compared with 12/37 (32%) in the cyclic corticosteroid cyclophosphamide group, OR 0.40 (95% CI 0.13 to 1.23). The number of adults in complete or partial remission: • at 6 months: 19/37 (51%) in the rituximab group compared with 24/37 (65%) in the cyclic corticosteroid cyclophosphamide group, OR 0.57 (95% CI 0.22 to 1.45). • at 12 months: 23/37 (62%) compared with 27/37 (73%) in the cyclic corticosteroid cyclophosphamide group, OR 0.61 (95% CI 0.23 to 1.63). Proteinuria: • baseline: rituximab 6.1 (IQR 4.0 to 10.1) compared with 6.2 (IQR 5.1 to 9.3) cyclic corticosteroid cyclophosphamide group, no analysis reported. • 24 months: rituximab 0.7 (IQR 0.2 to 2.2) compared with 0.7 (IQR 0.2 to 3.0), no analysis reported. **Excretory kidney function** Serum creatinine • baseline: rituximab 1.02 (SD 0.27) compared with 0.96 (SD 0.27) cyclic corticosteroid cyclophosphamide group, no analysis reported. • 24 months: rituximab 0.94 (SD 0.20) compared with 1.12 (SD 0.77), no analysis reported. **Important** **Anti-PLA2R antibodies** Anti-PLA2R antibody level in adults who were anti-PLA2R positive: • baseline: rituximab 58 (IQR 40 to 81) compared with 63 (IQR 52 to 87) in the cyclic corticosteroid cyclophosphamide group, p=0.50. • 6 months: rituximab 0 (IQR 0 to 44) compared with 13 (IQR 0 to 86) in the cyclic corticosteroid cyclophosphamide group, p=0.30	1.2. Yes 1.3. No Risk-of-bias judgement Low Domain 2: 2.1. Yes 2.2. Yes 2.3. Probably no 2.4. N/A 2.5. N/A 2.6. Yes Risk-of-bias judgement Low Domain 2: 2.1. Yes 2.2. Yes 2.3. Probably yes 2.4. Probably no 2.5. Probably no 2.6. Yes Risk-of-bias judgement Low Domain 3: Missing outcome data 3.1. No 3.2. Yes 3.3. N/A 3.4. N/A Risk-of-bias judgement Low Domain 4: 4.1. No

			• 12 months: rituximab 2 (IQR 0 to 44) compared with 0 (IQR 0 to 73) in the cyclic corticosteroid cyclophosphamide group, p=0.83 • 24 months: rituximab 0 (IQR 0 to 0) compared with 0 (IQR 0 to 53) in the cyclic corticosteroid cyclophosphamide group, p=0.26 • 36 months: rituximab 0 (IQR 0 to 18) compared with 0 (IQR 0 to 45) in the cyclic corticosteroid cyclophosphamide group, p=0.49 **Serum albumin** Serum albumin level (g/decilitre): • baseline: rituximab 2.4 (IQR 1.8 to 2.7) compared with 2.5 (IQR 1.9 to 2.7) in the cyclic corticosteroid cyclophosphamide group, no analysis reported • 6 months: rituximab 3.4 (IQR 2.8 to 3.8) compared with 3.6 (IQR 2.8 to 3.8) in the cyclic corticosteroid cyclophosphamide, no analysis reported • 12 months: rituximab 3.7 (IQR 2.9 to 4.2) compared with 3.7 (IQR 3.2 to 4.0) in the cyclic corticosteroid cyclophosphamide, no analysis reported • 18 months: rituximab 3.9 (IQR 3.4 to 4.2) compared with 3.8 (IQR 3.3 to 4.1) in the cyclic corticosteroid cyclophosphamide, no analysis reported • 24 months: rituximab 4.0 (IQR 3.5 to 4.2) compared with 3.8 (IQR 3.4 to 4.1) in the cyclic corticosteroid cyclophosphamide group, no analysis reported • 36 months: rituximab 3.8 (IQR 3.2 to 4.1) compared with 3.9 (IQR 3.3 to 4.3) in the cyclic corticosteroid cyclophosphamide, no analysis reported **Safety** The incidence of serious adverse events was 7/37 (19%) in the rituximab group compared with 5/37 (14%) in the cyclic corticosteroid cyclophosphamide group, p=0.75. The incidence of adverse events was 16/37 (43%) in the rituximab group compared with 16/37 (43%) in the cyclic corticosteroid cyclophosphamide group, p>0.99.	4.2. Probably no 4.3. Yes 4.4. Probably no 4.5. N/A Risk-of-bias judgement Low Domain 5: 5.1. Yes 5.2. Probably no 5.3. Probably no Risk-of-bias judgement Low Overall risk-of-bias judgement Low Source of funding: None

			The number of adults with drug infusion-related reactions or intolerance was 9/37 (24%) in the rituximab group compared with 1/37 (3%) in the cyclic corticosteroid cyclophosphamide group, p=0.01. Treatment discontinuation occurred in 4/37 adults in the rituximab group compared with 1/37 in the cyclic corticosteroid cyclophosphamide group, no analysis reported.	

IMN, idiopathic membranous nephropathy; IQR, inter-quartile range; PLA2R, phospholipase A2 receptor; RCT, randomised controlled trial

Appendix F Quality appraisal checklists

Cochrane Risk of Bias tool for randomised controlled trials

Domain 1: Risk of bias arising from the randomization process

1.1 Was the allocation sequence random?

1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?

1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?

Risk-of-bias judgement Low / High / Some concerns

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

2.1. Were participants aware of their assigned intervention during the trial?

2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?

2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?

2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?

2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?

2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?

2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?

Risk-of-bias judgement Low / High / Some concerns

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

2.1. Were participants aware of their assigned intervention during the trial?

2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?

2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?

2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?

2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?

2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?

Risk-of-bias judgement Low / High / Some concerns

Domain 3: Missing outcome data

3.1 Were data for this outcome available for all, or nearly all, participants randomized?

3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?

3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?

3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?

Risk-of-bias judgement Low / High / Some concerns

Domain 4: Risk of bias in measurement of the outcome

4.1 Was the method of measuring the outcome inappropriate?

4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?

4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?

4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?

4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?

Risk-of-bias judgement Low / High / Some concerns

Domain 5: Risk of bias in selection of the reported result

5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?

Is the numerical result being assessed likely to have been selected, on the basis of the results, from...

5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?

5.3 ... multiple eligible analyses of the data?

Risk-of-bias judgement Low / High / Some concerns

Overall risk-of-bias judgement Low / High / Some concerns

Appendix G GRADE profiles

Table 2: Question: in people with idiopathic membranous nephropathy, what is the clinical effectiveness and safety of rituximab compared with ciclosporin?

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Rituximab	Ciclosporin	Result (95%CI)		
Remission of proteinuria (1 RCT)									
Complete and partial remission at 6 months[a] (higher result indicates benefit)									
1 RCT Fervenza 2019	No serious	No serious	Not applicable	Serious[1]	23/65 (35%)	32/65 (49%)	Risk difference (%): −14 (95% CI −31 to 3)	CRITICAL	MODERATE
Complete and partial remission at 12 months[a] (higher result indicates benefit)									
1 RCT Fervenza 2019	No serious	No serious	Not applicable	Serious[1]	39/65 (60%)	34/65 (52%)	Risk difference (%): 8 (95% CI −9 to 25)	CRITICAL	MODERATE
Complete and partial remission at 18 months[a v] (higher result indicates benefit)									
1 RCT Fervenza 2019	No serious	No serious	Not applicable	No serious	40/65 (62%)	15/65 (23%)	Risk difference (%): 38 (95% CI 23 to 54)	CRITICAL	HIGH
Complete and partial remission at 24 months[a] (higher result indicates benefit)									
1 RCT Fervenza 2019	No serious	No serious	Not applicable	No serious	39/65 (60%)	13/65 (20%)	Risk difference (%): 40 (95% CI 25 to 55), p<0.001	CRITICAL	HIGH
Excretory kidney function (1 RCT)									
Number of adults with ≥50% decrease in creatinine clearance at 6 months (lower result indicates benefit)									
1 RCT Fervenza 2019	No serious	No serious	Not applicable	Very serious[1,2]	1/65 (1.5%)	4/65 (6.2%)	Risk difference: −4.6 (95% CI −11.2 to 1.9)	CRITICAL	LOW
Number of adults with ≥50% decrease in creatinine clearance at 12 months (lower result indicates benefit)									
1 RCT	No serious	No serious	Not applicable	Serious[2]	1/65 (1.5%)	8/65 (12.3%)	Risk difference: −10.8 (95% CI −19.3 to −2.2)	CRITICAL	MODERATE

Fervenza 2019									
Number of adults with ≥50% decrease in creatinine clearance at 18 months (lower result indicates benefit)									
1 RCT Fervenza 2019	No serious	No serious	Not applicable	Serious[2]	1/65 (1.5%)	8/65 (12.3%)	Risk difference: −10.8 (95% CI −19.3 to −2.2)	CRITICAL	MODERATE
Number of adults with ≥50% decrease in creatinine clearance at 24 months (lower result indicates benefit)									
1 RCT Fervenza 2019	No serious	No serious	Not applicable	Serious[2]	1/65 (1.5%)	8/65 (12.3%)	Risk difference: −10.8 (95% CI −19.3 to −2.2)	CRITICAL	MODERATE
ESRD									
Number of adults with ESRD (lower result indicates benefit)									
1 RCT Fervenza 2019	No serious	No serious	Not applicable	Serious[3]	0/65	1/65	No analysis reported.	IMPORTANT	MODERATE
Quality of life									
SF-12 physical health composite subscale of the KDQOL-SF at 6 months (in adults with complete or partial remission) (higher result indicates benefit)									
1 RCT Fervenza 2019	No serious	No serious	Not applicable	Very serious[1,2]	N=20 Mean (SD) 45.1 (13)	N=29 Mean (SD) 45.0 (10)	Modelled difference in means: 2.0 (95% CI −3.5 to 7.5)	IMPORTANT	LOW
SF-12 mental health composite subscale of the KDQOL-SF at 6 months (in adults with complete or partial remission) (higher result indicates benefit)									
1 RCT Fervenza 2019	No serious	No serious	Not applicable	Very serious[1,2]	N=20 Mean (SD) 53.2 (8)	N=29 Mean (SD) 51.4 (9)	Modelled difference in means: 3.3 (95% CI −1.4 to 7.9)	IMPORTANT	LOW
Symptom/problem list subscale of the KDQOL-SF at 6 months (in adults with complete or partial remission) (higher result indicates benefit)									
1 RCT Fervenza 2019	No serious	No serious	Not applicable	Serious[2]	N=23 Mean (SD) 84.5 (13)	N=32 Mean (SD) 80.9 (15)	Modelled difference in means: 7.4 (95% CI 0.8 to 14.1)	IMPORTANT	MODERATE
Effects of kidney disease subscale of the KDQOL-SF at 6 months (in adults with complete or partial remission) (higher result indicates benefit)									
1 RCT Fervenza 2019	No serious	No serious	Not applicable	Very serious[1,2]	N=23 Mean (SD) 81.3 (20)	N=31 Mean (SD) 84.2 (17)	Modelled difference in means: 0.1 (95% CI −7.0 to 7.2)	IMPORTANT	LOW

Burden of kidney disease subscale of the KDQOL-SF at 6 months (in adults with complete or partial remission) (higher result indicates benefit)									
1 RCT Fervenza 2019	No serious	No serious	Not applicable	Very serious[1,2]	N=23 Mean (SD) 66.0 (24)	N=32 Mean (SD) 65.0 (25)	Modelled difference in means: 3.3 (95% CI −6.3 to 13.0)	IMPORTANT	LOW
SF-12 physical health composite subscale of the KDQOL-SF at 12 months (in adults with complete or partial remission) (higher result indicates benefit)									
1 RCT Fervenza 2019	No serious	No serious	Not applicable	Very serious[1,2]	N=36 Mean (SD) 46.2 (10)	N=31 Mean (SD) 47.9 (9)	Modelled difference in means: 0.2 (95% CI −3.8 to 4.2)	IMPORTANT	LOW
SF-12 mental health composite subscale of the KDQOL-SF at 12 months (in adults with complete or partial remission) (higher result indicates benefit)									
1 RCT Fervenza 2019	No serious	No serious	Not applicable	Serious[2]	N=36 Mean (SD) 52.0 (7)	N=31 Mean (SD) 50.1 (11)	Modelled difference in means: 4.1 (95% CI 0.6 to 7.6)	IMPORTANT	MODERATE
Symptom/problem list subscale of the KDQOL-SF at 12 months (in adults with complete or partial remission) (higher result indicates benefit)									
1 RCT Fervenza 2019	No serious	No serious	Not applicable	Very serious[1,2]	N=38 Mean (SD) 83.5 (13)	N=33 Mean (SD) 85.3 (15)	Modelled difference in means: 2.3 (95% CI −3.2 to 7.8)	IMPORTANT	LOW
Effects of kidney disease subscale of the KDQOL-SF at 12 months (in adults with complete or partial remission) (higher result indicates benefit)									
1 RCT Fervenza 2019	No serious	No serious	Not applicable	Very serious[1,2]	N=38 Mean (SD) 83.8 (19)	N=33 Mean (SD) 83.8 (19)	Modelled difference in means: 3.3 (95% CI −4.0 to 10.6)	IMPORTANT	LOW
Burden of kidney disease subscale of the KDQOL-SF at 12 months (in adults with complete or partial remission) (higher result indicates benefit)									
1 RCT Fervenza 2019	No serious	No serious	Not applicable	Very serious[1,2]	N=38 Mean (SD) 68.6 (27)	N=33 Mean (SD) 73.1 (30)	Modelled difference in means: −4.5 (95% CI −16.1 to 7.1)	IMPORTANT	LOW
SF-12 physical health composite subscale of the KDQOL-SF at 24 months (in adults with complete or partial remission) (higher result indicates benefit)									
1 RCT Fervenza 2019	No serious	No serious	Not applicable	Very serious[1,2]	N=37 Mean (SD) 47.8 (8)	N=11 Mean (SD) 49.9 (9)	Modelled difference in means: 0.2 (95% CI −4.9 to 5.3)	IMPORTANT	LOW
SF-12 mental health composite subscale of the KDQOL-SF at 24 months (in adults with complete or partial remission) (higher result indicates benefit)									
1 RCT Fervenza 2019	No serious	No serious	Not applicable	Very serious[1,2]	N=37 Mean (SD) 53.4 (7)	N=11 Mean (SD) 55.0 (4)	Modelled difference in means: 0.3 (95% CI −3.7 to 4.3)	IMPORTANT	LOW

Symptom/problem list subscale of the KDQOL-SF at 24 months (in adults with complete or partial remission) (higher result indicates benefit)									
1 RCT Fervenza 2019	No serious	No serious	Not applicable	Very serious[1,2]	N=38 Mean (SD) 86.5 (11)	N=12 Mean (SD) 87.8 (16)	Modelled difference in means: 2.2 (95% CI −4.3 to 8.8)	IMPORTANT	LOW
Effects of kidney disease subscale of the KDQOL-SF at 24 months (in adults with complete or partial remission) (higher result indicates benefit)									
1 RCT Fervenza 2019	No serious	No serious	Not applicable	Very serious[1,2]	N=38 Mean (SD) 90.2 (16)	N=12 Mean (SD) 84.4 (14)	Modelled difference in means: 6.9 (95% CI −2.4 to 16.3)	IMPORTANT	LOW
Burden of kidney disease subscale of the KDQOL-SF at 24 months (in adults with complete or partial remission) (higher result indicates benefit)									
1 RCT Fervenza 2019	No serious	No serious	Not applicable	Very serious[1,2]	N=38 Mean (SD) 80.8 (24)	N=12 Mean (SD) 80.6 (20)	Modelled difference in means: 1.2 (95% CI −12.5 to 14.9)	IMPORTANT	LOW
Safety									
Any adverse event (higher result indicates harm)									
1 RCT Fervenza 2019	No serious	No serious	Not applicable	Not calculable	46/65 (71%) Number of events (rate per 100 patients): 179 (275)	51/65 (78%) Number of events (rate per 100 patients): 218 (335)	p=0.31	IMPORTANT	HIGH
Adverse event, infusion-related reactions (higher result indicates harm)									
1 RCT Fervenza 2019	No serious	No serious	Not applicable	Serious[3]	16/65 (25%) Number of events (rate per 100 patients): 22 (34)	0/65 (0%) Number of events (rate per 100 patients): 0 (0)	P<0.001	IMPORTANT	MODERATE
Serious adverse events (higher result indicates harm)									
1 RCT Fervenza 2019	No serious	No serious	Not applicable	Not calculable	11/65 (17%) Number of events (rate per 100 patients): 13 (20)	20/65 (31%) Number of events (rate per 100 patients): 22 (34)	p=0.06	IMPORTANT	HIGH

Abbreviations

KDQOL-SF, Kidney Disease and Quality of Life Short Form; PLA2R, phospholipase A2 receptor; RCT, randomised controlled trial

1 Downgraded 1 level because of wide confidence intervals
2 The authors reported that widths of 95% CI were not adjusted for multiple comparisons and should not be used for inference about treatment effects.
3 Downgraded 1 level for imprecision because there were 0 events in one group

a Complete remission: proteinuria of no more than 0.3 g/24 hours and serum albumin of at least 3.5 g/decilitre. Partial remission: a reduction in proteinuria of at least 50% from baseline plus final proteinuria between 0.3 g and 3.5 g/day.

Table 3: Question: in people with idiopathic membranous nephropathy, what is the clinical effectiveness and safety of rituximab compared with cyclic cyclophosphamide and corticosteroid?

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Rituximab	Cyclic cyclophosphamide corticosteroid regimen	Result (95%CI)		
Remission of proteinuria (1 RCT)									
Complete or partial remission of proteinuria at 6 months (higher result indicates benefit)									
1 RCT Scolari 2021	No serious	No serious	Not applicable	Very serious[1,2]	19/37 (51%)	24/37 (65%)	OR 0.57 (95% CI 0.22 to 1.45)	CRITICAL	LOW
Complete or partial remission of proteinuria at 12 months (higher result indicates benefit)									
1 RCT Scolari 2021	No serious	No serious	Not applicable	Very serious[1,2]	23/37 (62%)	27/37 (73%)	OR 0.61 (95% CI 0.23 to 1.63)	CRITICAL	LOW
Complete or partial remission of proteinuria at 18 months (higher result indicates benefit)									
1 RCT Scolari 2021	No serious	No serious	Not applicable	Very serious[1,2]	21/32 (66%)	27/34 (79%)	OR 0.49 (95% CI 0.16 to 1.49)	CRITICAL	LOW
Complete or partial remission of proteinuria at 24 months (higher result indicates benefit)									
1 RCT Scolari 2021	No serious	No serious	Not applicable	Very serious[1,2]	22/26 (85%)	25/31 (81%)	OR 1.32 (95% CI 0.33 to 5.29)	CRITICAL	LOW
Complete or partial remission of proteinuria at 36 months (higher result indicates benefit)									
1 RCT Scolari 2021	No serious	No serious	Not applicable	Very serious[1,2]	17/20 (85%)	16/22 (73%)	OR 2.21 (95% CI 0.45 to 9.96)	CRITICAL	LOW
Complete remission of proteinuria at 6 months (higher result indicates benefit)									
1 RCT Scolari 2021	No serious	No serious	Not applicable	Very serious[1,2]	3/37 (8%)	2/37 (5%)	OR 1.54 (95% CI 0.24 to 9.8)	CRITICAL	LOW
Complete remission of proteinuria at 12 months (higher result indicates benefit)									
1 RCT Scolari 2021	No serious	No serious	Not applicable	Very serious[1,2]	6/37 (16%)	12/37 (32%)	OR 0.40 (95% CI 0.13 to 1.23)	CRITICAL	LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Rituximab	Cyclic cyclophosphamide corticosteroid regimen	Result (95%CI)		
Complete remission of proteinuria at 18 months (higher result indicates benefit)									
1 RCT Scolari 2021	No serious	No serious	Not applicable	Very serious[1,2]	10/32 (31%)	7/34 (21%)	OR 1.75 (95% CI 0.57 to 5.36)	CRITICAL	LOW
Complete remission of proteinuria at 24 months (higher result indicates benefit)									
1 RCT Scolari 2021	No serious	No serious	Not applicable	Very serious[1,2]	11/26 (42%)	11/31 (35%)	OR 1.33 (95% CI 0.46 to 3.89)	CRITICAL	LOW
Complete remission of proteinuria at 36 months (higher result indicates benefit)									
1 RCT Scolari 2021	No serious	No serious	Not applicable	Very serious[1,2]	6/20 (30%)	7/22 (32%)	OR 0.92 (95% CI 0.25 to 3.41)	CRITICAL	LOW
Proteinuria at 24 months, g/decilitre (lower result indicates benefit)									
1 RCT Scolari 2021	No serious	No serious	Not applicable	Serious[2]	Baseline: 6.1 (IQR 4.0 to 10.1) 24 months: 0.7 (IQR 0.2 to 2.2)	Baseline: 6.2 (IQR 5.1 to 9.3) 24 months: 0.7 (IQR 0.2 to 3.0)	No analysis reported.	CRITICAL	MODERATE
Excretory kidney function (1 RCT)									
Serum creatinine at 6 months, mg/decilitre (lower result indicates benefit)									
1 RCT Scolari 2021	No serious	No serious	Not applicable	Serious[2]	Baseline: 1.02 (SD 0.25) 6 months: 1.00 (SD 0.25)	Baseline: 0.96 (SD 0.27) 6 months: 0.98 (SD 0.47)	No analysis reported.	CRITICAL	MODERATE
Serum creatinine at 12 months, mg/decilitre (lower result indicates benefit)									
1 RCT Scolari 2021	No serious	No serious	Not applicable	Serious[2]	Baseline: 1.02 (SD 0.27)	Baseline: 0.96 (SD 0.27)	No analysis reported.	CRITICAL	MODERATE

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Rituximab	Cyclic cyclophosphamide corticosteroid regimen	Result (95%CI)		
					12 months: 0.98 (SD 0.29)	12 months: 0.98 (SD 0.48)			
Serum creatinine at 18 months, mg/decilitre (lower result indicates benefit)									
1 RCT Scolari 2021	No serious	No serious	Not applicable	Serious[2]	Baseline: 1.02 (SD 0.27) 18 months: 0.98 (SD 0.26)	Baseline: 0.96 (SD 0.27) 18 months: 1.14 (SD 0.90)	No analysis reported.	CRITICAL	MODERATE
Serum creatinine at 24 months, mg/decilitre (lower result indicates benefit)									
1 RCT Scolari 2021	No serious	No serious	Not applicable	Serious[2]	Baseline: 1.02 (SD 0.27) 24 months: 0.94 (SD 0.20)	Baseline: 0.96 (SD 0.27) 24 months: 1.12 (SD 0.77)	No analysis reported.	CRITICAL	MODERATE
Serum creatinine at 36 months, mg/decilitre (lower result indicates benefit)									
1 RCT Scolari 2021	No serious	No serious	Not applicable	Serious[2]	Baseline: 1.02 (SD 0.27) 36 months: 0.97 (SD 0.20)	Baseline: 0.96 (SD 0.27) 36 months: 1.22 (SD 0.77)	No analysis reported.	CRITICAL	MODERATE
End stage renal disease (ESRD)									
End stage renal disease (ESRD) (higher result indicates harm)									
1 RCT Scolari 2021	No serious	No serious	Not applicable	Very serious[23]	0/37 (0%)	2/37 (5.4%) One at 7 months, the other at 24 months. Both required renal	No analysis reported.	CRITICAL	LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Rituximab	Cyclic cyclophosphamide corticosteroid regimen	Result (95%CI)		
						replacement. eGFR at baseline was 69 ml/min and 41 ml/min respectively.			
Anti-PLA2R level									
Anti-PLA2R level in anti-PLA2R positive adults at 6 months, units/ml (higher result indicates harm)									
1 RCT Scolari 2021	No serious	No serious	Not applicable	Serious[2]	Baseline: 58 (IQR 40 to 81) 6 months: 0 (IQR 0 to 44)	Baseline: 63 (IQR 52 to 87) 6 months: 13 (IQR 0 to 86)	p=0.30	IMPORTANT	MODERATE
Anti-PLA2R level in anti-PLA2R positive adults at 12 months, units/ml (higher result indicates harm)									
1 RCT Scolari 2021	No serious	No serious	Not applicable	Serious[2]	Baseline: 58 (IQR 40 to 81) 12 months: 2 (IQR 0 to 44)	Baseline: 63 (IQR 52 to 87) 12 months: 0 (IQR 0 to 73)	p=0.83	IMPORTANT	MODERATE
Anti-PLA2R level in anti-PLA2R positive adults at 18 months, units/ml (higher result indicates harm)									
1 RCT Scolari 2021	No serious	No serious	Not applicable	Serious[2]	Baseline: 58 (IQR 40 to 81) 12 months: 0 (IQR 0 to 0)	Baseline: 63 (IQR 52 to 87) 12 months: 0 (IQR 0 to 57)	p=0.21	IMPORTANT	MODERATE
Anti-PLA2R level in anti-PLA2R positive adults at 24 months, units/ml (higher result indicates harm)									
1 RCT Scolari 2021	No serious	No serious	Not applicable	Serious[2]	Baseline: 58 (IQR 40 to 81) 24 months: 0 (IQR 0 to 0)	Baseline: 63 (IQR 52 to 87) 24 months: 0 (IQR 0 to 53)	p=0.26	IMPORTANT	MODERATE

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Rituximab	Cyclic cyclophosphamide corticosteroid regimen	Result (95%CI)		
Anti-PLA2R level in anti-PLA2R positive adults at 36 months, units/ml (higher result indicates harm)									
1 RCT Scolari 2021	No serious	No serious	Not applicable	Serious[2]	Baseline: 58 (IQR 40 to 81) 36 months: 0 (IQR 0 to 18)	Baseline: 63 (IQR 52 to 87) 36 months: 0 (IQR 0 to 45)	p=0.49	IMPORTANT	MODERATE
Serum albumin									
Serum albumin level at 6 months, g/decilitre (higher result indicates benefit)									
1 RCT Scolari 2021	No serious	No serious	Not applicable	Serious[2]	Baseline:2.4 (IQR 1.8 to 2.7) 6 months: 3.4 (IQR 2.8 to 3.8)	Baseline: 2.5 (IQR 1.9 to 2.7) 6 months: 3.6 (IQR 2.8 to 3.8)	No analysis reported.	CRITICAL	MODERATE
Serum albumin level at 12 months, g/decilitre (higher result indicates benefit)									
1 RCT Scolari 2021	No serious	No serious	Not applicable	Serious[2]	Baseline:2.4 (IQR 1.8 to 2.7) 12 months: 3.7 (IQR 2.9 to 4.2)	Baseline: 2.5 (IQR 1.9 to 2.7) 12 months: 3.7 (IQR 3.2 to 4.0)	No analysis reported.	CRITICAL	MODERATE
Serum albumin level at 18 months, g/decilitre (higher result indicates benefit)									
1 RCT Scolari 2021	No serious	No serious	Not applicable	Serious[2]	Baseline:2.4 (IQR 1.8 to 2.7) 18 months: 3.9 (IQR 3.4 to 4.2)	Baseline: 2.5 (IQR 1.9 to 2.7) 18 months: 3.8 (IQR 3.3 to 4.1)	No analysis reported.	CRITICAL	MODERATE

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Rituximab	Cyclic cyclophosphamide corticosteroid regimen	Result (95%CI)		
Serum albumin level at 24 months, g/decilitre (higher result indicates benefit)									
1 RCT Scolari 2021	No serious	No serious	Not applicable	Serious[2]	Baseline:2.4 (IQR 1.8 to 2.7) 24 months: 4.0 (IQR 3.5 to 4.2)	Baseline: 2.5 (IQR 1.9 to 2.7) 24 months: 3.8 (IQR 3.4 to 4.1)	No analysis reported.	CRITICAL	MODERATE
Serum albumin level at 36 months, g/decilitre (higher result indicates benefit)									
1 RCT Scolari 2021	No serious	No serious	Not applicable	Serious[2]	Baseline:2.4 (IQR 1.8 to 2.7) 36 months: 3.8 (IQR 3.2 to 4.1)	Baseline: 2.5 (IQR 1.9 to 2.7) 36 months: 3.9 (IQR 3.3 to 4.3)	No analysis reported.	CRITICAL	MODERATE
Safety									
Serious adverse events (higher result indicates harm)									
1 RCT Scolari 2021	No serious	No serious	Not applicable	Serious[2]	7/37 (19%)	5/37 (14%)	p=0.75	IMPORTANT	MODERATE
Adverse events (higher result indicates harm)									
1 RCT Scolari 2021	No serious	No serious	Not applicable	Serious[2]	16/37 (43%)	16/37 (43%)	p>0.99	IMPORTANT	MODERATE
Adverse events, infusion related reactions (higher result indicates harm)									
1 RCT Scolari 2021	No serious	No serious	Not applicable	Serious[2]	9/37 (24%)	1/37 (3%)	P=0.01	IMPORTANT	MODERATE
Treatment discontinuation (higher result indicates harm)									
1 RCT Scolari 2021	No serious	No serious	Not applicable	Serious[2]	4/37 3 because of severe	1/37 Because of cyclophosphami	No analysis reported.	IMPORTANT	MODERATE

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Rituximab	Cyclic cyclophosphamide corticosteroid regimen	Result (95%CI)		
					infusion related reaction, 1 because of mild reaction (cough, itchy throat)	de intolerance (severe nausea and vomiting)			

Abbreviations

PLA2R, phospholipase A2 receptor; RCT, randomised controlled trial

1 Downgraded 1 level. Wide confidence intervals.
2 Downgraded 1 level. Pilot RCT which does not use a noninferiority method and not powered to detect a difference between the intervention and comparator.
3 Downgraded 1 level for imprecision because there were 0 events in one group

a proteinuria at least 50% lower than the baseline and ≤3.5 g/day

Table 4: Question: in people with idiopathic membranous nephropathy, what is the clinical effectiveness and safety of rituximab and supportive therapy compared with supportive therapy?

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Rituximab and supportive therapy	Supportive therapy	Result (95%CI)		
Remission of proteinuria (1 RCT)									
Complete and partial remission at 6 months (higher result indicates benefit, reduction of proteinuria >50% and increase of serum albumin >30%)[a]									
1 RCT Dahan 2017	Serious[1]	No serious	Not applicable	Not calculable	13/37 (35.1%, 95% CI 19.7 to 50.5%)	8/38 (21.1%, 95% CI 8.1 to 34.0)	p=0.21	CRITICAL	MODERATE

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Rituximab and supportive therapy	Supportive therapy	Result (95%CI)		
Complete and partial remission at 17 months (higher result indicates benefit, reduction of proteinuria >50% and increase of serum albumin >30%)[a]									
1 RCT (observational follow-up period) Dahan 2017	Very serious[1,2]	No serious	Not applicable	Not calculable	24/37 (64.9%, 95% CI 49.5 to 80.2%)	13/38 (34.2%, 95% CI 19.1 to 49.3)	p<0.01	CRITICAL	LOW
Complete remission at 17 months (higher result indicates benefit)									
1 RCT (observational follow-up period) Dahan 2017	Very serious[1,2]	No serious	Not applicable	Not calculable	7/37	1/38	P=0.03	CRITICAL	LOW
Protein to creatinine ratio at 3 months, mg/g (lower result indicates benefit)									
1 RCT Dahan 2017	Serious[1]	No serious	Not applicable	Not calculable	Baseline: 7680.0 (IQR 4584.3 to 10399.0) 3 months: 4814.4 (IQR 3205.5 to 7398.6)	Baseline: 7195.1 (IQR 5363.1 to 8965.1) 3 months: 4832.1 (IQR 2424.9 to 7911.9)	p=0.94	CRITICAL	MODERATE
Protein to creatinine ratio at 6 months, mg/g (lower result indicates benefit)									
1 RCT Dahan 2017	Serious[1]	No serious	Not applicable	Not calculable	Baseline: 7680.0 (IQR 4584.3 to 10399.0) 6 months: 3531.2 (IQR 1796.6 to 6469.4)	Baseline: 7195.1 (IQR 5363.1 to 8965.1) 6 months: 5265.8 (IQR 2500.1 to 7690.7)	p=0.18	CRITICAL	MODERATE

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Rituximab and supportive therapy	Supportive therapy	Result (95%CI)		
Protein to creatinine ratio at 17 months, mg/g (lower result indicates benefit)									
1 RCT (observational follow-up period) Dahan 2017	Very serious[1,2]	No serious	Not applicable	Not calculable	2194.8 (IQR 1309.8 to 5310.0)	4701.1 (IQR 2027.8 to 8265.3)	p=0.02	CRITICAL	LOW
Excretory kidney function (1 RCT)									
eGFR at 3 months, ml/min/1.73 m^2 (higher result indicates benefit)									
1 RCT Dahan 2017	Serious[1]	No serious	Not applicable	Not calculable	Baseline: 66.7 (IQR 55.4 to 82.5) 3 months: 66.7 (IQR 57.2 to 87.1)	Baseline: 72.7 (IQR 58.1 to 88.6) 3 months: 68.9 (IQR 45.7 to 89.7)	p=0.95	CRITICAL	MODERATE
eGFR at 6 months, ml/min/1.73 m^2 (higher result indicates benefit)									
1 RCT Dahan 2017	Serious[1]	No serious	Not applicable	Not calculable	Baseline: 66.7 (IQR 55.4 to 82.5) 6 months: 65.6 (IQR 51.0 to 89.0)	Baseline: 72.7 (IQR 58.1 to 88.6) 6 months: 72.5 (IQR 52.4 to 89.7)	p=0.75	CRITICAL	MODERATE
eGFR at 17 months, ml/min/1.73 m^2 (higher result indicates benefit)									
1 RCT (observational follow-up period) Dahan 2017	Very serious[1,2]	No serious	Not applicable	Not calculable	61.1 (IQR 48.7 to 83.4)	73.1 (IQR 50.4 to 90.5)	p=0.48	CRITICAL	LOW
Serum creatinine at 3 months, µmol/litre (lower result indicates benefit)									
1 RCT Dahan 2017	Serious[1]	No serious	Not applicable	Not calculable	Baseline: 98.1 (IQR 82.2 to 122.9)	Baseline: 91.1 (IQR 74.3 to 122.0)	p=0.88	CRITICAL	MODERATE

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Rituximab and supportive therapy	Supportive therapy	Result (95%CI)		
					3 months: 94.6 (IQR 78.7 to 114.0)	3 months: 100.8 (IQR 81.3 to 115.8)			
Serum creatinine at 6 months, µmol/litre (lower result indicates benefit)									
1 RCT Dahan 2017	Serious[1]	No serious	Not applicable	Not calculable	Baseline: 98.1 (IQR 82.2 to 122.9) 6 months: 94.6 (IQR 75.1 to 130.8)	Baseline: 91.1 (IQR 74.3 to 122.0) 6 months: 97.2 (IQR 76.0 to 126.4)	p=0.67	CRITICAL	MODERATE
Serum creatinine at 17 months, µmol/litre (lower result indicates benefit)									
1 RCT (observational follow-up period) Dahan 2017	Very serious[1,2]	No serious	Not applicable	Not calculable	101 (IQR 87 to 135)	97.2 (IQR 78.5 to 133.5)	p=0.50	CRITICAL	LOW
Anti-PLA2R level									
Anti-PLA2R level at 3 months, RU/ml (higher result indicates harm)									
1 RCT Dahan 2017	Serious[1]	No serious	Not applicable	Not calculable	Baseline 40.5 (IQR 0.0 to 275.5) 3 months: 0.0 (IQR 0.0 to 49.1)	Baseline: 43.3 (IQR 0.0 to 457.5) 3 months: 54.6 (IQR 16.5 to 278.4)	p<0.001	IMPORTANT	MODERATE
Anti-PLA2R level at 6 months, RU/ml (higher result indicates harm)									
1 RCT Dahan 2017	Serious[1]	No serious	Not applicable	Not calculable	Baseline 40.5 (IQR 0.0 to 275.5) 6 months: 0.0 (IQR 0.0 to 34.0)	Baseline: 43.3 (IQR 0.0 to 457.5) 6 months: 45.7 (IQR 7.6 to 262.2)	P=0.002	IMPORTANT	MODERATE

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Rituximab and supportive therapy	Supportive therapy	Result (95%CI)		
Anti-PLA2R positive at 3 months (higher result indicates harm)									
1 RCT Dahan 2017	Serious[1]	No serious	Not applicable	Not calculable	Baseline: 27/37 (73.0%) 3 months: 11/37 (31.4%)	Baseline: 28/38 (73.7%) 3 months: 25/38 (83.3%)	p<0.001	IMPORTANT	MODERATE
Anti-PLA2R positive at 6 months (higher result indicates harm)									
1 RCT Dahan 2017	Serious[1]	No serious	Not applicable	Not calculable	Baseline: 27/37 (73.0%) 6 months: 13/37 (36.1%)	Baseline: 28/38 (73.7%) 6 months: 24/38 (75.0%)	p=0.001	IMPORTANT	MODERATE
Serum albumin									
Serum albumin at 3 months, g/litre (higher result indicates benefit)									
1 RCT Dahan 2017	Serious[1]	No serious	Not applicable	Not calculable	Baseline: 22 (IQR 18 to 25) 3 months: 27 (IQR 21 to 31)	Baseline: 22 (IQR 20 to 26) 3 months: 23 (IQR 19 to 27)	p=0.10	IMPORTANT	MODERATE
Serum albumin at 6 months, g/litre (higher result indicates benefit)									
1 RCT Dahan 2017	No serious	No serious	Not applicable	Not calculable	Baseline: 22 (IQR 18 to 25) 6 months: 30 (IQR 26 to 34)	Baseline: 22 (IQR 20 to 26) 6 months: 24 (IQR 20 to 29)	p=0.029	IMPORTANT	MODERATE
Serum albumin at 17 months, g/litre (higher result indicates benefit)									
1 RCT (observational follow-up period) Dahan 2017	Very serious[1,2]	No serious	Not applicable	Not calculable	32 (IQR 26 to 35)	27 (IQR 20 to 30)	p=0.03	IMPORTANT	LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Rituximab and supportive therapy	Supportive therapy	Result (95%CI)		
Safety									
Serious adverse events (higher result indicates harm)									
1 RCT Dahan 2017	Serious[1]	No serious	Not applicable	Not calculable	Frequency: 8 (3 occurred in the same person)	Frequency: 8 (3 occurred in the same person)	p=0.87	IMPORTANT	MODERATE

Abbreviations

PLA2R, phospholipase A2 receptor; RCT, randomised controlled trial

1 Downgraded 1 level – short period (3 months) of no immunosuppressive therapy before randomisation. For example, rituximab is detectable for at least 3 months after administration. Therefore previous therapy could affect treatment outcomes. No detail on how many participants in each arm had previously received immunosuppressive therapy.
2 Downgraded 1 level – this outcome was during the observational follow-up period and has been downgraded as there may have been differences in management between the treatment groups.

a Remission was defined according to 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines as (1) complete in the case of urinary protein excretion <500 mg/day or <500 mg/g creatinine and (2) partial in the case of urinary protein excretion <3.5 g/day or <3500 mg/g creatinine and ≥500 mg/g creatinine with ≥50% reduction compared with baseline.

Glossary

Cost-effectiveness analysis	An analysis that assesses the cost of achieving a benefit by different means. The benefits are expressed in non-monetary terms related to health, such as symptom-free days, heart attacks avoided, deaths avoided or life years gained (that is, the number of years by which life is extended as a result of the intervention). Options are often compared on the cost incurred to achieve 1 outcome (for example, cost per death avoided).
Dominated	A health economics term. When comparing tests or treatments, an option that is both less effective and costs more is said to be 'dominated' by the alternative.
End stage renal disease (ESRD)	Dependence on dialysis or an eGFR less than 15 ml/min
Incremental cost-effectiveness ratio (ICER)	The incremental cost-effectiveness ratio (ICER), is the difference in the change in mean costs in the population of interest divided by the difference in the change in mean outcomes in the population of interest.
Kidney Disease Quality of Life Short Form (KDQOL-SF)	A self-reported measure of quality of life for people with kidney disease. The short form includes questions on symptoms/problems, effects of kidney disease on daily life, burden of kidney disease, work status, cognitive function, quality of social interaction, sexual function, and sleep.
Renal replacement therapy	Life-supporting treatments for severe acute kidney injury or stage 5 chronic kidney disease. This includes haemodialysis, haemofiltration, haemodiafiltration, peritoneal dialysis and kidney transplantation.

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