CADTH

CADTH HEALTH TECHNOLOGY ASSESSMENT REPORT

Rituximab for the Treatment of Primary Membranous Nephropathy

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

ARB	angiotensin II receptor blocker
ACE	angiotensin converting-enzyme
ACTH	adrenocorticotropic hormone
AE	adverse event
BIA	budget impact analysis
BP	blood pressure
BSC	best supportive care
CI	confidence interval
CR	complete remission
CrI	credible interval
CTX	cyclophosphamide
CYC	cyclosporine
DBP	diastolic blood pressure
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
GI	gastrointestinal
HR	hazard ratio
HRQoL	health related quality of life
HTA	health technology assessment
ITC	indirect treatment comparison
ITT	intention to treat
KDIGO	Kidney Disease: Improving Global Outcomes Clinical Practice Guidelines for Glomerulonephritis
KDQOL-SF	Kidney Disease and Quality of Life Short Form
MCMC	Markov Chain Monte Carlo
MN	membranous nephropathy
NR	no remission
PMN	primary membranous nephropathy
NI	non-inferiority
NMA	network meta-analysis

NS	nephrotic syndrome
NSAID	non-steroidal anti-inflammatory drug
OL	open label
OR	odds ratio
PICOS	population(s), intervention(s), comparators(s), study design(s)
PLA2R	phospholipase A2 receptor
PR	partial remission
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	quality-adjusted life-years
RCT	randomized controlled trial
ROB	risk of bias
RoB 2	risk of bias assessment tool 2
SAE	serious adverse event
SAP	statistical analysis plan
SCr	serum creatinine
SLE	systemic lupus erythematosus
SBP	systolic blood pressure
TAC	tacrolimus
TR	total remission
VAS	visual analog scale

Protocol Amendments

Section	Amendment	Page	Rationale
Policy Questions	Revisions to second policy question. Amended policy questions were determined by the jurisdictional clients. 1. Based on the available evidence, where do you see the place in therapy of rituximab for the treatment of primary membranous nephropathy? 2. What specific characteristics should patients possess/satisfy for access to rituximab?	Page 7 in Protocol	An Implementation Advice Panel will be convened to assist the jurisdictional clients in determining policy options for rituximab in primary membranous nephropathy.

	(Please consider parameters like objective measures and previous therapies patients should have tried or failed, as well as what constitutes an appropriate trial [dose and duration] on a given drug[s].) 3. What is the most appropriate rituximab dosing regimen? (Please consider initial, retreatment, and maintenance therapy settings, as appropriate.) 4. What objective measures or outcomes, and at what time points, should be used to determine treatment success or failure in PMN? 5. Are there special populations (e.g., pregnant women; fertile women etc.) that require other considerations?		

Summary

Key Messages

- Membranous nephropathy is an autoimmune disease and one of the most common cause of nephrotic syndrome in adults. The incidence of membranous nephropathy is 1.2/100,000 persons per year worldwide. Approximately 80% of patients with membranous nephropathy are classified as primary (or idiopathic) membranous nephropathy. The treatment goal of patients with primary membranous nephropathy is to induce remission. Current treatment options include the calcineurin inhibitors (cyclosporine and tacrolimus), cyclophosphamide, and rituximab.
- Rituximab is not approved for the indication of primary membranous nephropathy in Canada. The review aimed to evaluate the evidence on the use of rituximab compared to cyclophosphamide, tacrolimus, and cyclosporine in adult patients with primary membranous nephropathy.
- A systematic review of the efficacy and safety of rituximab versus cyclosporine, tacrolimus or cyclophosphamide was conducted with 18 included randomized controlled trials. A network meta-analysis of 11 of the 18 included RCTs was uninformative due to the small number of studies, the heterogeneity in the studies, and unreliable point estimates and wide credible intervals obtained with the network meta-analysis.
- Due to the uninformative nature of the network meta-analysis, a narrative analysis was conducted of the head-to-head trials of rituximab instead. Two randomized controlled trials showed no evidence of a difference between rituximab and cyclophosphamide whereas rituximab resulted in a better response rate (complete remission and the composite outcome of partial or complete remission) at 24 months compared with cyclosporine. There were no head-to-head trials comparing rituximab to tacrolimus.
- Given the small network of studies, the heterogeneity in the included studies, and the limited information provided by the NMA and the pair-wise comparisons of MENTOR and RI-CYCLO, CADTH was unable to conduct an informative economic evaluation. Further, in addition to the clinical evidence gaps, there were also issues identifying information to inform key parameters to address the policy question of interest to decision makers. Given the limitations associated with the clinical evidence and absence of evidence to inform key model parameters, an economic evaluation would not be able to quantify all relevant incremental costs and effects of using rituximab over currently used alternatives. CADTH will work with the plans to assist with tools to support policy decisions.

Abstract

Background and Policy Context

Membranous nephropathy is an autoimmune disease and one of the most common cause of nephrotic syndrome in adults. The incidence of membranous nephropathy is 1.2/100,000 persons per year worldwide. Nephrotic syndrome is characterized by proteinuria, hypoalbuminemia, hyperlipidemia, and peripheral edema, and may lead to end-stage renal disease. Approximately 80% of patients with membranous nephropathy are classified as primary (or idiopathic) membranous nephropathy (PMN).

No patient groups or individual patients responded to CADTH's call for feedback on the project scope. Thus, excerpts from patients' experiences and perspectives shared on social media and other online sources were considered instead. As such, patients indicated that preventing or delaying end-stage renal disease and dialysis were important treatment goals.

There is evidence to show that immunosuppressive therapies such as cyclophosphamide and the calcineurin inhibitors reduce proteinuria, all-cause mortality, and progression to end-stage renal disease. However, the use of these medications may be associated with serious adverse events such as malignancy, infertility, and infection.

Rituximab is another treatment option for which there is evidence of efficacy. Rituximab is not approved for the indication of primary membranous nephropathy in Canada, and as a such is used off-label. The review aims to evaluate the evidence on the use of rituximab compared to existing treatments in adult patients with primary membranous nephropathy.

Clinical Evidence

A total of 18 randomized controlled trials (RCTs) were included in the systematic review, of which 11 were included in the network meta-analysis (NMA). Due to the small network of studies and inherent heterogeneity in the included studies, primarily from differences in study interventions, population characteristics, and definition of outcomes, no conclusions could be drawn from the available data. The limitations of the NMA for drawing conclusions was evident from the extremely wide 95% credible intervals estimated by both the fixed effect and random effects models. Hence, reported estimates from these models were considered unreliable for drawing conclusions.

The aim of the project was to determine the place of rituximab in the treatment of PMN. Given the uninformative nature of the NMA results, a narrative synthesis of the head-to-head trials of rituximab was conducted. There were no head-to-head trials comparing rituximab to tacrolimus. Relevant evidence was taken from the MENTOR study (rituximab vs. cyclosporine) and the RI-CYCLO study (rituximab vs. cyclophosphamide). While both trials were generally well-conducted, the findings from RI-CYCLO were inconclusive with regards to the comparative efficacy and safety of rituximab compared with cyclophosphamide for any of the outcomes measured at any of the timepoints, given that the study was not powered to detect a clinically meaningful difference. In MENTOR, rituximab was shown to be superior to cyclosporine in terms of two efficacy outcomes at 24 months: complete remission and the composite outcome of partial or complete remission, this last one being the primary endpoint of the RCT. In addition, conclusions could not be drawn regarding the difference in time to remission and the difference in health-related quality of life (HRQoL) among patients treated with rituximab versus cyclosporine. The lower response among patients who received cyclosporine could have been due to the inclusion of patients with more severe proteinuria.

Rituximab showed a similar safety profile compared to both cyclophosphamide and cyclosporine; adverse events occurred in similar frequency between treatment groups in both trials. With respect to notable harms, gastrointestinal events and infections were less common with rituximab relative to the respective comparator arm, although two cases of end-stage renal disease were reported with rituximab.

Economic Evidence

Given the small network of studies, the heterogeneity in the included studies, and the limited information provided by the NMA and the pair-wise comparisons of MENTOR and RI-CYCLO, CADTH was unable to conduct an informative economic evaluation. Further, in addition to the clinical evidence gaps, there were also issues identifying information to inform key parameters to address the policy question of interest to decision makers. Given the limitations associated with the clinical evidence and absence of evidence to inform key model parameters, an economic evaluation would not be able to quantify all relevant incremental costs and effects of using rituximab over currently used alternatives. CADTH will work with the plans to assist with tools to support policy decisions.

Conclusions and Implications for Decision- or Policy-Making

The evidence is inconclusive with regards to the comparative efficacy and safety of rituximab compared with cyclophosphamide. Limited evidence from one RCT suggested that rituximab may result in better treatment response outcomes than cyclosporine. There were no head-to-head trials comparing rituximab to tacrolimus.

The evidence did not lend itself to conducting an economic evaluation and as such, the cost-effectiveness of rituximab to treat Canadians with PMN is unknown. Patients have indicated their willingness to try different treatment options while taking into consideration the safety profile of each drug. [Place holder – IAP]

Introduction

Background and Rationale

Membranous nephropathy (MN) is an autoimmune disease and one of the most common cause of nephrotic syndrome (NS) in adults.[1,2] NS is characterized by proteinuria (>3.5 g/24 hours), hypoalbuminemia (<30 g/dL), hyperlipidemia, and peripheral edema. Patients are also at risk of thromboembolism.[3] Nephrotic syndrome may lead to end-stage renal disease (ESRD).[4]

The incidence of MN is 1.2/100,000 persons per year worldwide.[2] Approximately 80% of patients with MN have anti-phospholipase A2 receptor (anti-PLA2R) antibodies and are classified as primary (or idiopathic) MN; whereas 20% of patients have secondary MN due to a malignancy, an infection (e.g., hepatitis B or C), drugs (e.g., penicillamine, NSAIDs), an autoimmune disease (e.g., systemic lupus erythematosus), or a non-identified autoantibody.[1,2]

Spontaneous remission of primary MN (PMN) is seen in approximately 30% of patients by 14 months and in approximately 60% of patients by 5 years,[1,2,5] and 30% to 40% of patients will progress to ESRD within 10 years.[6] The occurrence of remission is more common in patients with low antibody levels.[1,2] Those with high levels of antibodies have higher risks of relapses, lower responses to therapy, and longer time to remission.[1,2]

The treatment goal of patients with PMN is to induce remission to reduce proteinuria and prevent kidney function loss.[2] Treatments include supportive therapies for hypertension, hyperlipidemia, edema, and for preventing thromboembolism.[1,2] There is evidence to show that immunosuppressive therapy reduces proteinuria, all-cause mortality and progression to ESRD. Alkylating drugs (cyclophosphamide [CTX] or chlorambucil) and calcineurin inhibitors (cyclosporine [CYC] or tacrolimus [TAC]) are immunosuppressive therapies recommended to treat patients with PMN.[2]The use of these medications is associated with serious adverse events. Patients administered CTX are at risk of malignancy, infertility, infection, bone marrow suppression, liver toxicity, and cardiovascular events.[1,2] Serious adverse events seen in patients on calcineurin inhibitors include hypertension and nephrotoxicity.

The recently updated guideline, *KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases,* makes recommendations for the use of rituximab, cyclophosphamide and calcineurin inhibitors in patients at moderate, high and very high risk of progressive kidney injury as well as for patients who relapse after therapy or who are treatment-resistant.[7]

- Rituximab is a monoclonal antibody directed against the CD20 receptor. It induces the depletion of CD20 positive B-cells. Its use in PMN was first reported in a case series in 2002 and subsequently in three single arm trials and one RCT that compared rituximab with supportive therapies.[2] Rituximab does not have a Health Canada approval for the indication of PMN, and as a such is used off-label. Recently, two phase III RCTs have been conducted to evaluate rituximab compared with other immunosuppressive treatments in PMN: cyclosporine in MENTOR and cyclophosphamide in RI-CYCLO.[8,9] A critical appraisal of the MENTOR study is posted on the CADTH website.[10] In PMN, KDIGO recommends the administration of rituximab 1 g intravenously (IV) twice within 2 weeks or 375 mg/m^2 1 to 4 times at weekly intervals.[7]
- Cyclophosphamide, a nitrogen mustard drug, is an antineoplastic and an immunosuppressant.[11] In Canada, it is indicated for various cancers.[12] Its used in PMN was first described in the 1970's.[13] To treat PMN, KDIGO recommends a dose of 2.5 mg/kg/day in months 2, 4, and 6 in combination with methylprednisolone 1 g IV for 3 consecutive days at the start of month 1, 3, and 5 and prednisone 0.5 mg/kg/day in months 2, 4, and 6.[7]
- Cyclosporine and tacrolimus are calcineurin inhibitors that inhibit phosphatase calcineurin which leads to a reduction in T-cell activation. Cyclosporine is indicated for the treatment of adults and children with nephrotic syndrome, including MN.[14] KDIGO recommends its administration at a dose of 3.5mg/kg/day to achieve serum trough level of 125 to 225 ng/mL (101 to 187 nmol/L).[7] Tacrolimus, a drug approved for use in organ transplantation and in rheumatoid arthritis, is administered at a dose of 0.05 to 0.1 mg/kg/day with a target trough level of 125 to 225 ng/mL (104 to 187 nmol/L) for 12 months for PMN.[7,15]

The calcineurin inhibitors may be given in combination with prednisone 10 mg/day which can be withdrawn after 4 months in case of non-response or tapered after 12 months to a lower dose in responders.[7]

With the publication of two key studies, MENTOR and RI-CYCLO, the government-sponsored drug plans requested a review of the use of rituximab in adult patients with PMN.

Objective

CADTH undertook a health technology assessment to review the available evidence on the use of rituximab for PMN to determine its effectiveness and cost effectiveness relative to other treatments.

Policy Questions

The following policy questions were addressed with this project:

1) Is there evidence to support the use of rituximab in adult patients with primary membranous nephropathy?
2) If so, what are the policy options for providing access to rituximab?

In a protocol amendment, the second policy question was replaced with these questions:

- Based on the available evidence, where do you see the place in therapy of rituximab for the treatment of primary membranous nephropathy?
- What specific characteristics should patients possess/satisfy for access to rituximab? (Please consider parameters like objective measures and previous therapies patients should have tried or failed, as well as what constitutes an appropriate trial [dose and duration] on a given drug[s].)
- What is the most appropriate rituximab dosing regimen? Please consider initial, retreatment, and maintenance therapy settings, as appropriate.)
- What objective measures or outcomes, and at what time points, should be used to determine treatment success or failure in PMN?
- Are there special populations (e.g., pregnant women; fertile women etc.) that require other considerations?

Research Questions

The project addressed the following research questions. Details on the specific interventions and outcomes are included in Table 1 — Selection Criteria.

1. What are the efficacy and safety of rituximab compared with current treatments in patients with primary membranous nephropathy?
2. What is the cost-effectiveness of rituximab compared with current treatments in patients with primary membranous nephropathy?

Opportunities for Stakeholder Feedback

Stakeholders were given the opportunity to comment on the proposed project scope that informed this report. Stakeholders were also given the opportunity to provide feedback on the list of included studies and the draft report.

Summary of Patient Perspectives

CADTH involves patients, families, and patient groups to improve the quality and relevance of our assessments. When we are unable to speak to people with lived experience, we take steps to consider patient perspectives by including views from online patient groups. CADTH has adopted a Framework for Patient Engagement in HTA.[16] The Framework includes Standards for Patient Involvement in Individual HTAs and is used to support and guide our activities involving patients and patient groups. For this Health

Technology Review, understanding that patients have knowledge, perspectives, and experiences that are unique and contribute to essential evidence, guided our approach for finding and collating patient insights.

CADTH wanted to speak with a patient with PMN to better understand the challenges of the disease and hear their first-hand experiences with rituximab. CADTH contacted relevant patient groups and posted a public call for patient involvement. However, we were unable to find and interview an individual with personal experience with PMN who had tried rituximab. As an alternative, we gathered excerpts from patient observations and experiences shared on social media and other online sources. Appendix 1 follows the Guidance for Reporting Involvement of Patients and the Public short form (GRIPP2 SF) checklist[17] to outline the process of collecting patient perspectives and where and how that information was used in the review.

Patient age at diagnosis varied, but most patients reported being diagnosed before the age of 40 years. Disease symptoms included but were not limited to swelling and pain in the legs, weight gain, foamy urine, and fatigue. Some patients achieved proteinuria remission with corticosteroids and immunosuppressive therapies but reported that these medications had significant side effects. The risk of infertility associated with cyclophosphamide was a major concern for one young female patient. Overall, patients expressed wanting to try a treatment if it meant preventing or delaying disease progression. It was not uncommon for them to have tried immunosuppressive therapies prior to rituximab. Effectiveness of rituximab, like immunosuppressive therapies, varied from one patient to the next. The consensus among patients seemed to be that they were willing to endure treatment side effects if it meant there was a chance to go into remission and delay progression to end-stage kidney disease.

The collection of patient perspectives enabled the research team to consider the evidence found in the literature alongside an understanding of the wider experiences of patients and family caregivers.

Methods

To inform the conduct of this HTA, a preliminary scoping review of the existing literature was conducted. A protocol was written *a priori*, using appropriate reporting guidelines (e.g., the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols ([PRISMA-P]) for guidance on clarity and completeness and they were followed throughout the study process.

Study Design

This clinical evaluation was designed as a systematic review (SR) and a network meta-analysis (NMA) to answer the first research question. The SR and NMA of the primary studies focused on the clinical effectiveness, safety, and impact of rituximab treatment on PMN. The SR was conducted following the core methods and review steps, including screening, data extraction, and risk of bias assessment. The NMA was conducted in accordance with ISPOR guidelines for NMAs.[18]

To answer the second research question, an economic analysis was planned to evaluate the cost-utility of rituximab using a de novo decision analytic model to assess the costs and health outcomes associated with interventions for the treatment of biopsy-proven PMN in adult patients who have NS and have not achieved spontaneous remission within six months of diagnosis. The interventions were those in the clinical review.

Literature Search Methods

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the PRESS Peer Review of Electronic Search Strategies checklist (https://www.cadth.ca/resources/finding-evidence/press). [19] The search strategy is presented in Appendix 2.

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, the Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid, and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and

keywords. The main search concept was membranous nephropathy. Clinical trial registries were also searched: the US National Institutes of Health's clinicaltrials.gov and the World Health Organization's International Clinical Trials Registry Platform (ICTRP) search portal.

Search filters were applied to limit retrieval to randomized controlled trials or controlled clinical trials. Retrieval was not limited by publication date and was limited to the English or French language. Conference abstracts were excluded from the search results.

The initial search was completed on April 22, 2020 with regular updates until the publication of the final report. The clinical trial registries search was updated prior to the completion of the stakeholder feedback period. Studies meeting the selection criteria of the review and identified in the alerts prior to the completion of the stakeholder feedback period were incorporated into the analysis of the final report.

Grey literature (literature that is not commercially published) was identified by searching sources listed in relevant sections of the Grey Matters: A Practical Tool For Searching Health-Related Grey Literature checklist (https://www.cadth.ca/grey-matters),[20] which included the websites of regulatory agencies, HTA agencies, clinical guideline repositories, systematic review repositories, patient-related groups, and professional associations. Google was also searched for additional internet-based materials. These searches were supplemented by reviewing bibliographies of key papers and through contacts with experts and industry, as appropriate. The grey literature search was updated prior to the completion of the stakeholder feedback period. See Appendix 2 for more information on the grey literature search strategy.

Selection and Eligibility Criteria

Studies were included if they met the eligibility criteria, including the specific population, intervention, comparators, outcomes, and study design, presented in Table 1. The inclusion criteria were informed by the informal scoping review of the existing literature, patient engagement, stakeholder feedback, and consultation with the clinical expert.

Table 1: Selection Criteria for Clinical Review

Population and Sub-groups
Adults with biopsy-proven primary membranous nephropathy with nephrotic syndrome Subgroups: • Risk for disease progression (e.g., age, severity of albuminuria, anti-PLA2R status) • Relapse • Resistance to disease or prior failure with immunosuppressants • Treatment history (treatment-naive or experienced)
Interventions and Comparators[a]
• Rituximab monotherapy or combination therapy (e.g., with calcineurin inhibitors) • Cyclophosphamide with corticosteroids • Calcineurin inhibitors (cyclosporine or tacrolimus) with or without corticosteroids • Placebo or no treatment
Outcomes
Clinical Effectiveness: • Outcomes assessing clinical response: complete remission, partial remission, time to remission, relapse • Outcomes assessing kidney function: Kidney failure with or without renal replacement/end stage renal disease (dialysis, kidney transplantation), doubling of SCr or 50% reduction in eGFR

• Health-related quality of life Safety: • Adverse events, serious adverse events, withdrawal due to adverse events, death • Notable harms: Infection, gastrointestinal complications, neutropenia, neurologic, and malignancy
Study Design
Published phase 3 randomized controlled trials

eGFR = Estimated Glomerular Filtration Rate; PLA2R = Phospholipase A2 receptor; Scr = serum creatinine

[a] Best supportive care may be given on an as-needed basis with all treatment regimens, which can include angiotensin converting-enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), a diet low in salt and protein, and statins, chlorambucil, ACTH, azathioprine, mizoribine, leflunomide.

Population and Subgroups

For this review, adult patients with biopsy-proven PMN with NS were included, although studies were not excluded if their definition of NS was ambiguous or largely captured with PMN. Subgroups relevant for this review were determined based on risk factors for disease progression, relapse, resistance to disease, and prior treatment history. The clinical expert indicated that there may be differences in treatment effectiveness between the subgroups and that risk factors for progression are essential for the decision to treat or not.

Interventions and Comparators

All currently available treatments for PMN were considered potentially relevant; however, the clinical expert noted that mycophenolate mofetil (MMF) was not a recommended intervention in this group of patients. The following interventions were therefore selected: Rituximab, cyclophosphamide, calcineurin inhibitors (cyclosporine or tacrolimus), and placebo. Recognizing that corticosteroids are sometimes given in combination with these drugs, no distinction was made between monotherapy or combination therapy for any of the included treatments.

It should be noted that best supportive care (BSC) was included as a background treatment, or as an add-on treatment to any of the included regimens as the clinical expert noted that BSC is generally given to all patients. Antihypertensive medications (angiotensin converting enzyme [ACE] inhibitors or angiotensin receptor blockers [ARBs]) constituted the most common classes of BSC.

Outcomes

Several potentially important outcomes were discussed to assess the clinical effectiveness and safety of the studied drugs. These included outcomes assessed clinical response, kidney function, and health-related quality of life (HRQoL). Outcomes that were noted less important from a clinical standpoint were excluded (e.g., biomarkers). Likewise, several safety endpoints were considered important for clinical decision-making and were therefore included in the protocol.

Study Design

Published phase III RCTs that met the previously described population; intervention and comparator criteria were eligible for inclusion.

Study Selection

Two reviewers independently screened titles and abstracts of all retrieved citations (i.e., literature searches of academic databases, grey literature searches, and clinical trial database) against eligibility criteria (Table 1). Exclusion by both reviewers was required for a record to be excluded at the title and abstract level. Full-text articles that were judged to be potentially relevant by at least one reviewer were retrieved for the second level of screening. The same two reviewers independently examined all full-text articles against the eligibility criteria, and consensus was required for inclusion in the review. Discrepancies between reviewers were resolved by discussion.

Studies identified via monthly database search alerts and semi-annual grey literature search alerts meeting the selection criteria of the review were incorporated into the analysis.

Quality Assessment

The risk of bias of the primary studies was systematically evaluated using the methods described in the Cochrane Risk of Bias assessment tool 2 for RCTs (RoB 2).[21]

The RoB 2 tool[21] allowed for the assessment of five sources of bias or "domains": bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. Each question within each domain was answered with a yes, probably yes, probably no, no, or no information. Afterwards, a judgment of "low risk of bias," "high risk of bias," or "some concerns" was assigned for each domain, with rationale for each decision included in the comments box field.

The risk of bias assessments of the included studies was performed by one reviewer. The tools were used as a guide to evaluate the risk of bias in the included studies, and additional insight beyond the items on the instruments have been provided, when applicable. Summary scores were not calculated; rather, the strengths and limitations of each included study and how they affect the study findings were described narratively. Results of the risk of bias assessment were not used to exclude studies from this review.

Data Extraction

The original, primary publication for each included RCT was used for data extraction. In situations where multiple publications for a unique RCT were available (e.g., supplemental online appendices, companion publications of specific outcomes, or populations from the original study), the most recently adjudicated data for each outcome were extracted, with preference given to published records.

Reviewers used Microsoft Excel to document and tabulate all relevant information from the included studies. Data were extracted by the lead author, with data checking done by a secondary reviewer. Discrepancies were resolved through discussion until consensus was reached; a third reviewer was involved when necessary. The following relevant information were extracted, where available:

- Study level: description of publication (e.g., first author last name, title, publication year), study characteristics (e.g., clinical trial registry identification number, trial acronym, study design, year of study conduct, sample size, study setting, country of study conduct, randomization ratio, blinding status, superiority or noninferiority design, eligibility criteria, study duration)
- Patient level: number of patients, age, sex (as reported by study authors), clinical situation of the diagnosis, duration of disease, baseline characteristics
- Intervention and comparator level: type, dose, total duration of treatment, dosing frequency, route of administration, and concurrent and previous relevant therapies
- Outcome level: description of outcomes (e.g., method of measurement, unit of measurement, length of follow-up)
- Type of analysis: intention-to-treat (ITT) or safety population. Data from figures were extracted if explicit numerical data were reported.

Data Analyses and Synthesis

After the conclusion of data extraction, a feasibility assessment was conducted for addressing the posed research questions which included evaluating sources of methodological and clinical heterogeneity between the included studies. Study design, patients baseline characteristics, treatment characteristics, as well as outcomes definition were compared between studies. A qualitative assessment of feasibility was determined through close collaboration between the reviewers, methodologists, and clinical experts working on the HTA.

When feasible, the efficacy and safety of rituximab versus other relevant comparators outlined in the Table 1 were evaluated through an indirect treatment comparison (ITC) using NMA.

All NMAs were conducted under a Bayesian framework. The modeling approach was suitably chosen for each outcome i.e., binomial likelihood models for dichotomous outcomes and normal likelihood models for continuous data. Random effects models was identified a priori as the primary approach when feasible to account for anticipated clinical and methodological heterogeneity across studies. Fixed effects models were considered when the available network for a given outcome was insufficient for estimating a random effects model. When possible, regardless of the primary analysis, both fixed effect and random effect models were reported along with diagnostic information criterion (DIC). Vague priors were used for all parameters in the model. Each NMA was estimated in a MCMC (Markov Chain Monte Carlo) simulation using three chains, and their convergence were assessed by examining the history, trace and Gelman-Rubin plots. A minimum of 10,000 burn-ins and 20,000 iterations were preformed in the simulation. In addition, statistical heterogeneity were assessed through comparing the residual deviance between the fixed and random effects model. An assessment of the consistency assumption was conducted through an inconsistency model. Additional sensitivity analysis were conducted by excluding studies with high risk of bias or studies with missing data to a relevant outcome.

Results of Clinical Evaluation

Quantity of Research Available

A total of 934 citations were identified in the literature search. Following screening of titles and abstracts, 14 studies were identified as potentially relevant and retrieved for full-text review. A total of 24 reports were retrieved from other sources (i.e., grey literature, hand search, and search alerts). Of these 38 potentially eligible reports, 19 reports presenting data from 18 unique studies met the inclusion criteria and were included for review. The report selection process is outlined in Appendix 3 using a PRISMA diagram. A list of included and excluded citations with details describing the rationale for those excluded, are presented in Appendix 4 and 5 respectively. Study and Patient Characteristics

Study Characteristics

Study Design

A total of 19 publications met the inclusion criteria of this review, of which two publications reported findings from the same study, resulting in a total of 18 included trials. The study characteristics are shown in Appendix 6. The trials by Cattran et al.[22] and Omrani et al.,[23] were single-blinded and double-blinded, respectively; 11 RCTs used an open-label design; and the remaining 5 trials did not specify the type of blinding. The sample sizes ranged from 26 patients to 130 patients across the studies; 10 studies had a sample size between 40 and 80 patients; 3 studies had a sample size of less than 40 patients; and 5 studies had a sample size greater than 80 patients. The duration of the studies (including follow-up) ranged from 6 months to 10 years, with 12 studies having a duration between 10 months and 25 months. Eight trials were multi-centre, and 10 trials were single centre. Two studies were conducted in North America.

Inclusion Criteria

All trials were conducted in adults, although the definition of adults varied, with a minimum age of 15 years. Overall, the trials included patients with PMN, diagnosed primarily based on proteinuria and serum albumin, and to a lesser extent, creatinine clearance. Of the trials that reported a threshold for proteinuria, most studies used a threshold of ≥ 3.5 g/day for inclusion of patients, although studies consisting of patients with severe proteinuria and/or NS used a higher threshold ranging from ≥ 5g/day to > 8 g/day. Serum albumin was generally used in combination with daily proteinuria as a criterion for defining PMN, with threshold ranging from < 20 g/L to ≤ 35 g/L across studies. Creatinine clearance was reported as a function of estimated glomerular filtration rate (eGFR) or serum (or plasma) creatinine. For eGFR, the threshold ranged from ≥ 30 to > 60 mL/min/1.73 m^2 across studies, whereas the threshold for serum creatinine ranged from < 221 µmol/L to <133 µmol/L (or plasma creatinine concentration of < 300 µmol/L).

Idiopathic membranous nephropathy (IMN) stage as an eligibility criterion was reported in 5 trials. Three of these trials included IMN stage I–III, and 2 trials included IMN stage I-IV. IMN was generally diagnosed using renal biopsy and other pathological tests.

Exclusion Criteria

All trials excluded patients with IMN from a secondary source (systemic lupus erythematosus [SLE]), or drug-associated nephropathy (phenytoin and gold salts). Patients with characteristics indicative of significant comorbidities were excluded, including any serious systemic infection or associated disorders requiring NSAIDS; liver function test abnormalities; severe renal diseases; patients with diabetes mellitus, malignancy, infections (including malaria, HIV, tuberculosis, and hepatitis B and hepatitis C), severe cardiovascular conditions (cardiac dysfunction, uncontrolled hypertension, thromboembolism, unstable angina pectoris, renal vein thrombosis), and gastrointestinal diseases. Several trials restricted recruiting patients on immunosuppressive drugs, steroids, plasma exchange therapy, or anti-lymphocyte products, gold, penicillamine, NSAIDs between 1 month and 2 years prior to study, and rituximab (if the intervention of interest was rituximab). Pregnant females or inadequate contraception and those with hypersensitivity to study drugs were also excluded.

Interventions and Comparators

Of the included studies, 2 trials included rituximab as a treatment arm (MENTOR[8] and RI-CYCLO[9]). In both trials, rituximab was administered in two separate intravenous (IV) doses (administered 14 days apart) of 1,000 mg over a period of six months, without concomitant or subsequent drug therapies, although the MENTOR study allowed subsequent retreatment at the same dosage in the absence of remission. Three main treatment regimens were used across the studies: TAC, CTX, and CYC. Each of the three major treatment regimens were administered in different dosages across trials, usually given in two stages: a loading dose, to reach a certain plasma level, followed by a continuation dose, usually at a lower dose than the loading dose, continued through the end of the treatment period. Most trials administered corticosteroids (prednisone, prednisolone, or methylprednisolone) in combination with the primary treatment regimen, and these were also administered in two stages (i.e., a loading dose to reach a certain plasma level, and a continuation/tapering dose administered through the end of the treatment period). Details of the treatment regimen in each trial are provided in Appendix 7.

TAC was used as the treatment or comparator arm in 10 of the included trials, and was compared with CTX, CYC or other standards of care, including the Ponticelli regimen. TAC was generally administered at a dose of 0.5 – 0.1 mg/kg/day, for a period ranging from 6 months to 24 months across studies. TAC was administered in combination with corticosteroids in all but one trial. Two trials compared TAC administered for different lengths of time, a short course (6 – 12 months), and a long-course (24 months).

CTX was used in 8 trials as an intervention or comparator (compared with TAC, CYC, rituximab, or BSC), in both IV and oral formulations, administered for a period ranging from 3 to 12 months across trials. IV doses were administered once a month, at a dose of 500 to 750 mg/m^2. Oral CTX doses ranged from 1 to 2 g/day. In all cases, IV or oral corticosteroids were given in combination or alternatively with CTX.

CYC was used in 7 trials as an intervention or comparator (against placebo, rituximab, CTX, chlorambucil or TAC), administered for a period of 6 to 12 months. CYC was administered orally, at a dose of 1.5 to 3.5 mg/kg/day across studies, with low doses for longer treatment period, and higher doses for shorter treatment period. CYC was given in combination with corticosteroids in all but one trial.

In addition to the study drugs, various medications were allowed in most trials. Antihypertensives were the most common medication, most notably ACE inhibitors or ARBs, administered as needed to maintain a target or stable BP level (120 to140 mmHg for SBP, 75 to 90 mmHg for DBP). Other medications included dietary modifications, cholesterol lowering drugs, and anticoagulants.

Outcomes

All included trials measured complete or partial remission (CR and PR, respectively) as a primary or major outcome, or outcomes based on CR and PR, such as remission rates, total remission (TR), no remission (NR), relapse or recurrence. Both CR and PR were based on proteinuria; however, the definition of CR and PR varied across studies (Table). For CR, proteinuria thresholds ranged

from ≤ 0.3 to 0.5 g/day for most trials. In addition, normal serum albumin level and stable or normal renal function were included in CR definition in a few trials. For PR, a wide range of definitions were used across the trials, including a proteinuria level ≤ 0.2 to ≤ 3.5 g/day, 50% proteinuria reduction, and stable renal function. TR, sometimes referred to as any remission, consisted of those achieving either CR or PR, and NR consisted of those who achieved neither. Relapse and recurrence were outcomes based on a similar definition, most notably proteinuria level reaching outside of the range that was designated as PR after achieving CR and/or PR in the respective trials.

A number of outcomes assessing the kidney function were reported based on baseline creatinine or creatinine clearance. Most notable of these outcomes include doubling of baseline creatinine, referred to as renal survival in some trials. The incidence of the following outcomes were assessed less commonly: end-stage renal disease (ESRD, defined as creatinine clearance of < 12 mL/min to ≤ 15 ml/minute, the initiation of dialysis, or renal transplantation), NS or nephrotic proteinuria (severe proteinuria).

HRQoL was assessed in two trials, using the modified Kidney Disease Quality of Life-Short Form (KD-QoL) version 1.3, and visual analogue scale (VAS, score ranging from 0 to 10, with 10 indicating the best quality of life).

Table 2: Remission Definitions in Included Studies

Definitions of Complete Remission	Studies
Proteinuria ≤ 0.3 g/day plus stable renal function	Cattran 2001, Chen 2010, He 2013
Proteinuria < 0.3 g/day, normal serum albumin level, and stable renal function	Di 2018, Li 2017, Peng 2015
Proteinuria ≤ 0.3 g/day and serum albumin level of ≥ 3.5 g/dl	Fervenza 2019
Protein–creatinine index ≤ 0.2 g/10 mmol Cr, and improved or stabilized renal function	Hofstra 2010
Proteinuria < 0.2g/day	Jha 2007
Proteinuria ≤ 0.3 g/day	Kosmadakis 2010, Saito 2014, Scolari 2021
Proteinuria < 0.5 g/day and stable/normal renal function	Praga 2007, Xu 2013
Proteinuria < 0.5 g/day, normal serum albumin, and normal serum creatinine	Ramachandran 2016 and 2017
Proteinuria < 0.4 g/day	Yuan 2013
Proteinuria ≤ 0.3 g/day at 1 year	Scolari 2021
Definitions of Partial Remission	**Studies**
50% proteinuria reduction, proteinuria < 3.5 g/day, and stable renal function	Cattran 2001, Chen 2010
Proteinuria 0.3-3.0 g/day. Or 50% proteinuria reduction, serum albumin ≥ 30 g/l, and stable renal function	Di 2018, Li 2017
50% proteinuria reduction, proteinuria < 3.5 g/day, and normal serum creatinine	He 2013
Protein–creatinine index <2.0 g/10 mmol Cr, and improved or stabilized renal function	Hofstra 2010
Proteinuria 0.2-2.0 g/d. Or 50% proteinuria reduction and stable renal function	Jha 2007
50% proteinuria reduction and proteinuria < 3.5 g/day	Kosmadakis 2010, Peng 2015, Praga 2007
Proteinuria 0.5 – 1.9 g/day or 50% proteinuria reduction from baseline and stable renal function	Ramachandran 2016 and 2017
Proteinuria 0.3 – 1.0 g/day	Saito 2014

Proteinuria 0.5 – 3.5 g/day	Xu 2013
50% proteinuria reduction from baseline, proteinuria 0.4-2.9 g/day, and serum albumin ≥ 30 g/l	Yuan 2013
50% proteinuria reduction from baseline and final proteinuria between 0.31 and 3.5 g/day	Fervenza 2019
50% proteinuria reduction from baseline and proteinuria < 3.5 g/day	Scolari 2021

Source: Cattran et al.,[22] Chen et al.,[24] Di et al.,[25] Fervenza et al.,[8] He et al.,[26] Hofstra et al.,[27] Howman et al.,[28] Jha et al.,[29] Kosmadakis et al.,[30] Li et al.,[31] Omrani et al.,[23] Peng et al.,[32] Praga et al.,[33] Ramachandran et al.,[34,35] Saito et al.,[36] Scolari et al.,[9] Xu et al.,[37] Yuan et al.[38]

Baseline Patient Characteristics

The baseline patient characteristics are shown in Appendix 8. The mean age of the participants ranged from 37 to 58 years; for most trials, the patients were between 40 and 60 years old (15 studies). The trials consisted of 42.7% to 93.5% males, with 12 trials consisting of more than 60% males. Of the studies with available baseline data, the trials had a mean eGFR of 60 to 100 mL/min/1.73 m^2 (15 studies), a mean SBP of 100 to 130 mmHg (10 studies), and mean or median serum albumin of 2 to 3 g/dL (12 studies).

The following baseline characteristics were reported in no more than 9 studies: disease duration, total cholesterol, and urine protein. Of the studies that reported disease duration, 5 studies had patients who have had the disease for less than 15 months, whereas one trial included patients with the disease for more than 50 months. Six trials had patients with a mean total cholesterol greater than 250 mg/dL, whereas one trial had patients with a mean total cholesterol of less than 150 mg/dL. Mean or median urine protein levels ranged between 6 to 12 g/day in all but 2 studies, which had protein levels less than 4 g/day.

Data Analysis and Synthesis

Findings of the Network Meta-Analysis

Among the studies identified for inclusion in the NMA, 11 studies reported results for outcomes of interest for this review. The outcomes for which a viable network was available for analysis were complete remission and the composite outcome of complete or partial remission. A total of 10, 11, and 6 studies reported results for complete remission measured at 6, 12, and 18 months, respectively. A total of 11, 11, and 6 studies reported results for the composite outcome of partial or complete remission at 6, 12, and 18 months, respectively. The network diagrams and model results for both fixed effects and random effects models for each of these endpoints are reported in Appendix 9. All models successfully converged; however, upon examining the results of each model, several of the estimated credible intervals were found to be extremely wide. These results suggest a high level of instability in these models, likely a result of small networks of available studies and excessive heterogeneity across the network. Thus, the estimated results were considered to be unreliable for drawing conclusions for how rituximab compares to the available comparators in the network.

Narrative Synthesis

Given the uninformative results of the NMA, a narrative synthesis was conducted of the head-to-head trials of rituximab. Relevant evidence was taken from the MENTOR study (rituximab vs. CYC) and the RI-CYCLO study (rituximab vs. CTX). Unless otherwise specified, all efficacy results were based on the ITT population of the respective studies. There were no head-to-head trials comparing rituximab to TAC.

Summary of Critical Appraisal

MENTOR and RI-CYCLO were considered well-conducted studies. These trials had a low risk of bias in each domain, with most signaling questions assessed adequately based on the level of detail provided in the publications. The critical appraisal of all of the included trials is available in Appendix 10.

A complete critical appraisal of the MENTOR study is posted on the CADTH website. [10] In summary, the CADTH critical appraisal of MENTOR reported as the key limitations of this study being small sample size which limited power and the open-label design of the

study which could introduce bias for subjectively measured endpoints. It was also noted that, due to the limited evidence, conclusions could not be made for the endpoints of health-related quality of life, creatinine clearance, and anti-PLA2R. While CADTH did not publish an in-depth peer-reviewed critical appraisal of RI-CYCLO, based on the assessment conducted as part of this broader review, the study has similar limitations of low sample size, which limited power to detect difference, and an open-label design which could introduce bias for subjectively measured endpoints.

Outcomes Assessing Clinical Response

Complete Remission

In MENTOR, complete remission was a secondary outcome which was not adjusted for multiple comparisons (Table 4). Thus, results must be interpreted cautiously with consideration to the increased risk of type 1 error. The risk difference comparing rituximab to CYC estimated a 2% decrease in CR at 6 months (95% CI: −5 to 2), a 9% increase in CR at 12 months (95% CI:−1 to 19), a 26% increase in CR at 18 months (95% CI:15to 37), and a 35% increase in CR at 24 months (95% CI:24to 47).[8]

In RI-CYCLO, complete remission at 12 months was the primary efficacy outcome in RI-CYCLO, although the study was conducted as a pilot study which was not powered to detect a clinically meaningful difference. As a result, the estimated 95% CI for each point estimate were extremely wide, and thus, do not provide sufficient evidence to support differences between rituximab and CTX for any endpoints. At 12 months, the odds ratio (OR) comparing rituximab to CTX estimated a numerically decreased odds of CR for rituximab compared to CTX with an estimated OR of 0.40 (95% CI: 0.13 to 1.23). Results from the RI-CYCLO trial were not adjusted for multiple comparisons; however, there is no increased risk of type 1 error from these results as none of the estimated 95% CI exclude the null hypothesis.[9]

Complete or Partial Remission (Composite Outcome)

Partial remission was reported as a composite outcome with complete remission (Table 3). In MENTOR, the composite outcome of complete or partial remission at 24 months was the primary outcome. A gatekeeping approach was used to control the family-wise type 1 error by first testing the primary outcome for the non-inferiority of rituximab compared to CYC and only testing for superiority if the test for non-inferiority was successful. The results supported the conclusion that rituximab was non-inferior to CYC at 24 months at a non-inferiority margin of 15%. The noninferiority margin of 15% was based on the assumption that 55% of the patients in the rituximab group and 45% of those in the CYC group had a CR or PR at 24 months; however, only 20% patients in the CYC arm achieved CR or PR through 24 months. The authors for the MENTOR study suggested that the lower response among CYC patients could have been due to the inclusion of patients with more severe proteinuria. The risk difference comparing rituximab to CYC was 40% (95% CI: 25 to 55, 1-sided P <0.001 for non-inferiority), at 24 months. The effect estimate was consistent regardless of age (≤50 years and >50 years), anti-PLA2R (≤40 u/mL and >40 u/mL), and history of immunosuppressive therapy at baseline. Superiority of rituximab over CYC for complete or partial remission at 24 months was also supported by the results (2-sided P < 0.001). The secondary outcomes of complete or partial remission at 24 months based on the per protocol population and at 12 months based on the ITT population were also included in the gatekeeping procedure for multiple testing and were simultaneously tested using a Bonferroni correction for multiple comparison resulting in an alpha threshold of 0.0125 for the 1-sided P-value testing NI for these endpoints. Results for the per protocol population have not been presented in this report. For the endpoint of complete or partial remission at 12 months, the results supported conclusions of non-inferiority of rituximab compared to CYC at a non-inferiority margin of 15%. The estimated risk difference showed a numerical increase of 8% (95%CI: −9 to 25) for rituximab compared to CYC. This endpoint was not tested for superiority as part of the pre-specified analysis nor was any other endpoint formally tested. Thus, any further conclusions drawn based on results from this study must consider the risk of increased type 1 error for such conclusions.[8]

In RI-CYCLO, the composite outcome of complete or partial remission was a secondary outcome (Table 4). At month 6, 12, and 18, numerically fewer percentage of patients in the rituximab arm achieved CR or PR compared to the CTX regimen arm (OR 0.57 [95% CI: 0.22 to 1.45], 0.61 [95%CI: 0.23 to 1.63], 0.49 [95%CI: 0.16 to 1.49], respectively), whereas more patient achieved this endpoint in the rituximab arm at 24 and 36 months (OR 1.32 [95%CI: 0.33 to 5.29], and 2.12 [95%CI: 0.45 to 9.96], respectively). Of the reported subgroups, the composite CR or PR probability remained consistent across age (≤55 years and >55 years) and serum albumin levels (≤2.5 g/dL and >2.5 g/dL) As previously mentioned, the precision around the results from this study were generally insufficient to support any conclusions that the efficacy of rituximab differed from CTX.[9]

Table 3: Remission in MENTOR and RI-CYCLO (ITT)

Outcome/ Time point (months)	MENTOR, n (%)			RI-CYCLO, n/N (%)		
	Rituximab (N=65)	CYC (N=65)	Risk difference (95% CI)	Rituximab (N=37)	CTX(N=37)	Odds Ratio (95% CI)
Complete remission						
6	0 (0)	1 (2)	−2 (−5 to 2)	3/37 (8)	2/37 (5)	1.54 (0.24 to 9.8)
12	9 (14)	3 (5)	9 (−1 to 19)	6/37 (16)	12/37 (32)	0.40 (0.13 to 1.23)[b]
18	18 (28)	1 (2)	26 (15 to 37)	10/32 (31)	7/34 (21)	1.75 (0.57 to 5.36)
24	23 (35)	0 (0)	35 (24 to 47)	11/26 (42)	11/31 (35)	1.33 (0.46 to 3.89)
36	ND	ND	ND	6/20 (30)	7/22 (32)	0.92 (0.25 to 3.41)
Complete or partial remission (composite outcome)						
6	23/65 (35)	32/65 (49)	−14 (−31 to 3)	19/37 (51)	24/37 (65)	0.57 (0.22 to 1.45)
12	39/65 (60)	34/65 (52)	8 (−9 to 25) NI margin: 15 percentage points P-value: 0.004[a]	23/37 (62)	27/37 (73)	0.61 (0.23 to 1.63)
18	40/65 (62)	15/65 (23)	38 (23 to 54)	21/32 (66)	27/34 (79)	0.49 (0.16 to 1.49)
24	39/65 (60)	13/65 (20)	40 (25 to 55) Inferiority result: NI margin: 15 percentage points P-value: <0.001[a,b]	22/26 (85)	25/31 (81)	1.32 (0.33 to 5.29)
			Superiority result: P-value: <0.001[a,b]			
36	ND	ND	ND	17/20 (85)	16/22 (73)	2.12 (0.45 to 9.96)

CYC = cyclosporine; CTX = cyclophosphamide; CI = confidence interval; ND = not done

Data in bold represents primary outcome of the respective trial

[a] Indicates analysis was controlled for family-wise type I error, with a stepwise approach (first testing the noninferiority of rituximab and then testing the superiority of rituximab if the noninferiority test was significant) or Bonferroni correction in MENTOR.

[b] primary outcome for the trial

Source: Fervenza et al.,[8] Scolari et al.[9]

Time to remission

Time-to-event curves for CR or PR during the 12-month treatment period was provided in MENTOR only. Patients in the CYC group tended to have remission earlier, with a later catch-up in patients in the rituximab group (hazard ratio [HR] for response at 12 months, 0.85; 95% CI: 0.55 to 1.32) (data not presented).[8]

Relapse

Relapse was reported in RI-CYCLO only. A total of nine participants relapsed after they had achieved remission at 12 months: three of 23 patients in the rituximab arm (13%), and six participants of the 27 patients in the comparator arm (22%).[9]

Health-Related Quality of Life

HRQoL was assessed in MENTOR only, using selected subscales of the Kidney Disease and Quality of Life Short Form (KDQOL-SF) in patients with CR or PR at months 6, 12 and 24. Results were only reported for patients that achieved complete or partial remission at a given time point. Thus, these results cannot be used to support conclusions regarding difference in HRQoL among patients treated with rituximab vs CYC (data not presented).[8]

Outcomes Assessing Harms

Adverse Events

Overall, both trials showed a similar AE profile for rituximab and the respective comparator arm (Table 4). A higher proportion of AEs were reported in MENTOR (71% and 78% in the rituximab and CYC arms, respectively) than in RI-CYCLO (43% in both rituximab and CTX arm). Subsequently, the number and rate of AEs per 100 patients were higher in MENTOR than in RI-CYCLO with 275 AEs per 100 patients and 335 AEs per 100 patients in the rituximab and CYC arm, respectively, in MENTOR and 54 AEs per 100 patients and 47 AEs per 100 patients in the rituximab and CTX arm, respectively, in RI-CYCLO. Only MENTOR reported AEs by grade; the proportion of patients with grade ≥3 AEs was 35% in the CYC group compared to 17% with rituximab.[8,9]

Withdrawals due to Adverse Events

Patients in the rituximab group in both trials had fewer treatment discontinuations than the respective comparator group: 2 with rituximab versus 11 with CYC in MENTOR, and 1 with rituximab versus 4 with CTX in RI-CYCLO.[8,9]

Serious Adverse Events

Both trials had a comparable number of serious AEs between the treatment arms (Table 4). One patient receiving rituximab in RI-CYCLO had a fatal serious AE due to lung cancer. The other serious AEs were nonfatal.[8,9]

Notable harms

Of the notable harms listed in the Selection Criteria outlined in Table 1, patients in the rituximab arm generally had a lower rate of gastrointestinal events and infections relative to the respective comparator arm (Table 4). No cancers or deaths occurred during MENTOR, whereas 3 patients developed cancer in RI-CYCLO: 2 in the rituximab arm (lung and breast carcinoma, patient with lung cancer died), and one in the CTX arm (prostate carcinoma). End-stage renal disease was reported in one patient in the CYC group in MENTOR, and 2 patients in the rituximab group in RI-CYCLO.[8,9]

Table 4: Harms in MENTOR and RI-CYCLO

Event	MENTOR				RI-CYCLO			
	Rituximab (N=65)		CYC (N=65)		Rituximab (N=37)		CTX(N=37)	
	Patients, n (%)	Events no. of events (rate per 100 patients)	Patients, n (%)	Events no. of events (rate per 100 patients)	Patients, n (%)	Events no. of events (rate per 100 patients)	Patients, n (%)	Events no. of events (rate per 100 patients)
AE	46 (71)	179 (275)	51 (78)	218 (335)	16 (43)	25 (47)	16 (43)	30 (54)
SAE	11 (17)	13 (20)	20 (31)	22 (34)	7 (19)	8 (11)	5 (14)	6 (7)
Fatal	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)	0 (0)	0 (0)
Nonfatal	11 (17)	13 (20)	20 (31)	22 (34)	7 (19)	7 (9)	5 (14)	6 (7)
Notable AEs[a]								
GI pain	1 (2)	2 (3)	9 (14)	9 (14)	-	-	-	-

Event	MENTOR				RI-CYCLO			
	Rituximab (N=65)		CYC (N=65)		Rituximab (N=37)		CTX(N=37)	
	Patients, n (%)	Events no. of events (rate per 100 patients)	Patients, n (%)	Events no. of events (rate per 100 patients)	Patients, n (%)	Events no. of events (rate per 100 patients)	Patients, n (%)	Events no. of events (rate per 100 patients)
GI infection	4 (6)	4 (6)	4 (6)	4 (6)	-	-	-	-
Infections	17 (26.2)	28 (43.1)	20 (30.8)	26 (40.0)	-	-	-	-
Influenza-like symptoms	6 (9)	8 (12)	3 (5)	3 (5)	-	-	-	-
Pneumonia	1 (2)	1 (2)	6 (9)	6 (9)	0 (0)	0 (0)	3 (8)	7 (8)
Other respiratory tract infection	9 (14)	12 (18)	9 (14)	10 (15)	-	-	-	-
Skin infection	4 (6)	5 (8)	0	0	-	-	-	-
Other infectious events	-	-	-	-	5 (14)	6 (8)	6 (16)	8 (10)
Cancer	0	0	0	0				
Lung	-	-	-	-	1 (3)	1 (1)	0 (0)	0 (0)
Prostate	-	-	-	-	0 (0)	0 (0)	1 (3)	1 (1)
Breast	-	-	-	-	1 (3)	1 (1)	0 (0)	0 (0)

AE = adverse event; CTX = cyclophosphamide; CYC = Cyclosporine; GI = gastrointestinal; SAE = serious adverse event

[a] Notable harms were only reported if they occurred in ≥4 patients in MENTOR and ≥5 patients in RI-CYCLO.

Source: Fervenza et al.,[8] Scolari et al.[9]

Results of Economic Evaluation

Given the small network of studies, the heterogeneity in the included studies, and the limited information provided by the NMA and the pair-wise comparisons of MENTOR and RI-CYCLO, CADTH was unable to conduct an informative economic evaluation. Further, in addition to the clinical evidence gaps, there were also issues identifying information to inform key parameters to address the policy question of interest to decision makers. Given the limitations associated with the clinical evidence and absence of evidence to inform key model parameters, an economic evaluation would not be able to quantify all relevant incremental costs and effects of using rituximab over currently used alternatives. CADTH will work with the plans to assist with tools to support policy decisions.

Discussion

Summary of Evidence

The aim of the review was to determine the place of rituximab in the treatment of PMN. To inform the project scope, CADTH searched online social platforms for first-hand experiences from individuals with membranous nephropathy, to get a better understanding of the challenges associated with the disease and its treatment. The selection criteria of the protocol were then

adjusted to reflect these patient perspectives. With that, a total of 19 publications met the inclusion criteria for this review, with a total of 18 included trials.

The included RCTs enrolled patients with PMN, diagnosed primarily based on proteinuria and serum albumin. The sample sizes ranged from 26 patients to 130 patients across the trials. The mean age of the participants ranged from 37 years to 58 years and were mostly male (42.7% to 93.5%). The duration of the studies (including follow-up) ranged from 6 months to 10 years. Two studies were conducted in North America. All trials excluded patients if their disease was due to a secondary source such as systemic lupus erythematosus, or drug-associated nephropathy. Various outcomes were reported including complete or partial remission, remission rates, total remission, no remission, relapse, or recurrence measured at various time points.

A total of 11 studies reported the results for complete remission or the composite outcome of partial or complete remission which were used in the NMA. The fixed effects and random effects models of the NMA successfully converged; however, upon examining the results of each model, several of the estimated credible intervals were found to be extremely wide. These results suggested a high level of instability in these models likely a result of small networks of available studies and excessive heterogeneity across the network. Thus, the estimated results were unreliable for drawing conclusions.

Because of the noninformative results from the NMA, a narrative synthesis of the head-to-head trials of rituximab was performed. Relevant evidence was taken from the MENTOR study (rituximab vs. cyclosporine) and the RI-CYCLO study (rituximab vs. cyclophosphamide). MENTOR and RI-CYCLO were considered well conducted and the findings well reported. These trials had a low risk of bias in each domain, with most signaling questions assessed adequately based on the level of detail provided in the publications. There were no head-to-head trials comparing rituximab to tacrolimus.

Rituximab vs. Cyclosporine (MENTOR results)

In MENTOR, the composite outcome of complete or partial remission at 24 months was the primary outcome. Rituximab was found to be non-inferior to cyclosporine at 24 months at a non-inferiority margin of 15% with a risk difference of 40%. Superiority of rituximab over cyclosporine for complete or partial remission at 24 months was also supported by the results.

Complete remission was a secondary outcome which was not adjusted for multiple comparisons. There was a decrease in the number of patients with complete remission (2%) at 6 months and an increase in the number of patients with a complete remission of 9%, 26% and 35% at 12 months, 18 months, and 24 months respectively, with rituximab compared to cyclosporine. Though the risk of increased type I error must be considered when interpreting these results, the magnitude of the effect observed particularly at later time points is unlikely to be explained by random chance. Patients in the cyclosporine group tended to have remission earlier, with a later catch-up in patients in the rituximab group.

Results using selected subscales of KDQOL-SF in patients with complete remission or partial remission at months 6, 12 and 24 could not be used to support conclusions regarding differences in HRQoL among patients treated with rituximab versus cyclosporine.

The percentage of adverse events reported in MENTOR was 71% and 78% in the rituximab and cyclosporine groups, respectively. The number of adverse events per 100 patients were 275 in the rituximab and 335 in the cyclosporine group. Patients in the rituximab group had fewer treatment discontinuations than cyclosporine (2 with rituximab versus 11 with cyclosporine).

Rituximab vs. Cyclophosphamide (RI-CYCLO results)

In RI-CYCLO, complete remission at 12 months was the primary efficacy outcome, although the study was conducted as a pilot study which was not powered to detect a clinically meaningful difference. As a result, the estimated 95% CI for each point estimate were extremely wide, and thus, do not provide sufficient evidence to support differences between rituximab and cyclophosphamide at any time points.

The composite outcome of complete or partial remission was a secondary outcome in RI-CYCLO. The results were insufficient to support any conclusions regarding the efficacy of rituximab versus cyclophosphamide for this outcome.

More patients relapse with cyclophosphamide compared with rituximab at 12 months: 3 of 23 patients in the rituximab arm and 6 of the 27 patients with cyclophosphamide.

The percentage of adverse events reported in RI-CYCLO was 43% with rituximab and 43% with cyclophosphamide. The number of adverse events per 100 patients were 54 with rituximab and 47 with cyclophosphamide. Patients in the rituximab group had fewer treatment discontinuations with cyclophosphamide (1 with rituximab versus 4 with cyclophosphamide).

Economic Evaluation

Given the small network of studies, the heterogeneity in the included studies, and the limited information provided by the NMA and the pair-wise comparisons of MENTOR and RI-CYCLO, CADTH was unable to conduct an informative economic evaluation. Further, in addition to the clinical evidence gaps, there were also issues identifying information to inform key parameters to address the policy question of interest to decision makers. Given the limitations associated with the clinical evidence and absence of evidence to inform key model parameters, an economic evaluation would not be able to quantify all relevant incremental costs and effects of using rituximab over currently used alternatives. CADTH will work with the plans to assist with tools to support policy decisions.

Interpretation of Clinical Results

The systematic review was undertaken at the request of the government-sponsored drug plans to answer the following policy questions: Is there evidence to support the use of rituximab in adult patients with primary membranous nephropathy? If so, what are the policy options for providing access to rituximab? While 18 RCTs were found, the findings of 2 RCTs only were pertinent to the review.

The evidence from RI-CYLCO was inconclusive with regards to the comparative efficacy and safety of rituximab compared with cyclophosphamide for any of the outcomes measured at any of the timepoints, given that the study was not powered to detect a clinically meaningful difference. MENTOR showed that rituximab may be superior to cyclosporine in terms of the following efficacy outcomes at 24 months: complete remission and the composite outcome of partial or complete remission. In this same trial, conclusions could not be drawn regarding the difference in time to remission and the difference in HRQoL among patients treated with rituximab versus cyclosporine. In the 2 RCTs, rituximab showed a similar safety profile compared to cyclophosphamide or to cyclosporine.

The clinical expert consulted for this review indicated that equity-related issues need to be taken into consideration when determining the place in therapy of rituximab:

> "Besides clinical efficacy, the decision to fund rituximab or not may also pose issues for equity. Patient surveys as well as clinical experience suggest that some younger female patients with MN may wish to become pregnant. Since cyclophosphamide has an age-dependent effect on fertility in females whereas rituximab does not,[39] a decision against funding rituximab could be seen as disproportionately affecting women.
>
> In addition, if cyclophosphamide is selected and used for treatment of MN in a woman who desires children, provincial drug plans may pay for costly medications like gonadotropin-releasing hormone (GnRH) agonists and the health ministry will likely bear the costs of other treatments and/or specialist visits to preserve fertility and/or allow assisted reproduction. It might be less costly to pay for rituximab in such cases, although this possibility was not addressed in the economic analysis.
>
> On the other hand, if publicly funded drug plans do not pay for fertility preservation or assisted reproduction following cyclophosphamide treatment, then a decision not to fund rituximab may be inequitable in that individuals with private drug coverage may be able to mitigate the consequences of cyclophosphamide-induced infertility, whereas those with only public coverage will not."

Strengths and Limitations of the Systematic Review

Strengths

The systematic review was developed using robust methodology and a protocol was developed a priori and registered with the PROPSERO database. The scoping plan was posted for stakeholder feedback. While no patient groups provided comments on the scoping plan, a search of various social platforms was undertaken to gather patient perspectives which was used to inform the protocol. All available RCTs were included, and this list was posted for stakeholder feedback.

Evidence collection, data extraction, and evaluation of the quality of the studies were done in duplicate, with conflicts adjudicated by a third reviewer. Heterogeneity across trials were carefully assessed. The analytical approach for the NMA was aligned with ISPOR guidelines and employed a standard methodology.

Limitations

The number of trials that contributed to the NMA was limited and reported results that were highly heterogeneous across the network. Due to the limited size of the network, it was not possible to adequately account for the level of heterogeneity, and as a result, the variation around estimated effects were extremely wide and generally not informative. Thus, we were unable to use the findings of the NMA to draw conclusions for the report.

Implementation Advice Panel

[Place holder – IAP]

Conclusions and Implications for Decision or Policy-Making

Membranous nephropathy is an autoimmune disease and one of the most common cause of nephrotic syndrome in adults. Approximately 80% of patients with membranous nephropathy are classified as primary (or idiopathic) membranous nephropathy. While no patient groups or individual patients responded to our call for feedback to better understand the challenges of PMN, excerpts from patients' experiences and perspectives shared on social media and other online sources were considered. Patients indicated that preventing or delaying end-stage renal disease and dialysis were important treatment goals.

Current treatment options for PMN include rituximab and immunosuppressive therapies such as cyclosporine, tacrolimus, and cyclophosphamide. Most patients indicated that they had tried immunosuppressive therapies prior to rituximab. Rituximab is not approved for the indication of primary membranous nephropathy in Canada. Hence, the government-sponsored drug plans requested a review to answer the following policy questions: Is there evidence to support the use of rituximab in adult patients with primary membranous nephropathy? If so, what are the policy options for providing access to rituximab?

To answer the policy questions, a systematic review was conducted and 18 RCTs that met the inclusion criteria were identified; of these, 11 trials were included in the NMA. Due to various factors, the estimates obtained from the NMA models were considered unreliable for drawing conclusions. Therefore, a narrative synthesis of two head-to-head trials, MENTOR and RI-CYCLO was conducted. The limited evidence from the available studies did not provide conclusive evidence on the comparative efficacy of rituximab versus cyclophosphamide; however, the findings from the MENTOR study suggest that rituximab may be superior to cyclosporine in terms of complete remission and the composite outcome of partial or complete remission. No conclusions could be drawn from the available evidence regarding the difference in time to remission and the difference in HRQoL among patients treated with rituximab versus cyclosporine. Finally, in the 2 RCTs, rituximab showed a similar safety profile compared to cyclophosphamide or to cyclosporine. Of note, the conclusions drawn from the results of the systematic review are limited as they are based on two RCTs only as no other head-to-head trials of rituximab were retrieved.

Given the small network of studies, the heterogeneity in the included studies, and the limited information provided by the NMA and the pair-wise comparisons of MENTOR and RI-CYCLO, CADTH was unable to conduct an informative economic evaluation. Further, in addition to the clinical evidence gaps, there were also issues identifying information to inform key parameters to address the policy question of interest to decision makers. Given the limitations associated with the clinical evidence and absence of evidence to inform key model parameters, an economic evaluation would not be able to quantify all relevant incremental costs and effects of using rituximab over currently used alternatives. CADTH will work with the plans to assist with tools to support policy decisions.

Patients whose views were obtained from social media and other online platforms, expressed their willingness to try a treatment if it meant preventing or delaying disease progression. As well, the adverse event profile of the drugs needs to be taken into consideration when choosing a treatment. The clinical expert consulted for this review also indicated that women of child-bearing age should be given special consideration for funding rituximab in light of the fertility adverse profile of cyclophosphamide.

[Place holder – IAP]

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APPENDIX 1: Patient Perspectives

Table 5: Results based on the Guidance for Reporting Involvement of Patients and the Public short form (GRIPP2 SF)

Section and topic	Item	Reported on page
1: Aim	As part of this Health Technology Review, CADTH collected patient perspectives through a summary of findings from online sources, to better understand all aspects of the disease and experiences with rituximab, and to identify concepts and assumptions to be explored further by CADTH.	11-12, 24-25
2: Methods	CADTH contacted the Kidney Foundation of Canada and the Canadian Organization for Rare Disorders to help identify interested individual patients with personal experience with taking rituximab as a treatment for PMN. The call for participants was also shared on CADTH's and the Kidney Foundation of Canada's Facebook pages. Despite our best efforts, we were unable to identify a patient who met those criteria. Alternatively, we opted to report patient experiences and perspectives through a summary of findings from various online sources. We searched for and gathered excerpts from patients' experiences and perspectives shared publicly on social media and other online sources. A total of 37 quotations were found, from 27 individuals [Facebook (n = 13), YouTube (n = 4), Inspire social network for health (n = 4), Reddit (n = 3), RareRenal (n = 2), and patient blog (n = 1)]. Quotations were anonymized; no identifying information was gathered.	11-12, 24-25
3: Study results	The researchers were made aware of several outcomes and themes, in particular: **Disease experience** Patient age at diagnosis varied from 11 years to 64 years, but most reported being diagnosed before the age of 40. Patients experienced symptoms such as swollen and aching legs, shortness of breath, frothy urine, raised blood pressure, fatigue, and weight gain, which typically led to a series of tests and confirmation of diagnosis via biopsy. **Variability of treatment experiences** Efficacy of rituximab, like calcineurin inhibitors and alkylating drugs, varied considerably from one patient to the next. Some patients were in remission, some saw minor improvements, some were unsuccessful with rituximab, and others were starting rituximab as a last resort after being unsuccessful with other treatments. Most patients appeared to have tried other treatments prior to rituximab. **Willingness to endure side effects** Most patients who shared their experiences on online social platforms were willing to endure side effects if it meant there was a chance of remission. Overall, patients reported wanting to try a treatment that offered the possibility of preventing or delaying end-stage renal disease and dialysis.	8-9, 11, 26
4: Discussion and conclusions	Finding a Canadian patient with experience taking rituximab for PMN was the main challenge for this project. In terms of finding and collating perspectives shared publicly online, there are limitations to this approach, mainly, finding (and confirming) patients' diagnoses and finding (and confirming) demographic information, both of which would help provide context to the experiences being used to in this Health Technology Review.	25
5: Reflections/critical perspective	The value in this approach to capture patient insights allowed us to learn about patients' experiences, albeit, in an unconventional way. We were also able to include multiple perspectives, to reflect a diversity of needs rather than a singular patient perspective.	25

	However, engaging with an individual patient would have allowed us to learn more about barriers to access and use of treatment, as well as patient-borne costs, to better understand the challenges that patients in Canada specifically, must face. Additionally, people with limited or no access to computers or the Internet, such as elderly patients, racial/ethnic minorities, and those of lower socioeconomic status, may be underrepresented. It is possible that the patients who shared their experiences on online platforms skewed toward a younger and more digitally connected population; therefore, this sample may not reflect the broad range of patients with PMN.	

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946-present) Embase (1974-present) Cochrane Central Register of Controlled Trials (CCTR) **Note:** Subject headings will be customized for each database. Duplicates between databases will be removed in Ovid.
Date of Search:	April 22, 2020
Alerts:	Monthly search updates will be run until project completion
Study Types:	Randomized controlled trials; controlled clinical trials
Limits:	Language limit: English and French-language Conference abstracts excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
?	Truncation symbol for one or no characters only
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ab	Abstract
.dq	Candidate term word
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.mp	Mapped term
.jw	Journal word title

medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily
cctr	Ovid database code; Cochrane Central Register of Controlled Trials

MULTI-DATABASE STRATEGY

1	glomerulonephritis, membranous/ or Heymann Nephritis Antigenic Complex/
2	((extra?membranous or membranous) adj5 (nephropath* or Glomerulo* or nephritis)).ti,ab,kf.
3	((glomerular basement membrane* or glomerular membrane basement or GMB or GBM) adj5 thick*).ti,ab,kf.
4	((PMN or MGN) adj5 (nephropath* or kidney* or glomerul*)).ti,ab,kf.
5	(Heymann* adj2 Nephritis).ti,ab,kf.
6	1 or 2 or 3 or 4 or 5
7	6 use medall
8	membranous glomerulonephritis/ or Heymann nephritis/
9	((extra?membranous or membranous) adj5 (nephropath* or Glomerulo* or nephritis)).ti,ab,kw,dq.
10	((glomerular basement membrane* or glomerular membrane basement or GMB or GBM) adj5 thick*).ti,ab,kw,dq.
11	((PMN or MGN) adj5 (nephropath* or kidney* or glomerul*)).ti,ab,kw,dq.
12	(Heymann* adj2 Nephritis).ti,ab,kw,dq.
13	8 or 9 or 10 or 11 or 12
14	13 use oemezd
15	7 or 14
16	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.
17	Randomized Controlled Trial/
18	exp Randomized Controlled Trials as Topic/
19	"Randomized Controlled Trial (topic)"/
20	Controlled Clinical Trial/
21	exp Controlled Clinical Trials as Topic/
22	"Controlled Clinical Trial (topic)"/
23	Randomization/
24	Random Allocation/

25	Double-Blind Method/
26	Double Blind Procedure/
27	Double-Blind Studies/
28	Single-Blind Method/
29	Single Blind Procedure/
30	Single-Blind Studies/
31	Placebos/
32	Placebo/
33	Control Groups/
34	Control Group/
35	(random* or sham or placebo*).ti,ab,hw,kf,kw.
36	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
37	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
38	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf,kw.
39	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.
40	allocated.ti,ab,hw.
41	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.
42	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.
43	(pragmatic study or pragmatic studies).ti,ab,hw,kf,kw.
44	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw.
45	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.
46	(phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf,kw.
47	or/16-46
48	15 and 47
49	48 and (english or french).lg.
50	exp animals/
51	exp animal experimentation/ or exp animal experiment/
52	exp models animal/
53	nonhuman/
54	exp vertebrate/ or exp vertebrates/

55	or/50-54
56	exp humans/
57	exp human experimentation/ or exp human experiment/
58	or/56-57
59	55 not 58
60	49 not 59
61	glomerulonephritis, membranous/ or Heymann Nephritis Antigenic Complex/
62	((extra?membranous or membranous) adj5 (nephropath* or Glomerulo* or nephritis)).ti,ab,kw.
63	((glomerular basement membrane* or glomerular membrane basement or GMB or GBM) adj5 thick*).ti,ab,kw.
64	((PMN or MGN) adj5 (nephropath* or kidney* or glomerul*)).ti,ab,kw.
65	(Heymann* adj2 Nephritis).ti,ab,kw.
66	61 or 62 or 63 or 64 or 65
67	66 use cctr
68	60 or 67
69	68 not conference abstract.pt.
70	remove duplicates from 69

CLINICAL TRIAL REGISTRIES	
ClinicalTrials.gov	Produced by the U.S. National Library of Medicine. Targeted search used to capture registered clinical trials. Search updated prior to the completion of stakeholder feedback period.
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. Search updated prior to the completion of stakeholder feedback period.

GREY LITERATURE

Search dates:	May 2020
Keywords:	Membranous nephropathy, glomerular basement membrane, GBM thickening, extramembranous nephropathy, Glomerular disease

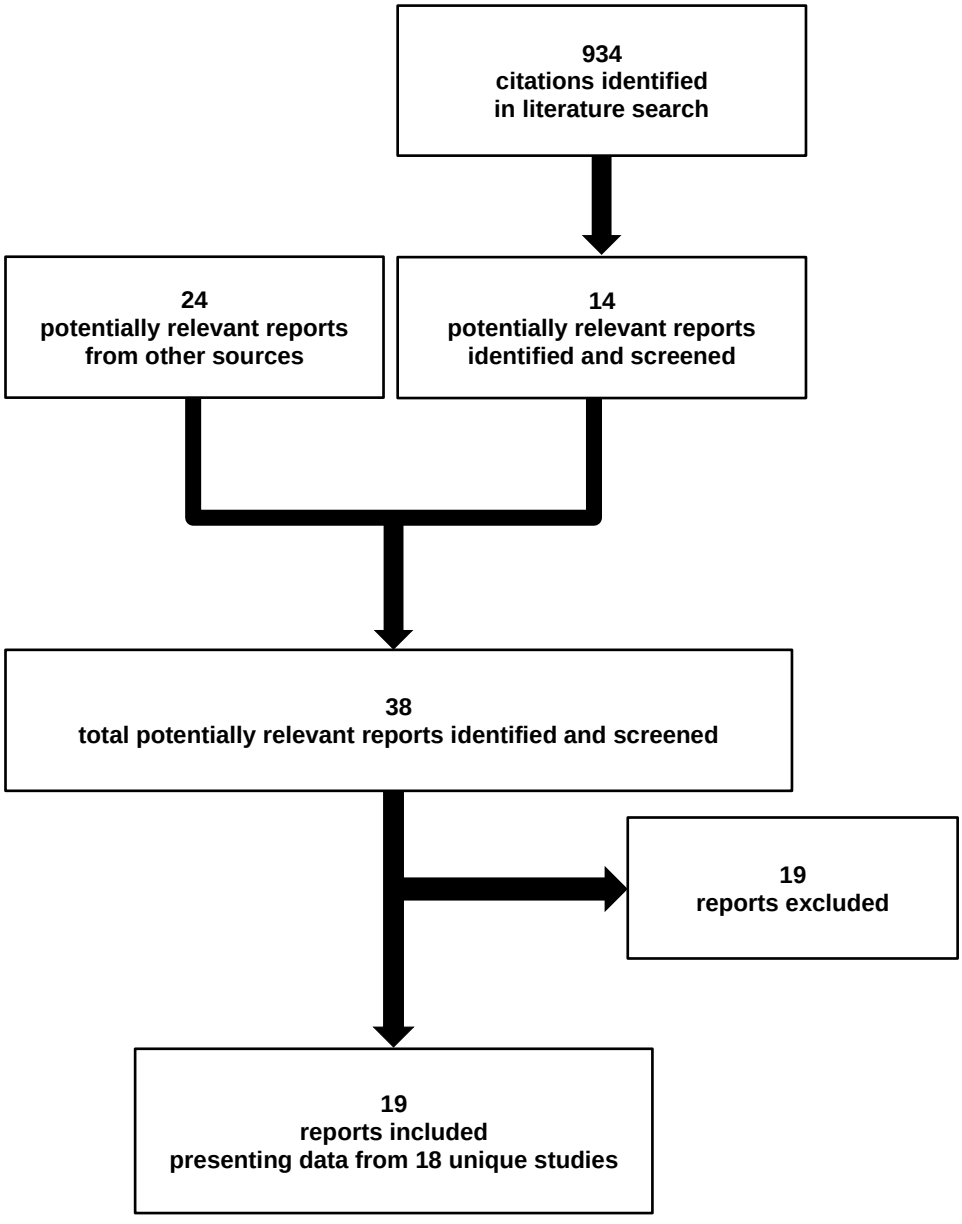
Limits:	English and French-language only documents
Updated:	Search updated prior to the completion of stakeholder feedback period

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* (https://www.cadth.ca/grey-matters) will be searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug Class Reviews
- Clinical Trial Registries
- Databases (free)
- Internet Search
- Open Access Journals

Appendix 3: PRISMA

Figure 1: Study Selection Process



Appendix 4: List of Included Studies

1. Cattran DC, Appel GB, Hebert LA, et al. Cyclosporine in patients with steroid-resistant membranous nephropathy: a randomized trial. Kidney Int. 2001;59(4):1484-1490.

2. Chen M, Li H, Li XY, et al. Tacrolimus combined with corticosteroids in treatment of nephrotic idiopathic membranous nephropathy: a multicenter randomized controlled trial. Am J Med Sci. 2010;339(3):233-238.

3. Di J, Qian Q, Yang M, et al. Efficacy and safety of long-course tacrolimus treatment for idiopathic membranous nephropathy. Exp Ther Med. 2018;16(2):979-984.

4. Fervenza FC, Appel GB, Barbour SJ, et al. Rituximab or cyclosporine in the treatment of membranous nephropathy. N Engl J Med. 2019;381(1):36-46.

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Appendix 5: List of Excluded Studies

Table 6: List of Excluded Studies and Reasons for Exclusion

Excluded studies	Reasons for exclusion
Austin et al. 2009[40]	Patient population not relevant
Cameron et al.2009[41]	Intervention/comparator not relevant
Cattran et al.1989[42]	Intervention/comparator not relevant
Choi et al. 2018[43]	Intervention/comparator not relevant
Coggins et al. 1979[44]	Intervention/comparator not relevant
D'Amico et al. 1991[45]	Intervention/comparator not relevant
Fernandez-Juarez et al. 2021[46]	Intervention/comparator not relevant
Guo et al. 2020[47]	Intervention/comparator not relevant
Liang et al. 2017[48]	Study design not relevant
Nikolopoulou et al. 2019[49]	Intervention/comparator not relevant
Ponticelli et al. 1982[50]	Intervention/comparator not relevant
Ponticelli et al. 1984[51]	Intervention/comparator not relevant
Ponticelli et al. 1989[52]	Intervention/comparator not relevant
Ponticelli et al. 1992[53]	Intervention/comparator not relevant
Ponticelli et al. 1995[54]	Intervention/comparator not relevant
Ponticelli et al. 1998[55]	Intervention/comparator not relevant
Reichert et al. 1994[56]	Intervention/comparator not relevant
Saito et al. 2007[57]	Intervention/comparator not relevant
West et al. 1987[58]	Study design not relevant

Appendix 6: Study Characteristics

Table 7: Characteristics of the Included Randomized Controlled Trials

Study	Blinding	Number of Centres (Countries)	Total Sample Size	Follow-up
Cattran et al. 2001	single-blind	11 (North America)	51	78 weeks
Chen et al. 2010	open label	6 (China)	73	12 months
Di et al. 2018	not specified	1 (China)	76	24 months
Fervenza et al. 2019	open label	22 (North America)	130	24 months
He et al. 2013	open label	1 (China)	56	12 months
Hofstra et al. 2010	open label	multi centre (Netherlands)	26	12 months
Howman et al. 2013	open label	37 (UK)	103	3 years
Jha et al. 2007	open label	1 (India)	93	10 years
Kosmadakis et al. 2010	open label	1 (Greece)	28	9 months
Li et al. 2017	not specified	1 (China)	31	6 months
Omrani et al. 2017	double-blind	1 (Iran)	68	6 months
Peng et al. 2016	not specified	1 (China)	90	9 months
Praga et al. 2007	open label	13 (Spain)	48	18 months
Ramachandran et al. 2016 /17	open label	1 (India)	70	24 months
Saito et al. 2014	open label	30 (Japan)	48	48 weeks
Scolari et al. 2021	open label	11 (10 in Italy, 1 in Switzerland)	74	6 months
Xu et al. 2013	not specified	1 (China)	100	18 months
Yuan et al. 2013	not specified	1 (China)	42	24 months

Appendix 7: Interventions and Comparators

Table 8: Treatment Regimens in Included Studies

Study	Treatment regimen	Comparator regimen	Concomitant and background therapy for BP
Cattran et al. 2001	Oral CYC 3.5 mg/kg/day [q12h] for 26 weeks then tapered off over 4 weeks period Target levels of 125 to 225 µg/L	Placebo 0.035 mL/kg/day [q12h] for 26 weeks then tapered off over 4 weeks period	Concomitant: Prednisone 0.15 mg/kg/day for 26 weeks (maximum dose 15 mg) then tapered off by thirds at 4-week intervals and stopped after 8 weeks. Background: Continuation of ACEI/ARB regimen as per usual – patients previously taking ACEI/ARB dose maintained their dose, patients not taking ACEI/ARB prescribed other antihypertensives, introduction of ACEI/ARB was forbidden, other dietary modifications made
Chen et al. 2010	TAC (0.1 mg/kg/day [q12h] for 9 months 1st 6 months – plasma concentration 5-10 µg/l Last 3 months – plasma concentration 2-5 µg/l	Oral CTX 100 mg/d for 4 months (accumulated dose 12 g) Dosage reduced by 50 mg/d if WBC < 4000/µl (dosage increased when WBC returned to the normal range)	Concomitant: Oral prednisone 1 mg/kg/d for 4 weeks, tapered gradually, and discontinued by 8 months Background: Continuation of ACEI/ARB regimen as per usual – patients previously taking ACEI/ARB dose maintained their dose, patients not taking ACEI/ARB prescribed other antihypertensives to maintain target BP 125/75 mm Hg
Di et al. 2018	Short-course: Oral TAC (0.1 mg/kg/day) [q12h] for 12 months 1st 6 months – plasma concentration 5-10 µg/l After 6 months – plasma concentration 2-4 µg/l	Long-course: Oral TAC (0.1 mg/kg/day) for 24 months 1st 6 months - plasma concentration 5-10 µg/l After 6 months – plasma concentration 2-4 µg/l	Concomitant: Prednisone (0.5 mg/kg/day), dose reduced by 5 mg every 4 weeks, then maintained at a total of 10 mg/day
Fervenza et al. 2019	Rituximab 1,000 mg IV on days 1 and 15, no second dose if complete remission achieved, second course administered if proteinuria reduced from baseline by ≥ 25% at 6 months	Oral CYC 3.5 mg/kg/day [q12h] for 6 months then tapered off over 2 months period (applicable for complete remission or failure, partial remission repeated treatment for 6 months); plus Prednisone 0.15 mg/kg/day for 26 weeks then tapered off for 8 weeks Target CYC levels of 125 to 175 ng/L	No concomitant corticosteroids Background: Renin–angiotensin system blockers, BP management targeting < 130/80 mm Hg, dietary sodium restriction to < 4 g/day, and dietary protein restriction to 0.8 – 1 g of protein/kg/d 3 months prior treatment
He et al. 2013	Oral TAC 1 mg/day for 1 week then alternating 1 mg and 2 mg per day [q12h] for 12	IV CTX 750 mg/m^2 once every 4 weeks for 24 weeks +	Concomitant: Oral prednisone 1 mg/kg/day for 4 weeks (max 60 mg/day)

Study	Treatment regimen	Comparator regimen		Concomitant and background therapy for BP
	months + Prednisone (1 mg/kg/day for 4 weeks tapered) Plasma concentration at 2-4 ng/l	Prednisone (1 mg/kg/day for 4 weeks tapered)		Prednisone tapered gradually by 5 mg/2 weeks till 30 mg/day, then further tapered at 5 mg/month rate till 10 mg/d for the rest of the 12 months treatment period Background: ACEI/ARB or other antihypertensives as needed to meet target BP of 125/75 mm Hg
Hofstra et al. 2010	Early start (immediately after randomization): Oral CTX 1.5 mg/kg/day for 12 months	Late start (when renal function deteriorated): Same as early start group		Concomitant: methylprednisolone 1 g intravenously on Days 1, 2, 3, 60, 61, 62, 120, 121 and 122, and oral prednisone 0.5 mg/kg/day for 6 months, prednisone tapered at 5 mg/week rate Background: ACEI/ARB as needed to maintain target BP of 130/80 mmHg, 3-Hydroxy-3- methylglutaryl coenzyme A reductase inhibitors to decrease serum cholesterol levels, moderately salt-restricted diet, anticoagulant drugs (not routinely), famotidine for GI symptoms, trimethoprim–sulfamethoxazole for pneumocystis jiroveci pneumonia
Howman et al. 2013	CYC 5 mg/kg/day for 12 months Target levels of 100 to 200 µg/L, dose reduced if toxicity developed	Prednisolone: IV methyl prednisolone 1 g/day for 3 consecutive days then oral prednisolone 0.5 mg/kg/day for 28 days during months 1, 3, and 5; plus Oral chlorambucil: 0.15 mg/kg/day during months 2, 4, and 6, dose reduced if leucopenia developed		Concomitant: renin-angiotensin blockade, statins, and anticoagulants as needed Background: ACEI, ARB, and other BP control medications as needed.
Jha et al. 2007	6-month course of alternate months of steroid and CTX: IV methylprednisolone 1 g/d for 3 consecutive days followed by oral prednisolone 0.5 mg/kg/d for 27 d in month 1, 3, and 5 and oral CTX at 2 mg/kg/d in month 2, 4, and 6	Supportive therapy: Dietary sodium restriction, diuretics, and antihypertensive agents		Background: ACEI, ARB were not allowed in the first year
Kosmadakis et al. 2010	Oral CYC 3–3.5 mg/kg/day plus oral methylprednisolone 12.5 mg/day for 9 months Target levels of 100 to 120 µg/L ACEI, ARB not allowed	Oral CTX 2 mg/kg/day plus oral methylprednisolone 1.5 mg/kg/48 hour for 9 months (dose adjusted per WBC count) ACEI, ARB not allowed	ACEI: lisinopril for 9 months	Background: low-sodium diet (5 g/day), doses of loop diuretics if indicated, antihypertensive agents (beta-blockers and/or dihydropyridine calcium-blockers), to maintain BP of 140/90 mmHg

Study	Treatment regimen	Comparator regimen		Concomitant and background therapy for BP
Li et al. 2017	TAC 0.05-0.1 mg/kg/day [q12h]) for 6 months Plasma concentration 5-10 ng/mL	CYC 3–5 mg/kg/day [q12h] for 6 months Target levels of 100 to 200 ng/mL		Concomitant: Oral Prednisone 0.5 mg/kg/d, tapered at 5 mg/month rate till 10 mg/d, maintained through 6 month
Omrani et al. 2017	TAC 0.05 mg/kg/d for 6 months.	CYC 3 - 6 mg/kg/d for 6 months		Concomitant: low dose of prednisolone for 6 months
Peng et al. 2016	TAC 0.05 mg/kg/day [q12h] for 9 months + corticosteroid (0.5 mg/kg/d [tapered down after 2 months] 1st 6 months - plasma concentration 4 - 8 ng/l Last 3 months – plasma concentration 2-4 ng/l	IV CTX 750 mg/m^2 once a month for 6 months, then reduced to every 3 months	Oral MMF 1.5 to 2.0 g/d	Concomitant: Oral corticosteroid 0.5 mg/kg/d (TAC) or 1 mg/kg/d (CTX and MMF) for 2 months Corticosteroids tapered by 5 mg/d every 2 weeks until 20 mg/d then tapered to zero based on patient's condition Background: Antihypertensive agents to maintain target BP (130/80 mm Hg). ACEI/ARB not initiated, but continued among previous users. Anticoagulant drugs and simvastatin as needed.
Praga et al. 2007	TAC 0.05 mg/kg/d [q12h] for over 12 months with a 6-month taper by 25% Plasma concentration 3–5 ng/mL, or 5–8 ng/mL if remission not achieved by 2 months	Control group (no information available)		Background: Antihypertensive agents to maintain target BP (130/80 mm Hg). ACEI/ARB dose continued among previous users. Statins as indicated.
Ramachandran et al. 2016 /17	Oral TAC 0.1 mg/kg/day [q12h] for 12 months plus prednisolone 0.5 mg/kg/day for 6 months, tapered by 0.1 mg/kg/week 1st 6 months – plasma concentration 5–10 ng/mL Last 6 months – plasma concentration 4–8 ng/mL	Modified Ponticelli regimen: IV methylprednisolone 1 g/d for 3 consecutive days followed by oral prednisolone 0.5 mg/kg/d for 27 d in month 1, 3, 5 and oral CTX at 2 mg/kg/d in month 2, 4, 6.		Background: All received max ACEI or ARBs and statins
Saito et al. 2014	CYC 2 - 3 mg/kg/d [once daily] for 48 weeks	CYC 1.5 mg/kg/12h for 48 weeks		Concomitant: Prednisolone 40 mg/day, tapered until <10 mg/day by 48 weeks
Scolari et al. 2021	Rituximab 1,000 mg IV on days 1 and 15	Cyclical corticosteroid/CTX therapy: 3 consecutive cycles of 2-month duration each (for a total of 6 months) Month 1, 3, 5: 1 g IV methylprednisolone daily for 3 days, thereafter oral methylprednisolone (0.4 mg/kg/day) or prednisone (0.5		Any medications not in the list of exclusion, at the discretion of the investigator

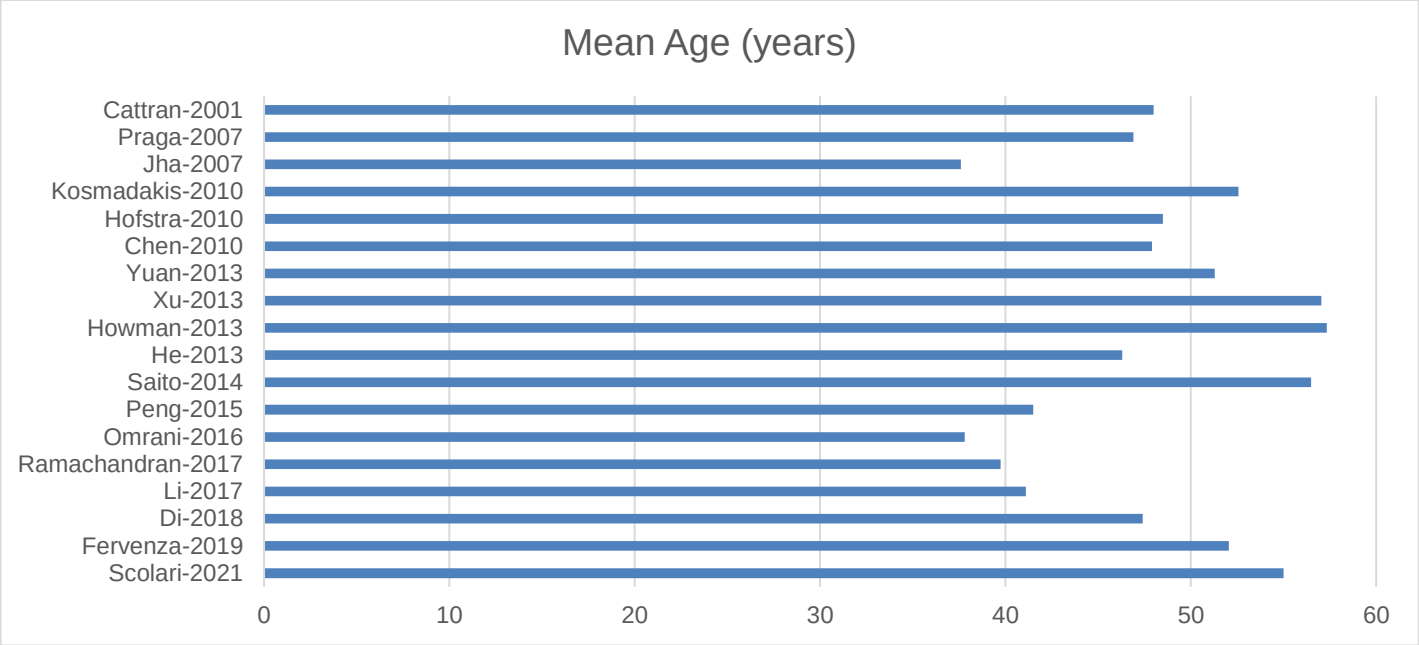
Study	Treatment regimen	Comparator regimen	Concomitant and background therapy for BP
		mg/ kg/day) for the remainder of the month. Month 2, 4, 6: Oral CTX daily (2.0 mg/kg/day)	
Xu et al. 2013	TAC (0.1 mg/kg/day) for 10 months plus prednisolone (0.5 mg/kg per day [then tapered]	IV CTX 0.5–0.75 g/m^2/month (maximum dosage 1.0 g/month) once a month for 6 months, then reduced to every 3 months Oral prednisone 0.5-1 mg/kg/d for 2 months	Background: ACEI, ARB allowed for BP control
Yuan et al. 2013	Short-term: TAC 0.05-0.08 mg/kg/day [q12h] for 6 months Plasma concentration 5–8 ng/ml (maximum 0.15 mg/kg/day)	Long-term: TAC 0.05-0.08 mg/kg/day [q12h] for 24 months, tapered by 2 mg/day during months 6–12, then 0.5 mg BID for months 12–24	Concomitant: Oral prednisone 30 mg/day for 8 weeks, tapered by 5 mg every 4 weeks till 10 mg/day, maintained throughout Background: NSAIDS, ACEI, ARB use prohibited, except for prior user of ACEI or ARB

ACEI = Angiotensin-converting enzyme; ARB = Angiotensin II receptor blockers; CYC = cyclosporine; CR= complete remission; CTX = cyclophosphamide; IV = intravenous; MMF = mycophenolate mofetil; NSAID= nonsteroidal anti inflammatory drug; q12h = every 12 hours; TAC = tacrolimus; WBC = white blood cell

Source: Cattran et al.,[22] Chen et al.,[24] Di et al.,[25] Fervenza et al.,[8] He et al.,[26] Hofstra et al.,[27] Howman et al.,[28] Jha et al.,[29] Kosmadakis et al.,[30] Li et al.,[31] Omrani et al.,[23] Peng et al.,[32] Praga et al.,[33] Ramachandran et al.,[34,35] Saito et al.,[36] Scolari et al.[9] Xu et al.,[37] Yuan et al.[38]

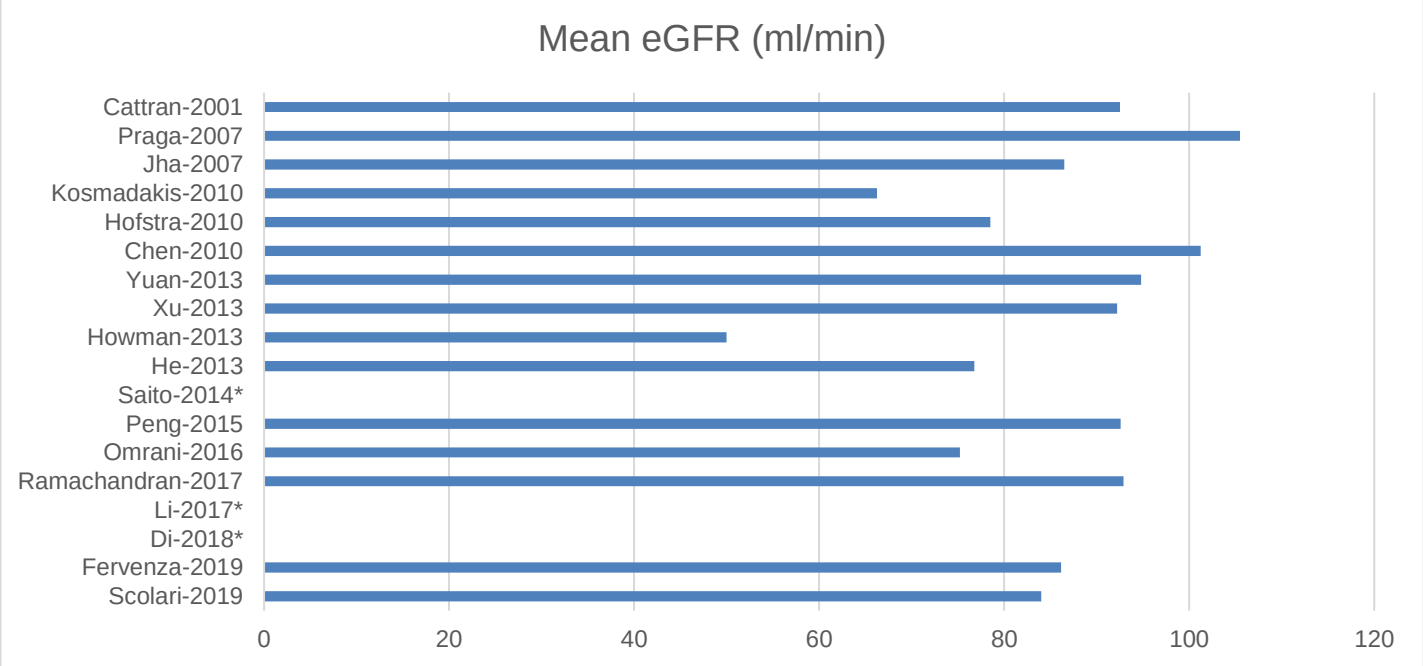
Appendix 8: Baseline Patient Characteristics

Figure 2: Age



Source: Cattran et al.,[22] Chen et al.,[24] Di et al.,[25] Fervenza et al.,[8] He et al.,[26] Hofstra et al.,[27] Howman et al.,[28] Jha et al.,[29] Kosmadakis et al.,[30] Li et al.,[31] Omrani et al.,[23] Peng et al.,[32] Praga et al.,[33] Ramachandran et al.,[34,35] Saito et al.,[36] Xu et al.,[37] Yuan et al.[38] Scolari et al.[9]

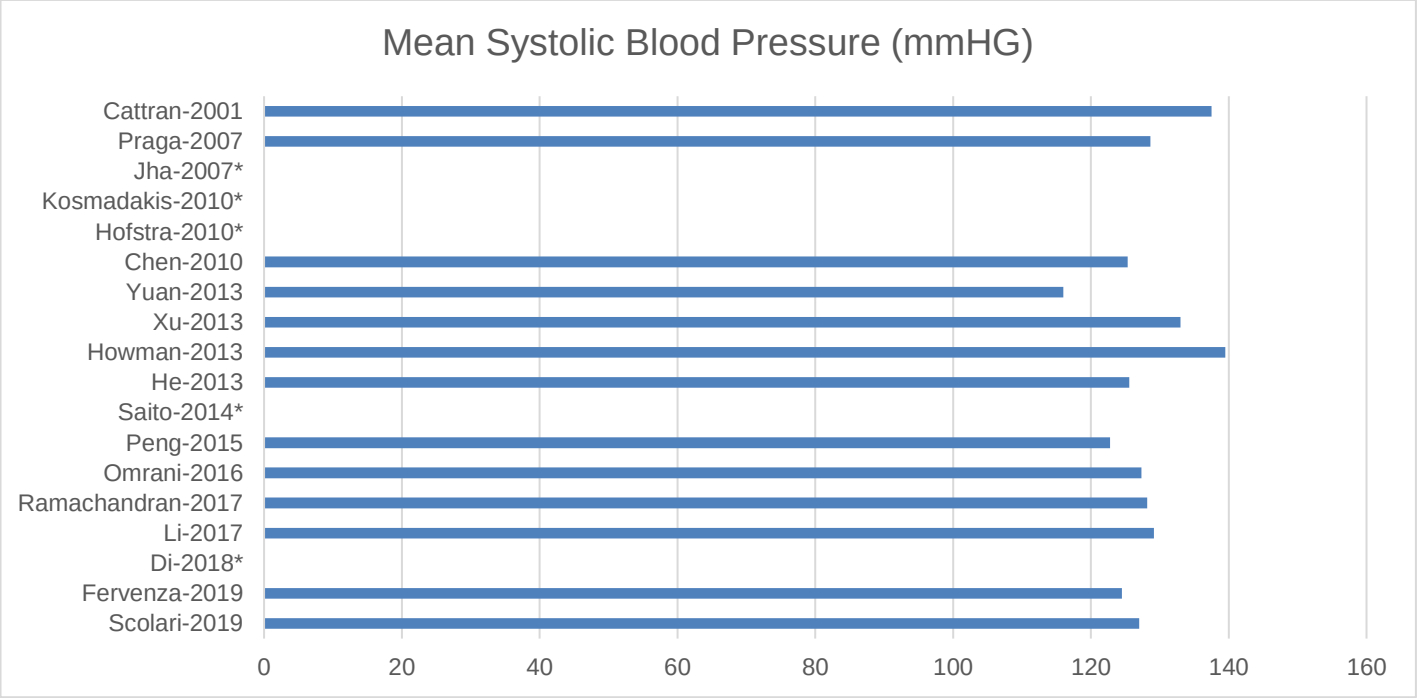
Figure 3: Estimated Glomerular Filtration Rate



*Data not reported

Source: Cattran et al.,[22] Chen et al.,[24] Di et al.,[25] Fervenza et al.,[8] He et al.,[26] Hofstra et al.,[27] Howman et al.,[28] Jha et al.,[29] Kosmadakis et al.,[30] Li et al.,[31] Omrani et al.,[23] Peng et al.,[32] Praga et al.,[33] Ramachandran et al.,[34,35] Saito et al.,[36] Xu et al.,[37] Yuan et al.[38] Scolari et al.[9]

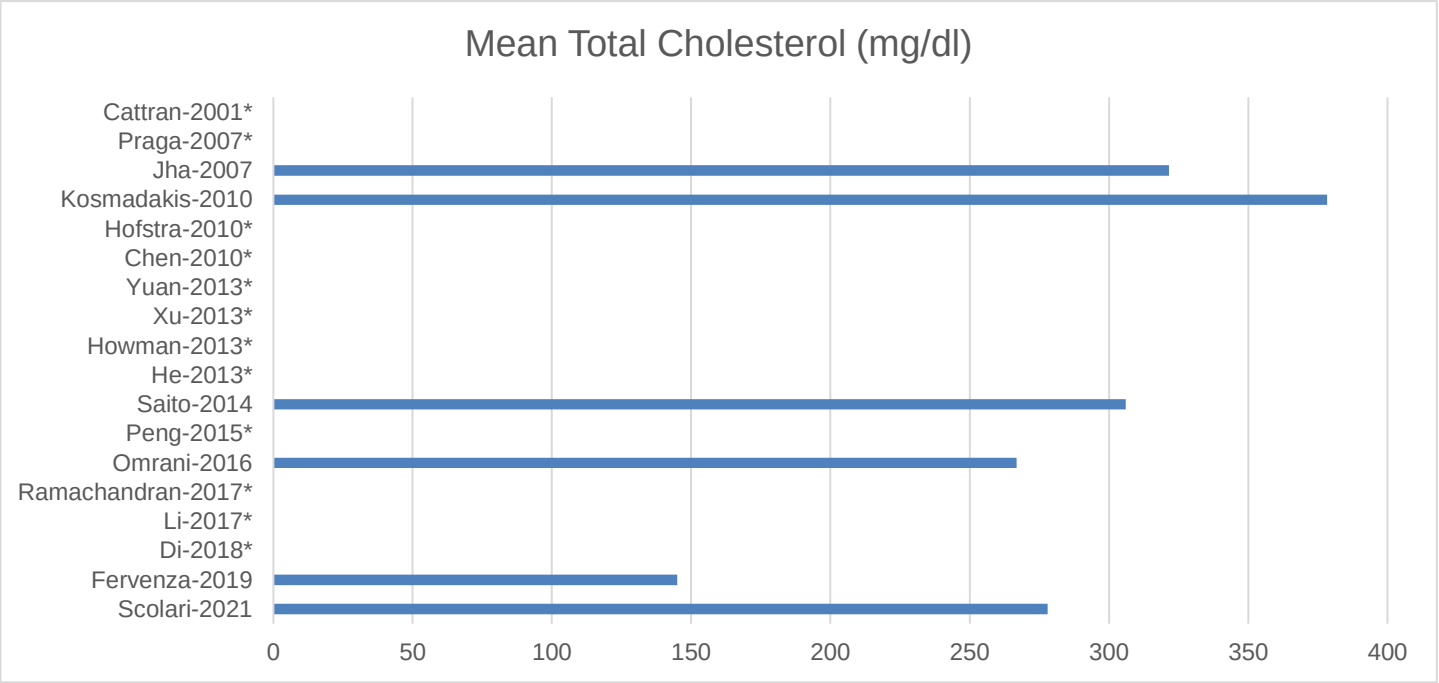
Figure 4: Systolic Blood Pressure



*Data not reported

Source: Cattran et al.,[22] Chen et al.,[24] Di et al.,[25] Fervenza et al.,[8] He et al.,[26] Hofstra et al.,[27] Howman et al.,[28] Jha et al.,[29] Kosmadakis et al.,[30] Li et al.,[31] Omrani et al.,[23] Peng et al.,[32] Praga et al.,[33] Ramachandran et al.,[34,35] Saito et al.,[36] Xu et al.,[37] Yuan et al.[38] Scolari et al.[9]

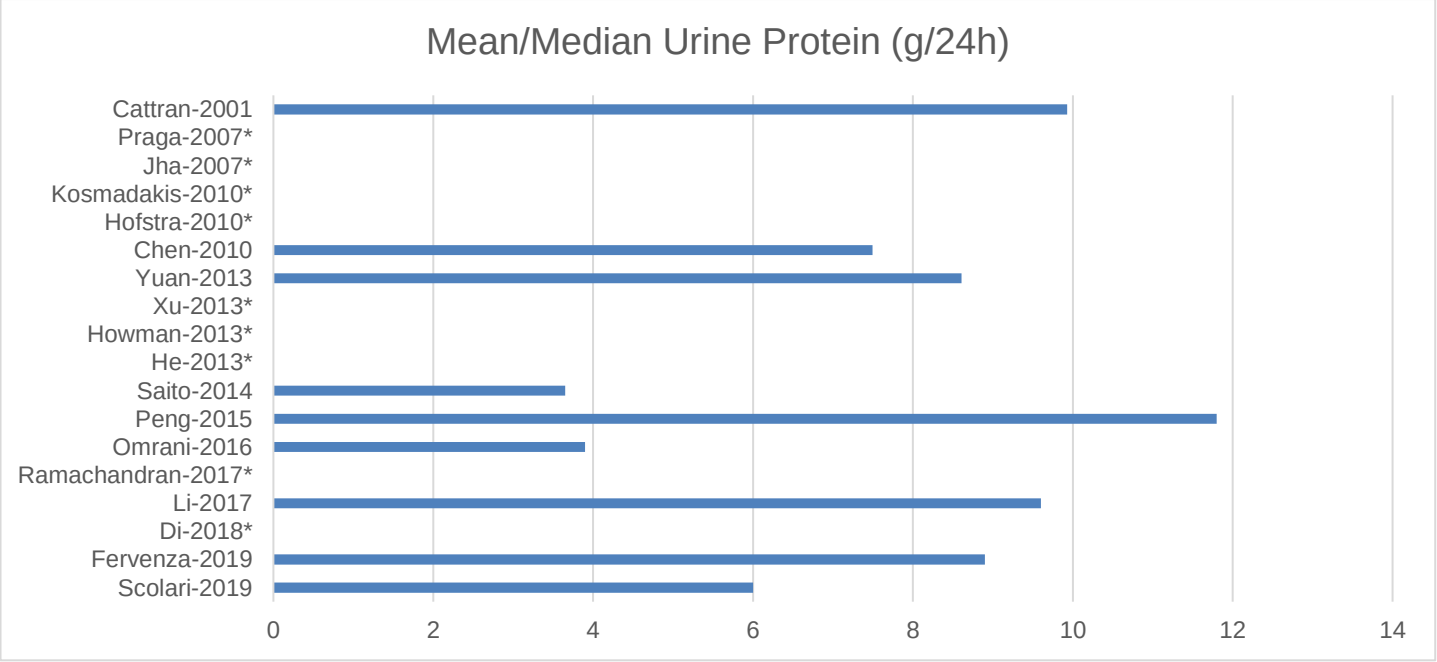
Figure 5:Total Cholesterol



*Data not reported

Source: Cattran et al.,[22] Chen et al.,[24] Di et al.,[25] Fervenza et al.,[8] He et al.,[26] Hofstra et al.,[27] Howman et al.,[28] Jha et al.,[29] Kosmadakis et al.,[30] Li et al.,[31] Omrani et al.,[23] Peng et al.,[32] Praga et al.,[33] Ramachandran et al.,[34,35] Saito et al.,[36] Xu et al.,[37] Yuan et al.[38] Scolari et al.[9]

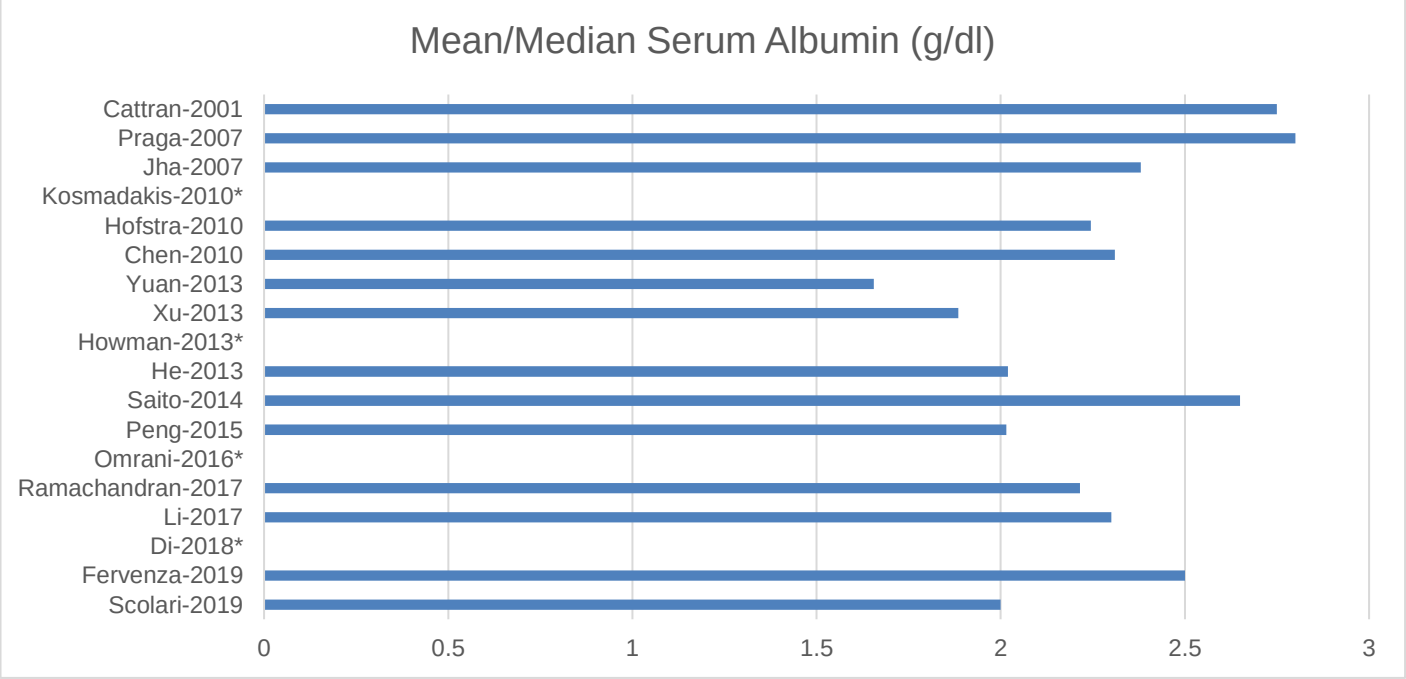
Figure 6: Urine Protein



*Data not reported

Source: Cattran et al.,[22] Chen et al.,[24] Di et al.,[25] Fervenza et al.,[8] He et al.,[26] Hofstra et al.,[27] Howman et al.,[28] Jha et al.,[29] Kosmadakis et al.,[30] Li et al.,[31] Omrani et al.,[23] Peng et al.,[32] Praga et al.,[33] Ramachandran et al.,[34,35] Saito et al.,[36] Xu et al.,[37] Yuan et al.[38] Scolari et al.[9]

Figure 7: Serum Albumin



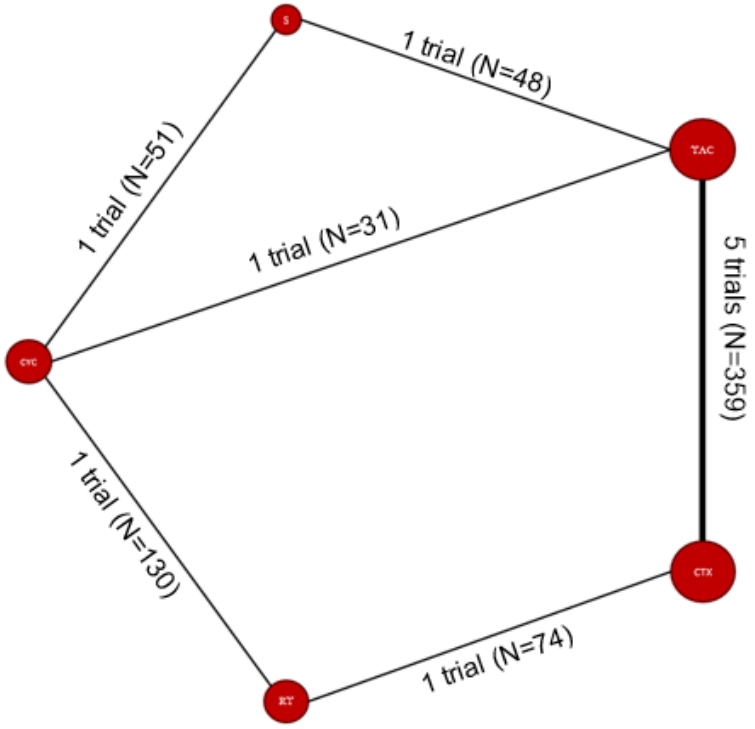
*Data not reported

Source: Cattran et al.,[22] Chen et al.,[24] Di et al.,[25] Fervenza et al.,[8] He et al.,[26] Hofstra et al.,[27] Howman et al.,[28] Jha et al.,[29] Kosmadakis et al.,[30] Li et al.,[31] Omrani et al.,[23] Peng et al.,[32] Praga et al.,[33] Ramachandran et al.,[34,35] Saito et al.,[36] Xu et al.,[37] Yuan et al.[38] Scolari et al.[9]

Appendix 9: Network Meta-Analysis

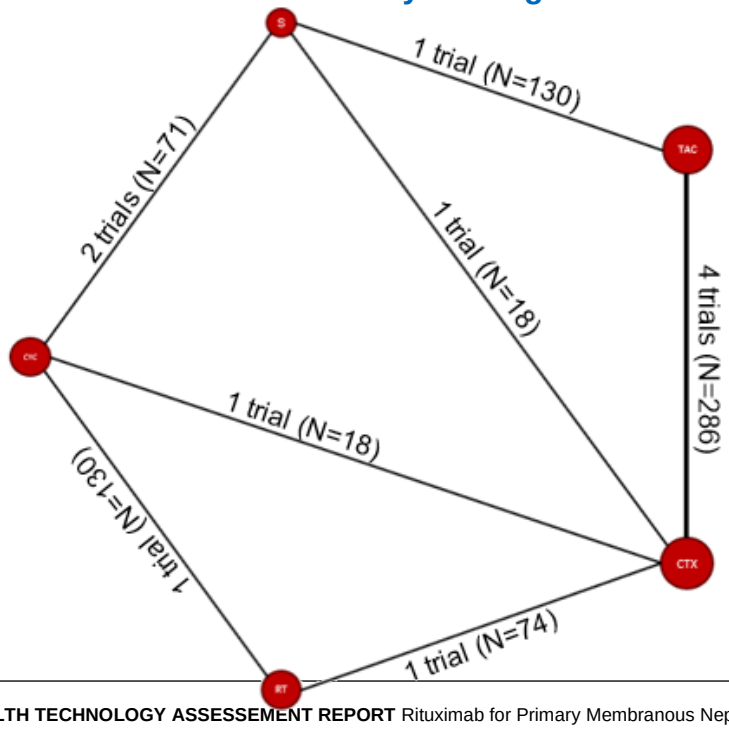
The network meta-analysis (NMA) was based on comparisons between rituximab and tacrolimus, cyclosporine, cyclophosphamide, and supportive care. Odds ratios were calculated for each rituximab treatment comparison. It should be noted that the results of the NMA cannot support any conclusions due to the high degree of uncertainty as demonstrated by the wide credible intervals (CrI).

Figure 9: Network Meta-Analysis Diagram for Complete Remission at 6 months



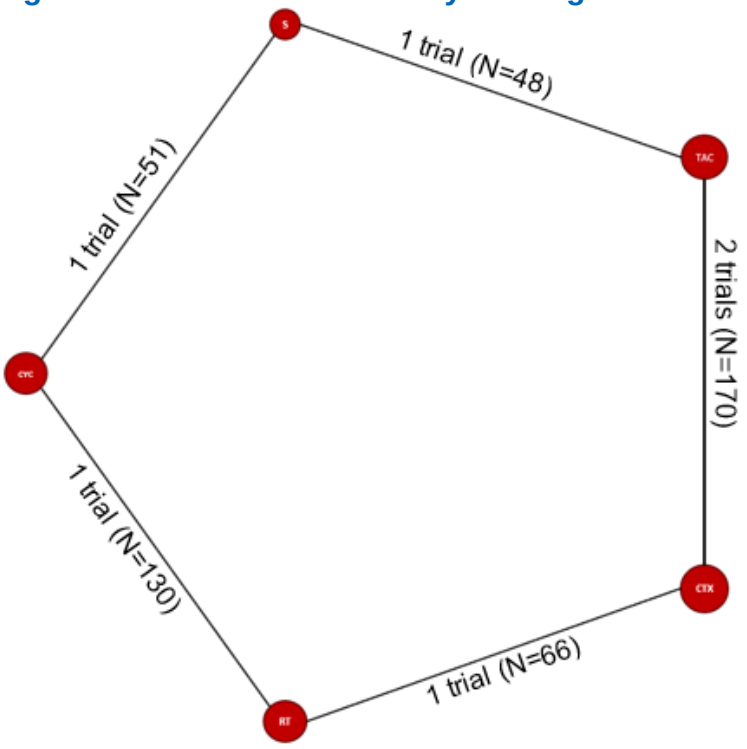
Legend	
Drug	**Abbreviation**
Cyclosporine	CYC
Rituximab	RT
Cyclophosphamide	CTX
Tacrolimus	TAC
Supportive care	S
Base Node Size = 30	

Figure 10: Network Meta-Analysis Diagram for Complete Remission at 12 months



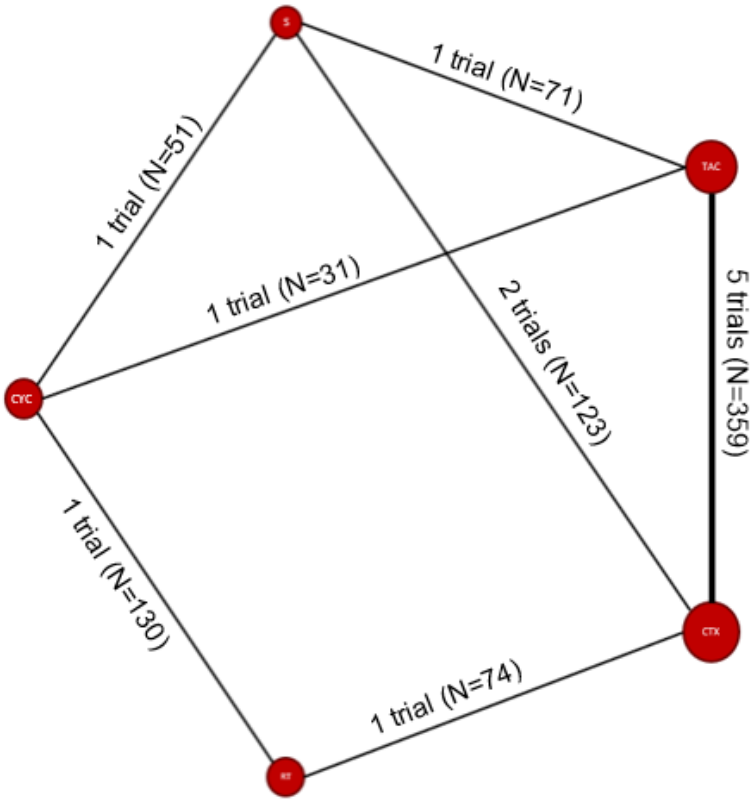
Legend	
Drug	**Abbreviation**
Cyclosporine	CYC
Rituximab	RT
Cyclophosphamide	CTX
Tacrolimus	TAC
Supportive care	S
Base Node Size = 30	

Figure 11: Network Meta-Analysis Diagram for Complete Remission at 18 months



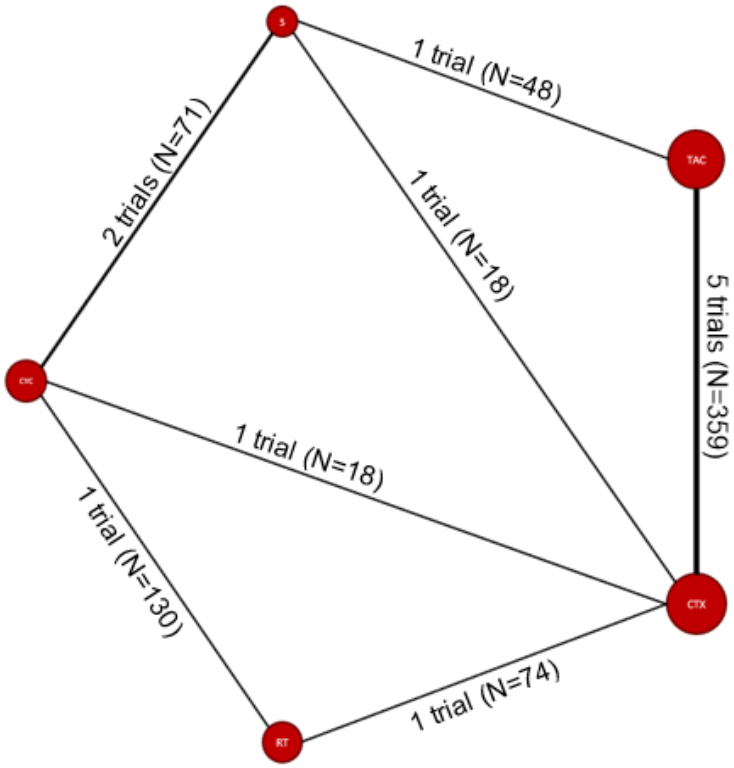
Legend	
Drug	**Abbreviation**
Cyclosporine	CYC
Rituximab	RT
Cyclophosphamide	CTX
Tacrolimus	TAC
Supportive care	S
Base Node Size = 30	

Figure 12: Network Meta-Analysis Diagram for Any Remission at 6 months



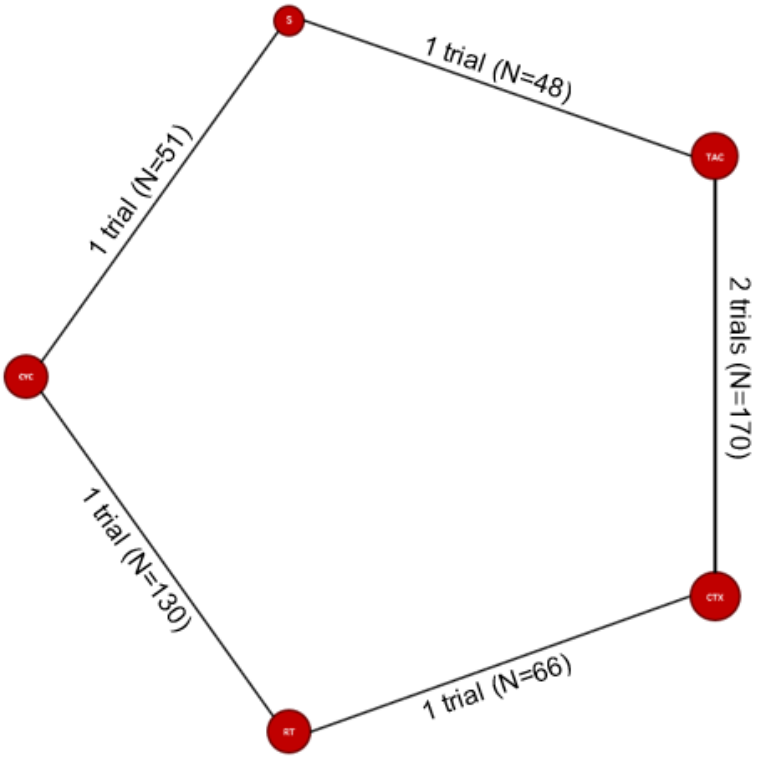
Legend	
Drug	**Abbreviation**
Cyclosporine	CYC
Rituximab	RT
Cyclophosphamide	CTX
Tacrolimus	TAC
Supportive care	S
Base Node Size = 30	

Figure 13: Network Meta-Analysis Diagram for Any Remission at 12 months



Legend	
Drug	**Abbreviation**
Cyclosporine	CYC
Rituximab	RT
Cyclophosphamide	CTX
Tacrolimus	TAC
Supportive care	S
Base Node Size = 30	

Figure 14: Network Meta-Analysis Diagram for Any Remission at 18 months



Legend	
Drug	**Abbreviation**
Cyclosporine	CYC
Rituximab	RT
Cyclophosphamide	CTX
Tacrolimus	TAC
Supportive care	S
Base Node Size = 30	

Table 10: Fixed and Random Effects Model Results for Complete Remission at 6, 12, and 18 months

Treatment Comparison	Odds Ratio (CrI) from Fixed Effects Model	Odds Ratio (CrI) from Random Effects Model	Fixed Effects Model DIC	Random Effects Model DIC
6-month Study Time Point				
Rituximab vs. cyclophosphamide	1.08 (0.17 – 6.76)	1.00 (0.09 – 9.23)	99	99
Rituximab vs. cyclosporine	0.68 (0.08-5.88)	0.54 (0.03 – 7.25)		
Rituximab vs. supportive care	1.03 (0.09 – 12.72)	0.87 (0.04 – 16.78)		
Rituximab vs. tacrolimus	0.59 (0.09-3.85)	0.51 (0.04 – 4.96)		
12-month Study Time Point				
Rituximab vs. cyclophosphamide	0.48 (0.17-1.28)	0.51 (0.06 – 4.60)	105	99
Rituximab vs. cyclosporine	2.62 (0.88 – 8.81)	2.70 (2.91 – 26.60)		
Rituximab vs. supportive care	1.81 (0.42 – 8.49)	0.86 (0.02 – 4.54)		
Rituximab vs. tacrolimus	0.36 (0.12-1.05)	0.39 (0.04 – 4.82)		
18-month Study Time Point				
Rituximab vs. cyclophosphamide	1.99 (0.67 – 6.11)	2.13 (0.29 - 18.84)	63	64
Rituximab vs. cyclosporine	22.20 (5.24 – 145.80)	23.33 (2.39 - 356.70)		
Rituximab vs. supportive care	25.07 (4.63 – 155.50)	28.13 (2.01 - 583.09)		
Rituximab vs. tacrolimus	5.97 (1.76 – 20.99)	6.42 (0.65 - 81.23)		

CrI = credible interval; DIC = deviance information criterion

Table 11: Fixed and Random Effects Model Results for Any Remission at 6, 12, and 18 months

Treatment Comparison	Odds Ratio (CrI) from Fixed Effects Model	Odds Ratio (CrI) from Random Effects Model	Fixed Effects Model DIC	Random Effects Model DIC
6-month Study Time Point				
Rituximab vs. cyclophosphamide	0.49 (0.22-1.09)	0.48 (0.11 – 2.13)	115	114
Rituximab vs. cyclosporine	0.61 (0.32-1.15)	0.63 (0.15 - 2.76)		
Rituximab vs. supportive care	8.75 (3.13 – 26.10)	9.12 (1.61 – 57.50)		
Rituximab vs. tacrolimus	0.27 (0.11-0.65)	0.24 (0.05 - 1.12)		
12-month Study Time Point				

Treatment Comparison	Odds Ratio (CrI) from Fixed Effects Model	Odds Ratio (CrI) from Random Effects Model	Fixed Effects Model DIC	Random Effects Model DIC
Rituximab vs. cyclophosphamide	0.49 (0.20-1.18)	0.35 (0.03 - 3.54)	124	112
Rituximab vs. cyclosporine	1.52 (0.79 – 2.95)	2.25 (0.23 – 29.53)		
Rituximab vs. supportive care	3.71 (1.31 – 10.84)	2.54 (0.13 – 39.23)		
Rituximab vs. tacrolimus	0.45 (0.57-1.47)	0.27 (0.02 – 3.30)		
18-month Study Time Point				
Rituximab vs. cyclophosphamide	0.52 (0.19-1.39)	0.51 (0.09 – 2.89)	65	67
Rituximab vs. cyclosporine	5.31 (2.60 – 11.17)	5.29 (1.04 – 25.78)		
Rituximab vs. supportive care	22.60 (6.80 – 81.70)	22.59 (2.98 – 187.83)		
Rituximab vs. tacrolimus	2.12 (0.69 – 6.51)	2.13 (0.31 – 15.43)		

CrI = credible interval; DIC = deviance information criterion

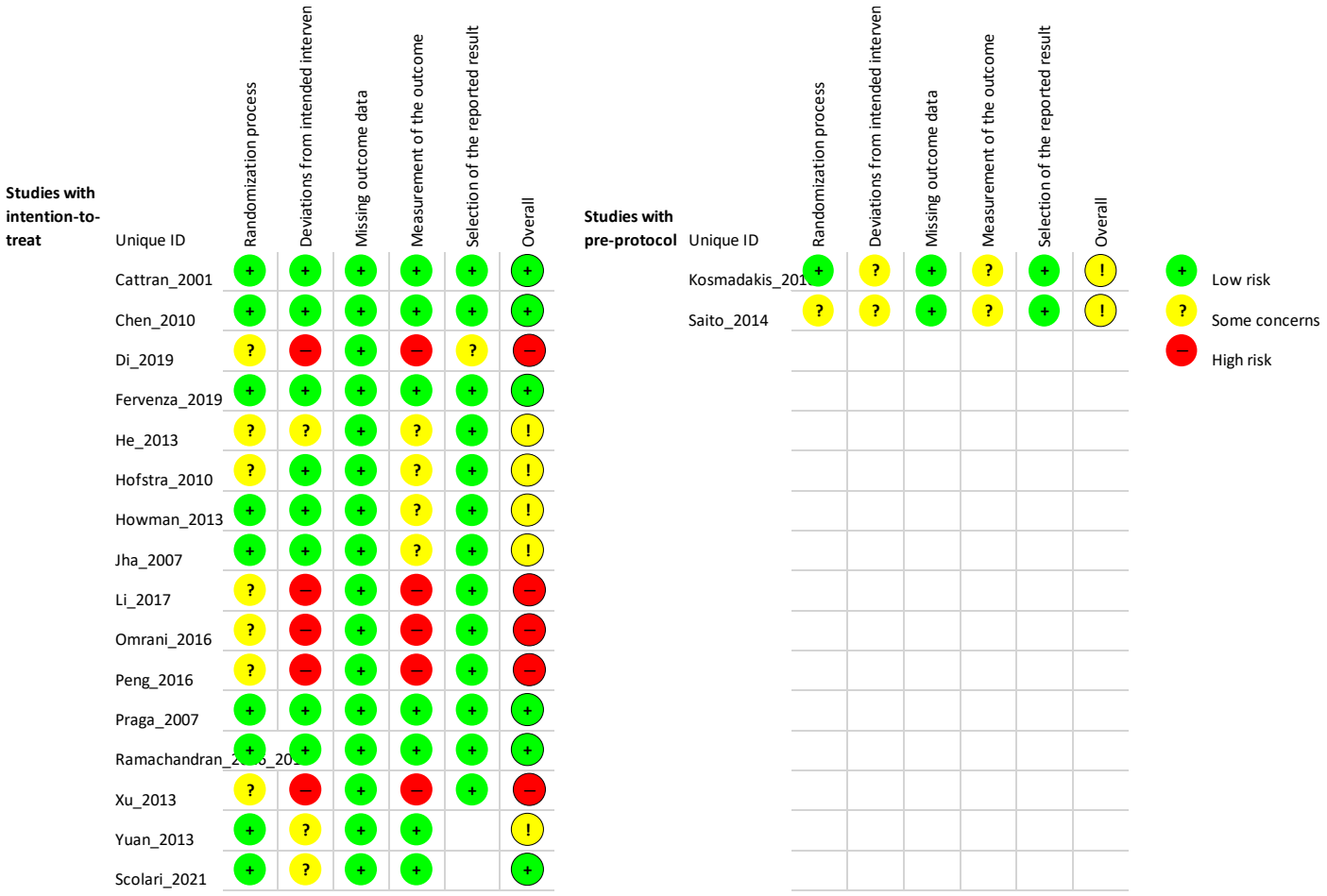
Appendix 10: Critical Appraisal

The included studies had a broad range of reporting quality, despite being published within the last two decades. Several domains in the Cochrane ROB tool could not be assessed as intended due to the context of the study. Firstly, not all studies reported if the analysis (at least for the primary outcomes) was done in the ITT population; however, the review team's aim was to assess the ITT effect (assignment to intervention), as opposed to the per-protocol effect (adhering to intervention). Secondly, all but 2 trials were open-label, therefore the possibility remains that the assignment of treatment (including dosage determination or adjustment and adherence to treatment) and the assessment of outcomes were biased to a certain degree. However, all trials had an active comparator, and the dosage of the treatment and comparator arm could, in theory, be adjusted independently. Therefore, any bias resulting from the knowledge of treatment assignment is likely minimal. The outcomes in the trials were defined based on cutoffs from laboratory parameters, generally measured using appropriate procedure and instrument. Therefore, biases resulting from differential assessment of outcomes based on treatment knowledge is less likely, irrespective of whether the outcome assessors were blinded or not. Finally, the signaling questions in the "selection of reported result" domain were not applicable for most trials (see Cochrane ROB tool for signaling questions). Even though results were analyzed in accordance with a pre-specified analysis plan for most trials, the analysis plan was not finalized before unblinded outcome data became available since most trials were open-label. The numerical results were neither selected on the basis of results from multiple eligible outcome measurements (e.g., scales, definitions, timepoints), nor from multiple eligible analyses of the data. **Error! Reference source not found.** provides a ROB plot showing an assessment of risk of bias in the individual domains as well as overall bias for each of the included trials.

Six trials were considered well conducted and reported, including Cattran et al., Chen et al., Fervenza et al., Praga et al., Scolari et al., and Ramachandran et al. These trials had a low risk of bias in each domain, with most signaling questions assessed adequately based on the level of detail provided in the publications. Seven trials had moderate risk of bias, including He et al., Hofstra t al., Howman et al., Jha et al., Kosmadakis et al., Saito et al., and Yuan et al. The trials had some concerns primarily with respect to randomization and treatment allocation as the publications did not provide adequate detail to assess the appropriateness of these processes. In addition, most of these trials provided no information if the outcome assessors were blinded to treatment assignment, therefore, the possibility that the results could be biased due to the knowledge of treatment assignment cannot be discounted. **Error! Reference source not found.** provides additional details of the strengths and limitations of each trial based on risk of bias assessment.

Overall, 5 trials had a high risk of bias, including Di et al., Li et al., Omrani et al., Peng et al., and Xu et al. The high risk of bias primarily resulted from poor reporting of study methodology, specifically within the domains of "intended interventions" and "outcome measurement". Except for Omrani et al., it was not clear if the other trials were open-label or not, as this information was not available, and could not be assessed from the respective publications. In addition, aspects of randomization, blinding, and allocation concealment were described with little information, or not at all. Additionally, it was not clear if the trial data were pre-specified to be analyzed in ITT population; however, the efficacy analyses were adjudicated to be conducted in the ITT population since data were available for all or almost all patients.

Figure 8: Risk of Bias Assessment Plot



Source: Cattran et al.,[22] Chen et al.,[24] Di et al.,[25] Fervenza et al.,[8] He et al.,[26] Hofstra et al.,[27] Howman et al.,[28] Jha et al.,[29] Kosmadakis et al.,[30] Li et al.,[31] Omrani et al.,[23] Peng et al.,[32] Praga et al.,[33] Ramachandran et al.,[34,35] Saito et al.,[36] Xu et al.,[37] Yuan et al.[38]

Table 9: Strengths and Limitations of Included Studies

First Author, Publication Year	Strengths	Limitations
Cattran 2001	• Trial was single-blinded, with patients blinded to treatment allocation. Only a couple studies in the evidence base that was not open-label. Additionally, outcomes were measured by blinded assessors. • Randomization method was appropriate, conducted centrally, allocation was concealed. No significant difference in baseline characteristics either. • Outcomes were objective laboratory measures, with acceptable definitions, assessed using standard methods, less likely to be biased. • Analysis method was appropriate, with ITT principle used. • Missing data was not an issue of concern.	

First Author, Publication Year	Strengths	Limitations
Chen 2010	• Randomization method was appropriate, conducted centrally, allocation was concealed. No significant difference in baseline characteristics either. • Outcomes were objective laboratory measures, with acceptable definition, assessed using standard method, and outcome assessors were blinded. • Analysis method was appropriate, with ITT principle used. • Missing data was not an issue of concern.	• Trial was open-label, therefore, both patients and study investigators were aware of treatment allocation. • High dropout rate, short follow-up duration, noted by the authors.
Di 2018	• Baseline characteristics were well-balanced; therefore, randomization appears to be done reasonably. • Outcomes were objective laboratory measures, with acceptable definition, assessed using standard method. • Missing data was not an issue of concern.	• Reporting of study methodology was poor. Aspects of study design, randomization, blinding, allocation concealment, ITT analysis could not be assessed.
Fervenza 2019	• Randomization method was appropriate, conducted centrally, allocation was concealed. No significant difference in baseline characteristics either. • Outcomes were objective laboratory measures, with acceptable definition, assessed using standard method, and outcome assessors were blinded. • Analysis method was appropriate, with ITT principle used. • Missing data was not an issue of concern.	• OL design has the possibility to affect the treatment of the patient and the assessment of disease status. • Laboratory outcomes and QoL measures were not assessed in the ITT population, as noted by the authors.
He 2013	• Randomization method was appropriate, although no information if allocation was concealed. No significant difference in baseline characteristics either. • Outcomes were objective laboratory measures, with acceptable definition, assessed using standard method, although no information if outcome assessors were blinded. • Analysis method was appropriate, although no information if ITT principle was used. • Missing data was not an issue of concern.	• OL design has the possibility to affect the treatment of the patient and the assessment of disease status. • Study authors noted a lack of homogeneous study population with an adequate number of patients.
Hofstra 2010	• Randomization method was appropriate, although no information if allocation was concealed. No significant difference in baseline characteristics either. • Outcomes were objective laboratory measures, with acceptable definition, assessed using standard method, although no information if outcome assessors were blinded. • Analysis method was appropriate, although no information if ITT principle was used. • Missing data was not an issue of concern.	• OL design has the possibility to affect the treatment of the patient and the assessment of disease status. • Study authors noted that the frequency of follow-up visits was different in the two groups
Howman 2013	• Randomization method was appropriate, conducted centrally, independent of the study. No significant difference in baseline characteristics either. • Outcomes were objective laboratory measures, with acceptable definition, assessed using standard method, and outcome assessors were blinded. • Analysis method was appropriate, with ITT principle used. • Missing data was not an issue of concern.	• Trial was open-label, therefore, both patients and study investigators were aware of treatment allocation.

First Author, Publication Year	Strengths	Limitations
Jha 2007	• Randomization method was appropriate, although no information if allocation was concealed. No significant difference in baseline characteristics either. • Outcomes were objective laboratory measures, with acceptable definition, assessed using standard method, although no information if outcome assessors were blinded. • Analysis method was appropriate, with ITT principle used. • Missing data was not an issue of concern.	• OL design has the possibility to affect the treatment of the patient and the assessment of disease status.
Kosmadakis 2010	• Baseline characteristics were well-balanced; therefore, randomization appears to be done reasonably. • Outcomes were objective laboratory measures, with acceptable definition, assessed using standard method. • Missing data was not an issue of concern.	• Reporting of study methodology was poor. Aspects of study design, randomization, allocation concealment, ITT analysis could not be assessed. Randomization method was not described with adequate detail, other than patients were randomized by a person blinded and independent of the study.
Li 2017	• Randomization method was appropriate, although no information if allocation was concealed. No significant difference in baseline characteristics either. • Outcomes were objective laboratory measures, with acceptable definition, assessed using standard method. • Missing data was not an issue of concern.	• Reporting of study methodology was poor. Aspects of study design, allocation concealment, ITT analysis could not be assessed. • Study authors noted a limited sample size, short follow-up time, and drug levels was not monitored rigorously.
Omrani 2016	• Double-blind design • Outcomes were objective laboratory measures, with acceptable definition, although interestingly none of the binary endpoints were reported, instead continuous outcomes were reported.	• Reporting of study methodology was poor. Aspects of study design, randomization, blinding, allocation concealment, ITT analysis could not be assessed.
Peng 2016	• Outcomes were objective laboratory measures, with acceptable definition, assessed using standard method. • Missing data was not an issue of concern.	• Reporting of study methodology was poor. Aspects of study design, randomization, blinding, allocation concealment, ITT analysis could not be assessed. • Study authors noted a limited sample size, short follow-up time.
Praga 2007	• Randomization method was appropriate, conducted centrally, allocation was concealed. No significant difference in baseline characteristics either. • Outcomes were objective laboratory measures, with acceptable definition, assessed using standard method, although no information if outcome assessors were blinded. • Analysis method was appropriate, with ITT principle used. • Missing data was not an issue of concern.	• OL design has the possibility to affect the treatment of the patient and the assessment of disease status.
Ramachandran 2016 and 2017	• Randomization method was appropriate, conducted centrally, allocation was concealed. No significant difference in baseline characteristics either. • Outcomes were objective laboratory measures, with acceptable definition, assessed using standard method, although outcome assessors were not blinded. • Analysis method was appropriate, with ITT principle used.	• OL design has the possibility to affect the treatment of the patient and the assessment of disease status.

First Author, Publication Year	Strengths	Limitations
	• Missing data was not an issue of concern.	
Saito 2014	• Baseline characteristics were well-balanced; therefore, randomization appears to be done reasonably. • Outcomes were objective laboratory measures, with acceptable definition, assessed using standard method, although no information if outcome assessors were blinded. • Analysis method was appropriate, with ITT principle used. • Missing data was not an issue of concern.	• OL design has the possibility to affect the treatment of the patient and the assessment of disease status. • Reporting of study methodology was poor. Aspects of randomization, allocation concealment, ITT analysis could not be assessed.
Xu 2013	• Baseline characteristics were well-balanced; therefore, randomization appears to be done reasonably. • Outcomes were objective laboratory measures, with acceptable definition, assessed using standard method. • Missing data was not an issue of concern.	• Reporting of study methodology was poor. Aspects of study design, randomization, blinding, allocation concealment could not be assessed.
Yuan 2013	• Baseline characteristics were well-balanced; therefore, randomization appears to be done reasonably. • Outcomes were objective laboratory measures, with acceptable definition, assessed using standard method. • Missing data was not an issue of concern.	• Reporting of study methodology was poor. Aspects of study design, randomization, blinding, allocation concealment could not be assessed.
Scolari 2021	• Randomization method was appropriate, conducted centrally, allocation was concealed. No significant difference in baseline characteristics either. • Outcomes were objective laboratory measures, with acceptable definition, assessed using standard method, although outcome assessors were not blinded. • Analysis method was appropriate, with ITT principle used. • Missing data was not an issue of concern.	• OL design has the possibility to affect the treatment of the patient and the assessment of disease status.

Source: Cattran et al.,[22] Chen et al.,[24] Di et al.,[25] Fervenza et al.,[8] He et al.,[26] Hofstra et al.,[27] Howman et al.,[28] Jha et al.,[29] Kosmadakis et al.,[30] Li et al.,[31] Omrani et al.,[23] Peng et al.,[32] Praga et al.,[33] Ramachandran et al.,[34,35] Saito et al.,[36] Xu et al.,[37] Yuan et al.[38], Scolari et al.[9]