

BMJ Open Efficacy and safety of different dosing regimens of rituximab in primary membranous nephropathy: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Primary membranous nephropathy (PMN) is a major cause of nephrotic syndrome in adults. Rituximab has been recommended in the treatment of PMN by the updated Kidney Disease Improved Outcome guideline. However, the optimal dosing regimen of rituximab for the initial treatment of patients with PMN is unclear.

Methods and analysis A comprehensive screening will be performed by searching PubMed, Embase and the CENTRAL (Cochrane Central Register of Controlled Trials) without language restriction. Studies evaluating the efficacy of rituximab monotherapy using the following types of dosing regimens will be included: high-dose regimen; standard regimen and low-dose regimen. Studies with less than 10 participants will be excluded. The primary outcome is the remission rate at 12 months. The secondary outcomes are remission rate at 6 and 24 months, complete remission rate at 6, 12 and 24 months, relapse at 6, 12 and 24 months, and side effects. Risk of Bias In Non-randomised Studies of Interventions tool will be used to assess the risk of bias for non-randomised studies and the Cochrane risk of bias assessment tool will be used for randomised controlled trials. The pooled remission rate, complete remission rate, relapse rate and side effects will be estimated using the metaprop command. All analyses will be calculated using Stata software (V.15.0; StataCorp).

Ethics and dissemination Ethics approval is not required. The results of our study will be submitted to a peer-review journal.

PROSPERO registration number CRD42022319401

INTRODUCTION

Membranous nephropathy (MN), representing a spectrum of histopathological abnormalities, is characterised by immunoglobulin and complement-containing immune deposits in a subepithelial position.¹ MN is a major cause of nephrotic syndrome in adults.² Primary MN (PMN) is a kidney-specific disease with autoantibodies against certain podocyte membrane antigens, whereas secondary MN is associated with other diseases or exposures.³ In recent years, the progress of the mechanism and

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This meta-analysis and prespecified subgroup analysis may enable the comparative analysis of the efficacy of different dosing regimens for rituximab on primary membranous nephropathy.
- ⇒ This meta-analysis may provide useful information for medical decision-making and guide further research.
- ⇒ A comprehensive literature screening including conference abstracts will be performed without language restriction.
- ⇒ Heterogeneity and risks of bias among included studies may influence the results of the meta-analysis.

treatment strategy of PMN are developing rapidly. A majority of patients with PMN have anti-phospholipase A2 receptor (PLA2R) antibodies.⁴ Several new target antigens have recently been identified in PMN.⁵ As the efficacy of rituximab in PMN is confirmed in a series of landmark randomised controlled trials, Rituximab vs Steroids and Cyclophosphamide in the Treatment of Idiopathic Membranous Nephropathy (RI-CYCLO),⁶ Membranous Nephropathy Trial of Rituximab (MENTOR)⁷ and Evaluate Rituximab Treatment for Idiopathic Membranous Nephropathy (GEMRITUX)⁸ studies, rituximab is recommended in the treatment of PMN by updated Kidney Disease Improved Outcome (KDIGO) guideline.⁹

However, the optimal dosing regimen of rituximab for the initial treatment of patients with PMN is unclear.⁹ In the MENTOR and RI-CYCLO trial, rituximab was given 1 g twice, 14 days apart.^{6,7} In some prospective studies, rituximab was administered 4 weekly infusions of 375 mg/m².^{10–12} In the GEMRITUX study, rituximab was given 375 mg/m² weekly for 2 weeks.⁸ While, in the B cell-driven rituximab regimen, a single dose of 375 mg/m² was initially administered, and the second dose of 375 mg/m² is given if ≥5 circulating

B cells/microl.¹³ In some observational studies, single-dose rituximab (375 mg/m²) was given.^{14 15} Debate exists regarding the efficacy of various dosing regimens, especially the so-called low-dose rituximab.¹⁵

Although previous meta-analyses have evaluated the efficacy of rituximab in PMN compared with other medications,^{16–19} the study focusing on the efficacy of different dosing regimens of rituximab at different time points is lacking. Because head-to-head trial regarding specific dosing regimens is scarce so far, direct comparisons are difficult. However, subgroup analysis based on dosing regimens in a meta-analysis may enable comparative analysis. Our meta-analysis will investigate whether a difference in treatment response exists among different dosing regimens of rituximab in PMN by subgroup analysis.

METHODS

The proposed review protocol conforms to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols²⁰ (online supplemental file 1).²⁰ This review protocol has been registered within the International Prospective Register of Systematic Reviews (PROSPERO). Any important protocol amendments will also be documented in PROSPERO. This systematic review was initiated in May 2022. We plan to finish this study in October 2023.

Eligibility criteria and prespecified outcomes

Inclusion criteria are as follows: (A) studies evaluating the efficacy of rituximab monotherapy (not in combination with other immunosuppressive therapy/corticosteroid) with one type of dosing regimen in PMN patients; (B) the following types of dosing regimen of rituximab were used: high-dose regimen (two infusions of 1 g rituximab at 2-week intervals); standard regimen (four infusions of 375 mg/m² at 1-week interval; low-dose regimen (defined as one or two infusions of 375 mg/m² at 1-week interval,¹⁴ or two infusions of 500 mg rituximab²¹); (C) treatment response (remission rate (complete remission+partial remission), complete remission rate or relapse) were reported. Eligible study designs will include interventional studies (such as randomised controlled clinical trials and non-randomised trials) and observational studies (such as cohort studies, case-control studies and case series). Studies reported in conference abstracts will also be considered. Studies with less than 10 participants will be excluded.

The primary outcome is the remission rate (complete remission+partial remission) at 12 months. The secondary outcomes are remission rate at 6 and 24 months, complete remission rate at 6, 12 and 24 months, relapse at 6, 12 and 24 months, and side effects. The outcomes were used as defined by investigators in individual studies.

Search methods for identification of relevant studies

Popular databases will be searched including PubMed, Embase and CENTRAL (Cochrane Central Register of

Controlled Trials) without language restriction. The relevant text words and medical subject headings will be used. The search strategy for PubMed is given in online supplemental file 1. The reference list of the eligible articles and relevant reviews will be manually searched to identify additional studies.

Records and data management

Literature search results will be stored in EndNote, a bibliographic management software and duplicates will be removed. The screening of remaining citations will be conducted by using Endnote, too. The data extraction will be performed on Microsoft Excel 2016.

Study selection

Two authors will independently examine the studies against eligibility criteria. In the title and abstract screening stage, two authors will independently screen initial subsets of studies until convergence is reached. Subsequently, full-text records of the selected abstracts will be retrieved. The full-text screening will be performed in full independent double screening. Full-text records selected for inclusion by both authors will be included in the review. Any disagreements during this stage will be resolved through discussion. Studies in languages other than English or Chinese will be translated into English using Google Translate. We will record the selection process with reasons for exclusion. When there are multiple studies from the same cohort, the study with the largest sample size will be used.

Data extraction

Two authors will independently extract data, including first author, year of publication, study design, setting, baseline characteristics (such as age, proteinuria, serum albumin level, serum creatinine, kidney function, antibodies to the M-type phospholipase A2 receptor), dosing regimen, actual doses and the maximum doses of rituximab administered, follow-up time, study outcomes, side effects and so on. We will extract data from the parts of the studies that met the selection criteria.

Assessing the risk of bias

The risk of bias in the included studies will be assessed independently by two reviewers. Any disagreement will be discussed by consultation. Two authors will independently assess the risk of bias using the Risk of Bias In Non-randomised Studies of Interventions tool for non-randomised studies²² or the Cochrane risk of bias assessment tool for randomised controlled trials.²³

Statistical analysis

The pooled remission rate, complete rate, relapse and side effects will be estimated using the metaprop command, a statistical programme in Stata.²⁴ Subgroup analyses will be undertaken to explore whether there are differences in treatment response among different dosing regimens of rituximab. Referring to previous publications,^{25–27} we will conduct bivariate meta-regression analysis to evaluate

the impact of the dosing regimen of rituximab on the primary outcome and also perform multivariate meta-regression analyses to examine whether the result will remain unchanged while adjusting for other prognostic factors (such as age, sex, proteinuria, kidney function) if sufficient studies are available. The heterogeneity between studies will be investigated statistically using the χ^2 test and I^2 statistic.²⁸ Funnel plots, Egger's regression asymmetry test, and Begg's test will be used to evaluate publication bias.^{29 30} A two-sided $p < 0.05$ will be regarded as significant for all analyses. All analyses will be calculated using Stata software (V.15.0; StataCorp).

Patient and public involvement

Patients are not involved in any stage of the study including but not limited to the development of the research question, outcome measure and study design.

DISCUSSION

Although an increasing body of evidence suggests the efficacy of rituximab treatment in PMN recently, dosing regimens of rituximab used across studies are different.^{6 7 31 32} The updated KDIGO guideline on PMN offers a wide scope of options either two infusions of 1 g, apart 14 days, or 375 mg/m² ranging from 1 single dose to 4 weekly doses.⁹ Meanwhile, the low-dose regimen of rituximab was used in recent years.^{14 15} However, due to the absence of head-to-head trials, the optimal dosing regimen of rituximab is unclear.

To date, although some previous meta-analyses have been published regarding the efficacy of rituximab on the PMN, the efficacy of different dosing regimens of rituximab at different time points was not assessed in these studies.^{16–19} Unlike these above-mentioned meta-analyses, our work will focus on the efficacy of different dosing regimens of rituximab at different time points. Our meta-analysis may enable the comparative analysis of various dosing regimens of rituximab in PMN patients under the condition that head-to-head trials are not available presently. In addition, a comprehensive screening will be performed by searching PubMed, Embase and CENTRAL without language restriction and conference abstracts will also be included in this systematic review. It needs to be noted that heterogeneity and risks of bias among included studies may influence the results of the meta-analysis and prevent drawing solid conclusions. However, our work may provide useful information for medical decision-making and guide further research.

Ethics and dissemination

For this type of study, ethics approval is unnecessary because the data of individual patients will not be included and no privacy will be involved. The results of this review will be published in a peer-reviewed journal. Amendments to the basic protocol will be documented in the comprehensive review.

Contributors YX and YG conceptualised and designed the current study. YX, QY, CF, EH and YG drafted this protocol. The search strategy was designed by YX and the literature search will be performed by QY. YX, QY and CF were involved in the methodological aspects and analysis sections of the protocol. YX and YG are the guarantors of this review.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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Correction: *Editorial assignment*

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The article is corrected since it was published, the article title is updated from “Editorial assignment to “Efficacy and safety of different dosing regimens of rituximab in primary membranous nephropathy: protocol for a systematic review and meta-analysis”.

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Supplementary File 1: PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	PAGE
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Not applicable
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	11
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Not applicable
Support:			
Sources	5a	Indicate sources of financial or other support for the review	1
Sponsor	5b	Provide name for the review funder and/or sponsor	1
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	1
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6-7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2 , Kendall's τ)	9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	No

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Supplementary File 2: PubMed search strategy

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- 1 "glomerulonephritis, membranous"[MeSH Terms]
 - 2 membranous nephropathy[Text word]
 - 3 "membranous glomerulo*"[Text word]
 - 4 extramembranous glomerulopathy[Text word]
 - 5 inm[Text word]
 - 6 OR/1-5
 - 7 "Rituximab"[Mesh]
 - 8 "IDEC C2B8"[Text Word]
 - 9 Rituxan[Text Word]
 - 10 rituximab[Text Word]
 - 11 mabthera[Text Word]
 - 12 OR/7-11
 - 13 6 AND 12
-