

# BMJ Open Editorial Assignment

Yongxing Xu <sup>1</sup>, Qing Yang,<sup>1</sup> Chen Fu,<sup>2</sup> Enhong Han,<sup>1</sup> Yuehua Gao<sup>1</sup>

**To cite:** Xu Y, Yang Q, Fu C, *et al.* Editorial Assignment. *BMJ Open* 2023;**13**:e064220. doi:10.1136/bmjopen-2022-064220

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2022-064220>).

YX, QY and CF contributed equally.

Received 26 April 2022

Accepted 02 December 2022

## 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.<sup>1</sup> MN is a major cause of nephrotic syndrome in adults.<sup>2</sup> 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.<sup>3</sup> In recent years, the progress of the mechanism and treatment strategy of PMN are developing rapidly. A majority of patients with PMN have anti-phospholipase A2 receptor (PLA2R) antibodies.<sup>4</sup> Several new target antigens have recently been identified in PMN.<sup>5</sup> As the efficacy of rituximab in PMN is confirmed in a

## 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.

series of landmark randomised controlled trials, Rituximab vs Steroids and Cyclophosphamide in the Treatment of Idiopathic Membranous Nephropathy (RI-CYCLO),<sup>6</sup> Membranous Nephropathy Trial of Rituximab (MENTOR)<sup>7</sup> and Evaluate Rituximab Treatment for Idiopathic Membranous Nephropathy (GEMRITUX)<sup>8</sup> studies, rituximab is recommended in the treatment of PMN by updated Kidney Disease Improved Outcome (KDIGO) guideline.<sup>9</sup>

However, the optimal dosing regimen of rituximab for the initial treatment of patients with PMN is unclear.<sup>9</sup> In the MENTOR and RI-CYCLO trial, rituximab was given 1 g twice, 14 days apart.<sup>6,7</sup> In some prospective studies, rituximab was administered 4 weekly infusions of 375 mg/m<sup>2</sup>.<sup>10–12</sup> In the GEMRITUX study, rituximab was given 375 mg/m<sup>2</sup> weekly for 2 weeks.<sup>8</sup> While, in the B cell-driven rituximab regimen, a single dose of 375 mg/m<sup>2</sup> was initially administered, and the second dose of 375 mg/m<sup>2</sup> is given if ≥5 circulating B cells/microl.<sup>13</sup> In some observational studies, single-dose rituximab (375 mg/m<sup>2</sup>) was given.<sup>14,15</sup> Debate exists regarding the efficacy of various dosing regimens, especially the so-called low-dose rituximab.<sup>15</sup>

Although previous meta-analyses have evaluated the efficacy of rituximab in PMN compared with other medications,<sup>16–19</sup> 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



© Author(s) (or their employer(s)) 2023. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

<sup>1</sup>Department of Nephrology, People's Liberation Army Strategic Support Force Medical Center, Beijing, China

<sup>2</sup>Department of Nephrology, Beijing Jishuitan Hospital, Beijing, China

### Correspondence to

Dr Yuehua Gao; [kidneygyh@163.com](mailto:kidneygyh@163.com)

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 Protocols<sup>20</sup> (online supplemental file 1).<sup>20</sup> 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/m<sup>2</sup> at 1-week interval; low-dose regimen (defined as one or two infusions of 375 mg/m<sup>2</sup> at 1-week interval,<sup>14</sup> or two infusions of 500 mg rituximab<sup>21</sup>); (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 studies<sup>22</sup> or the Cochrane risk of bias assessment tool for randomised controlled trials.<sup>23</sup>

## Statistical analysis

The pooled remission rate, complete rate, relapse and side effects will be estimated using the metaprop command, a statistical programme in Stata.<sup>24</sup> Subgroup analyses will be undertaken to explore whether there are differences in treatment response among different dosing regimens of rituximab. Referring to previous publications,<sup>25-27</sup> 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

$\chi^2$  test and  $I^2$  statistic.<sup>28</sup> Funnel plots, Egger's regression asymmetry test, and Begg's test will be used to evaluate publication bias.<sup>29,30</sup> 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.<sup>6,7,31,32</sup> The updated KDIGO guideline on PMN offers a wide scope of options either two infusions of 1 g, apart 14 days, or 375 mg/m<sup>2</sup> ranging from 1 single dose to 4 weekly doses.<sup>9</sup> Meanwhile, the low-dose regimen of rituximab was used in recent years.<sup>14,15</sup> 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.<sup>16–19</sup> 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.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**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.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

### ORCID iD

Yongxing Xu <http://orcid.org/0000-0003-1216-235X>

### REFERENCES

- 1 Alsharhan L, Beck LH, Jr. Membranous nephropathy: core curriculum 2021. *American Journal of kidney diseases. the official journal of the National Kidney Foundation* 2021 Mar;77:440–53.
- 2 Ronco P, Beck L, Debiec H, et al. Membranous nephropathy. *Nat Rev Dis Primers* 2021;7:69.
- 3 Couser WG. Primary membranous nephropathy. *Clin J Am Soc Nephrol* 2017;12:983–97.
- 4 Beck LH, Bonegio RGB, Lambeau G, et al. M-Type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. *N Engl J Med* 2009;361:11–21.
- 5 Caravaca-Fontán F, Fernandez-Juarez GM, Floege J. *The management of membranous nephropathy - an update. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*, 2021.
- 6 Scolari F, Delbarba E, Santoro D, et al. Rituximab or cyclophosphamide in the treatment of membranous nephropathy: the RI-CYCLO randomized trial. *J Am Soc Nephrol* 2021;32:972–82.
- 7 Fervenza FC, Appel GB, Barbour SJ, et al. Rituximab or cyclosporine in the treatment of membranous nephropathy. *N Engl J Med* 2019;381:36–46.
- 8 Dahan K, Debiec H, Plaisier E, et al. Rituximab for severe membranous nephropathy: a 6-month trial with extended follow-up. *J Am Soc Nephrol* 2017;28:348–58.
- 9 KDIGO. Clinical practice guideline for the management of glomerular diseases. *Kidney international*. 2021;2021;100.
- 10 Ruggenti P, Chiurciu C, Brusegan V, et al. Rituximab in idiopathic membranous nephropathy: a one-year prospective study. *J Am Soc Nephrol* 2003;14:1851–7.
- 11 Remuzzi G, Chiurciu C, Abbate M, et al. Rituximab for idiopathic membranous nephropathy. *Lancet* 2002;360:923–4.
- 12 Fervenza FC, Abraham RS, Erickson SB, et al. Rituximab therapy in idiopathic membranous nephropathy: a 2-year study. *Clin J Am Soc Nephrol* 2010;5:2188–98.
- 13 Cravedi P, Ruggenti P, Sghirlanzoni MC, et al. Titrating rituximab to circulating B cells to optimize lymphocytolytic therapy in idiopathic membranous nephropathy. *Clin J Am Soc Nephrol* 2007;2:932–7.
- 14 Moroni G, Depetri F, Del Vecchio L, et al. Low-Dose rituximab is poorly effective in patients with primary membranous nephropathy. *Nephrol Dial Transplant* 2017;32:1691–6.
- 15 Fenoglio R, Baldovino S, Sciascia S, et al. Efficacy of low or standard rituximab-based protocols and comparison to Ponticelli's regimen in membranous nephropathy. *J Nephrol* 2021;34:565–71.
- 16 Lu W, Gong S, Li J, et al. Efficacy and safety of rituximab in the treatment of membranous nephropathy: a systematic review and meta-analysis. *Medicine* 2020;99:e19804.
- 17 Huang L, Dong Q-R, Zhao Y-J, et al. Rituximab for the management of idiopathic membranous nephropathy: a meta-analysis. *Int Urol Nephrol* 2021;53:111–9.
- 18 Bose B, Chung EYM, Hong R, et al. Immunosuppression therapy for idiopathic membranous nephropathy: systematic review with network meta-analysis. *J Nephrol* 2022;35:1159–70.



- 19 Ou J-Y, Chen Y-W, Li T-L, JY O, TL L, *et al.* Evaluation of efficacy of rituximab for membranous nephropathy: a systematic review and meta-analysis of 11 studies. *Nephrol Ther* 2022;18:104-112.
- 20 Shamseer L, Moher D, Clarke M, *et al.* Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;349:g7647.
- 21 Bagchi S, Subbiah AK, Bhowmik D, *et al.* Low-Dose rituximab therapy in resistant idiopathic membranous nephropathy: single-center experience. *Clin Kidney J* 2018;11:337-41.
- 22 Sterne JAC, Hernán MA, Reeves BC, *et al.* ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016 Oct 12;355:i4919.
- 23 Higgins J, Thomas J, Chandler J. Cochrane Handbook for systematic reviews of interventions version 6.2 (updated February 2021). Cochrane, 2021. Available: [www.trainingcochrane.org/handbook](http://www.trainingcochrane.org/handbook)
- 24 Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. *Arch Public Health* 2014;72:39.
- 25 Malhotra R, Nguyen HA, Benavente O, *et al.* Association between more intensive vs less intensive blood pressure lowering and risk of mortality in chronic kidney disease stages 3 to 5: a systematic review and meta-analysis. *JAMA Intern Med* 2017;177:1498-505.
- 26 Cuijpers P, Karyotaki E, Eckshtain D, *et al.* Psychotherapy for depression across different age groups: a systematic review and meta-analysis. *JAMA Psychiatry* 2020;77:694-702.
- 27 Liu J, Liu D, Li J, *et al.* Efficacy and safety of everolimus for maintenance immunosuppression of kidney transplantation: a meta-analysis of randomized controlled trials. *PLoS One* 2017;12:e0170246.
- 28 Higgins JPT, Thompson SG, Deeks JJ, *et al.* Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60.
- 29 Begg CB, Mazumdar M. Operating characteristics of a RANK correlation test for publication bias. *Biometrics* 1994;50:1088-101.
- 30 Egger M, Davey Smith G, Schneider M, *et al.* Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-34.
- 31 Ruggenti P, Cravedi P, Chianca A, *et al.* Rituximab in idiopathic membranous nephropathy. *J Am Soc Nephrol* 2012;23:1416-25.
- 32 Ramachandran R, Nayak S, Kumar V. Rituximab in primary membranous nephropathy: a comparative study of three dosing regimens. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*, 2021