

BMJ Open Rituximab versus steroids and cyclophosphamide for the treatment of primary membranous nephropathy: protocol of a pilot randomised controlled trial

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ABSTRACT

Introduction Primary membranous nephropathy (MN) is a common cause of nephrotic syndrome in adults. The disease may have different long-term outcomes. After 10 years of follow-up, 35%–50% of the untreated patients with persistent nephrotic syndrome may die or progress to end stage renal disease. The 2012 KDIGO (Kidney Disease Improving Global Outcomes) guidelines recommend that initial therapy should consist of alternating steroids and an alkylating agent for 6 months. Recent observational studies showed that the anti-CD20 antibody rituximab may be effective in inducing remission. We designed a pilot multicentre randomised trial to inform the design of a larger trial testing the efficacy and safety of treatment with steroids and cyclophosphamide versus rituximab in patients with primary MN and heavy proteinuria (>3.5 g/24 hours).

Methods and analysis This pilot, open-label, two-parallel-arm, randomised clinical trial will enrol 70 patients with primary MN and heavy proteinuria. Patients will be randomised in a 1:1 ratio to either the intervention arm (rituximab) or the active comparator arm (corticosteroid/alkylating-agent therapy). The study will provide estimates of the probability of complete remission of proteinuria and risk of serious side effects at 12 months to inform the design of a larger trial. We will also assess the recruitment potential of each participating centre to address study feasibility.

Ethics and dissemination The trial received ethics approval from the local ethics boards. We will publish pilot data to inform the design of a larger clinical trial.

Trial registration numbers NCT03018535; 2011-006115-59.

INTRODUCTION

Primary membranous nephropathy (MN) is a common cause of nephrotic syndrome in adults. MN is an autoimmune disease mediated by the deposition of antibodies (usually IgG₄) produced by autoreactive B

Strengths and limitations of this study

- This is a pilot trial that will inform the design of a larger trial comparing rituximab versus standard care in MN with heavy proteinuria (>3.5 g/24 hours); being a pilot study, this study will not address intervention questions.
- Complete remission of proteinuria (primary endpoint) is a clinically important and more frequent outcome than kidney failure (final outcome). A trial looking at kidney failure for outcome may not be feasible.
- Recruitment potential of a trial comparing rituximab to cyclophosphamide is unknown; we will provide preliminary estimates and reasons for exclusion which may be used to increase the feasibility of a larger study.

cells directed against antigens located in the subepithelial area of the glomerular basement membrane. In 60%–70% of patients with primary MN, the antibodies are directed against the receptor1 of phospholipase A2 (PLA2R)^{1 2}; in 10% of patients, circulating antibodies against thrombospondin type-1 domain-containing 7A (THSD7A) have been detected.^{3 4} Additional autoantibodies of unknown clinical significance directed to podocyte neo-expressed cytoplasm proteins have been described, including aldose reductase, Mn-superoxide dismutase (SOD2) and alpha-enolase (alpha-ENO).⁵

The disease has heterogeneous outcomes. A complete or partial remission of proteinuria may develop spontaneously in 30%–50% of patients,^{6 7} but relapses may occur and a number of patients will continue to have proteinuria and progress slowly. In longer

follow-up studies (10 years or more), 35%–50% of the untreated patients may die or progress to end-stage kidney failure.^{8–11}

The pathogenetic background of MN suggests that there is a rationale to stop the production of these auto-antibodies with therapies targeting B cells. A number of different treatments have been used in MN, including corticosteroids, cyclophosphamide, calcineurin inhibitors and AdrenoCorticotropichormone (ACTH). Based on evidence from randomised controlled trials of the effect of alternating steroids and alkylating agent on disease remission and long-term progression, the 2012 KDIGO (Kidney Disease Improving Global Outcomes) guidelines recommend that initial therapy consist of a 6-month course of alternating monthly cycles steroids and an oral alkylating agent, preferably cyclophosphamide.¹² However, cyclophosphamide use increases the risk of myelotoxicity, infection and cancer. The ideal treatment of MN should target the B cells but display a more favourable safety profile.

In the last years, a therapy based on the anti-CD20 monoclonal antibody rituximab has been successfully used in MN.^{13–15} While a randomised clinical study testing whether treatment with rituximab is non-inferior to cyclosporine (second line therapy) in inducing long-term remission of proteinuria in patients with MN has recently been published,¹⁶ there is no head-to-head comparison in a randomised controlled trial between rituximab and gold standard treatment (cyclical corticosteroid/cyclophosphamide therapy).

For this, we planned a pilot multicentre randomised trial to inform the design of a larger trial testing the efficacy and safety of treatment with steroids and an alkylating agent versus rituximab in patients with primary MN and heavy proteinuria.

METHODS AND DESIGN

Design of the study

This is an open-label, two-parallel-arm, pilot randomised controlled trial assessing the recruitment potential of each participant centre and providing estimates of the possible benefits of rituximab versus cyclical corticosteroid/cyclophosphamide therapy in inducing disease remission. Estimates from this pilot will not address the clinical question of efficacy but will inform the feasibility and design of a larger trial. We will study complete remission of proteinuria at 12 months (primary objective) in patients with MN and heavy proteinuria, and other outcomes. After 3 months of therapy with renin-angiotensin system (RAS) inhibitors and reduction of blood pressure <130/80 mm Hg (run-in/conservative phase of the study), patients with estimated Glomerular Filtration Rate (GFR) ≥ 30 mL/min (Modification of Diet in Renal Disease (MDRD) formula) and proteinuria >3.5 g/24 hours will be eligible for the study. We will follow participants up to 36 months.

Study enrolment has been completed in December 2018.

Setting

Interventions will be administered in an inpatient setting at the following nephrology units: Montichiari (coordinating centre), Bari, Cagliari, Messina, Viterbo, Gorizia, Bologna, Bern, Novara, Modena, Milano. Each participant will be followed at the same institution where the induction treatment will be administered.

Eligibility criteria

Inclusion criteria include: patients aged 18 years and older; biopsy-proven diagnosis of MN performed within 24 months before enrolment; proteinuria >3.5 g/24 hours on three 24-hour urine collections (once a week for 3 weeks following the run-in phase); estimated GFR ≥ 30 mL/min/1.73 m² (MDRD formula); postmenopausal females, or females surgically sterile or practising a medically approved method of contraception; blood pressure <130/80 mm Hg; Idrossimetilglutaril-CoA (HMG-CoA) reductase inhibitor therapy; RAS inhibition therapy.

Exclusion criteria include serum creatinine >2.0 mg/dL or estimated GFR <30 mL/min/1.73 m²; previous treatment with rituximab, steroids, alkylating agents, calcineurin inhibitors, synthetic ACTH, Micofenolate Mofetil (MMF), azathioprine; presence of active infection; secondary cause of MN (eg, hepatitis B and C, Systemic Lupus Erythematosus (SLE), malignancies; testing for HIV, hepatitis B and C should have occurred <6 months prior to enrolment into the study); type 1 or 2 diabetes mellitus; pregnancy or nursing for safety reasons; renal vein thrombosis documented prior to entry by renal ultrasound (US) or CT scan.

Participant identification process

All patients affected by primary MN and proteinuria >3.5 g/24 hours followed by the participating institutions will be screened for eligibility. A local study coordinator will illustrate the project, deliver the information material (information sheet and informed consent form) and collect written informed consent. Participants will be told that they will be able to withdraw consent at any time.

Randomisation

Participants will be randomised 1:1 to the intervention or active comparator arm. A distant site with no clinical involvement in the trial will generate a randomisation list. Assignments will be notified electronically after obtaining signed consent. A local study coordinator responsible for recruitment will assign a unique participant study number and request assignment from the institution responsible for randomisation. An analyst from a distant site, not involved in patient care, where the randomisation lists have been generated and kept concealed from the clinical investigators, will communicate the allocation arm to the study coordinator.

Treatment arms

Intervention

Patients randomised to the intervention arm will receive two courses of the chimeric monoclonal anti-CD20

antibody rituximab at a dose of 1 g on days 1 and 15 without concomitant or subsequent drug therapies. Rituximab will be diluted in 500 mL of normal saline and administered at 9 mL/hour for the first 30 min; thereafter, the infusion rate will be doubled every 30 min up to a maximum of 72 mL/hour. In order to reduce common reactions, patients will receive a premedication with methylprednisolone (2 mg/kg infused in 30 intravenous diluted in 100 mL of normal saline), oral cetirizine (0.2 mg/kg) and oral paracetamol (15 mg/kg). Registered nurses will deliver the premedication and the intervention drug in the nephrology units of participating centres.

Active comparator

Patients randomised to active comparator will receive cyclical corticosteroid/cyclophosphamide therapy, consisting of three consecutive cycles of 2-month duration each (for a total of 6 months), one based on steroids and one based on cyclophosphamide. The first month of each 2-month cycle (months 1, 3 and 5) will begin with a 1 g pulse of intravenous methylprednisolone repeated daily for three consecutive days followed by oral methylprednisolone (0.4 mg/kg/day) or prednisone (0.5 mg/kg/day) for the remaining days of that month. In the second month of each 2-month cycle (months 2, 4 and 6), the steroid will be stopped and oral cyclophosphamide (2.0 mg/kg/day) will be given daily for that month.⁹

Relevant concomitant care

Any medications not listed in the exclusion criteria may be given at the discretion of the investigator. The investigator will record all concomitant medications taken by the participant in the appropriate section of the case report form.

Outcomes

The primary outcome measure is complete remission (proteinuria to ≤ 0.3 g/day) at 1 year.¹⁷ The secondary end-points will be change from baseline in proteinuria at 6, 12, 18, 24 and 36 months following treatment. We will estimate the probability of complete (primary outcome measure) or partial remission (reduction in proteinuria of at least 50% over the baseline and between 0.31 and 3.5 g/day) at 6, 12, 18, 24 and 36 months. Other outcomes summarised at the same time points will include eGFR and serum creatinine level (mg/dL). We will summarise data on time to relapse of heavy proteinuria, the levels of autoantibodies and their relation to therapy and proteinuria response in a subgroup of patients at baseline and 3 days, 1 month, 3 months, 6 months and 12 months after treatment. We will summarise data on serious side effects: death, life-threatening event, hospitalisation, disability, quality of life, permanent impairment or damage. We will also assess the recruitment potential of a trial comparing rituximab to cyclophosphamide in MN, and track reasons for exclusion (including those who may be eligible but refuse to participate).

Safety data

We will collect any untoward medical occurrence in the form of signs, symptoms, abnormal laboratory finding or disease that emerge or worsen relative to baseline (ie, present at the initial study visit).

Data collection methods and adherence during follow-up

Study visits will be done at baseline and after 3, 7, 14 days and 3, 6, 12, 24 and 36 months, unless complications or relapses occur. Determination of 24-hour proteinuria will be performed at baseline and after 1, 3, 6, 12, 24 and 36 months at a local laboratory. Complete blood count will be evaluated at baseline, after 3 and 7 days and at 3, 6, 12, 24 and 36 months. In patients undergoing cyclical therapy, during the administration of cyclophosphamide, monitoring blood cells will be performed every week, in order to prevent bone marrow toxicity. Kidney function, plasma proteins and cholesterol levels will be obtained at baseline and after 1, 3, 6, 12, 18, 24 and 36 months. Levels of anti-PLA2R (ELISA method), anti-THSD7A (IF assay) and anti-AR, anti-SOD2 and anti-alpha-ENO (ELISA method) auto-antibodies will be evaluated in a subgroup of patients at baseline and 3 days, 1 month, 3 months, 6 months and 12 months after treatment. In patients undergoing rituximab, lymphocyte subpopulations (for CD20 lymphocytes B count) will be evaluated at baseline, after 3 days and after 3, 6, 9, 12, 18, 24 and 36 months. Time schedule of enrolment, interventions assessments and visits for participants are shown in figure 1. A local study coordinator will maintain ongoing contact with the patients to collect potential adverse events also in order to minimise loss to follow-up/dropout.

Data management

The investigators will be responsible for recording study data in the case report form and entering study data in the electronic database prepared by the study coordinating centre. The data management and analysis centre at the University of Calgary will be responsible for data processing and analysis. Database will be locked once quality assurance procedures have been completed.

Statistical methods

Analyses will be mainly descriptive and will focus on CI estimation. We will use standard statistical methods to summarise the sample characteristics overall and by arm assignment, using statistics for quantitative (mean and SD) and qualitative (frequencies) data as appropriate. We will do comparative analysis acknowledging the nature and purpose of this pilot study. Given the relatively small study size, its feasibility objective and the lack of a power calculation, we will treat any comparative analyses as preliminary and interpret them with caution. We expect that there could be imbalance in baseline covariates which would need adjustment in the analyses, and that the CIs will likely to be imprecise regardless of statistical testing results. Following this approach, we will consider the following analyses: logistic regression to compare

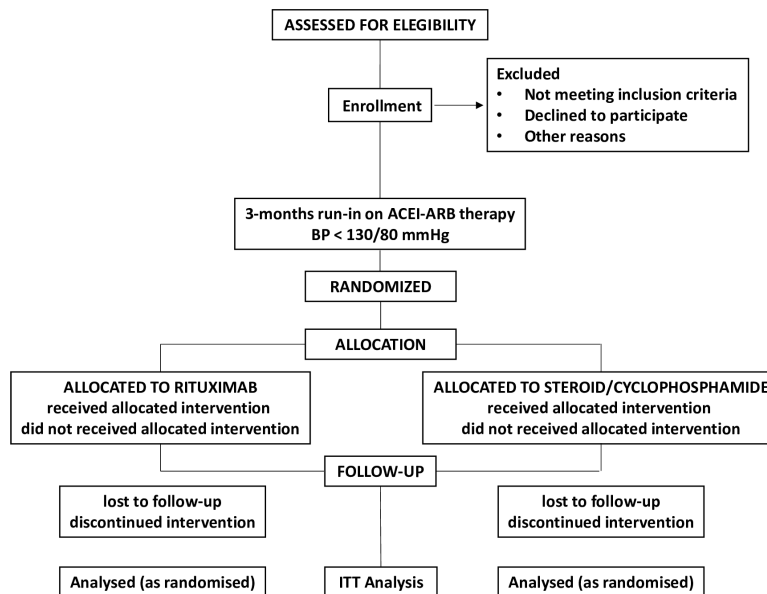


Figure 1 Schematic view of trial design. BP, blood pressure; ITT, intention to treat. ACEI-ARB, Angiotensin Covering Enzyme Inhibitor-Angiotensin II receptor Blockers.

the probability of achieving complete remission at 12 months and other binary outcomes, and methods for continuous, count or survival data for time to event analyses (secondary outcome). In all analyses, we will use an intention-to-treat approach, whereby participants will be analysed as randomised regardless of protocol adherence. We will replace missing data in two ways: first carrying forward the last available measure; second, assuming the worst-case scenario by considering the missing data in the active comparator group as successes and missing data in the active intervention as failures.

Sample size

The main reason for conducting the present pilot study is to gather preliminary outcome data for the primary outcome measure (disease remission) in order to perform a sample size calculation for a larger trial.¹⁸ To estimate the probability of achieving complete remission in the two treatment groups, we will include 35 participants per arm, following a general rule of thumb (ie, at least 30 statistical unit per parameter).¹⁸ We will follow participants for at least 1 year. We expect that each centre would enrol between 6 and 8 participants over 2 years. This pilot study will provide preliminary effect estimate to inform the design of a larger study, as it will not be powered to address intervention questions.

Patient and public involvement

Neither patients or the public were directly involved in the study design or conduct of the study. No plans were established a priori for sharing the results of the study with participants.

Study termination

Participants will be informed that they have the right to withdraw from the study at any time, without prejudice to their medical care. Any withdrawal will be fully

documented in the case report form. Follow-up will be considered complete when the participant has completed all study procedures and assessments up to the month-12 visit (primary end-point). Termination of receipt of study drug for a patient will be mandatory in the following situations: pregnancy, significant worsening of renal function (defined as doubling of serum creatinine), onset of malignancy, serious hypersensitivity or allergic reaction, any serious adverse events, serious intercurrent illness, administrative reasons, or investigator's or participant's request.

The study will continue from the enrolment of the first participant until 1 year from the enrolment of the last participant. Participants enrolled earlier will be followed for a longer period of time; the last participant will be followed for 1 year. Participant's participation in the treatment phase of the study will be stopped if any of the event mentioned above occurs. In these situations, patient's participation in the study will be maintained for follow-up if the participant agrees to be followed for safety and outcome measures. We have no plans for interim analyses or prespecified stopping rules. The Sponsor (Spedali Civili Hospital of Brescia) may temporarily or permanently discontinue the study for safety, ethical, compliance or other reasons; in this case, the main investigator will be responsible for promptly informing the Independent Ethics Committee.

Study monitoring

The safety and monitoring board (Board of Safety; BoSa) at the Spedali Civili di Brescia Hospital will be responsible for study monitoring. The BoSa is an independent team with functional autonomy, specifically created for no profit studies, consisting of qualified personnel expert in clinical research methodology and not directly involved in the clinical study. The frequency of monitoring visits

will be determined by the site enrolment rate. On study completion, the study monitor will visit the site to conduct a study termination visit.

DISSEMINATION

The completed randomised controlled trial study will be summarised in a final report accurately presenting the study objectives, methods, results, limitations of the study and interpretation of findings. The authors of this study protocol will inform the contributing investigators in advance about any plans to publish or present data. Any publication and presentation of the results (abstract in journals or newspapers, oral presentations, etc), either in whole or in part, by investigators or their representatives will require presubmission review by the authors of this study protocol and all coauthors.

DISCUSSION

This is the first step towards a clinical trial comparing the effectiveness of rituximab versus gold standard therapy in MN with heavy proteinuria. Being a pilot study, this study will address feasibility and design questions, as opposed to intervention questions. This pilot randomised trial is needed to provide preliminary data on outcome frequencies following each treatment strategy in comparable groups (ie, randomised groups), including benefits and harms.

A study with sample size large enough to ensure sufficient power is not feasible. Baseline probabilities to achieve disease remission with standard therapy are based on estimates obtained decades ago, and we need more recent estimates on recruitment potential. We also do not have estimates of effects in comparable groups to inform power analysis for a larger study of efficacy. Recruitment may be challenging for the low incidence of MN, the high cost of rituximab (in the absence of pharma support) and the large off-label use of the drug by nephrologists.

This pilot study has strengths. We selected a high-risk population (MN with heavy proteinuria) and designed methods to reduce bias (randomised design, steps to ensure complete follow-up and blinding of outcome adjudicators to treatment assignment). Only centres with clinical and research expertise in nephrology were engaged in the study. A careful collection of safety data has been implemented.

The study also has limitations. First, interventions are not blinded. Second, the primary end-point is a surrogate end-point rather than a clinically meaningful end-point. However, the laboratory-based measures we adopted to define disease remission are objective and predict more distant outcomes, particularly progression of kidney disease to kidney failure, usually observed after 10–20 years of treatment exposure. While a very large multi-national trial will be necessary to study these hard end-points, remission of proteinuria is an important outcome for the patients with MN.^{19 20}

In summary, this study addresses a study design question that is relevant to improve outcomes of adults with MN and heavy proteinuria. Results from this study will be key to the design of a larger trial, if feasible.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Ethics approval for the study has been received from Local Independent Ethics Committees (Ethics Committees of Brescia, Bari, Messina, Cagliari, Bern, Gorizia, Milano, Modena, Novara; the ethic committees approval number at the coordinating center of Brescia was NP 1063). We also obtained approval from the Italian Drug Agency (Agenzia Italiana del Farmaco). Where required by local regulations, the Sponsor will be responsible for ensuring Independent Ethics Committee approval of the study.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

- 1 Beck LH Jr., 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.
- 2 Ronco P, Debiec H. Antigen identification in membranous nephropathy moves toward targeted monitoring and new therapy. *J Am Soc Nephrol* 2010;21:564–9.
- 3 Tomas NM, Beck LH, Meyer-Schwesinger C, *et al*. Thrombospondin type-1 domain-containing 7A in idiopathic membranous nephropathy. *N Engl J Med* 2014;371:2277–87.



- 4 Beck LH. PLA2R and THSD7A: disparate paths to the same disease? *J Am Soc Nephrol* 2017;28:2579–89.
- 5 Murtas C, Bruschi M, Candiano G, *et al*. Coexistence of different circulating anti-podocyte antibodies in membranous nephropathy. *Clin J Am Soc Nephrol* 2012;7:1394–400.
- 6 Polanco N, Gutiérrez E, Covarsí A, *et al*. Spontaneous remission of nephrotic syndrome in idiopathic membranous nephropathy. *J Am Soc Nephrol* 2010;21:697–704.
- 7 Kanigicherla DAK, Short CD, Roberts SA, *et al*. Long-term outcomes of persistent disease and relapse in primary membranous nephropathy. *Nephrol Dial Transplant* 2016;31:2108–14.
- 8 Hogan SL, Muller KE, Jennette JC, *et al*. A review of therapeutic studies of idiopathic membranous glomerulopathy. *Am J Kidney Dis* 1995;25:862–75.
- 9 Ponticelli C, Zucchelli P, Passerini P, *et al*. A 10-year follow-up of a randomized study with methylprednisolone and Chlorambucil in membranous nephropathy. *Kidney Int* 1995;48:1600–4.
- 10 du Buf-Vereijken PWG, Branten AJW, Wetzels JFM. Idiopathic membranous nephropathy: outline and rationale of a treatment strategy. *Am J Kidney Dis* 2005;46:1012–29.
- 11 Jha V, Ganguli A, Saha TK, *et al*. A randomized, controlled trial of steroids and cyclophosphamide in adults with nephrotic syndrome caused by idiopathic membranous nephropathy. *J Am Soc Nephrol* 2007;18:1899–904.
- 12 KDIGO. KDIGO clinical practice guideline for glomerulonephritis. *Kidney Int* 2012;2S:1–274.
- 13 Fervenza FC, Cosio FG, Erickson SB, *et al*. Rituximab treatment of idiopathic membranous nephropathy. *Kidney Int* 2008;73:117–25.
- 14 Ruggenti P, Cravedi P, Chianca A, *et al*. Rituximab in idiopathic membranous nephropathy. *J Am Soc Nephrol* 2012;23:1416–25.
- 15 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.
- 16 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.
- 17 Thompson A, Cattran DC, Blank M, *et al*. Complete and partial remission as surrogate end points in membranous nephropathy. *JASN* 2015;26:2930–7.
- 18 Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. *J Eval Clin Pract* 2004;10:307–12.
- 19 Ponticelli C, Passerini P. Can prognostic factors assist therapeutic decisions in idiopathic membranous nephropathy? *J Nephrol* 2010;23:156–63.
- 20 Cattran DC, Kim ED, Reich H, *et al*. Membranous nephropathy: quantifying remission duration on outcome. *J Am Soc Nephrol* 2017;28:995–1003.