

# A comparison of rituximab and modified Ponticelli regimen (alternating steroids and cyclophosphamide) for treatment of primary membranous nephropathy

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<b>Registration date</b> 15/04/2022	<b>Overall study status</b> Completed	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
<b>Last Edited</b> 23/05/2022	<b>Condition category</b> Urological and Genital Diseases	<input type="checkbox"/> Individual participant data <input type="checkbox"/> Record updated in last year

## Plain English summary of protocol

### Background and study aims

Membranous nephropathy (MN) is one of the most common causes of nephrotic syndrome in adults, which is characterised by the presence of protein in the urine. There are two treatment options for this disease, both of which aim to achieve remission – the reduction of protein excretion in the urine. The modified Ponticelli regimen with cyclical steroids and cyclophosphamide is used as first-line treatment but is associated with several adverse effects such as infections, infertility and low blood cell counts. Rituximab has emerged as a newer option for treatment but it has not been compared against the modified Ponticelli regimen in head-to-head trials. The aim of this study is to assess the effectiveness of rituximab versus the modified Ponticelli regimen in inducing remission in MN.

### Who can participate?

Patients aged over 18 years with primary membranous nephropathy with more than 3.5 g protein excretion in urine

### What does the study involve?

Some patients can have spontaneous resolution of protein excretion in urine. Therefore all patients with primary MN will be given a 3-month observation period to watch for spontaneous resolution. Patients with severe symptoms or those with persistent protein excretion will be randomly allocated into one of the two groups and will receive either rituximab or the modified Ponticelli regimen. The rituximab group will receive two injections of rituximab on days 1 and 15. Their CD19 level (which indicates their B cell levels) will be checked at 1 and 6 months. B cells are suppressed by rituximab and a low level indicates that the rituximab was effective at suppressing the B cells. The modified Ponticelli regimen consists of alternating months of steroids and cytotoxic agents for a total of 6 months. Steroids are given in months 1, 3 and 5 which will include three injections of methylprednisolone on days 1-3 followed by prednisolone tablets. Cyclophosphamide tablets will be given in months 2, 4 and 6.

What are the possible benefits and risks of participating?

The participants would receive two treatments that are routinely being used for this disease. All drugs used in this study have an established role in treatment of MN and all are associated with specific side effects. Steroids can cause weight gain, high blood sugar, bone weakness, muscle wasting and an increased risk of infections. Cyclophosphamide can cause infections, infertility, bladder problems, low blood counts as well as cancer. Rituximab is typically associated with reactions during infusion including flushing, itching and sometimes low blood pressure.

Where is the study run from?

Muljibhai Patel Urological Hospital, Nadiad (India)

When is the study starting and how long is it expected to run for?

June 2018 to June 2021

Who is funding the study?

Muljibhai Patel Society for Research in Nephrology, Nadiad, Gujarat (India)

Who is the main contact?

Dr Sandhya Suresh

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## Contact information

### Type(s)

Principal Investigator

### Contact name

Dr Sandhya Suresh

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## Additional identifiers

### EudraCT/CTIS number

Nil known

### IRAS number

### ClinicalTrials.gov number

Nil known

## Secondary identifying numbers

525

# Study information

## Scientific Title

INDian CONtrolled trial of RITuximab vs Modified Ponticelli regimen for treatment of primary membranous nephropathy

## Acronym

INCORIT-M

## Study objectives

Rituximab is non-inferior to modified Ponticelli regimen in inducing remission (complete or partial) at 6 months in patients with primary membranous nephropathy (PMN).

## Ethics approval required

Old ethics approval format

## Ethics approval(s)

Approved 16/08/2018, Muljibhai Patel Society for Research in Nephro-Urology Ethics Committee (Muljibhai Patel Urological Hospital, Dr. Virendra Desai Road, Nadiad - 387001, Gujarat, India; +91 (0)268 2520330; info@mpuh.org), ref: EC/525/2018

## Study design

Interventional randomized controlled trial

## Primary study design

Interventional

## Secondary study design

Randomised controlled trial

## Study setting(s)

Hospital

## Study type(s)

Treatment

## Participant information sheet

See additional files

## Health condition(s) or problem(s) studied

Primary membranous nephropathy

## Interventions

Intervention arm - Rituximab injection 500mg IV given on days 1 and 15

Control arm - Modified Ponticelli regimen (cyclical steroids/cyclophosphamide for 6 months)

Months 1, 3 and 5: 1 g IV methylprednisolone daily (Days 1–3), then oral prednisolone (0.5 mg/kg/day) for 27 days (Days 4–30).

Months 2, 4 and 6: Oral cyclophosphamide (2.0 mg/kg/day) for 30 days.

The researchers used a random number-producing algorithm for block randomisation using sealed envelope online software. Randomisation and treatment allocation were then done by the primary investigator using this randomisation list in a concealed manner in a 1:1 manner using sealed envelopes.

## **Intervention Type**

Drug

## **Phase**

Not Applicable

## **Drug/device/biological/vaccine name(s)**

Rituximab, cyclophosphamide, steroids

## **Primary outcome measure**

The proportion of patients reaching complete or partial remission at 6 months, defined according to the 2012 KDIGO guidelines as follows:

Complete remission: a reduction of proteinuria to  $<0.3$  g/24 h (uPCR  $<300$  mg/g) with normal serum albumin concentration and normal serum creatinine

Partial remission: a reduction of proteinuria to  $<3.5$  g/day (uPCR  $<3500$  mg/g) and a 50% or greater reduction from peak values accompanied by an improvement or normalisation of serum albumin concentration and stable serum creatinine

1. Proteinuria measured using the urine protein creatinine ratio (using Pyrogallol red and Jaffe kinetic reaction test methodology) at baseline and 6 months

2. Serum albumin concentration measured using the Bromocresol green test at baseline and 6 months

3. Serum creatinine measured using the Jaffe kinetic test at baseline and 6 months

## **Secondary outcome measures**

1. The proportion of patients reaching either complete or partial remission at 12 months after therapy (measured as per the primary outcome measure)

2. The proportion of patients with relapsing nephrotic syndrome measured among patients who previously underwent partial remission or complete remission at any time during the study period as determined by proteinuria (measured as per the primary outcome measure)

3. The time to relapse of nephrotic syndrome after initial remission as determined by proteinuria (measured as per the primary outcome measure)

4. Serum anti-PLA2R levels measured using EUROIMMUN Anti-PLA2R ELISA (quantitative method) before treatment and at 6 and 12 months post-therapy

5. Efficacy outcome variables during the study period including the trend of the magnitude of proteinuria, serum albumin, serum proteins, serum creatinine and estimated GFR (measured by the CKD-EPI formula) at baseline, 6 and 12 months

6. Proportion of patients developing the following adverse events during the study period, as determined by clinical evaluation including patient interviews and patient notes and lab investigations:

6.1. Infections: symptoms such as fever, cough, dysuria; signs of infection such as fever, respiratory system signs including rales/crepitations, skin lesions of Tinea; lab investigations including total white blood cell (WBC) count (by automated cell counter machine), urine routine

analysis (using Multistix and microscopic examination of urine sediment after centrifugation), chest X-ray

6.2. Leucopenia determined by total WBC count (by automated cell counter machine)

6.3. Infusion reaction determined by clinical evaluation

6.4. Acute kidney injury after the start of therapy determined by measuring serum creatinine using the Jaffe kinetic reaction

### **Overall study start date**

06/06/2018

### **Completion date**

30/06/2021

## **Eligibility**

### **Key inclusion criteria**

1. Patients older than 18 years who provide written informed consent.

2. Biopsy-proven primary MN within 2 years of enrolment with nephrotic range proteinuria denoted by 24-hour urine protein  $\geq 3.5$  g or UPCR (urine protein:creatinine ratio)  $\geq 3500$  mg/g as well as the following:

2.1. Serology or biopsy positive for AntiPLA2R

2.2. Serology or biopsy negative for AntiPLA2R and secondary causes ruled out

2.3. Evaluation for secondary causes was done in all patients, even in patients who were positive for Anti-PLA2R antibodies on serology or PLA2R antigen on biopsy because these have also been found in some cases of secondary MN

3. Estimated GFR  $\geq 30$  ml/min/1.73m<sup>2</sup>. The CKD-EPI creatinine equation was used for the calculation of the eGFR

4. Treatment with an ACEI or ARB for at least 3 months before enrolment

### **Participant type(s)**

Patient

### **Age group**

Adult

### **Lower age limit**

18 Years

### **Sex**

Both

### **Target number of participants**

By sample size estimation, the trial required 132 patients in each arm. This trial was done as a short-term pilot study over a period of 3 years from 2018 to 2021

### **Total final enrolment**

68

### **Key exclusion criteria**

1. Secondary MN
2. Active serious infections
3. Pregnant women
4. Suspected or known hypersensitivity to either interventional drug
5. Patients with persistently low estimated GFR  $<30 \text{ ml/min/1.73m}^2$  in the absence of acute causes such as acute tubular injury, renal vein thrombosis and others

**Date of first enrolment**

26/08/2018

**Date of final enrolment**

03/10/2020

## **Locations**

**Countries of recruitment**

India

**Study participating centre**

**Muljibhai Patel Urological Hospital**

Dr. Virendra Desai Road

Nadiad

India

387001

## **Sponsor information**

**Organisation**

Muljibhai Patel Urological Hospital

**Sponsor details**

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**Sponsor type**

Hospital/treatment centre

**Website**

<http://www.mpuh.org/>

ROR

<https://ror.org/059h1d250>

## Funder(s)

### Funder type

Research organisation

### Funder Name

Muljibhai Patel Society for Research in Nephro-Urology

## Results and Publications

### Publication and dissemination plan

Planned publication in a high-impact peer-reviewed journal

### Intention to publish date

30/06/2022

### Individual participant data (IPD) sharing plan

The datasets generated and/or analysed during the current study will be published as a supplement to the subsequent results publication

### IPD sharing plan summary

Published as a supplement to the results publication

### Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">Participant information sheet</a>			05/04/2022	No	Yes
<a href="#">Protocol file</a>			12/04/2022	No	No