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Clinical profile, response and outcome of various immunosuppressive regimens used for treatment of idiopathic membranous nephropathy—a retrospective cohort study

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Abstract

Background: Membranous nephropathy (MN) is a glomerular disease commonly presenting as a nephrotic syndrome in adults. Various immunosuppressive medications have been used in the treatment of the same with different levels of success. Hence we have undertaken a retrospective analysis of "Clinical profile, response and outcome of various immunosuppressive regimens used for treatment of membranous nephropathy" to determine the efficacy of each treatment regimen. **Methods**: A retrospective observational cohort study was conducted in a single tertiary care centre in southern India. Patients with proven primary membranous nephropathy from 2010 to June 2020 with a minimum duration of follow-up of one year and treated with different immunosuppressive regimens were included in the study. **Results**: The total number of patients in the study was 129. Mean age of onset was 39 years with a follow-up of a minimum of 1 year and a maximum of 10 years, the mean follow-up being 3 years. 46.5% achieved complete remission, 23.3% had partial remission and 10.9% had relapse, doubling of serum creatinine was seen in 5 (3.9%) and chronic kidney failure requiring kidney replacement therapy in 3 (2.3%) respectively. Presence of interstitial fibrosis and tubular atrophy (IFTA) had a significant correlation *p*-value 0.02, patients with IFTA less than 30% performed the best with 54/71 patients (60%) achieving remission. **Conclusions**: Hypertension and IFTA at presentation were predictors for worse outcomes. modified Ponticelli, followed by rituximab, were the most effective in inducing and maintaining remission.

Keywords: Glomerular diseases; Membranous nephropathy; Immunosuppression; Outcome

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Introduction

Membranous nephropathy (MN) is a widespread glomerular disease among all age groups. In the majority of cases, there is no underlying cause (primary MN); in rare cases, it may be associated with other diseases such as systemic lupus erythematosus, viral infections or malignancies.

Many different immunosuppressive combinations have been tried to induce remission in membranous nephropathy patients, these include the modified Ponticelli regimen (6 months of alternating pulse steroids of 1 gram (gm) intravenous methyl prednisolone for 3 days followed by oral steroid dose of 0.5 milligram (mg) per kilogram (kg) per day for 27 days on 1, 3 and 5 months and cyclophosphamide at 2 mg per kg per day on 2, 4 and 6 months, calcineurin inhibitors (CNI), mycophenolate mofetil (MMF) and rituximab.

MN has an intermediate prognostic course with about one-third of patients achieving spontaneous remission, one-third remaining stable and one-third having progressive disease not responding to treatment. Early immunosuppression treatment has been recommended to achieve remission of proteinuria and to prevent kidney dysfunction. We have undertaken a retrospective analysis to study the clinical profile, response and outcomes of various treatment protocols among patients with biopsy-proven primary membranous nephropathy attending a single tertiary care centre in South India.

Methodology

This is a record-based retrospective observational analytical study conducted on patients with biopsy-proven primary membranous nephropathy from 2010 to June 2020 with a minimum duration of follow-up of one year [1].

General supportive measures which were initiated in all patients of primary membranous nephropathy attending the centre included diuretics to control edema and maintenance of adequate nutrition, with dietary sodium and protein restriction, blood pressure control, minimization of proteinuria with renin-angiotensin system inhibition, treatment of dyslipidemia, and, in select patients (depending on their level of proteinuria and risk of bleeding) anticoagulation therapy was given with warfarin or aspirin with regular monitoring of their prothrombin time and international normalized ratio (INR).

Various regimens that were used for treatment of membranous nephropathy based on risk stratification depending on proteinuria and estimated glomerular filtration rate (eGFR) on presentation and after 6 months of conservative therapy with renin angiotensin inhibitors like angiotensin convertase enzyme inhibitor (ACE-I) or angiotensin receptor blockade (ARB') were modified Ponticelli regimen which was—1 gram intravenous methyl prednisolone for 3 days followed by oral steroid dose of 0.5 mg per kg per day for 27 days on 1, 3 and 5 months and cyclophosphamide at 2 mg per kg per day on 2, 4 and 6 months. Calcineurin inhibitor (CNI)-tacrolimus 0.05–0.075 mg/kg daily in two divided doses adjusted to level of 3–5 mg/for 12–18 months and tapered slowly. Rituximab was given either weekly for 4 weeks as doses of 375 mg/m^2 intravenously (iv) or, as two iv doses of 1000 mg 375 mg/m^2, 15 days apart. Effectiveness/response was measured via decline in proteinuria. 6 monthly maintenance dose of rituximab 500 mg was given based on patient's Cluster of Differentiation (CD) 19/20 levels with aim to maintain these levels at less than 1%.

Combination therapy was started if the patient received 1 cycle modified Ponticelli regimen and did not respond after a period of 6 months, they were started on various combination therapies including CNI (tacrolimus) 0.05–0.075 mg/kg daily in two divided doses adjusted to level of 3–5 mg/for 12–18 months or mycophenolate mofetil (MMF) at 1.5–2 gm per day in 2 divided doses for 12 months or rituximab at weekly for 4 weeks as doses of 375 mg/m^2 intravenously (iv) or, as two iv doses of 1000 mg 15 days apart and 6 monthly maintenance dose of 500 mg.

All patients of primary membranous nephropathy on various treatment protocols were registered and a follow-up visit was scheduled in the glomerular clinic on monthly basis. The following parameters were recorded on each visit: Spot urine protein/creatinine ratio/24 hours urine for proteinuria, complete blood picture, kidney & liver function tests, lipid profile. These were then analysed at 1, 3, 6, 12, 18, 36, 48 and 60 months to record the study outcome. Adverse effects were classified from grade 1–5 based on the Common Terminology Criteria for Adverse Events Grade and clinical severity (CTCAE) [2] and were noted during regular visits. All immunosuppressive drugs were tapered down or discontinued gradually in all patients as per clinical response.

The study outcomes were defined as per Kidney Disease Improving Global Outcomes (KDIGO) guidelines and included time to achieve remission (complete/partial), non-responders, doubling of serum creatinine, other adverse events and progression to end-stage kidney disease. Complete response in our study was defined as 24-hour urine protein as less than 500 mg/day. Partial response was defined as more than 50% reduction of proteinuria from baseline and between 500 mg and 3.5 gm/day with stable eGFR. No response was defined as less than 50% reduction in proteinuria from baseline. Relapse was defined as recurrence of proteinuria of more than 3.5 gm/day after achieving complete/partial remission. Doubling of serum creatinine was defined as decrease in eGFR by more than 50%. Chronic kidney failure was defined as an eGFR of less than 15 mL/min or requirement for dialysis/transplant.

All statistical analysis was done with IBM SPSS version 20.0 for Windows® (Armonk, NY, USA). An unpaired *t*-test or Pearson's test was used for comparing values with Gaussian distribution, and Mann-Whitney (Wilcoxon rank) test or Spearman's test was used for continuous variables without normal distribution. Gaussian distribution was determined using the Kolmogorov-Smirnov test. Categorical data were compared using chi-square test. Logistic regression analysis was done to define factors determining response to treatment. *p*-values were 2 tailed and *p*-value of < 0.05 was considered significant.

Results

Retrospective records of 129 patients were retrieved and analysed. The demographic profile of the patients, along with the biochemical parameters at presentation, was recorded and described in Table 1.

Eighteen patients (14%) with non-nephrotic range proteinuria were managed conservatively with only ACE-I and ARBs. 58 (45%) of the patients were started on modified Ponticelli regimen, and 7 (5.4%) were started on *de novo* rituximab. For the rest of the patients, 46 (35.7%) were started on "(combination therapy, which mainly included one cycle of modified Ponticelli, and if no response was observed, it was followed by any other immunosuppression that is either mycophenolate mofetil (MMF), calcineurin inhibitors (CNI) or rituximab)". Five patients following with us who had started treatment with CNI, MMF or rituximab from the onset.

The complications secondary to the treatment therapy were seen in 48 patients (37.2%) and were graded from 1–5 based on the CTCAE grading. Grade 1 mild asymptomatic with no intervention was seen in 9 patients who presented with steroid induced cushingoid facies. Grade 2 moderate requiring minimal intervention was seen in 16 patients including upper respiratory tract infection in 4 patients, lower respiratory tract infection in 3 patients, herpes zoster in 6 patients, gastritis in 2 patients and esophagitis in 1 patient. Grade 3 severe complication requiring hospitalization was seen in 19 patients including cellulitis in 11 patients, tuberculosis in 4 patients and Covid 19 infection in 4 patients. Grade 4 life threatening complications were seen in 2 patients in form of severe pancreatitis requiring hospitalization and intensive care management and grade 5 death related to adverse event was seen in 2 patients which were due to acute

Table 1. Baseline characteristics of patients.

Variable at presentation	N = 129
Age at onset (yr) Median (IQR)	39 (30–50)
Male:Female	85:44
Duration of illness (mon) Median (IQR)	3.0 (2.0–5.7)
Duration of follow up (mon) Median (IQR)	24.0 (12.0–48.0)
Serum creatinine (mg/dL) Median (IQR)	1.1 (0.8–1.6)
Estimated Glomerular filtration Rate (eGFR) (mL/min) Median (IQR)	84.0 (50.0–96.5)
Serum hemoglobin (gm/dL) Median (IQR)	11.6 (10.0–12.7)
Serum. protein (gm/dL) Median (IQR)	5.2 (4.2–5.9)
Serum albumin (gm/dL) Median (IQR)	2.8 (2.0–3.3)
24 hour proteinuria (gm/day) Median (IQR)	4.1 (2.9–6.2)
Serum total cholesterol (mg/dL) Median (IQR)	218.0 (191.0–306.0)
Serum low density lipid (mg/dL) Median (IQR)	146.0 (115.0–204.0)
Serum triglycerides (mg/dL) Median (IQR)	152.0 (107.5–210.0)
Serum thyroid stimulating hormone (mIU/mL) Median (IQR)	3.0 (1.8–4.8)
Comorbidities present at the time of diagnosis	
Coronary artery disease (N) (%)	3 (2.32)
Diabetes mellitus (N) (%)	13 (10.07)
Hypothyroid (N) (%)	23 (17.82)
Systemic Hypertension (N) (%)	30 (23.25)
No comorbidities (N) (%)	50 (38.75)
Light Microscopy at the time of presentation	
Membranous (N) (%)	107 (82.94)
Membranous With Crescents (N) (%)	2 (1.55)
Membranous With Focal segmental glomerulosclerosis (N) (%)	20 (15.50)
NIL Interstitial fibrosis and tubular atrophy (IFTA) (N) (%)	71 (55.03)
IFTA <30% (N) (%)	44 (34.10)
IFTA >30% (N) (%)	14 (10.85)
Serum Anti Phospholipase A2 Receptor Antibody (PLA2R) Median (IQR)	129.0 (62.5–216.9)

IQR: Interquartile range; N: Number of patients.

myocardial infarction and multi organ dysfunction secondary to Covid 19 infection. The majority, 81 (62.8%), did not have any complications after receiving the prescribed treatment. After receiving the treatment, the patients were followed up for up to 5 years (60 months), with minimum follow-up being 1 year and mean follow-up being 33.25 months (2 years and 9 months), and they were categorised into the following based on their response: 60 (46.5%) patients had a complete remission, 30 (23.3%) had partial remission and 14 (10.9%) relapsed with nephrotic range of proteinuria. Doubling of baseline creatinine and requirement of kidney replacement therapy was seen in 5 (3.9%) and 3 (2.3%), respectively.

The number of, patients who were lost to follow up were 15 (11.6%).

The various long-term outcomes in different treatment protocols were compared for all patients including lost to follow-up patients as a part of intention to treat analysis as seen in Table 2.

In our study, out of the 129 patients, 90 (69.8%) achieved remission (complete plus partial), whereas 39 (30.2%) did not achieve remission. Rituximab therapy given at onset showed the best results, with complete remission seen in 6/7 (85.7%).

Table 2. Treatment regimen and their result among the study population.

Result	Treatment				Total
	Conservative[a]	Ponticelli[b]	Combination[c]	Rituximab	
Complete Remission, N (%)	4 (22.2%)	19 (32.8%)	31 (67.4%)	6 (85.7%)	60 (46.5%)
Partial Remission, N (%)	5 (27.8%)	15 (25.9%)	10 (21.7%)	0	30 (23.3%)
Relapse, N (%)	2 (11.1%)	9 (15.5%)	2 (4.3%)	1 (14.3%)	14 (10.9%)
Doubling of Serum Creatinine, N (%)	1 (5.6%)	4 (6.9%)	0	0	5 (3.9%)
Chronic kidney failure, N (%)	0	1 (1.7%)	2 (4.3%)	0	3 (2.3%)
Death, N (%)	0	2 (3.4%)	0	0	2 (1.6%)
Lost to follow up, N (%)	6 (33.3%)	8 (13.8%)	1 (2.2%)	0	15 (11.6%)
Total, N (%)	18 (100.0%)	58 (100.0%)	46 (100.0%)	7 (100.0%)	129 (100.0%)

Chi square = 35.657, p value = 0.008 (S) Confidence interval (31.78–40.64).
Conservative[a]: conservative therapy; Ponticelli[b]: modified Ponticelli therapy; Combination[c]: combination therapy; (a, b, c: details in methodology section); N: Number of patients.

This was followed by combination therapy 31/46 (67.4%). The modified Ponticelli regimen for one cycle showed a complete remission in 19/58 (32%) and partial remission in 15/38 (25.9%). Maximum number of relapses 9/58 (15.5%), doubling of serum creatinine 4/58 (6.9%), lost to follow-up 8/58 (13.8%), and death 2/58 (3.4%) was also seen with the Ponticelli regimen. Chronic kidney failure requiring kidney replacement therapy was seen maximally in resistant cases requiring combination therapy 2/46 (4.3%).

The baseline variables and whether they play any role in determining remission (complete/partial) were studied in Table 3.

In our study, it was seen that having chronic hypertension as a comorbid condition at the time of diagnosis was associated with a worse prognosis, with 74/90 (82.2%) who achieved remission were non-hypertensive and only 16/90 (17.8%) chronic hypertensive patients achieved remission. This was statistically significant, with *p*-value being 0.025. The presence of interstitial fibrosis and tubular atrophy (IFTA) had a significant correlation *p*-value of 0.02, with 60% patients with IFTA less than 30, achieving remission.

Discussion

Our study had a complete remission rate of 22.2%, which was comparable to the studies by Dahan *et al.* [3] and Polenakovik *et al.* [4], with rates of 20 and 21%, respectively, and lower than that of Vivekanand Jha *et al.* [5] (72.3%). This, however, may be due to the natural course of membranous nephropathy, which is said to resolve spontaneously in one-third of patients without any treatment. Doubling of serum creatinine and progression to chronic kidney failure was seen in 70% of the patients in Polenakovik *et al.* [4] and 35% in the study by Vivekanand Jha *et al.* [5] demonstrating the harmful exposure of long-standing proteinuria to the kidney's structure and function. Since it was a retrospective study, there was attrition of 33% patients were on conservative treatment.

Our study had a remission rate of 58.7% (complete plus partial), which was similar to the original Ponticelli (61%) and R Ram *et al.* [6, 7] (58.5%) however it was lower as compared to Ramachandran *et al.* [8], Vivekanand Jha *et al.* [5] and Polenakovik *et al.* [4] at 88.2%,72.3% and 76.8% respectively. One reason is maybe the patients enrolled in our study had lower eGFR as compared to the above studies.

As compared to other studies, our study had more patients who were lost to follow-up owing to the retrospective nature and duration period of the study (10 years).

Combination therapy in the form of rituximab (375 mg/m^2 weekly for 4 weeks or 1gm in two divided doses 15 days apart) or CNI (tacrolimus 0.05–0.75 mg/kg in 2 divided doses) or MMF 1.5–2 gm in two divided doses twice daily or a second cycle of modified Ponticelli regimen was started in treatment-resistant cases based on the treating physician discretion. As seen in our study and the study by Ramachandran *et al.* [8]. The remission rates in combination therapy are more than 89%, thus proving an effective way of treating resistant cases.

The efficacy of rituximab has been studied in various RCTs. Like the GEMRITUX trial [9], after 23 months of follow-up, the remission rate was 66% in patients treated with rituximab and 45% in those who received conservative treatment. In the MENTOR trial [9], remission at 12 months after withdrawal of therapy was 60% in the rituximab group versus 20% in the other group. In the STARMEN trial [10] the remission rate was 58% in the rituximab group at 24 months. In comparison, to these studies, Dahan *et al.* [3] and our study showed a remission rate of 64.9% and 85.7%, respectively. Our study had a very small number of patients who were started on *de novo* rituximab, the majority of our cases received rituximab as a rescue/combination therapy in treatment-resistant cases.

In our study, a significant correlation was found between hypertension at presentation with fewer patients who are hypertensive achieving remission versus people who are not suffering from the same (82% and 17.8%), respectively, with a significant *p*-value of 0.025. This finding can be explained by the fact that hypertension is a chronic condition and can lead to kidney damage and secondary FSGS. Hence leading to the

Table 3. Baseline characteristics of the study population and their association with response to treatment.

Baseline Variable	Remission		Non-Remission		OR [CI], *p*-value
	Mean	SD	Mean	SD	
Age (yr)	40.21	13.72	39.28	9.66	1.06 [0.97–1.03], 0.70
Serum PLA2R (RU)	151.20	139.41	160.38	90.72	0.99 [0.99–1.06], 0.87
Duration of symptoms (mon)	3.91	2.63	4.03	2.77	0.98 [0.85–1.3], 0.80
Hypertension present, n (%)	74	82.2%	16	17.8%	0.38 [0.16–0.90], 0.02
Serum. protein (g/dL)	5.29	1.07	4.80	0.90	1.61 [1.08–2.38], 0.15
Serum. albumin (g/dL)	2.80	0.80	2.52	0.92	1.49 [0.94–2.37], 0.08
24 hour urine protein (gm/day)	4.97	2.97	4.86	3.46	1.01 [0.89–1.13], 0.86
Serum. creatinine (mg/dL)	1.39	1.18	1.40	0.91	0.98 [0.70–1.38], 0.94
Estimated Glomerular filtration Rate (eGFR) (mL/min)	72.57	31.80	70.31	32.86	1.02 [0.99–1.01], 0.71
Serum cholesterol (mg/dL)	250.78	81.05	253.92	84.78	1.00 [0.99–1.00], 0.84
Low density lipoprotein (mg/dL)	162.57	65.74	164.31	63.24	1.00 [0.99–1.00], 0.88
Serum triglyceride (mg/dL)	167.49	89.79	196.36	121.72	0.99 [0.99–1.00], 0.13
Serum haemoglobin (gm%)	11.31	2.04	12.09	2.56	0.85 [0.72–1.01], 0.06
Thyroid stimulating hormone (mIU/mL)	3.52	2.33	4.22	3.03	0.90 [0.78–1.04], 0.15
Light Microscopy	Count (N)	(%)	Count (N)	(%)	OR [CI], *p* value
Interstitial fibrosis with tubular atrophy (IFTA) less than or equal to 30%	54	60	14	35.90	0.27 [0.08–0.8], 0.02
IFTA more than 30%	36	40	25	64.10	0.99 [0.98–1.0], 0.77

PLA2R: Serum Anti Phospholipase A2 Receptor; SD: Standard deviation; OR: Odds Ratio; CI: Confidence interval.

persistence of proteinuria and labelling of no remission in these cases despite immunosuppression therapy.

Another factor that plays an important role in the remission of membranous nephropathy was found to be the presence of significant interstitial inflammation and tubular atrophy (IFTA >30%). Patients having more IFTA had lesser remission compared to their counterparts with IFTA <30% and nil IFTA (6.7% *vs.* 33.3% and 60% respectively) with *p*-value being 0.02. This finding can also be due to chronic kidney damage, as explained above. Other studies like Dahan *et al.* [3] have found serum albumin at presentation to be significant in remission, whereas it is not significant in our study. This may be secondary to collection and lab reagents along with different standards of reporting among laboratories.

Another variable significant to remission among both the studies by Dahan *et al.* [3] and Ramachandran *et al.* [8] is an antibody to serum PLA2R with higher values seen among responders, indicating its usefulness as a potential biomarker for predicting response among patients and avoiding invasive procedures like biopsy. Our study was a retrospective study, and due to the poor financial status of our patients, the antibody to serum PLA2R test was done in only 33 out of the 129 patients, and it was not found to correlate with remission rates (*p*-value 0.87). Since the test was not performed uniformly at the time of presentation for all patients, its significance in predicting the remission cannot be commented upon in our study.

Our study thus provides evidence that immunosuppressive therapy is probably superior to non-immunosuppressive therapy in inducing remission and reducing the number of patients progressing to chronic kidney disease. However, some limitations of this study include retrospective nature single centre design and small sample sizes in each treatment group hence more uniformity and trials are needed to prove one combination's superiority over another.

Availability of Data and Materials

The data are contained within this article.

Author contributions

MS and SG—designed the research study; wrote the manuscript. MS—performed the research; analyzed the data. GT—provided help and advice on data collection. All authors contributed to editorial changes in the manuscript. All authors

read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the institutional ethics board of Nizam's Institute of Medical Sciences vide letter number (EC/NIMS/2771/2021) and written informed consent was waived.

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Conflict of interest

The authors declare no conflict of interest.

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