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Original Research Article

Which one is the best-comparison of three treatment modalities in membranous glomerulonephropathy?

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ABSTRACT

Background: This retrospective study explores the efficacy of Modified Ponticelli, Rituximab and Tacrolimus in treating membranous nephropathy, focusing on remission rates.
Methods: This retrospective study analyzed 41 membranous nephropathy cases treated with Modified Ponticelli, Rituximab, or Tacrolimus. Statistical analyses included Kruskal-Wallis and Chi-Square tests to evaluate treatment responses, renal markers and remission outcomes, providing comprehensive insights into treatment efficacy.
Results: Modified Ponticelli demonstrated substantial reductions in proteinuria (-88.20%) and favorable increases in albumin (15.80%), outperforming Rituximab and Tacrolimus. Significant differences (p=0.0014) in remission outcomes underscore Modified Ponticelli's efficacy, with the highest complete remission rate (26.7%) and notable partial remission rate (73.3%). Rituximab (Complete 0%, Partial 46.2%) and Tacrolimus (Complete 15.4%, Partial 30.8%) exhibited lower rates.
Conclusions: In conclusion, Modified Ponticelli demonstrates superior efficacy in achieving both complete and partial remission in membranous nephropathy patients.

Keywords: Membranous Nephropathy, Rituximab, Tacrolimus

INTRODUCTION

Primary membranous nephropathy (MN) is a glomerular disease that is one of the primary causes of nephrotic syndrome in adults. Membranous nephropathy (MN) is a condition characterized by the accumulation of immune complexes in the subepithelial space of the glomerulus.[1] In the primary form of the disease (PMN), immune complex formation is triggered by autoantibodies, with the most common autoantigen being the M type phospholipase A2 receptor (PLA2R) , a protein typically found in podocytes.[2] In PMN, disease activity and prognosis are still evaluated by proteinuria and renal excretory function, with a decrease in proteinuria lowering the risk of renal deterioration.[3] Control of proteinuria, with or without immunosuppression, is thus a major indicator of therapy success in PMN . Alkylating drugs and steroids tend to be used in conjunction to cause such immunosuppression, as demonstrated in research conducted by Ponticelli et al.

Since its first description in 1984, the standard of care has consisted of alternating high-dose intravenous steroids and immunosuppression. Later on, methylprednisolone and cyclophosphamide were added to the original combination of methylprednisolone and chlorambucil.[4,5] Since the late 1990s, rituximab has been used extensively in cancer therapy, more recently, it has been utilised to

treat autoimmune illnesses. In randomized controlled trials, Rituximab has proven effective in achieving proteinuria remission, surpassing the renin-angiotensin system blockade or cyclosporine.[6,7] GEMRITUX study showed a positive effect of rituximab on proteinuria remission occurred after 6 months.[8]

The use of calcineurin inhibitors (CNIs) in Membranous Glomerulonephropathy (MGN) is supported by clinical studies. Trials demonstrated that Tacrolimus, a CNI, effectively reduced proteinuria and enhanced renal function in MGN patients.[9] We conducted a study to compare the three modalities of treatment in patients with MGN.

METHODS

Study type

This was a retrospective observational data collection study.

Study duration

January 2018 to December 2022 at Manipal Hospitals, Bangalore.

Data collection

This study was a hospital-based observational data collection study conducted in a tertiary care referral institute. Data was collected according to the Data collection proforma from hospital electronic system and from medical records department.

Inclusion criteria

Primary Membranous nephropathy diagnosed by renal biopsy. Age 18–80 years inclusive. Nephrotic-range proteinuria >4 g/day of the baseline value). Moderate to High risk of progression according to KDIGO guidelines.

Exclusion criteria

Diagnosis of secondary causes of PMN, diagnosis of cancer, systemic autoimmune diseases (e.g., Systemic lupus erythematosus) or any other acute or chronic inflammatory disease. Previous treatment with corticosteroids or any other immunosuppressive agent. Previous treatment with rituximab or any other biological agent in the 2-year period. Pregnant or breastfeeding.

Ethical Considerations

This study adhered to all relevant ethical principles and guidelines for the use of patient data. The Study was conducted in accordance with the Declaration of Helsinki, and all data were anonymized to protect patient confidentiality and privacy. Ethical approval for the study was obtained from the Institutional Ethics Committee of Manipal Hospitals, Bangalore.

Treatment protocol

(Cyclical corticosteroid/ alkylating agent therapy “the Ponticelli Regimen”). Month 1, Intravenous methylprednisolone 1g daily for three doses, then oral methylprednisolone 0.5 mg/kg/d for 27 days.

Month 2, Oral cyclophosphamide 2.0 mg/kg/d for 30 days. Month 3, Repeat Month 1. Month 4, Repeat Month 2. Month 5, Repeat Month 1. Month 6, Repeat Month 2

Rituximab protocol

375 mg/m2 given 2-4 times at weekly intervals.

Tacrolimus protocol

0.05-0.1 mg/kg/day for 12 months, maintaining trough levels of 3-8 ng/ml.

Definition of outcomes

We reported the remission rates (Both complete and partial), relapses at the end of 6 month and 1 Year. The patients in this study were classified according to the treatment response criteria of the KDIGO clinical practice guidelines for glomerulonephritis (kidney disease improving global outcomes, 2021), in the following response groupsComplete remission, proteinuria <0.3 g/d, partial remission proteinuria between 0.3 g/d and 3.5 g/d and no remission proteinuria >3.5g/d.

Statistical analysis

The study followed an open-label, non-blinded, observational, retrospective comparative design from.

Data analysis involved calculating means, standard deviations, frequencies and percentages. Repeated measures ANOVA was used to compare changes from baseline among different groups. Statistical analysis employed SPSS® (version 23.0) and Microsoft Excel®.

RESULTS

Patient enrollment

41 patients were included in the study, out of which 15 patients received modified ponticelli (36.58%), 13 patients received rituximab (31.71%), 13 patients received tacrolimus (31.71%).

Age distribution

Mean age was 47.27 years and the standard deviation was 15.06.

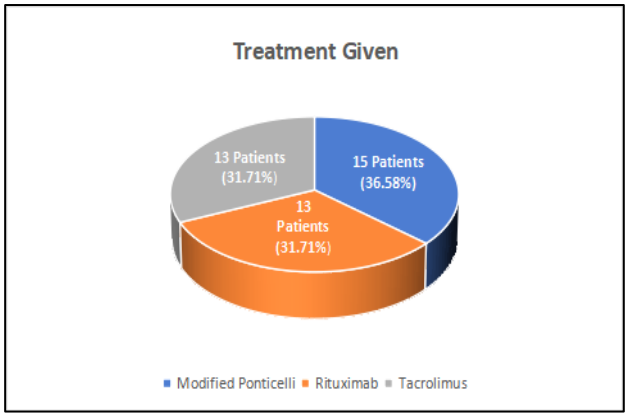

Figure 1: Percentage of the treatment regimen received by the Patients.

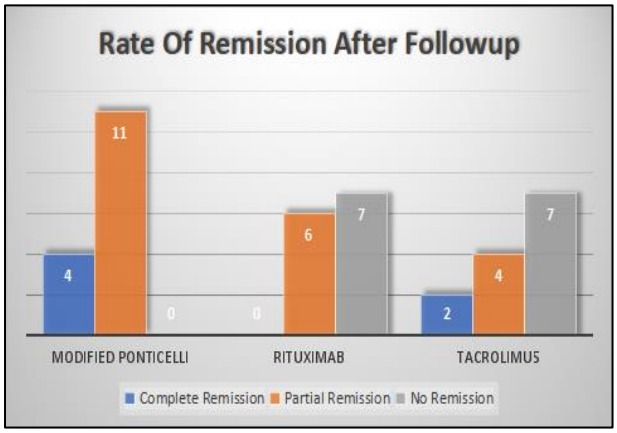

Figure 2: Rate of complete/partial remission after 6 and 12 months of follow up.

Gender distribution

Out of the 41 patients included in the study males comprised 58.54% (N-24) and females comprised 41.46% (n=17) of the population.

Treatment given

Of 41 Patients, 15 patients have been given with Modified Ponticelli (36.58%),13 patients have been given with Rituximab (31.71%) and 13 patients have been given with Tacrolimus (31.71%).

Follow up

After 6 and 12 months of follow up, 4 out of 15 patients achieve complete remission and 11 out of 15 patients achieved partial remission with modified ponticelli regimen.

6 out of 13 achieve partial remission and 7 out of 13 achieve no remission on rituximab regimen. 2 out of 13 achieve complete remission and 4 out of 13 achieve partial remission with tacrolimus regimen.

Table 1: Baseline characteristics of patients.

Clinical parameters	Total (n=41)
Age, years (mean±SD)	47.27±15.06
Male, N (%)	24 (58.54%)
Female, N (%)	17 (41.46%)
Diabetic mellitus, N (%)	22 (53.66%)
Hypertension, N (%)	21 (51.22%)

Table 2: Biochemical parameters at baseline of the patients in the three treatment arms.

Biochemical parameters	Treatment given			P value
	Modified ponticelli	**Rituximab**	**Tacrolimus**	
PCR (mean±SD)	10.20±6.35	6.38±4.60	9.35±4.20	0.0863
SR creatinine (mean±SD)	0.81±0.33	1.71±0.76	0.74±0.28	0.0004
eGFR (mean±SD)	108.85±30.00	53.90±31.50	114.05±26.10	0.0004
Albumin (mean±SD)	2.07±0.66	3.05±0.71	2.42±0.61	0.0063

Remark: p values are based on Kruskal-Wallis Test

Table 3: Outcomes of PCR, SrCreatinine, eGFR, Albumin after the regimen.

Biochemical parameters	Treatment given			
	Modified ponticelli (% change)	**Rituximab (% change)**	**Tacrolimus (% change)**	
PCR	-88.2	-36.5	-56.1	% decrease
SrCreatinine	8.42	67.6	48.3	% increase
eGFR	-24.9	-28.2	-26.8	% decrease
Albumin	15.8	3.27	16.9	% increase

DISCUSSION

This retrospective observational study spanning from January 2018 to December 2022, provides a comprehensive exploration into the labyrinth of primary membranous nephropathy (PMN). The patient cohort, totaling 41 individuals, offers a nuanced understanding of PMN in the context of varied demographics and treatment modalities. In scrutinizing the patient characteristics, it becomes evident that PMN, a condition with a predilection for the aging population, manifests predominantly in individuals above 40 years as seen in table 1. The gender distribution leans towards males, a trend often observed in renal disorders.

The treatment landscape, diversified into Modified Ponticelli, Rituximab and Tacrolimus arms, presents a unique opportunity to unravel the effectiveness of distinct therapeutic strategies. The distribution among these regimens-36.58%, 31.71% and 31.71%, respectively-ensures a balanced evaluation, facilitating comparisons among the treatment groups (figure 1). Modified Ponticelli, a cyclical corticosteroid/alkylating agent therapy, is juxtaposed with the biologic agent Rituximab and the immunosuppressant Tacrolimus, each with its distinctive pharmacological footprint.

As the study advances, the biochemical parameters emerge as critical indicators of treatment response (table 2). The Kruskal-Wallis test unveils intriguing patterns, with Rituximab exhibiting a statistically significant increase in serum creatinine compared to its counterparts. This signals a potential impact on renal function, prompting a deeper exploration of the delicate balance between therapeutic efficacy and potential adverse effects. In contrast, Modified Ponticelli and Tacrolimus showcase promising reductions in proteinuria, hinting at a renoprotective potential (table 3).

The percentage changes in biochemical parameters provide additional layers to the narrative. Modified Ponticelli, with an impressive -88.2% decrease in PCR, underscores its efficacy in ameliorating proteinuria. Tacrolimus, with a -56.1% decrease, aligns with this trend, albeit to a slightly lesser extent. Rituximab, while displaying a less pronounced decrease (-36.5%), introduces a counterpoint with a substantial increase in serum creatinine, posing questions about the delicate equilibrium between proteinuria reduction and potential renal implications (figure 2). One of the limitations of the study is that we did not have the data for PLA2R antibody and its levels for our patients.

The outcomes at the conclusion of the study period offer a dynamic snapshot of remission rates. Modified Ponticelli emerges as a frontrunner, with 4 out of 15 patients achieving complete remission and 11 achieving partial remission after 6 and 12 months of follow-up. Rituximab, while showcasing a higher rate of partial remission (6 out of 13), grapples with a considerable proportion (7 out of 13) experiencing no remission. Tacrolimus presents a mixed outcome, with 2 out of 13 patients achieving complete remission, 4 achieving partial remission and 7 experiencing no remission.

Comparisons with existing literature, STARMEN study showed that complete and partial remissions occurred in 36 patients (83.7%) in the corticosteroid-cyclophosphamide group and in 25 patients (58.1%) in the tacrolimus-rituximab group (relative risk 1.44; 95% confidence interval 1.08 to 1.92).[10] Similarly, Scolari et al.'s RI-CYCLO trial, focusing on Rituximab and Cyclophosphamide, which showed At 12 months, six of 37 patients (16%) randomized to rituximab and 12 of 37 patients (32%) randomized to the cyclic regimen experienced complete remission resonates with our findings, underlining the challenges and varied responses associated with Rituximab.[11]

MENTOR study showed that Rituximab was noninferior to cyclosporine in inducing complete or partial remission of proteinuria at 12 months and was superior in maintaining proteinuria remission up to 24 months.[12] Contrary to our study which showed tacrolimus to be better than Rituximab with respect to achieving complete or partial remissions.

Limitations of the study were data for Anti- PLA2R (Phospholipase A2 receptor) wasn’t available for the patients which could have added value for assessment of remission. Small number of patients included in the study

CONCLUSION

In conclusion, this study not only illuminates the intricate tapestry of patient characteristics and treatment responses in PMN but also contributes valuable insights into the comparative effectiveness of Modified Ponticelli, Rituximab and Tacrolimus.

The outcomes, when viewed through the lens of existing literature, underscore the multifaceted nature of PMN management and beckon further exploration into personalized therapeutic approaches tailored to individual patient profiles. As we navigate the complexities of PMN, this study invites a broader discourse on refining treatment strategies to optimize patient outcomes in this intricate nephrological landscape.

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