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Original Article

Short-term clinical remission rates and adverse reactions of rituximab compared to cyclosporine in patients with refractory membranous nephropathy (MN)

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Abstract: Objective: To compare short-term remission rates, adverse events, and laboratory trends between rituximab (RTX) and cyclosporine A (CsA) in refractory membranous nephropathy (MN), and to identify independent predictors of 12-month remission. Methods: This retrospective cohort study enrolled 165 patients with refractory MN (RTX: 85, CsA: 80). Primary outcome was clinical remission (complete or partial) at 6 and 12 months. Cumulative remission was assessed by Kaplan-Meier analysis. Multivariable logistic regression identified factors associated with 12-month remission. Adverse events were recorded throughout follow-up. Results: Baseline characteristics were largely balanced, although the RTX group had lower proteinuria (6.47±1.84 vs. 7.14±1.70 g/24 h, P=0.016) and eGFR (66.71±9.80 vs. 74.82±9.50 mL/min/1.73 m^2, P<0.001). At 6 months, total remission rates were similar (34.1% vs. 46.2%, P=0.152). At 12 months, CsA achieved significantly higher total remission (78.8% vs. 49.4%, P<0.001) and superior cumulative remission (log-rank P=0.013). Multivariable analysis confirmed RTX treatment was independently associated with lower remission odds (OR=0.138, 95% CI 0.052-0.363, P<0.001). Baseline proteinuria was a negative predictor (OR=0.416, 95% CI 0.309-0.560), whereas baseline eGFR was protective (OR=1.070, 95% CI 1.023-1.119). Overall adverse events were less frequent with RTX (49.4% vs. 82.5%, P<0.001), though severe event rates were comparable. Conclusions: Over 12 months, CsA induced higher remission rates than RTX in refractory MN, albeit with more adverse events and a measurable effect on renal function. RTX offered a better safety profile but slower onset of action. Baseline proteinuria and eGFR independently predicted remission.

Keywords: Membranous nephropathy, refractory, rituximab, cyclosporine, clinical remission, adverse reactions, retrospective cohort study

Introduction

Membranous nephropathy (MN) is an autoimmune glomerular disease characterized by subepithelial immune complex deposition along the glomerular basement membrane. It is one of the most common pathologic types of nephrotic syndrome in adults, accounting for approximately 20-30% of primary glomerular diseases. The underlying pathogenic mechanism primarily involves the binding of autoantigens on the podocyte surface (such as phospholipase A2 receptor, PLA2R; thrombospondin type-1 domain-containing 7A, THSD7A) to their corresponding autoantibodies, forming *in situ* immune complexes. These complexes activate the complement system, leading to podocyte injury, thickening of the basement membrane, and the subsequent production of proteinuria [1].

Clinically, MN presents with proteinuria, hypoalbuminemia, edema, and hyperlipidemia to varying degrees. Approximately 30-40% of patients progress to end-stage renal disease (ESRD) within 5-10 years.

Although traditional treatment regimens for MN involve glucocorticoids combined with alkylating agents (e.g., cyclophosphamide) or calcineurin inhibitors (e.g., cyclosporine, tacrolimus), approximately 20-30% of patients fail to respond adequately to initial immunosuppressive therapy. These patients exhibit persistent nephrotic syndrome (24-hour urine protein >3.5 g/24 h and serum albumin <30 g/L) or progres-

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sive deterioration of renal function and are defined as having refractory MN [2]. The pathophysiologic mechanisms of refractory MN are complex and may be associated with persistent production of pathogenic antibodies, defects in immune tolerance, impaired podocyte repair, and genetic susceptibility. Currently, there is no uniform standard for treating refractory MN, posing significant challenges for clinical decision-making and creating an urgent need to explore more effective and safer therapeutic strategies [3, 4].

Rituximab (RTX) is a chimeric monoclonal antibody that specifically targets the CD20 antigen on B cells. It rapidly depletes B cells in peripheral blood and lymphoid tissues through mechanisms including antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and induction of apoptosis, thereby reducing the production of pathogenic autoantibodies [5].

In recent years, the application of RTX in MN treatment has become increasingly widespread. Ronco et al. first reported that RTX effectively reduces proteinuria and induces clinical remission in MN patients [6]. Subsequently, the randomized controlled trial (MENTOR study) conducted by Fernández et al. [7] confirmed that RTX was non-inferior to cyclosporine in inducing remission at 12 months and demonstrated higher remission rates and lower relapse rates at 24 months. For refractory MN, multiple observational studies have also shown that RTX enables patients who have only partial remission to achieve clinical remission, improves renal function, and delays disease progression [8-10]. However, further evidence is still needed regarding the optimal timing, dosing regimens, indications for retreatment, and long-term safety of RTX.

Cyclosporine A (CsA) is a lipophilic cyclic undecapeptide. It exerts immunosuppressive effects by binding to intracellular cyclophilin, thereby inhibiting calcineurin activity. This inhibition blocks the dephosphorylation and subsequent nuclear translocation of the nuclear factor of activated T-cells (NF-AT), leading to the suppression of cytokine transcription (such as IL-2) and T-cell proliferation [11-13].

As a second-line therapeutic agent for MN, CsA can rapidly reduce proteinuria with an efficacy rate of 60-80%, making it particularly suitable for patients who are intolerant to or unresponsive to glucocorticoids and alkylating agents. The randomized controlled trial by Cai et al. demonstrated that the remission rate in MN patients treated with CsA was significantly higher than that of the placebo group at 6 months, with a notable renoprotective effect [9]. However, the long-term application of CsA is limited by its adverse effects, including nephrotoxicity (acute tubular injury, chronic interstitial fibrosis), hypertension, hyperlipidemia, gingival hyperplasia, and hirsutism. Furthermore, the relapse rate after discontinuation was high (exceeding 50%) [14, 15].

Currently, clinical studies directly comparing RTX and CsA in the treatment of refractory MN remain limited. Although the MENTOR study included some refractory patients, it focused primarily on treatment-naïve and relapsed patients, and the subgroup analysis indicated that the efficacy advantage of RTX in the refractory subgroup still requires validation. The single-center retrospective study by Xu et al. [16] compared the efficacy of RTX and CsA in refractory MN, finding that the total remission rates in the RTX group were 45.2% and 71.0% at 6 and 12 months, respectively, versus 40.0% and 56.0% in the CsA group. However, the differences between the groups did not reach statistical significance, which may be attributed to the small sample size. Köllner et al. treated refractory MN with high-dose RTX and achieved a 12-month total remission rate of 75% with favorable safety [17, 18]. Nevertheless, the aforementioned studies suffer from small sample sizes, short follow-up durations, and a lack of multivariate adjustment, making it difficult to provide high-quality evidence [18, 19].

Furthermore, the factors influencing the prognosis of patients with refractory MN are not yet fully elucidated. Baseline renal function, proteinuria levels, serum albumin, and PLA2R antibody titers may affect treatment response. As a core indicator reflecting renal function, the modifying effect of eGFR on the efficacy of RTX and CsA has not been sufficiently investigated. The nephrotoxicity of CsA may be more detrimental to patients with poorer baseline renal function, whereas the immunosuppressive effect of RTX may be more effective in patients with high antibody titers. Therefore, adjusting

for these confounding factors by multivariate analysis is crucial for accurately assessing the relative efficacy of the two drugs.

Based on the aforementioned context, this study adopted a single-center retrospective cohort design. We consecutively enrolled patients diagnosed with refractory membranous nephropathy at the AFFILIATED HOSPITAL OF PUTIAN UNIVERSITY between January 2018 and December 2024. We systematically compared the differences between rituximab and cyclosporine in the following aspects: (1) Short-term clinical remission rates (overall remission, complete remission, and partial remission at 6 and 12 months); (2) Adverse event incidence and safety profiles; (3) Trends in laboratory indicators (e.g., 24-hour urine protein, serum albumin, and serum creatinine) from baseline to 12 months. Multivariate Logistic regression models were employed to adjust for potential confounding factors such as age, sex, baseline proteinuria, baseline albumin, and baseline eGFR. This was done to further validate the independent association between the treatment group and 12-month remission, as well as to explore other factors influencing the prognosis. This study aimed to provide real-world evidence for clinical treatment decisions in refractory MN, assisting clinicians in making optimal choices between RTX and CsA.

Materials and methods

Study design and patient selection

This was a single-center, retrospective cohort study designed to compare the clinical efficacy and safety of rituximab (RTX) and cyclosporine A (CsA) in the treatment of refractory membranous nephropathy (MN). The study protocol was approved by the Ethics Committee of the Putian University Affiliated Hospital.

We consecutively enrolled patients diagnosed with refractory MN at our hospital between January 2018 and December 2024. Refractory MN was defined according to international consensus and previous studies [20-22] as follows: after receiving adequate dosage and full-course (≥6 months) treatment with at least one immunosuppressant (including cyclophosphamide, tacrolimus, and mycophenolate mofetil), patients still exhibited one or more of the following conditions: (1) persistent 24-hour urine protein >3.5 g/24 h and serum albumin <30 g/L; (2) estimated glomerular filtration rate (eGFR) decreased by ≥30% from baseline or showed progressive deterioration; (3) occurrence of severe complications related to nephrotic syndrome (e.g., thrombosis, severe infection). All patients were pathologically diagnosed with membranous nephropathy by renal biopsy and clinically evaluated based on pathologic stage (Stage I-IV) and phospholipase A2 receptor (PLA2R) antibody levels.

Exclusion criteria were: (1) secondary membranous nephropathy (e.g., systemic lupus erythematosus, hepatitis B virus-associated glomerulonephritis, tumor-associated, etc.); (2) active infection (including active hepatitis B, hepatitis C, tuberculosis, etc.); (3) severe comorbidities involving the heart, liver, lungs, hematologic system, or malignancies; (4) pregnancy or lactation; (5) known allergy to rituximab or cyclosporine; (6) incomplete follow-up data or loss to follow-up.

Ultimately, a total of 165 patients were included in the final analysis and divided into two groups based on their treatment regimen: the RTX group (n=85) and the CsA group (n=80). The assignment of treatment regimens was determined by the attending physicians based on the patient's condition, financial status, and personal preference, representing a non-randomized clinical practice (**Figure 1**).

Treatment regimens

RTX group: Patients received intravenous rituximab (brand name: MabThera; F. Hoffmann-La Roche Ltd., Shanghai, China) at a standard dose of 1000 mg on Day 1 and Day 15. Premedication with an antihistamine (diphenhydramine 25 mg) and an antipyretic analgesic (acetaminophen 500 mg) was administered before each infusion to prevent infusion-related reactions. Complete blood count, liver function, and hepatitis B markers were monitored before each infusion. The need for re-treatment was determined based on clinical response and CD19+ B-cell count (if measured). However, the primary analysis focused on efficacy within 12 months after the initial treatment.

CsA group: Patients received oral cyclosporine soft capsules (brand name: Xinsaisiping; Huadong Pharmaceutical Co., Ltd.) at a starting

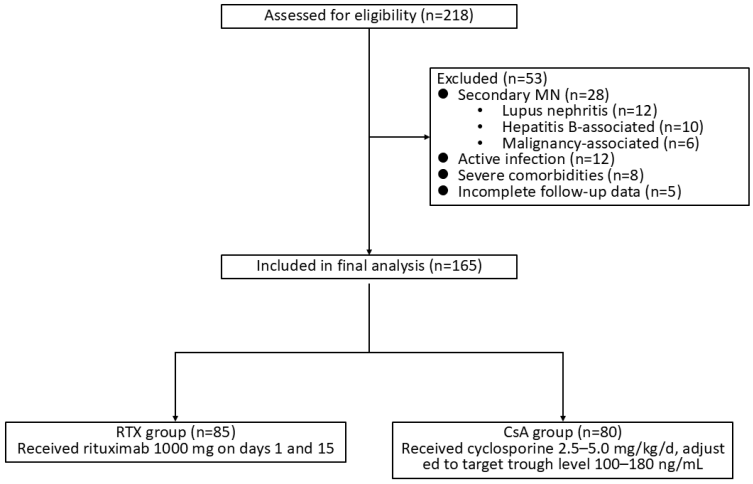

Figure 1. Patient selection flowchart. Abbreviations: MN, membranous nephropathy; RTX, Rituximab; CsA, cyclosporine A.

dose of 3-5 mg/kg/day, divided into two doses. The dosage was adjusted according to the trough blood concentration (C0), with a target range of 100-180 ng/mL. Blood drug concentration, blood pressure, renal function, and electrolytes were monitored every 1-2 weeks during treatment.

Concomitant therapy: Both groups were permitted to receive low-dose glucocorticoids (prednisone ≤10 mg/day or equivalent methylprednisolone) to control nephrotic syndrome symptoms or as adjunctive immunosuppression. All patients received angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) as baseline supportive therapy, with a blood pressure target of <130/80 mmHg. Lipid-lowering agents (statins) and anticoagulants were administered as clinically indicated for dyslipidemia and thrombosis prophylaxis, respectively.

Data collection and follow-up

Baseline data were retrospectively collected by the electronic medical record system, including: Demographic characteristics: age, sex; Clinical indices: 24-hour urine protein, serum albumin, serum creatinine, estimated glomerular filtration rate (eGFR, calculated using the CKD-EPI formula), serum total cholesterol, systolic blood pressure, diastolic blood pressure; History of prior immunosuppressant use: cyclophosphamide (CTX) and tacrolimus (Tac) (yes/no); Treatment details: RTX administration regimen, CsA starting dose, target trough concentration, concomitant glucocorticoid use (yes/no).

All patients were followed up at 3, 6, 9, and 12 months post-treatment. At each visit, the following were recorded: 24-hour urine protein, serum albumin, serum creatinine; Clinical remission status (see Outcome Measures); Adverse events (see Outcome Measures). Follow-up data were entered into the database by two independent researchers and cross-verified to ensure accuracy.

Outcome measures

Primary outcome: Clinical remission rate at 6 and 12 months post-treatment. Clinical remission was defined according to international consensus with minor modifications: Complete Remission (CR): Meeting all of the following criteria: (1) 24-hour urine protein <0.3 g/24 h; (2) serum albumin ≥35 g/L; (3) stable serum creatinine, defined as <25% increase from baseline or <25% decrease in eGFR. Partial Remission (PR): Meeting all of the following criteria: (1) 24-hour urine protein 0.3-3.5 g/24 h; (2) ≥50% reduction in 24-hour urine protein from baseline; (3) improved or ≥30 g/L serum albumin from baseline. No Remission (NR): Failure to meet CR or PR criteria. Total Remission (TR) was defined as the sum of CR and PR.

Secondary outcomes: Adverse event incidence: Any adverse event occurring within 12 months of treatment was recorded. Definitions were as follows: Infection: Any event requiring antimicrobial therapy (including respiratory, urinary tract, or skin/soft tissue infections); Hepatic dysfunction: Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation to more than 2 times the upper limit of normal; Renal injury: Serum creatinine increase >25% from baseline; Infusion reaction: Fever, chills, rash, or hypotension during or within 24 hours after rituximab infusion; Hepatitis B reactivation: Hepatitis B virus (HBV) DNA increase ≥10-

fold from baseline or conversion to positivity in HBsAg-positive or anti-HBc-positive patients; Gingival hyperplasia, hirsutism, tremor, new-onset hypertension (new diagnosis requiring antihypertensive treatment), new-onset hyperglycemia (fasting glucose ≥7.0 mmol/L or requiring antidiabetic treatment), hyperlipidemia (cholesterol or triglycerides requiring pharmacologic treatment), leukopenia (white blood cell count $<3.0\times10^9$/L); Severe adverse events: Events requiring dose reduction, discontinuation, hospitalization, or life-threatening events.

Trends in laboratory values: Mean changes in 24-hour urine protein, serum albumin, and serum creatinine at baseline and at 3, 6, 9, and 12 months.

Statistical analysis

Statistical analyses were performed using SPSS 26.0 (IBM Corp., Armonk, NY, USA) and Python 3.9 (SciPy 1.7, statsmodels 0.13). All tests were two-sided, and a *P*-value <0.05 was considered significant. Continuous variables are presented as mean ± standard deviation or median (interquartile range) and were compared using the independent t-test or Mann-Whitney U test as appropriate. Categorical variables are presented as frequencies and percentages and were compared using the chi-square test or Fisher's exact test. Cumulative remission probabilities were estimated using the Kaplan-Meier method and compared with the log-rank test. Independent predictors of 12-month remission were identified using multivariable logistic regression with the Enter method, with results expressed as odds ratios (OR) and 95% confidence intervals (CI). Model goodness-of-fit was assessed using the Hosmer-Lemeshow test. Missing data were minimal (<5% for key variables) and were handled using listwise deletion. Sample size and power considerations. Based on previously reported data [23], we hypothesized that the 12-month remission rate would be approximately 70% in the cyclosporine group versus 45% in the control group. To detect this 25% absolute difference with a two-sided alpha level of 0.05 and a statistical power of 80%, a minimum of 58 patients per group was required. Accounting for an anticipated 10% dropout rate, the target enrollment was set at 64 patients per group. While the overall cohort meets this threshold, we acknowledge that the smaller sample sizes within specific subgroup analyses (e.g., by gender or age quartile) are underpowered to detect small-to-moderate effects, and these findings should be interpreted as exploratory and hypothesis-generating.

Results

Baseline characteristics

A total of 165 patients with refractory membranous nephropathy were enrolled in this study, comprising 85 patients in the RTX group and 80 patients in the CsA group. The baseline characteristics of the two groups are presented in **Table 1**. No significant differences were observed between the groups regarding age, sex, serum albumin, serum creatinine, or total cholesterol (all P>0.05).

The baseline 24-hour urine protein was slightly lower in the RTX group compared to the CsA group (6.47±1.84 g/24 h vs. 7.14±1.70 g/24 h, P=0.016). The eGFR was significantly lower in the RTX group than in the CsA group (66.71 ±9.80 ml/min/1.73 m^2 vs. 74.82±9.50 ml/min/1.73 m^2, P<0.001), indicating relatively poorer baseline renal function in the RTX group. The rates of prior cyclophosphamide and tacrolimus use were well-balanced between the two groups (both *P*>0.05).

Clinical remission rates

The clinical remission status at 6 and 12 months is shown in **Table 2**. At the 6-month follow-up, no cases of complete remission (CR) were observed in either the RTX or CsA group. The partial remission (PR) rates were 34.1% and 46.2%, respectively, and the total remission (CR+PR) rates were 34.1% and 46.2%, respectively. The difference between the groups was not significant (χ^2=2.047, P=0.152).

At the 12-month follow-up, one patient (1.2%) in the RTX group achieved CR, whereas no CR cases were observed in the CsA group. The PR rates were 48.2% and 78.8%, and the total remission rates were 49.4% and 78.8%, respectively. The CsA group showed a significantly higher remission rate compared to the RTX group (χ^2=14.088, P<0.001).

Table 1. Baseline characteristics

Variable	RTX (n=85)	CsA (n=80)	t/χ^2	*P*-value
Age (years)	52.05±13.08	53.20±13.78	-0.550	0.583
24 h urine protein (g/24 h)	6.47±1.84	7.14±1.70	-2.444	0.016
Serum albumin (g/L)	23.57±3.38	24.19±3.21	-1.221	0.224
Serum creatinine (μmol/L)	126.78±32.16	127.58±28.75	-0.170	0.865
eGFR (ml/min/1.73 m^2)	66.71±9.80	74.82±9.50	-5.397	<0.001
Serum cholesterol (mmol/L)	8.63±2.07	8.41±2.07	0.681	0.497
Gender			0.037	0.848
Female	32 (37.6%)	28 (35.0%)		
Male	53 (62.4%)	52 (65.0%)		
Previous_CTX			0.153	0.696
No	7 (8.2%)	9 (11.2%)		
Yes	78 (91.8%)	71 (88.8%)		
Previous_Tac			0.177	0.674
No	23 (27.1%)	25 (31.2%)		
Yes	62 (72.9%)	55 (68.8%)		

Abbreviations: RTX, Rituximab; CsA, Cyclosporine A; eGFR, estimated glomerular filtration rate; SCr, serum creatinine; CTX, cyclophosphamide; Tac, tacrolimus; SMD, standardized mean difference.

Table 2. Remission rates

Timepoint	Remission status	RTX (n=85)	CsA (n=80)	χ^2	*P*-value
6 months	CR	0 (0.0%)	0 (0.0%)		
6 months	PR	29 (34.1%)	37 (46.2%)		
6 months	NR	56 (65.9%)	43 (53.8%)		
6 months	Total remission (CR+PR)	29 (34.1%)	37 (46.2%)	2.047	0.152
12 months	CR	1 (1.2%)	0 (0.0%)		
12 months	PR	41 (48.2%)	63 (78.8%)		
12 months	NR	43 (50.6%)	17 (21.2%)		
12 months	Total remission (CR+PR)	42 (49.4%)	63 (78.8%)	14.088	<0.001

Abbreviations: CR, complete remission; PR, partial remission; NR, no remission; TR, total remission.

Kaplan-Meier survival analysis demonstrated that the cumulative probability of remission was significantly higher in the CsA group than in the RTX group (Log-rank test P=0.013, **Figure 2**). The median time to remission for both groups was 12 months.

Adverse reactions

The incidence of adverse events is summarized in **Table 3**. The overall incidence of adverse reactions was 49.4% in the RTX group, which was significantly lower than that of the CsA group (82.5%) (χ^2=18.518, P<0.001).

The most common adverse events in the RTX group were infection (16.5%), renal injury (16.5%), and infusion reactions (11.8%). In contrast, the CsA group primarily exhibited infection (23.8%), new-onset hypertension (22.5%), renal injury (20.0%), and hepatic dysfunction (15.0%).

Adverse events specific to the RTX group included infusion reactions, hepatitis B reactivation, and leukopenia. The CsA group exhibited characteristic adverse events such as gingival hyperplasia (15.0%), hirsutism (8.8%), tremor (15.0%), and hyperlipidemia (12.5%).

The incidence of severe adverse events was 4.7% in the RTX group and 10.0% in the CsA group, with no significant difference between the groups (P=0.313).

Trends in laboratory values

Figure 3 depicts longitudinal changes in laboratory values over 12 months. For 24-hour urine protein (**Figure 3A**), mean levels declined from

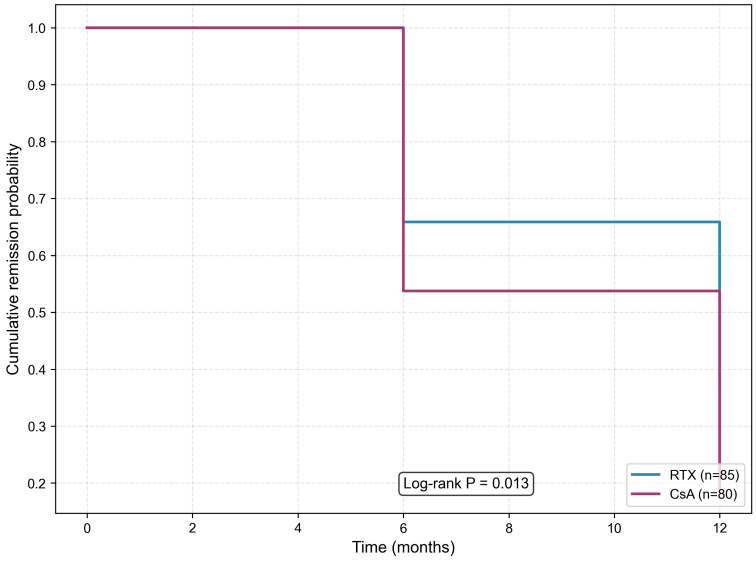

Figure 2. Kaplan-Meier curves for cumulative remission. Abbreviations: RTX, Rituximab; CsA, Cyclosporine A.

6.47 to 2.97 g/24 h in the RTX group and from 7.14 to 2.73 g/24 h in the CsA group, with CsA showing a more rapid early reduction (4.30 vs. 4.58 g/24 h at 3 months). Serum albumin (**Figure 3B**) increased steadily in both groups, rising from 23.57 to 32.02 g/L with RTX and from 24.19 to 32.69 g/L with CsA. Serum creatinine (**Figure 3C**) remained stable in the RTX group (126.78 to 130.75 μmol/L), whereas the CsA group exhibited an early increase to 144.17 μmol/L at 3 months that persisted through 12 months (142.34 μmol/L), indicating a measurable renal hemodynamic effect.

Multivariate logistic regression analysis

A multivariate Logistic regression analysis was performed with remission status at 12 months (CR+PR) as the dependent variable. The model included treatment group, age, sex, baseline urine protein, baseline albumin, and baseline eGFR. The results are presented in **Table 4** and **Figure 4**. After adjusting for other factors, CsA treatment was independently associated with a higher remission rate (compared to RTX: OR=0.138, 95% CI 0.052-0.363, P<0.001). For every 1 g/24 h increase in baseline urine protein, the odds of remission decreased by 58.4% (OR=0.416, 95% CI 0.309-0.560, P<0.001). For every 1 ml/min/1.73 m^2 increase in baseline eGFR, the odds of remission increased by 7.0% (OR=1.070, 95% CI 1.023-1.119, P= 0.003). Age, sex, and baseline albumin showed no significant association with 12-month remission (all P> 0.05).

Discussion

The principal finding of this investigation was the marked temporal dissociation in proteinuria reduction between calcineurin inhibition and alternative immunosuppressive strategies. Specifically, the superior early-phase response observed with cyclosporine is most likely attributable to a synergistic dual mechanism: (i) the direct stabilization of the podocyte actin cytoskeleton by synaptopodin dephosphorylation and (ii) the rapid reduction in glomerular filtration pressure. Unlike B-cell depletion strategies that require a lag phase for antibody titer decay and podocyte repair, CsA induced a near-immediate biomechanical shielding of the filtration barrier. This mechanistic distinction provides a plausible explanation for the early separation of the survival curves observed within the first 3 months of therapy, a finding that underscores the value of CsA as a bridge therapy in severe nephrotic syndrome pending definitive immunological remission.

Mechanistic Basis for Accelerated CsA Response. Beyond T-cell inhibition, the rapid antiproteinuric efficacy of CsA is increasingly attributed to non-immune, podocyte-centric effects. Calcineurin inhibition prevents the dephosphorylation of synaptopodin, a key regulator of RhoA signaling and actin filament organization in foot processes [24, 25]. By preserving the integrity of the slit diaphragm complex independent of immune complex clearance, CsA provides an immediate architectural reinforcement to the damaged glomerular capillary wall. Furthermore, afferent arteriolar vasoconstriction induced by CsA reduces intraglomerular hydraulic pressure, thereby diminishing convective drag forces that drive macromolecule leakage. This combination of biomechanical protection and structural stabilization explains why patients with severe hypoalbuminemia often exhibit a steep decline in urine protein-to-creatinine ratio within the first 4-8 weeks, a trajec-

Table 3. Adverse events

Adverse event	RTX (n=85)	CsA (n=80)	χ^2	*P*-value
Any adverse event	42 (49.4%)	66 (82.5%)	18.518	<0.001
Infection (any)	14 (16.5%)	19 (23.8%)	0.948	0.330
Liver dysfunction	1 (1.2%)	12 (15.0%)	9.029	0.003
Renal impairment (SCr ↑ >25%)	14 (16.5%)	16 (20.0%)	0.149	0.700
Infusion-related reaction	10 (11.8%)	0 (0.0%)	8.059	0.005
HBV reactivation	2 (2.4%)	0 (0.0%)	0.447	0.504
Leukopenia	10 (11.8%)	0 (0.0%)	8.059	0.005
Gingival hyperplasia	0 (0.0%)	12 (15.0%)	11.616	<0.001
Hirsutism	0 (0.0%)	7 (8.8%)	5.762	0.016
Tremor	0 (0.0%)	12 (15.0%)	11.616	<0.001
New-onset hypertension	4 (4.7%)	18 (22.5%)	9.805	0.002
New-onset hyperglycemia	6 (7.1%)	11 (13.8%)	1.338	0.247
Hyperlipidemia	0 (0.0%)	10 (12.5%)	9.221	0.002
Serious adverse events	4 (4.7%)	8 (10.0%)	1.018	0.313

Abbreviations: SCr, serum creatinine; HBV, hepatitis B virus.

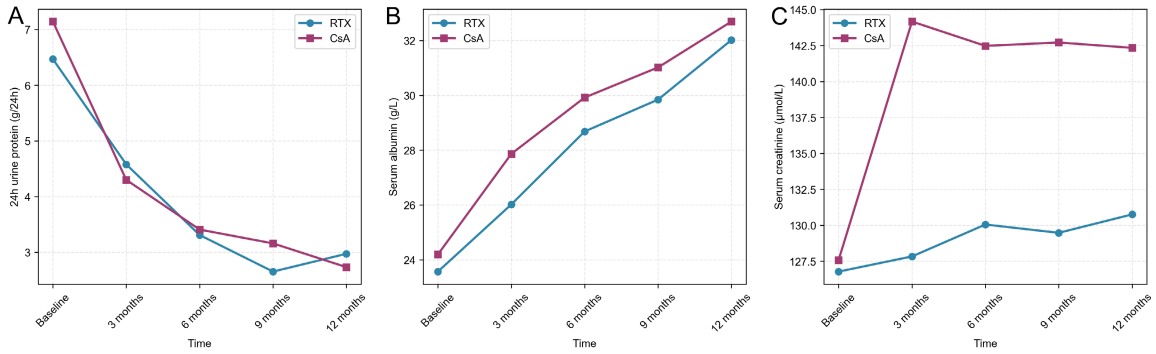

Figure 3. Trends in laboratory values. (A) 24-hour urine protein, (B) serum albumin, and (C) serum creatinine are shown from baseline to 12 months for the RTX (n=85) and CsA (n=80) groups. Error bars represent standard deviation. Abbreviations: RTX, Rituximab; CsA, cyclosporine A; SCr, serum creatinine.

Table 4. Multivariable logistic regression for 12-month remission

Variable	OR (95% CI)	β	SE	z	*P*-value
Treatment_RTX	0.138 (0.052-0.363)	-1.981	0.494	-4.010	<0.001
Age	1.009 (0.978-1.040)	0.009	0.016	0.536	0.592
Gender_male	0.427 (0.175-1.041)	-0.852	0.455	-1.873	0.061
Baseline_Upro	0.416 (0.309-0.560)	-0.878	0.152	-5.780	<0.001
Baseline_Alb	0.949 (0.835-1.079)	-0.052	0.066	-0.794	0.427
Baseline_eGFR	1.070 (1.023-1.119)	0.068	0.023	2.946	0.003

Abbreviations: RTX, Rituximab; eGFR, estimated glomerular filtration rate; Upro, urine protein; Alb, albumin; OR, odds ratio; CI, confidence interval; SE, standard error.

tory seldom matched by therapies reliant on *de novo* immunoglobulin synthesis cessation. Notably, beyond the glomerular filtration barrier, evidence indicates that inducible cytoprotective mechanisms within the renal tubular epithelium - such as heat shock protein 70 (HSP70) upregulation - can mitigate ischemia-reperfusion and toxin-induced tubular injury [26]. While the direct role of HSP70 in CNI-related tubular toxicity in membranous ne-

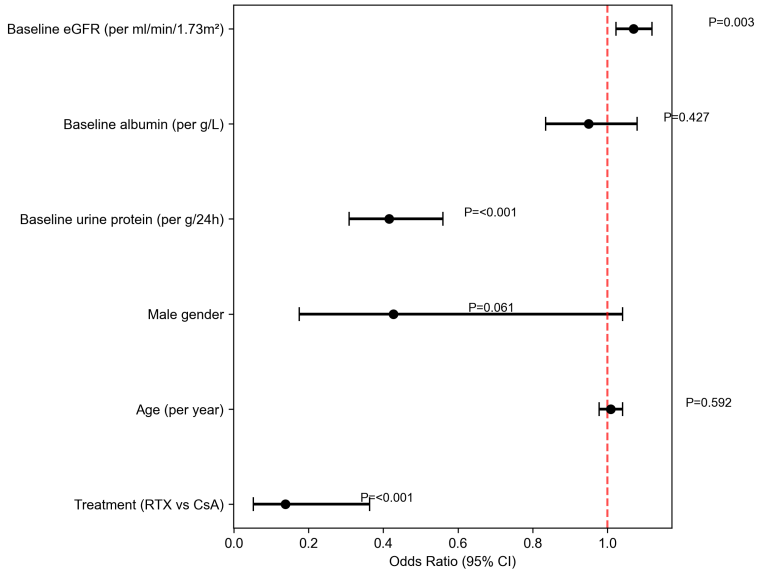

Figure 4. Forest plot of multivariable logistic regression. Abbreviations: RTX, Rituximab; eGFR, estimated glomerular filtration rate; Upro, urine protein; Alb, albumin; OR, odds ratio; CI, confidence interval.

phropathy remains unexplored, these findings raise the possibility that CsA's net renal effect may reflect a balance between its adverse hemodynamic and tubulointerstitial actions and potential sublethal cellular adaptive responses. Whether pharmacologic preconditioning of tubular cells by HSP induction could ameliorate CsA-associated nephrotoxicity warrants further investigation.

The 12-month total remission rate of 78.8% in the CsA group is consistent with previously reported rates of 60-80% [27, 28], whereas the 49.4% rate in the RTX group is partially consistent with the 45.2-71.0% range reported by Wang et al. [29], though lower than the 75% reported by Scolari et al. [30] using high-dose RTX. These discrepancies likely reflect differences in patient populations, RTX dosing regimens, and the refractory nature of our cohort. Notably, the MENTOR trial found no significant difference between RTX and CsA at 12 months in treatment-naïve and relapsed MN, with RTX demonstrating superiority at 24 months [25]. The divergence from our findings underscores that refractory MN represents a distinct therapeutic challenge, where the rapid hemodynamic and podocyte-stabilizing effects of CsA may confer a short-term advantage that dissipates with longer follow-up or upon drug withdrawal.

Multivariable analysis confirmed baseline proteinuria as an independent negative predictor of 12-month remission (OR=0.416 per g/24 h increase, P<0.001), consistent with the notion that higher proteinuria reflects more extensive podocyte injury and immune complex burden. Baseline eGFR was an independent protective factor (OR=1.070 per ml/min/1.73 m^2 increase, P=0.003), suggesting that preserved renal functional reserve facilitates both drug tolerance and intrinsic repair capacity. The marginally significant association of male gender with lower remission odds (OR= 0.427, P=0.061) warrants further investigation. Notably, the lower baseline eGFR in the RTX group (66.71 vs. 74.82 mL/min/1.73 m^2, P<0.001) may have contributed to the observed efficacy difference despite multivariable adjustment, and residual confounding cannot be excluded.

The adverse event profiles aligned with the known pharmacologic properties of each agent. RTX demonstrated a favorable safety profile, with infusion reactions (11.8%), leukopenia (11.8%), and infection (16.5%) representing the most common events. The 2.4% incidence of HBV reactivation underscores the importance of routine screening and antiviral prophylaxis in endemic regions. In contrast, CsA was associated with a higher overall adverse event burden (82.5% vs. 49.4%, P<0.001), primarily driven by nephrotoxicity, new-onset hypertension (22.5%), gingival hyperplasia (15.0%), and metabolic disturbances. The acute rise in serum creatinine observed in the CsA group at 3 months (144.17 μmol/L) with incomplete recovery at 12 months (142.34 μmol/L) highlights the need for vigilant therapeutic drug monitoring and blood pressure management.

A notable constraint of the current analysis was the absence of serial anti-phospholipase A2 receptor (PLA2R) antibody titers, a cornerstone biomarker for defining immunological remission in contemporary MN practice. The lack of

PLA2R stratification introduces a potential confounding variable in interpreting the observed short-term superiority of CsA. It is plausible that the rapid proteinuria reduction observed with CsA reflects a direct hemodynamic and podocyte-stabilizing effect, occurring independently of any change in underlying autoantibody production. In contrast, the slower onset of remission in the RTX group may actually signify a more definitive immunological cure. Therefore, the observed divergence in Kaplan-Meier curves at 6-12 months (**Figure 2**) must be interpreted with caution; it may represent a pharmacodynamic surrogate rather than a disease-modifying advantage.

Several limitations warrant consideration. First, the 12-month observation window is insufficient to capture differential relapse rates or the insidious onset of CNI-induced interstitial fibrosis, which typically manifests beyond 24 months. Second, the single-center retrospective design and relatively modest sample size preclude definitive conclusions. Despite these constraints, the present data inform specific directions for subsequent trial design: future prospective cohorts should mandate centralized PLA2R antibody monitoring at baseline and quarterly intervals to differentiate hemodynamic remission from true immunological quiescence, and a minimal follow-up threshold of 24 months is essential to accurately capture CNI-dependency relapse and long-term renal outcomes. From a methodological perspective, emerging strategies that leverage drug-protein interactions to redirect nephrotoxic drug biodistribution - such as albumin nanoparticle-based formulations for amphotericin B reported by Liu et al. - offer a conceptual framework for mitigating off-target kidney injury [31]. Although directly applicable to calcineurin inhibitors remains speculative, such approaches highlight the potential value of carrier-mediated drug delivery in reducing renal accumulation of nephrotoxic agents, which may inspire future formulation strategies for CNI-sparing or CNI-detoxifying regimens in membranous nephropathy. Future research should focus on the following aspects: (1) Conducting multicenter, prospective, randomized controlled trials to compare the long-term efficacy and safety of RTX and CsA in treating refractory MN. (2) Exploring individualized treatment strategies based on biomarkers (e.g., PLA2R antibodies, B-cell subsets). (3) Extending the follow-up duration to evaluate relapse rates, long-term changes in renal function, and cumulative drug toxicity. (4) Establishing a prognostic prediction model for refractory MN by integrating clinical, pathologic, and immunological indicators. (5) Comparing the efficacy of different dosing regimens (e.g., fixed-dose RTX versus B-cell count-guided adjustment).

In clinical practice, treatment selection should be individualized. CsA may be preferable for patients requiring rapid control of severe proteinuria or those with acceptable renal function and adequate access to drug monitoring. RTX may offer greater long-term advantages for younger patients concerned about cumulative CNI toxicity, although its slower onset necessitates patience and possibly longer observation to fully appreciate a therapeutic benefit.

Conclusion

This single-center retrospective cohort study demonstrated that, within a 12-month follow-up period, cyclosporine (CsA) achieved significantly higher clinical remission rates than rituximab (RTX) in treating refractory membranous nephropathy (MN). However, CsA was associated with a higher incidence of adverse events and some effect on renal function. RTX exhibited a better overall safety profile but had a slower onset of action. High baseline proteinuria is an independent risk factor for 12-month remission, whereas high baseline eGFR is an independent protective factor. In clinical practice, the choice between these agents should involve a careful weighing of risks and benefits based on individual patient characteristics and therapeutic goals to formulate a personalized treatment plan. This study provides evidence comparing the short-term efficacy and safety of these two drugs in refractory MN. However, due to the limitations of the retrospective design, these conclusions warrant further validation through prospective randomized controlled trials.

Disclosure of conflict of interest

None.

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