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ORIGINAL RESEARCH

# Evaluating Efficacy and Safety of Tacrolimus Treatment in Membranous Nephropathy: Results of a Retrospective Study of 182 Patients

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**Purpose:** Tacrolimus is recommended by KDIGO Clinical Practice Guidelines as an initial therapy for the treatment of membranous nephropathy (MN). However, little is known about the factors that influence response and recurrence of the disease after tacrolimus therapy, and there are limited data regarding the duration of tacrolimus treatment. Here, we present a real-world retrospective cohort study of 182 MN patients treated with tacrolimus, aiming to assess the efficacy and safety of tacrolimus in the treatment of MN.

**Patients and Methods:** The clinical data of 182 patients with MN treated with tacrolimus and followed up for at least one year were analyzed retrospectively for the efficacy and safety of tacrolimus.

**Results:** The mean follow-up period was 27.3 (19.3–41.6) months. A total of 154 patients (84.6%) achieved complete or partial remission, and 28 patients (15.4%) did not. Multivariate Cox regression analysis showed that male and higher baseline BMI were independently associated with lower, while higher serum albumin was associated with higher probability of remission. Among the responders, 56 patients (36.4%) relapsed. After adjustments for age and sex, Cox regression analysis revealed that the longer period of full-dose tacrolimus was administered, the lower the incidence of relapse. However, high levels of serum creatinine and proteinuria at the onset of tacrolimus discontinuation were risk factors for relapse. During the treatment of tacrolimus, a decline in renal function (≥50% increase in serum creatinine after the onset of tacrolimus treatment) was the most common adverse reaction, observed in 20 (11.0%) patients, followed by elevated blood glucose and infection, but the latter two occurred mostly during treatment with tacrolimus plus corticosteroids.

**Conclusion:** Tacrolimus is effective in the treatment of MN, but the relapse rate is high. Clinical studies with larger sample sizes are needed to further explore the use of tacrolimus in the treatment of membranous nephropathy.

**Keywords:** membranous nephropathy, tacrolimus, response, relapse, safety

## Introduction

Membranous nephropathy (MN) is one of the most common pathologies that cause adult nephrotic syndrome (NS) and its prevalence has increased significantly in recent years.[1–4] The prognosis of MN is variable, and approximately 40% of patients with MN can achieve complete remission of NS. However, approximately 20% are poorly responsive to immunosuppressive therapy and eventually progress to end-stage renal disease (ESRD).[5–7]

It is widely accepted that corticosteroid monotherapy for the treatment of MN is ineffective.[8] Calcineurin inhibitors (CNIs), either cyclosporine or tacrolimus, and rituximab, were recommended by the KDIGO Clinical Practice Guidelines as the major regimens for initial therapy in patients with MN.[9] Tacrolimus, which has been used more frequently in clinical practice, serves an immunosuppressive role through blocking transcription in early T cell lymphocytes and



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inhibiting the activation and proliferation of T cells.[10] Several studies have revealed the efficacy of tacrolimus treatment in MN, with a relatively high remission rate and mild toxicity and side effects.[11–13] But the relapse rate of MN is high during tacrolimus withdrawal.[13,14] Little is known about the factors that influence response and recurrence of the disease after tacrolimus therapy, and there are limited data regarding the duration of tacrolimus treatment. Here, we present a real-world retrospective cohort study of 182 MN patients treated with tacrolimus, aiming to assess the efficacy and safety of tacrolimus in the treatment of MN and identify factors that could predict the remission and relapse.

# Materials and Methods

## Subjects

A total of 182 patients with biopsy-proven MN hospitalized at the First Medical Center of PLA General Hospital from January 1, 2014, to December 31, 2019, were included. The inclusion criteria were as follows: age ≥18 years; the follow-up period ≥1 year; having received treatment with tacrolimus. We excluded participants if they (1) were diagnosed as secondary membranous nephropathy (including membranous nephropathy caused by hepatitis B, autoimmune disease, tumor, etc.); (2) had other concomitant glomerulonephritis; (3) had end-stage renal disease (ESRD), i.e., estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 $m^2$, on dialysis or other renal replacement therapy; (4) had severe complications upon renal biopsy, such as severe infection, neoplasm, active hepatitis B, HIV, and severe liver injury; (5) were during pregnancy and lactation. Demographics and clinical data were collected from patients who met the eligibility criteria. The date each patient started receiving tacrolimus was the baseline time of the study. Events that occurred during follow-up were recorded, including complete remission, partial remission, relapse, and adverse reactions. The follow-up period was the time interval (in months) between the start of tacrolimus treatment and the last visit. The follow-up period ended in February 2022.

## Treatment Regimen

All patients were treated with tacrolimus, initially administered orally in two daily doses, 12 hours apart. The regimen of tacrolimus taper was judged by the clinician based on the efficacy and the patient's tolerability. In this study, we defined full-dose tacrolimus treatment as a tacrolimus dose ≥0.04 mg/kg/d, and results in a plasma concentration ranging between 4 and 10 ng/mL. In cases with a combined use of corticosteroids, the starting dose of the corticosteroid was recorded (mg/kg/d).

## Definitions

Nephrotic syndrome is defined by urinary protein excretion ≥3.5 g/24 h and serum albumin ≤30 g/L. Complete remission (CR) is defined by urinary protein excretion <0.3 g/24 h and serum albumin >35 g/L. Partial remission (PR) is defined by urinary protein excretion 0.3–3.5g/24 h, and a ≥50% reduction in the 24h proteinuria from baseline, accompanied by stable renal function. Non-remission is defined by serum albumin <30 g/L, a decrease in the 24h urinary protein excretion <50% from baseline, and worsening of renal function. Relapse is defined by the recurrence of proteinuria consistent with nephrotic syndrome (three consecutive measurements of protein in urine >3.5 g/24 h) after complete or partial remission. ESRD is defined by an eGFR <15 mL/min/1.73 $m^2$, or requiring renal replacement therapy. Nephrotoxicity is defined by an increase in serum creatinine of ≥50% from baseline after ruling out and adjusting for functional factors.[13] eGFR is estimated by the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formula.

## Statistical Analysis

Data were processed and statistically analyzed using SPSS software version 26.0 (IBM SPSS, USA). Normality of data was tested by Kolmogorov–Smirnov test. Continuous variables with normal or symmetrical distribution were expressed as mean ± standard deviation, where those of non-normal distribution as median (interquartile range), i.e. [M (O1, Q3)]. Group differences were analyzed by *t*-test or rank sum test of two independent samples. Categorical variables are expressed as absolute value n (%), and group comparisons were performed by Chi-square test. Kaplan–Meier curves and multivariate Cox proportional hazards analysis were used to evaluate the associations between baseline variables and

outcomes. Parameters with a $p$-value <0.15 in univariate analysis were then introduced in multivariate Cox regression analysis. All tests were two-sided, and a $p$-value <0.05 is considered statistically significant.

# Results

## Baseline Characteristics of Subjects

A total of 182 patients with MN who met the eligibility criteria were included in this study and the main clinical characteristics at baseline are presented in Table 1. The majority of patients had normal renal function at baseline. A total of 37 patients (20.3%) had used corticosteroids and/or immunosuppressants before starting treatment with tacrolimus, including cyclophosphamide, mycophenolate mofetil (MMF), calcineurin inhibitors, leflunomide, and *Tripterygium wilfordii*.

## Tacrolimus Use

The mean follow-up period was 27.3 (19.3–41.6) months. Tacrolimus was used for an average of 19.2 (12.5–27.9) months. A total of 13 patients used tacrolimus for less than six months. Among them, five discontinued tacrolimus due to pulmonary infection, one due to diabetes, one due to herpes zoster and diabetes, three due to non-remission and a change of the treatment regimen, one due to partial remission, and two due to poor compliance. Of the 182 patients included in the study, nine did not take full-dose tacrolimus from the start to the end (five of whom were co-administered with corticosteroids); 12 did not take full-dose tacrolimus initially but did during the course of visits; and information on the length of full-dose tacrolimus use was missing in seven patients. The mean course of full-dose tacrolimus was 8.7 (3.8–14.6) months, and the mean duration of tacrolimus taper was 7.8 (0–15.2) months.

**Table 1** Baseline Characteristics of Enrolled Subjects

| Items | Total (n=182) |
|---|---|
| Age (years) | 46 (32–56) |
| Male (n, %) | 116 (63.7%) |
| BMI (kg/m$^2$) | 26.2 (23.7–28.7) |
| Baseline eGFR (mL/min/1.73 m$^2$) | 98.68±20.55 |
| eGFR<60 (n, %) | 8 (4.4%) |
| Blood creatinine (μmol/L) | 75.67±20.75 |
| Proteinuria (g/24 h) | 4.67 (3.22–6.55) |
| Serum albumin (g/L) | 25.89±5.76 |
| PLA2R (Ru/mL) | 27.86 (5.30–96.85) |
| Plasma tacrolimus concentration (ng/mL) | 5.10 (3.90–7.65) |
| Nephrotic syndrome (n, %) | 114 (62.6%) |
| Initial dose of tacrolimus (mg/kg/d) | 0.045±0.014 |
| Concomitant RAS blockers (n, %) | 121 (66.5%) |
| Concomitant corticosteroids (n, %) | 70 (38.5%) |
| Prior use of corticosteroids and/or immunosuppressants (n, %) | 37 (20.3%) |
| Pathological stage (n, %) | |
| I | 90 (49.5%) |
| II | 85 (46.7%) |
| III | 7 (3.8%) |
| IV | 0 |
| With intrarenal arteriosclerosis (n, %) | 26 (14.3%) |
| With chronic tubulointerstitial injury (n, %) | 6 (3.3%) |

**Abbreviations**: BMI, body mass index; eGFR, estimated glomerular filtration rate; PLA2R, anti-phospholipase A2 receptor antibody.

## Remission and Its Influencing Factors

A total of 154 patients (84.6%) achieved a remission. Of them, 91 (50.0%) achieved complete remission and 63 (34.6%) achieved partial remission. There were 28 patients (15.4%) who did not respond to tacrolimus treatment. The mean time from baseline to partial remission was 3.7 (1.7–7.3) months, and the mean time from baseline to complete remission was 10.1 (6.4–15.6) months. The numbers of patients who achieved a remission (including partial remission and complete remission) at 3, 6, 9, 12, 18, and 24 months were 33 (18.1%), 57 (31.3%), 78 (42.9%), 105 (57.7%), 138 (75.8%), and 146 (80.2%), respectively (Figure 1). Table 2 shows the characteristics of the responder and the non-responder group. The serum albumin levels at baseline were significantly higher, while BMI, and the anti-phospholipase A2 receptor antibody (PLA2R) titers at baseline were significantly lower in the responder group compared with those in the non-responder group. There were no significant differences in other parameters at baseline between the two groups. Multivariate Cox regression analysis showed that male and higher baseline BMI were independently associated with lower probability of remission, while higher serum albumin was associated with higher probability of remission (Table 3).

Of the 28 patients who did not respond to tacrolimus treatment, 11 continued to receive tacrolimus; eight switched to a regimen of corticosteroids plus cyclophosphamide (one switched to tacrolimus alone later and another to rituximab); four switched to cyclosporine (one switched to full-dose tacrolimus later and another to rituximab); one switched to a regimen of corticosteroids plus *Tripterygium wilfordii*, then to tacrolimus later; one switched to *Tripterygium wilfordii* alone; two switched to corticosteroids alone; and one did not receive corticosteroids and/or immunosuppressants, and was treated with RAAS (renin-angiotensin-aldosterone-system) inhibitors and Chinese patent medicine.

## Relapse and Its Influencing Factors

Of the 154 patients in remission, 56 (36.4%) experienced a relapse. A total of 21 (23.1%) of the 91 patients with complete remission relapsed, with a mean time from complete remission to relapse of 13.5 (7.5–36.7) months (Figure 2), while 35 of the 63 patients (55.6%) with partial remission relapsed, with a mean time from partial remission to relapse of 8.3 (3.8–14.3) months (Figure 3). In terms of the point of relapse, 20 patients relapsed during tacrolimus tapering, 22 relapsed after discontinuation of tacrolimus, three did not take full-dose tacrolimus from the start to the end, and 11 relapsed on full-dose tacrolimus. There was no significant difference in age, gender, baseline BMI, eGFR, serum albumin, proteinuria, initial dose of tacrolimus, and concomitant use of corticosteroids or RAS blockers, the period of full-dose tacrolimus and the duration of tacrolimus tapering between patients who relapsed and those who did not. The amount of proteinuria at the onset of tacrolimus tapering was significantly higher in patients who relapsed compared with those who did not. And serum creatinine and proteinuria upon discontinuation of tacrolimus were significantly higher in relapsing patients. In the multivariable COX analysis adjusting for age and gender, the longer the course of full-dose tacrolimus, the lower the chance of relapse. Higher serum creatinine and proteinuria upon discontinuation of tacrolimus were found to be risk factors for disease relapse (Table 4).

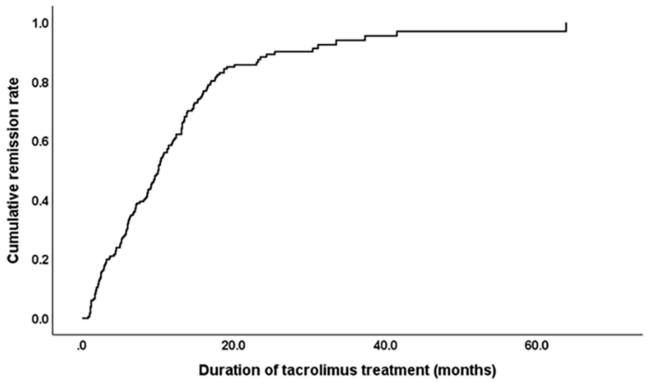


**Figure 1** Cumulative remission rate during tacrolimus treatment.

**Table 2** Characteristics of Responders and Non-Responders

| Items | Responders (n=154) | Non-Responders (n=28) | *p*-value |
|---|---|---|---|
| Age (years) | 46 (32–56) | 43 (32–57) | 0.964 |
| Male (n, %) | 95 (61.7%) | 21 (75.0%) | 0.178 |
| BMI (kg/m$^2$) | 26.1 (23.3–28.4) | 28.4 (24.8–33.6) | 0.008 |
| eGFR (mL/min/1.73 m$^2$) | 98.73±20.90 | 98.41±18.79 | 0.940 |
| Blood creatinine (μmol/L) | 75.36±20.42 | 77.41±22.79 | 0.631 |
| Proteinuria (g/24 h) | 4.58 (3.15–6.44) | 5.37 (3.32–6.99) | 0.204 |
| Serum albumin (g/L) | 26.36±5.73 | 23.26±5.28 | 0.008 |
| PLA2R (Ru/mL) | 24.90 (4.73–88.29) | 42.43 (23.76–261.48) | 0.023 |
| Nephrotic syndrome (n, %) | 94 (61.0%) | 20 (71.4%) | 0.296 |
| Initial dose of tacrolimus (mg/kg/d) | 0.046±0.013 | 0.040±0.015 | 0.056 |
| Concomitant RAS blockers (n, %) | 102 (66.2%) | 19 (67.9%) | 0.867 |
| Concomitant corticosteroids (n, %) | 59 (38.3%) | 11 (39.3%) | 0.922 |
| Prior use of corticosteroids and/or immunosuppressants (n, %) | 30 (19.5%) | 7 (25%) | 0.504 |
| Period of full-dose tacrolimus (months) | 9.4 (4.5–15.4) | 7.2 (2.8–12.0) | 0.144 |

**Abbreviations**: BMI, body mass index; eGFR, estimated glomerular filtration rate; PLA2R, anti-phospholipase A2 receptor antibody.

**Table 3** Factors Predicting Remission of Tacrolimus Treatment in Univariate and Multivariate Analysis

| Items | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | *p*-value | HR | 95% CI | *p*-value |
| Age (years) | 0.991 | 0.979–1.003 | 0.126 | | | |
| Gender (M vs F) | 0.721 | 0.518–1.003 | 0.052 | 0.633 | 0.406–0.989 | 0.045 |
| BMI (kg/m$^2$) | 0.948 | 0.915–0.982 | 0.003 | 0.941 | 0.893–0.993 | 0.026 |
| eGFR (mL/min/1.73 m$^2$) | 1.004 | 0.996–1.013 | 0.304 | | | |
| Proteinuria (g/24h) | 0.927 | 0.868–0.990 | 0.024 | | | |
| Serum albumin (g/L) | 1.047 | 1.017–1.078 | 0.002 | 1.053 | 1.003–1.106 | 0.037 |
| PLA2R (Ru/mL) | 0.998 | 0.996–1.000 | 0.015 | | | |
| Nephrotic syndrome (n, %) | 0.760 | 0.548–1.055 | 0.101 | | | |
| Concomitant RAS blockers (n, %) | 1.192 | 0.851–1.670 | 0.307 | | | |
| Concomitant corticosteroids (n, %) | 1.229 | 0.885–1.706 | 0.218 | | | |
| Prior use of corticosteroids and/or immunosuppressants (n, %) | 0.988 | 0.662–1.475 | 0.953 | | | |
| Period of full-dose tacrolimus (months) | 0.972 | 0.955–0.990 | 0.002 | | | |

**Abbreviations**: BMI, body mass index; eGFR, estimated glomerular filtration rate; PLA2R, anti-phospholipase A2 receptor antibody.

For treatment regimen after relapse, eight patients were treated with other corticosteroids and/or immunosuppressants (two with corticosteroids alone, one with cyclophosphamide alone, one with corticosteroids plus cyclosporine, two with corticosteroids plus cyclophosphamide, one with corticosteroids plus leflunomide and later with tacrolimus, one with rituximab, and one with rituximab plus corticosteroids); 14 patients received an increased dose of tacrolimus, with two of them also receiving corticosteroids and two also receiving cyclophosphamide; 11 patients continued to receive the original dose of tacrolimus, with one of them also receiving corticosteroids; tacrolimus was reintroduced in 12 patients, and three of these also received corticosteroids; one patient was treated with Chinese herbal medicines; and the treatment was unknown for five patients.

## Adverse Events

A total of 38 patients (20.9%) developed adverse reactions during the treatment of tacrolimus. A decline in renal function (≥50% increase in serum creatinine after the onset of tacrolimus treatment) was observed in 20 (11.0%) patients, and 15 of them serum creatinine normalized after taper or discontinuation of tacrolimus. Newly developed hyperglycemia

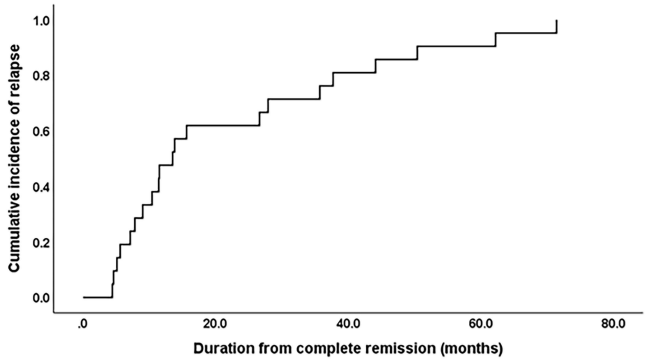


**Figure 2** Cumulative incidence of relapse after complete remission.

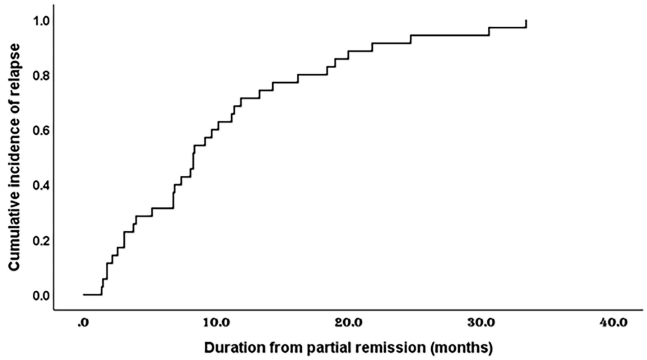


**Figure 3** Cumulative incidence of relapse after partial remission.

occurred in 13 patients (7.1%), eight of whom occurred during treatment with tacrolimus plus corticosteroids. There were seven cases of infection (3.8%), all occurring during treatment with tacrolimus plus corticosteroids, including six cases of severe pulmonary infection and one case of herpes zoster. There were two cases of hypertension (1.1%), which both

**Table 4** Factors Predicting Relapse of Tacrolimus Treatment in Univariate and Multivariate Analysis

| Items | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | *p*-value | HR | 95% CI | *p*-value |
| Age (years) | 0.996 | 0.977–1.015 | 0.675 | | | |
| Gender (M vs F) | 1.387 | 0.796–2.418 | 0.248 | | | |
| BMI (kg/m$^2$) | 1.038 | 0.970–1.111 | 0.276 | | | |
| eGFR (mL/min/1.73 m$^2$) | 0.997 | 0.984–1.010 | 0.667 | | | |
| Proteinuria (g/24 h) | 1.042 | 0.939–1.156 | 0.443 | | | |
| Serum albumin (g/L) | 1.017 | 0.970–1.065 | 0.489 | | | |
| PLA2R (Ru/mL) | 0.999 | 0.996–1.003 | 0.736 | | | |
| Concomitant RAS blockers (n, %) | 0.954 | 0.549–1.657 | 0.866 | | | |
| Concomitant corticosteroids (n, %) | 1.278 | 0.747–2.186 | 0.370 | | | |
| Prior use of corticosteroids and/or immunosuppressants (n, %) | 1.493 | 0.811–2.748 | 0.198 | | | |
| Nephrotic syndrome (n, %) | 0.946 | 0.549–1.629 | 0.840 | | | |
| Course of full-dose tacrolimus (months) | 0.964 | 0.932–0.997 | 0.034 | 0.816 | 0.674–0.988 | 0.037 |
| Duration of tacrolimus tapering (months) | 0.984 | 0.959–1.009 | 0.197 | | | |
| Blood creatinine upon tacrolimus taper (n=103) | 1.003 | 0.987–1.019 | 0.725 | | | |
| Proteinuria upon tacrolimus tapering (n=103) | 1.300 | 1.082–1.561 | 0.005 | | | |
| Serum creatinine upon discontinuation of tacrolimus (n=64) | 1.032 | 1.012–1.053 | 0.002 | 1.084 | 1.005–1.168 | 0.036 |
| Proteinuria upon discontinuation of tacrolimus (n=64) | 1.623 | 1.383–1.903 | 0.000 | 1.832 | 1.216–2.759 | 0.004 |

**Abbreviations**: BMI, body mass index; eGFR, estimated glomerular filtration rate; PLA2R, anti-phospholipase A2 receptor antibody.

occurred during tacrolimus monotherapy. There was one case (0.5%) of infectious eczema-like dermatitis and one case (0.5%) of gastric ulcer, both occurring during treatment with tacrolimus plus corticosteroids.

## Discussion

The introduction of novel immunosuppressants offers hope for effective, low toxicity treatment of patients with MN. Calcineurin inhibitors (CNIs), such as cyclosporine and tacrolimus, can inhibit the activation and proliferation of T cells and has been widely used as an immunosuppressive agent.[15,16] In addition, CNIs can directly target podocytes, thereby reducing proteinuria.[17] The 2012 KDIGO Clinical Practice Guideline for Glomerulonephritis recommends rituximab or cyclophosphamide and alternate month glucocorticoids for 6 months, or CNI-based therapy for ≥6 months for patients with MN and at least one risk factor for disease progression.[18] One clinical study showed that CNIs increased the likelihood of partial or complete remission of proteinuria compared with no treatment (72–75% vs 22%) and that the remission rate at 12 months of treatment was comparable to and numerically higher than that of cyclophosphamide (71–89% for CNIs; 65–77% for cyclophosphamide).[19] In a retrospective study, tacrolimus induced remission of membranous nephropathy in 84% of patients.[20] A randomized, controlled, multicenter study conducted in China showed that tacrolimus led to a significantly higher rate of remission of NS compared with cyclophosphamide in the treatment of MN (85% vs 65%).[21] Our study revealed that 84.6% patients achieved remission, and the rates of remission were 18.1%, 31.3%, 57.7%, 75.8%, and 80.2% at 3, 6, 12, 18, and 24 months, respectively, which were generally consistent with the remission rates reported in literatures.

The serum albumin levels at baseline were significantly higher, while BMI, and the PLA2R titers were significantly lower in the responder group than in the non-responder group. Multivariate Cox regression analysis showed that male and higher baseline BMI were independently associated with lower probability of remission, while higher serum albumin was associated with higher probability of remission. The identification of PLA2R is a landmark in the better understanding and management of MN. The level of PLA2R correlates with the severity of disease; thus can help monitor disease interaction and predict prognosis.[22–24] Cohort studies on IgA nephropathy and polycystic kidney disease suggest that BMI is a risk factor for the progression of chronic kidney disease.[25,26] Obesity increases the risk of kidney injury through mechanisms such as insulin resistance, lipotoxicity, dysregulation of adipocytokines, elevated blood pressure, and elevated glomerular blood pressure.[27,28] In the current study, although the dose of tacrolimus was calculated by weight, BMI was significantly higher in the non-responder group compared with the responder group and it was deemed a risk factor for remission. Previous studies have reported that low serum albumin levels at baseline are a risk factor for a lack of spontaneous remission of membranous nephropathy and progression to NS,[29] which was consistent with findings in this study.

One of the shortcomings of tacrolimus in the treatment of MN was the high rate of relapse. Several studies suggest a high relapse rate of MN when treated with CNIs.[30,31] In a randomized control trial, 40% of patients treated with tacrolimus and 7% of patients treated with cyclophosphamide relapsed within 12 months after remission.[14] In a retrospective study of 408 patients with MN, 37.3% patients relapsed after complete or partial remission.[29] However, the factors that associated with relapse remain unclear. The results of this study showed that 36.4% patients relapsed after remission. After adjustments for age and sex, a longer period of full-dose tacrolimus was found to be associated with a lower probability of relapse, whereas high levels of serum creatinine and proteinuria at the onset of tacrolimus discontinuation were risk factors for disease relapse. At present, the duration of tacrolimus treatment, and the timing and indications for tacrolimus taper and discontinuation remains inclusive. The 2012 KDIGO Clinical Practice Guideline for Glomerulonephritis recommends tapering CNIs to 50% of the initial dose within 4–8 weeks if a complete or partial remission has been achieved and if no CNI-related nephrotoxicity occurs, with a total course of at least 12 months (2C) with tacrolimus for MN.[9] However, some studies have shown that a longer course of treatment (24 months)[32] or a longer period of dose tapering can reduce relapse.[20,29] Studies also suggested that relapsing patients had higher levels of proteinuria at the start of tacrolimus taper,[20] which is consistent with the findings of this study. These results shed light on clinical practice, as they suggest that for patients with higher levels of proteinuria, a longer course of tacrolimus may be desirable, but a longer course of tacrolimus may be related to the adverse event of increased nephrotoxicity. Therefore, the relationships of the dose and course of tacrolimus with the long-term efficacy and relapse rate should be further studied in MN.

Tacrolimus has a narrow therapeutic window and should be monitored for possible adverse effects. Nephrotoxicity is the most common adverse reaction of tacrolimus. Tacrolimus-related nephrotoxicity is associated with reversible or irreversible histological damage to the kidney, which can occur in the glomeruli, arterioles, and tubular interstitium, but most lesions are non-specific.[33,34] In addition, elevated blood glucose, gastrointestinal symptoms, hepatotoxicity, hypertension, gouty arthritis, tremor, infection, and rarely epilepsy have been reported during treatment with tacrolimus.[35] In this study, 11.0% patients experienced a ≥50% increase in serum creatinine. Blood glucose increased in 7.2% patients, infection occurred in 3.8% patients, hypertension in 1.1% patients, infectious eczema-like dermatitis in one patient, and gastric ulcer in one patient. However, it is important to note that the majority of these adverse effects occurred during the use of tacrolimus in combination with corticosteroids and they may therefore be side effects of corticosteroids as elevated blood glucose, infection, and gastric ulcer are known common adverse effects of corticosteroids. The findings on adverse effects suggest that patients with membranous nephropathy should be followed up regularly and should take protective measures, such as wearing a mask, and also clinicians should closely monitor the patient's response and adverse reactions to treatment.

There exit some limitations. Because of the retrospective nature, it is difficult to control the patient adherence and the duration of tacrolimus treatment, which may influence the efficacy of tacrolimus. What is more, data in the current study were collected from the medical records. There was no standardized induction and maintenance therapy regimen for tacrolimus and concomitant medications such as corticosteroids, so the remission rate observed in this study might be overestimated to some extent. To more precisely explore the efficacy and safety of tacrolimus for MN, well-controlled clinical trials with larger sample size and longer follow-up period are needed.

## Conclusions

The results of this study suggest that tacrolimus is effective in the treatment of MN, providing a high remission rate. A high rate of relapse was also observed in our study. High levels of serum creatinine and proteinuria at the onset of tacrolimus discontinuation were risk factors for relapse. In addition, we found that the longer the period of full-dose tacrolimus, the lower the chance of relapse. However, longer course of tacrolimus also associated with increased risk of adverse reactions. Clinical studies with larger sample sizes are needed to further explore the use of tacrolimus, especially the optimal full-dose and tapering strategy, in the treatment of membranous nephropathy.

## Ethics Approval Statement

The study protocol was approved by the Medical Ethics Committee of the Chinese PLA General Hospital (Approval No. of Ethics Committee S2022-588-01). The requirement for written informed consent was waived by this institution due to the retrospective nature of the study. Decisions letter of Ethics Committee covered patient data confidentiality and compliance with the Declaration of Helsinki.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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