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ORIGINAL RESEARCH

How to Choose Treatment Regimens for Idiopathic Membranous Nephropathy Patients with PLA2R-Negative: A Single-Center Retrospective Cohort Study

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Background: Cyclophosphamide, tacrolimus, and rituximab (RTX) are first-line treatments for idiopathic membranous nephropathy (IMN), regardless of PLA2R status. While the efficacy of RTX in IMN patients with PLA2R-positive has been well-documented, its effectiveness in IMN patients with PLA2R-negative remains understudied. This study aimed to evaluate the efficacy and adverse events of these three treatment regimens in IMN patients with PLA2R-negative.

Methods: This study included 46 PLA2R-negative IMN patients confirmed by renal biopsy and immunofluorescence from the Department of Nephrology, the Second Affiliated Hospital of Nanchang University between September 2021 and October 2023. We compared clinical remission rates, and side effects at 3, 6, and 12 months follow-up in 14 patients who received prednisolone combined with cyclophosphamide (cyclophosphamide group), in 11 patients who treated with prednisolone combined with tacrolimus (tacrolimus group), and 21 patients who treated with rituximab (RTX group).

Results: Baseline characteristics were similar among the three groups. At the 12-month follow-up, the complete response rate was significantly higher in the cyclophosphamide and tacrolimus groups compared to the RTX group ($p = 0.029$). However, there were no significant differences in cumulative complete remission rates or cumulative composite remission rates among the three groups during the follow-up period ($p = 0.192$, $p = 0.212$). Severe adverse events occurred in all groups, but the differences were not statistically significant ($p > 0.05$).

Conclusion: Cyclophosphamide and tacrolimus appear to offer long-term benefits for PLA2R-negative IMN patients, with tacrolimus demonstrating superior efficacy among the treatment options evaluated. These insights offer important guidance for clinical decision-making in the management of PLA2R-negative IMN. However, further large-scale, multicenter studies with long-term follow-up are necessary to confirm these findings.

Keywords: idiopathic membranous nephropathy, PLA2R-negative, cyclophosphamide, tacrolimus, rituximab

Introduction

Idiopathic membranous nephropathy (IMN) is an autoimmune kidney disease, and the treatment of this disease has made great progress in recent years.[1] M-type phospholipase A2 receptor (PLA2R) is a major target antigen expressed in podocytes, and autoantibodies to PLA2R are responsible for 70–80% IMN patients.[2] Therefore, MN patients with serum anti-PLA2R antibody positive can be diagnosed with PLA2R-associated IMN without the need for renal biopsy.[1,3]

Rituximab (RTX), a chimeric IgG1 monoclonal antibody targeting CD20, depletes CD20 pre-B cells and mature B cells. Mechanically, RTX alleviates IMN by promoting B cell depletion and causing the titer of target antibodies

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decreased, mainly anti-PLA2R and Thrombospondin type-1 domain-containing 7 A antibodies, resulting in reduced immune complex formation in the kidney.[4] In the 2021 KDIGO guidelines, cyclophosphamide, calcineurin inhibitor (CNI)-based therapy such as tacrolimus, and RTX are recommended for IMN patients with or without PLA2R-positive.[3] Multiple studies also confirmed the therapeutic effects of these three regimens.[5–7] Our previous study also revealed no significant difference in complete remission rates of proteinuria between RTX and conventional therapy in IMN patients with or without PLA2R-positive.[8] However, RTX is not effective in all patients with IMN,[5–7] mainly used in IMN patients with PLA2R-positive,[9] there has been scarce research reporting on the efficacy of RTX in IMN patients with PLA2R-negative. In this retrospective study, 46 eligible IMN patients with PLA2R-negative were enrolled and divided into three groups based on treatment. The clinical remission rate, including complete response rate and partial response rate, and adverse event, in these patients were explored. The aim of this study was to investigate the efficacy and adverse events of these three regiments in IMN patients with PLA2R-negative.

Methods

Study Patients

This study is a single-center retrospective analysis. From September 2021 to October 2023, 46 IMN patients with PLA2R-negative confirmed by renal biopsy were recruited from the Department of Nephrology, the Second Affiliated Hospital of Nanchang University (Figure 1). This study was conducted in strict accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Second Affiliated Hospital of Nanchang University (No. 20210912B). All patients signed the informed written consent. Inclusion criteria: (i) Patients diagnosed with

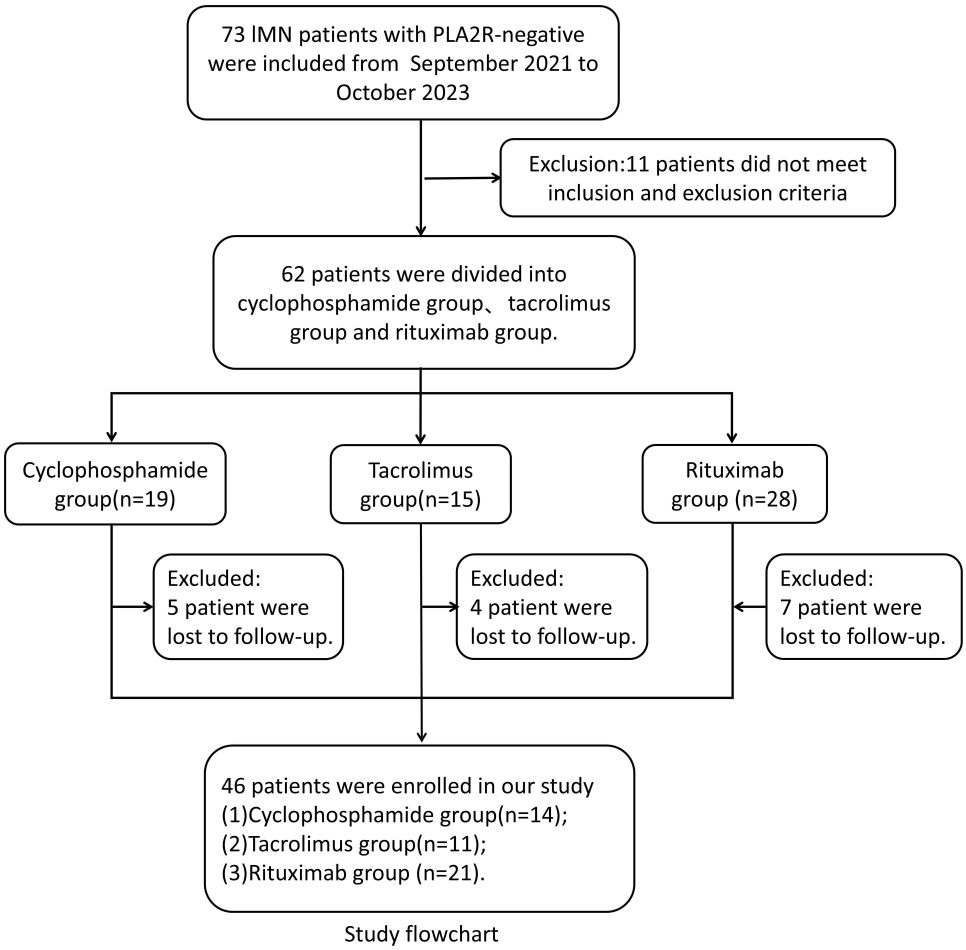

Figure 1 Flowchart of the study.

IMN by renal biopsy, and the expression of PLA2R in kidney tissue was confirmed negative by the immunofluorescence; (ii) Patients met the diagnostic criteria for nephrotic syndrome; (iii) No treatment with glucocorticoids or immunosuppressants before renal biopsy. (iv) The neoplastic lesions were excluded by PET-CT.

Exclusion criteria: (i) Patients with type 1 or type 2 diabetes; (ii) Secondary MN, such as connective tissue disease, malignancy, or hepatitis B virus; (iii) The presence of active infection, or pregnancy or breastfeeding; (iv) Having received glucocorticoids or immunosuppressants therapy within the last 3 months; (v) Severe liver dysfunction or cardiovascular disease.

Interventions

According to the guideline recommendations, the RTX regimen involved an infusion of 1000 mg on day 1 and day 15. Cyclophosphamide was administered by intravenous infusion (0.5 to 0.75 g/m^2/month, maximum dose is 1 g/month). Stop dosing when the cumulative dose of cyclophosphamide reaches 9 to 10g. The tacrolimus regimen was oral tacrolimus (0.05 mg/Kg/day), and the target blood concentration is 5–7 ng/mL. The dose of tacrolimus was reduced in cases of impaired renal function. The initial dose of prednisone is 0.5 mg/kg/d during administration of cyclophosphamide or tacrolimus for 1 month, thereafter, tapered gradually over 6 months until discontinuation.

Data Collection and Follow-Up

Patients' medical information, such as age, gender, blood pressure, albuminuria, serum albumin, creatinine, eGFR (calculated by the CKD-EPI formula), and renal pathology data, was collected. All basic tests were completed before immunotherapy. All severe adverse reactions were treated and recorded both in hospitalization and follow-up.

Follow-up will be conducted on all patients at 3, 6, and 12 months after treatment to collect relevant clinical data.

Outcomes

The main outcome of this study is the clinical response rate during the follow-up period. Clinical response includes complete response (CR) and partial response (PR). CR:Urinary protein excretion≤0.3g/d; Serum albumin≥35g/L. PR: Urinary protein<3.5 g/d, 50% lower than baseline; Serum albumin≥35g/L. Composite remission comprises CR or PR.

The severe adverse events were documented, such as infection, leukopenia, and steroid-induced diabetes as secondary clinical outcomes.

Statistical Analysis

Nonnormally distributed data are represented by the median (Q25 and Q75), and continuous variables are compared using the Wilcoxon rank sum test. Normal distribution data is represented by mean ± SD, and continuous variable comparison is performed using *t*-test. Categorical data are represented by counts and percentages, while nominal variables are compared using chi-square tests. The cumulative response rate was calculated using Kaplan–Meier method and evaluated by log rank. Double tailed P<0.05 is considered statistically significant. SPSS version 22.0 (SPSS Inc., Chicago, Illinois, USA) was used to analyze all data.

Results

Study Participants

As presented in Table 1, 46 IMN patients with PLA2R-negative were enrolled in this retrospective study. Among the 46 patients, fourteen patients in cyclophosphamide group, the average age is 49.5 years (42.75,58.25), the average level of proteinuria is 7.80 g/d (5.41,13.73), eleven patients in tacrolimus group, the average age is 48 years (37,59), the average level of proteinuria is 8.32 g/d (5.61,13.11), twenty-one patients in RTX group, the average age is 55 years (38.5,64), the average level of proteinuria is 8.46 g/d (6.60,12.46).

Other clinical indices at baseline included age, sex, blood pressure, albumin, scr, and eGFR. These data were similar among three groups.

Table 1 Baseline Characteristics of IMN Patients with PLA2R-Negative in Cyclophosphamide, Tacrolimus and Rituximab Groups

Characteristics	Cyclophosphamide Group	Tacrolimus Group	Rituximab Group	*P*
Number of patients	14	11	21	
Age (years)	49.5(42.75,58.25)	48(37,59)	55(38.5,64)	0.707
Gender, n(%)				0.119
Males	10(71.4%)	5(45.5%)	17(81.0%)	
Females	4(28.6%)	6(54.5%)	4(19.0%)	
BP(mmHg)				
SBP	126.86±17.31	125.45±20.82	129.81±21.16	0.822
DBP	90.80±16.14	83.18±12.78	83.48±11.66	0.314
Proteinuria (g/24 h)	7.80(5.41,13.73)	8.32(5.61,13.11)	8.46(6.60,12.46)	0.888
ALB (g/L)	25.66(22.07,27.58)	27.34(20.93, 28.32)	24.74(21.70, 27.56)	0.852
scr (μmol/L)	87.59±29.28	82.65±25.13	93.84±37.73	0.641
eGFR(mL/min/1.73 m^2)	88.96±30.37	94.72±25.88	86.18±25.66	0.703

Note: *P*< 0.05 was statistical difference.
Abbreviations: ALB, albumin; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; scr, serum creatinine; eGFR, estimated glomerular filtration rate.

Primary Outcomes Comparison Among Three Groups

The primary outcomes by the end of 12 months are summarized in Table 2. The CR rates at 3 months and 6 months for cyclophosphamide, tacrolimus and RTX group showed no statistical significance (17.1%(1/14), 9.1%(1/11), 0.0%(0/21), *p*=0.29; 21.4%(3/14), 9.1%(1/11), 19%(4/21), *p*=0.782) (Figure 2A and B). By the end of 12 months, the CR rates were 50% (7/14), 72.7% (8/11), and 23.8% (5/21) for cyclophosphamide group, tacrolimus group and RTX group, respectively, and there was a statistically significant difference (*p*=0.029). Furtherly, we found that tacrolimus is the most effective regimen among three treatments (cyclophosphamide vs tacrolimus, *p*=0.414; cyclophosphamide vs RTX, *p*=0.153; tacrolimus vs RTX, *p*=0.021). The composite remission rates for three groups showed no statistical significance at 3 months (71.4%, 63.6%, 47.6%, *p*=0.198), 6 months (78.6%, 90.9%, 66.7%, *p*=0.346), and 12 months (92.9%, 100%, 85.7%, *p*=0.546) (Figure 2A and B). Moreover, the cumulative CR rate and the cumulative composite remission rate were similar among three groups analyzed by Kaplan–Meier method (*p* = 0.192, *p* = 0.212) (Figure 2C and D).

By the end of 12 months, the levels of proteinuria for three groups were 0.3g/d (0.18, 0.61), 0.23 g/d (0.17, 0.59), and 0.65 g/d (0.27, 1.92), and there was no statistical significance (*p*=0.173). Besides, the levels of serum ALB for three groups at 12 months were 41.18g/L (39.55, 43.46), 41.54g/L (39.10, 44.80), and 40.08g/L (37.46, 42.95), and there was no statistical significance (*p*=0.335).

At 3, 6, and 12 months, there was no statistically significant difference in the changes of clinical indicators among three groups (Figure 3A–E). Compared with baseline, proteinuria was significantly reduced in all three groups at 12 months (p<0.001).

Table 2 Comparison of Outcomes and Laboratory Index in Cyclophosphamide, Tacrolimus and Rituximab Groups for the 12-months Follow-up

Characteristics	Cyclophosphamide Group(n=14)	Tacrolimus Group(n=11)	Rituximab Group(n=21)	*P*
Composite remission, n (%)	13(92.9%)	11(100%)	18(85.7%)	0.546
Complete remission, n (%)	7(50.0%)	8(72.7%)	5(23.8%)	**0.029**
Proteinuria (g/24 h)	0.30(0.18,0.61)	0.23(0.17,0.59)	0.65(0.27,1.92)	0.173
ALB (g/L)	41.18(39.55,43.46)	41.54(39.10, 44.80)	40.08(37.46,42.95)	0.335
scr (μmol/L)	84.79±26.13	86.01±41.92	80.57±18.74	0.885
eGFR(mL/min/1.73 m^2)	89.11±25.01	87.03±36.54	90.71±20.16	0.947

Note: P< 0.05 was statistical difference. The data in bold means the complete remission rate among three groups is of significant.
Abbreviations: ALB, albumin; scr, serum creatinine; eGFR, estimated glomerular filtration rate.

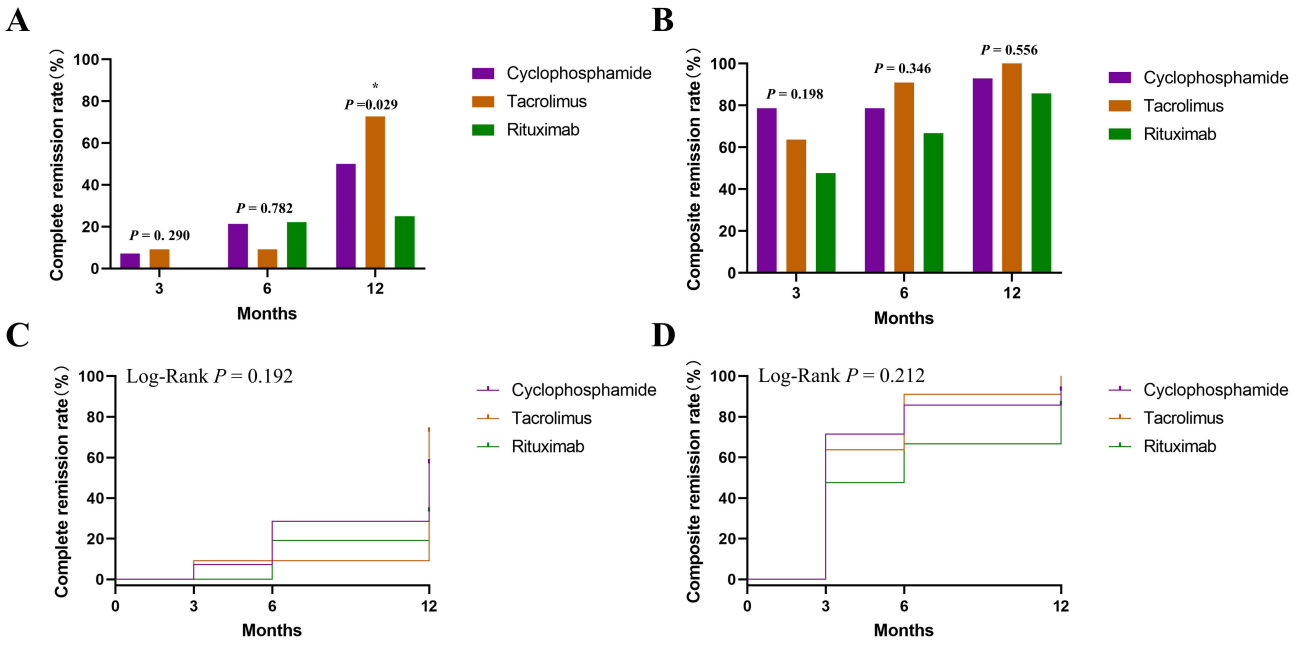

Figure 2 Complete remission rate and composite remission rate in the patients with IMN with PLA2R-negative. (**A**) Complete remission rate among three groups. (**B**) composite remission rate among three groups. (**C** and **D**) Kaplan-Meier survival analysis showed that the cumulative complete remission rate and the cumulative composite remission rate among three groups.
Note: *p<0.05.

Safety Evaluation

The main adverse events during 12 months follow-up were observed among three groups (Table 3).

During the whole follow-up period, there were 4 patients (28.6%) experienced new-onset steroid induced-diabetes in cyclophosphamide group (median time to onset: 2.5 months), and three of them recovered after medication or insulin therapy. There was the only one patient with leucopenia occurred in cyclophosphamide group.

One patient suffered infection in cyclophosphamide group (7.1%) and tacrolimus group (9.1%). In terms of steroid induced-diabetes, one patient (9.1%) was observed in tacrolimus group at the first month.

Additionally, 3 patients (14.3%) experienced infections in RTX group. The main organs affected include the lungs, urinary tract and digestive system, with a median onset of 3 months.

There is no significantly different of adverse events occurred among three groups (p= 0.11, p= 0.31, p=0.78).

Discussion

In the 2021 KDIGO guidelines, cyclophosphamide, CNI-based therapy such as tacrolimus, and RTX are recommended for IMN patients with or without PLA2R-positive.[3] In clinical practice, it is really difficult to choose the treatment regimen for IMN patients with PLA2R-negative. In this single-center retrospective study, we compared the therapeutic effects of cyclophosphamide, tacrolimus and rituximab in IMN patients with PLA2R-negative. The results showed that the rate of CR in cyclophosphamide or tacrolimus group at 12 months was higher than that in the RTX group, which means that cyclophosphamide or tacrolimus may be more suitable for PLA2R-negative IMN patients.

Rituximab (RTX), a chimeric IgG1 monoclonal antibody targeting CD20, depletes CD20 pre-B cells and mature B cells. Mechanically, RTX alleviates IMN mainly by promoting B cell depletion and causing the titer of target antibodies decreased, mainly anti-PLA2R and thrombospondin type-1 domain-containing 7 A antibodies, resulting in reduced immune complex formation in the kidney.[4] However, the complement system plays an activating role in the pathogenesis of IMN.[10] In addition to causing depletion of B cells, RTX has been reported to inhibit complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity,[11] particularly in systemic lupus erythematosus and anti-neutrophil cytoplasmic antibody (ANCA)-related vasculitis where RTX is widely used.[12,13] More importantly, RTX has been proposed as a treatment for C3 glomerulopathy, where the complement system plays an important role in

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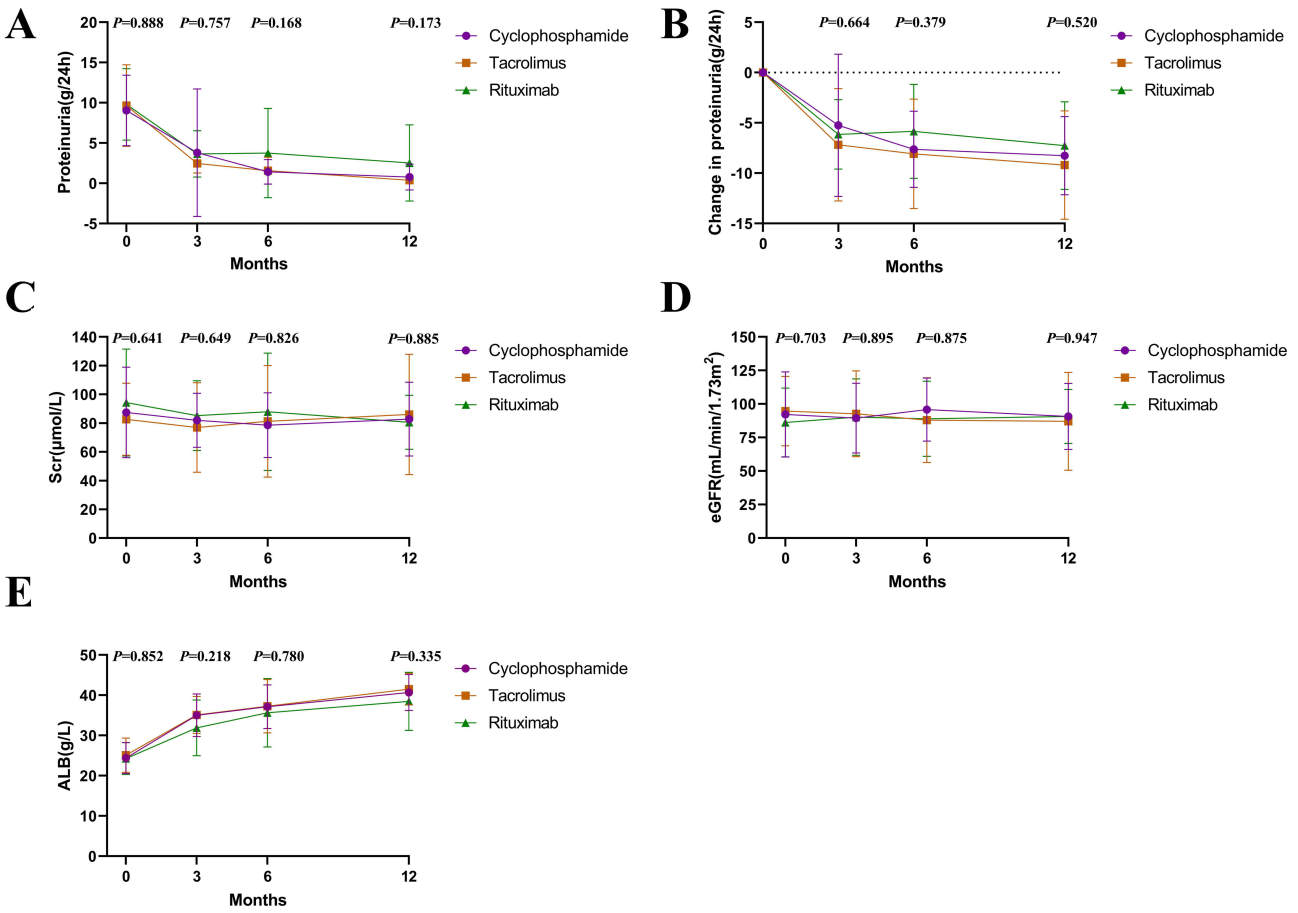

Figure 3 Changes in clinical indicators during follow-up in IMN patients with PLA2R-negative. (**A**) 24h proteinuria. (**B**) change in proteinuria. (**C**) Scr (Serum creatinine). (**D**) eGFR (estimated glomerular filtration rate). (**E**) Serum albumin (ALB).

the absence of immunoglobulin deposition.[14] In addition, RTX can significantly downregulate genes involved in immune cell recruitment, lymphoid tissue and antigen presentation, as well as T cell co-stimulation pathways.[15] These may explain why RTX is effective in IMN patients with PLA2R-negative, but the complete remission rate is low after 12 months of RTX treatment.

Meanwhile, our research findings indicate that patients in the tacrolimus group have an earlier remission period, which is consistent with the results of the MENTOR study.[7] Nevertheless, there was no statistical difference in the rate of complete remission at 12 months of follow-up between the cyclophosphamide and tacrolimus groups. However, the complete remission in RTX group is lower at 12 months of follow-up. Besides, we found that tacrolimus is the most

Table 3 Summary of Adverse Events (AEs) in Cyclophosphamide, Tacrolimus and Rituximab Groups for the 12-months Follow-up

Event	Cyclophosphamide Group (n=14)	Tacrolimus Group (n=11)	Rituximab Group (n=21)	*P*
Any adverse event(n/No.)[a]	5/6	2/2	4/4	0.269
Steroid diabetes n (%)[b]	4(28.6)	1(9.1)	1(4.8)	0.11
Leucopenia	1	0	0	0.31
Infection	1(7.1)	1(9.1)	3(14.3)	0.78

Notes: (n/No.)[a]is the number of patients with adverse events and the number of events. n(%)[b]indicates that the following are expressed in terms of number of patients and percentage.

effective regimen among three treatments in IMN patients with PLA2R-negative. Previous study reported that combining tacrolimus with low-dose prednisone markedly improved IMN with a remission rate of 90% at 6 months,[16] which is similar to the results of this study. Mechanically, as a macrolide lactone antibiotic with potent immunomodulatory properties, tacrolimus effectively inhibits T lymphocytes, and prevents B lymphocyte mitogenesis.[17] Moreover, tacrolimus reduced podocyte apoptosis and inhibited the damaging effects of angiotensin II on podocytes.[18] Additionally, tacrolimus treatment reduces glomerular angiopoietin-like 4, glomerular immune deposits, and circulating IgG levels, decreases proteinuria, and promotes podocyte repair.[19] Cyclophosphamide, as an old drug for the treatment of IMN, also has multifarious immunosuppressive mechanisms. Therefore, cyclophosphamide or tacrolimus seem to show a long-term benefit for IMN patients with PLA2R-negative.

Consistent with published studies, side effects were similar among three groups.[5–7] Serious events were slightly frequent with rituximab than other two groups, especially infection. The MENTOR study found that patients in the cyclosporine group experienced a significant decline in kidney function compared to patients in the rituximab group.[6] However, our study found that the effect of three regiments on kidney function was mild, which was consistent with previous studies.[7,20] Collectively, the safety of three regimens in IMN patients with PLA2R-negative is acceptable.

This study has some limitations. Firstly, the sample size we studied is relatively small. Due to PLA2R is expressed in 70–80% of IMN patients, PLA2R-negative IMN patients are difficult to collect, which may lead to partial bias in the results of this study, and a large multi-center randomized controlled trial is needed. Second, our follow-up period was only 12 months, which limits our ability to observe the potential relapse rate of the medication over a longer duration.

Conclusions

Compared to RTX, cyclophosphamide and tacrolimus appear to offer long-term benefits for PLA2R-negative IMN patients, with tacrolimus demonstrating superior efficacy among the treatment options evaluated. These insights offer important guidance for clinical decision-making in the management of PLA2R-negative IMN. However, this conclusion needs to be further validated through a larger multi-center randomized controlled trial.

Data Sharing Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Ethical Approval

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Bioethics Committee of The Second Affiliated Hospital to Nanchang University (IRB approval no.: The Second Affiliated Hospital to Nanchang University, 20210912B).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Acknowledgments

We are grateful to all the patients who participated in this study.

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 have declared that no conflict of interest exists.

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