Balkan Med J 2023;40:287-93

Combination of Rituximab and Low-dose Tacrolimus in the Treatment of Refractory Membranous Nephropathy: A Retrospective Cohort Study

Xian Chen, Sumin Jiao, Shaomei Li, Juan Li, Pei Li, Fang Song, Zhe Yan

Department of Nephrology, The Second Hospital of Hebei Medical University, Shijiazhuang, China

Background: Conventional regimens for refractory idiopathic membranous nephropathy (IMN) still have limitations. Rituximab (RTX) has a good effect in the treatment of refractory IMN. However, whether RTX single or combined with immunosuppressive therapy is more effective and whether adverse events will increase are still inconclusive.

Aims: To investigate the efficacy and safety of RTX combined with low-dose tacrolimus (TAC) versus RTX alone in the treatment of refractory IMN.

Study Design: A retrospective cohort study.

Methods: We retrospectively studied 91 cases of refractory IMN diagnosed between January 2018 and June 2021, all of which immunosuppressive regimens had failed. Thirty-four patients received RTX combined with TAC (RTX + TAC group), and 57 patients were treated with RTX alone (RTX group). The RTX + TAC group was given RTX 1 g once every 2 weeks, two times, and TAC 0.03 mg/kg/day orally. In the RTX group, RTX was given at the same dosage as the RTX + TAC group. Clinical data were collected at 12 months of follow-up to compare the complete and partial remission rates and the incidence of adverse reactions between the two groups.

Results: The overall effectiveness rate of RTX + TAC in the treatment of refractory IMN was 87.14%, of which the partial and complete remission rates were 50.01% and 37.13%, respectively, and the median time to complete remission was 9 (interquartile range [IQR] 6.0, 12.0) months. The overall effectiveness rate of RTX was 65.87%, of which the partial and complete remission rates were 39.48% and 26.39%, respectively, and the median time to complete remission was 10.5 (IQR 6.0, 12.0) months. Adverse events occurred in 6 (17.65%) patients in the RTX + TAC group and in 11 (19.30%) in the RTX group ($P = 0.473$). Proteinuria and high titer of PLA2R are risk factors for non-remission.

Conclusion: The complete and partial remission rates of RTX combined with low-dose TAC in the treatment of refractory IMN are higher than those of RTX alone, and no significant increase in adverse events was noted.

INTRODUCTION

Idiopathic membranous nephropathy (IMN) is the main pathological type of adult nephrotic syndrome in China.[1] The incidence of IMN has increased significantly in recent years. Refractory membranous nephropathy is more likely to progress to end-stage renal disease (ESRD).[2] Conventional regimens for the treatment of membranous nephropathy include glucocorticoids combined with cyclophosphamide and low-dose glucocorticoids combined with cyclosporine or tacrolimus (TAC), and the therapeutic effect is good. However, for refractory IMN, the above treatment options still have limitations.[3] Antibodies produced by autoreactive B cells in patients with IMN are involved in the formation of glomerular subepithelial immune complexes, resulting in glomerular filtration barrier damage and proteinuria. Therefore, the selective intervention of antibody production by B-cells can be an ideal choice for the treatment of IMN.[4]

Rituximab (RTX) is a kind of human/mouse chimeric monoclonal antibody that specifically binds to the CD20 receptor on the cell membrane of precursor B-cells and mature B-cells and induces antibody-dependent cytotoxicity and complement-dependent cytotoxicity B-lymphocyte apoptosis.[5] The remission rate of RTX in the treatment of IMN is approximately 60-70%. For patients with IMN in whom traditional immunosuppressive regimens are not effective, RTX still has a good effect.[6] The 2021 KDIGO Clinical Practice Guideline for the Management of Glomerular Diseases recommends using RTX in patients with high- and very-high-risk

Corresponding author: Zhe Yan, Department of Nephrology, The Second Hospital of Hebei Medical University, Shijiazhuang, China
e-mail: yanzhe74@sina.com

Received: September 28, 2022 Accepted: April 27, 2023 Available Online Date: July 12, 2023 • DOI: 10.4274/balkanmedj.galenos.2023.2022-9-7

Available at www.balkanmedicaljournal.org

ORCID iDs of the authors: X.C. 0000-0001-8229-6463; S.J. 0000-0001-9202-4883; S.L. 0000-0001-5797-2810; J.L. 0000-0002-2084-5321; P.L. 0000-0001-6368-7944; F.S. 0000-0003-1801-9474; Z.Y. 0000-0002-7992-1472.

Cite this article as:
Chen X, Jiao S, Li S, Li J, Li P, Song F, Yan Z. Combination of Rituximab and Low-dose Tacrolimus in the Treatment of Refractory Membranous Nephropathy: A Retrospective Cohort Study. *Balkan Med J*.; 2023; 40(4):287-93.

membranous nephropathy and suggests that RTX and calcineurin inhibitor combination therapy can be applied in patients who showed relapses after remission.[7] However, whether RTX single or combined with immunosuppressive therapy is more effective is still inconclusive, and whether adverse events will increase is unclear. To find a better treatment plan, this study aimed to investigate whether RTX combined with low-dose TAC is superior to RTX alone in the treatment of refractory IMN.

MATERIALS AND METHODS

Study participants

The enrollment criteria were as follows: (1) age ≥ 18 years, (2) IMN diagnosed by renal biopsy within 24 months before enrollment, (3) urinary protein > 50% of baseline or nephrotic syndrome after regular treatment with immunosuppressive therapy other than RTX and TAC, and (4) estimated glomerular filtration rate (eGFR) ≥ 45 ml/min/1.73 m^2.

The exclusion criteria were as follows: (1) secondary membranous nephropathy, i.e., membranous nephropathy caused by type 1 or 2 diabetes mellitus, systemic lupus erythematosus, hepatitis B, hepatitis C, and heavy metals; (2) pregnancy or lactation; (3) presence of tumors and local or systemic infection; and (4) eGFR < 45 ml/min/1.73 m^2.

Study design

All patients had at least one or more failed standard immunosuppressive regimens such as cyclophosphamide or cyclosporine but without TAC before RTX infusion, and all patients received conventional therapy such as angiotensin-converting enzyme inhibitors/angiotensin receptor blockers. They were divided into the RTX combined with TAC (RTX + TAC) group and the RTX alone (RTX) group. The RTX + TAC group received an RTX infusion of 1 g/time on days 1 and 15, twice in total. In the second month, 0.03 mg/kg/day of TAC was added at an interval of 12 h in the morning and at night for 6 months, and the average blood concentration was maintained at 4-5 ng/ml. At 6 months and 12 months, serum albumin and urinary protein levels were monitored. If complete remission was not achieved, one dose of RTX 375 mg/m^2 was given again at 6 months. The dose of RTX in the RTX group was the same as that in the RTX + TAC group. Both groups were followed up for at least 12 months.

Monitoring indicators

The clinical and biological data of patients were recorded, and blood routine, liver and kidney function, blood lipids, serum uric acid, 24-h protein, GFR, phospholipase A2 receptor antibody titer, and $CD20^+$ B-cell counts were monitored at baseline and 3, 6, and 12 months of follow-up.

Study Outcomes

Primary outcomes

Complete remission: 24-h urinary protein < 0.3 g, serum albumin ≥ 35 g/l, and normal renal function.

Partial remission: 24-h urinary protein between 0.3 and 3.5 g, or 24-h urinary protein decreased by ≥ 50% from baseline, serum albumin of ≥ 30 g/l, and stable renal function.

Secondary outcomes

Adverse reactions: infusion reaction, infection, dizziness, gastrointestinal symptoms, and granulocytopenia.

Withdrawal criteria: creatinine increased by 50% from baseline, and ESRD that required renal replacement therapy.

Statistical Analysis

Statistical analysis was performed using Statistical Product and Service Solutions (SPSS) 20.0 (IBM Corp., NY, USA). Continuous variables with normal distribution were expressed as mean ± standard deviation, and continuous variables with non-normal distribution were expressed as between-group medians and quartiles. T-test or Wilcoxon rank-sum test was used for between-group comparison. The chi-square test or Fisher's exact test was used to determine differences between groups of categorical variables. Cox regression was used to identify non-remission risk factors. The Kaplan-Meier survival analysis was performed to compare the complete and partial remission rates between the two groups. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 107 patients with refractory membranous nephropathy received RTX. Nine patients were excluded for reasons such as secondary membranous nephropathy, pregnancy, tumors or infections, and eGFR of < 45 ml/min/1.73 m^2. The RTX + TAC group and RTX group included 38 and 60 patients, respectively. Seven patients withdrew from the study because of incomplete data, lost to follow-up, or progression to ESRD. Finally, 34 patients in the RTX + TAC group and 57 patients in the RTX group completed the study (Figure 1).

No significant differences in sex, serum albumin, GFR, and urine protein were found between the two groups. Type I membranous nephropathy was the main pathological type in both groups. The level of anti-PLA2R in the RTX + TAC group was slightly lower than that in the RTX group [89.44 (30.34, 169.88) vs. 102.87 (48.74, 198.43), $P = 0.172$] without statistical significance. The uric acid level in the RTX + TAC group was higher than that in the RTX group (368.8 ± 102.02 vs. 328.12 ± 78.79, $P = 0.040$), and the triglyceride level was lower than that in the RTX group (1.93 ± 0.12 vs. 2.56 ± 0.92, $P = 0.029$). The difference between the two groups was statistically significant (Table 1).

The median follow-up time was 13 (interquartile range [IQR] 12.0, 18.0) months. The results indicated that urinary protein levels gradually decreased, albumin gradually increased, and eGFR decreased slightly during the follow-up. The anti-PLA2R titer decreased gradually; however, no statistical difference was found between the two groups (Figure 2).

At 12 months, the urinary protein level in the RTX + TAC group was significantly lower than that in the RTX group [1.45 (0.18,

3.62) vs. 3.36 (0.58, 4.61), $P = 0.033$), and the albumin level was higher than that in the RTX group (38.57 ± 7.86 vs. 33.98 ± 8.89, $P = 0.018$); a statistical difference was noted between the two groups. eGFR, anti-PLA2R titers, and proportion of anti-PLA2R-positive patients in the RTX + TAC group and RTX group all decreased compared between baseline and at 12 months. In the 12-month follow-up, the anti-PLA2R titers and proportion of anti-PLA2R-positive patients in the RTX + TAC group were lower than that in the RTX group; however, no statistical difference was found between the two groups (Table 2).

In this study, 44 (77.19%) patients in the RTX group received RTX again at the 6-month follow-up compared with 23 (67.65%) patients in the RTX + TAC group. At 12 months, the overall effectiveness rate of RTX + TAC in the treatment of refractory IMN was 87.14%, of which the partial and complete remission rates were 50.01% and 37.13%, respectively. In the RTX group, the overall effectiveness rate of RTX was 65.87%, of which the partial and complete remission rates were 39.48% and 26.39%, respectively (P = 0.008, $P = 0.019$, $P = 0.037$ respectively). In the RTX + TAC group, the median time to complete remission was 9 (IQR 6.0, 12.0) months, and the median time to partial remission was 6 (IQR 3.0, 9.0) months. In the RTX group, the median time to complete remission was 10.5 (IQR 6.0, 12.0) months, and the median time to partial response was 6 (IQR 3.0, 9.0) months. The complete remission time was not statistically different between the two groups (Figure 3).

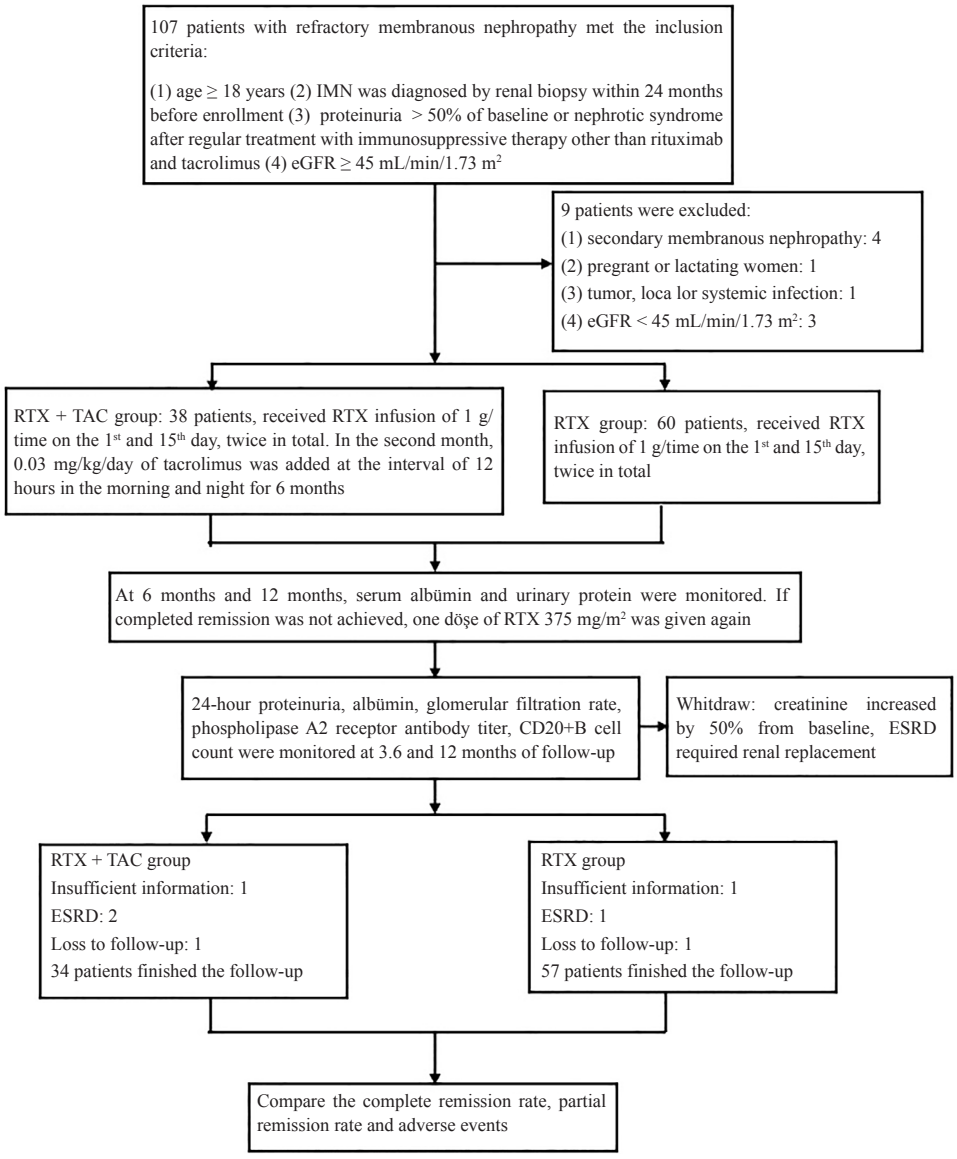

FIG. 1. Flow chart of the trial. The flowchart shows the patient selection process in this retrospective cohort study. The cohort included 107 patients with refractory membranous nephropathy between January 2018 and November 2021. After screening under the conditions shown in this figure, 91 eligible patients (RTX + TAC group, n = 34; TAC group, n = 57) were included in the final analysis.

The non-remission risk factors of IMN after treatment were analyzed by multivariate analysis (Cox regression). Proteinuria (hazard ratio [HR] =1.15, 95% confidence interval [CI] 1.02, 2.03) and high titer PLA2R antibody levels (HR = 1.04, 95% CI 1.01, 1.73) were risk factors for non-remission. Higher albumin levels and higher cumulative doses of RTX were remission-promoting factors (Table 3).

A total of 6 (17.65%) patients in the RTX + TAC group and 11 (19.30%) in the RTX group experienced adverse events. The proportion of adverse reactions in the two groups was comparable (P = 0.473). Infusion adverse reactions were the most common adverse events (Table 4).

DISCUSSION

Membranous nephropathy is the primary cause of adult nephrotic syndrome. Refractory nephrotic syndrome has a poor response to treatment and will likely progress to ESRD.[8] RTX has become a new treatment option for membranous nephropathy.[9] In this retrospective, single center analysis of refractory IMN, the efficacy and safety of RTX combined with low-dose TAC and RTX alone in the treatment of refractory IMN were compared. The results showed that the overall response rate of 87.14% and complete remission rate of 37.13% in the treatment of membranous nephropathy with RTX + TAC were higher than those with RTX alone. No significant difference in adverse reactions was found between the two groups.

TABLE 1. Baseline Characteristics of Patients with Non-responsive IMN in RTX + TAC and RTX Groups.

	RTX + TAC	RTX	P
	N = 34	N = 57	
Age (years)	43.47 ± 13.83	46.63 ± 13.03	0.030
Male (n)	25 (73.53%)	43 (75.44%)	0.964
Body weight (kg)	77.91 ± 15.06	74.85 ± 12.87	0.096
Height (m)	1.72 ± 0.85	1.69 ± 0.68	0.154
Body mass index (kg/m^2)	27.32 ± 4.25	26.12 ± 3.84	0.187
Body surface area (m^2)	2.14 ± 0.22	2.06 ± 0.25	0.384
Systolic blood pressure (mmHg)	126.25 ± 10.92	129.88 ± 11.43	0.158
Diastolic blood pressure (mmHg)	80.76 ± 6.34	78.82 ± 9.45	0.694
Proteinuria, (g/24 h)	7.25 (3.53, 9.35)	8.06 (4.27, 11.35)	0.428
Albumin (g/l)	25.74 ± 5.27	23.36 ± 8.13	0.183
eGFR (ml/min/1.73 m^2)	103.4 ± 21.1	98.54 ± 25.06	0.513
Cholesterol (mmol/l)	7.59 ± 0.78	8.06 ± 1.22	0.142
Triglyceride (mmol/l)	1.93 ± 0.12	2.56 ± 0.92	0.029
Uric acid (μmol/l)	368.8 ± 102.02	328.12 ± 78.79	0.040
Hemoglobin (mmol/l)	130.36 ± 29.9	124.14 ± 18.77	0.057
Complications			
Hypertension, n (%)	21 (61.76%)	36 (63.16%)	0.633
Coronary heart disease, n (%)	1 (2.94%)	3 (5.26%)	0.095
Diabetes, n (%)	6 (17.65%)	11 (19.30%)	0.606
Stroke, n (%)	2 (5.88%)	5 (8.77%)	0.103
Disease stage, n (%)			
I	25 (73.53%)	41 (71.93%)	0.801
II	6 (17.65%)	10 (17.54%)	0.195
III	3 (8.82%)	6 (10.53%)	0.243
Anti-PLA2R level (RU/ml)	89.44 (30.34,169.88)	102.87 (48.74, 198.43)	0.172
Patients positive for anti-PLA2R, n (%)	23 (69.70%)	37 (66.07%)	0.330
CD20$^+$B count (/μl)	234.78 ± 35.25	256.38 ± 48.39	0.919
Previous protocol			
GC + CTX, n (%)	22 (65.00%)	38 (64.71%)	0.990
GC + CSA, n (%)	25 (73.53%)	43 (75.44%)	0.832
GC + CTX and GC + CSA, n (%)	13 (38.24%)	24 (42.11 %)	0.826

CSA, cyclosporine A; CTX, cyclophosphamide; eGFR, estimated glomerular filtration rate; GC, glucocorticoid; GC + CTX and GC + CSA means both protocols were used during the different periods.

RTX + TAC may be a new treatment option for membranous nephropathy.

RTX is a CD20 receptor antibody that can bind to CD20 antigens located on the B-cell surface, removing B cells and reducing the formation of antibody and immune complexes, to achieve disease remission.[10] At present, RTX has been applied to membranous nephropathy, lupus nephritis, small vasculitis renal damage, and other renal diseases, showing good therapeutic effects, and RTX has good compliance because of its mild side effects.[11,12] The MENTOR trial was a randomized controlled trial (RCT) comparing RTX and cyclosporine in the treatment of primary membranous nephropathy. After 12 months of follow-up, the partial or complete remission rate of RTX (60%) was noninferior to that of the cyclosporine (59%), and at 24 months, the partial or complete remission rate of the RTX group (60%) was significantly higher than that of the cyclosporine group (20%). The MENTOR trial suggests considering RTX as a first-line agent when alkylating agents are inappropriate.[13] Hanset reported that RTX is more effective in the treatment of membranous nephropathy, with fewer adverse reactions and a low recurrence rate.[14] The 2021 KDIGO guidelines have suggested that RTX can be used in high-risk and

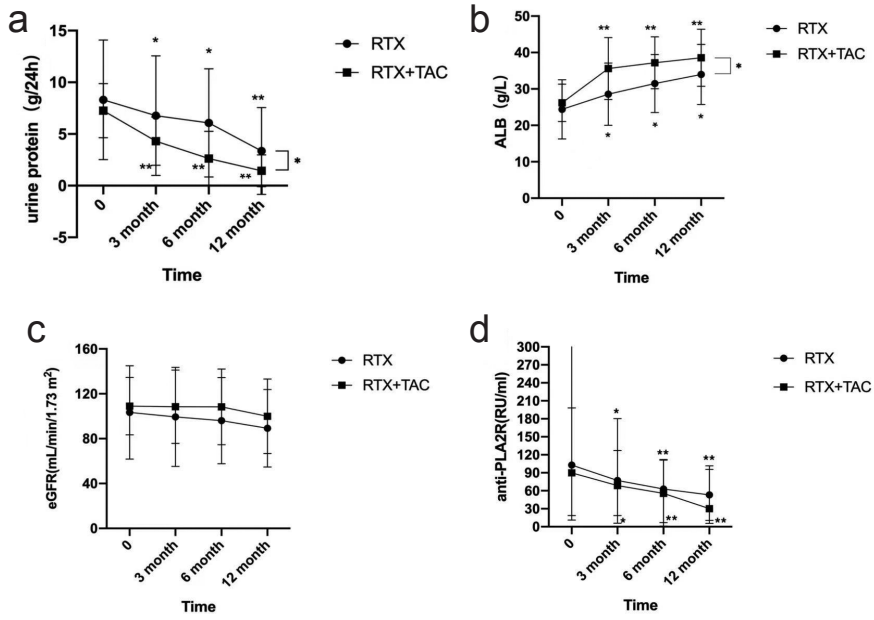

FIG. 2. Changes in indices in the two groups during follow-up. Changes in the levels of 24-h proteinuria (a), serum albumin (b), eGFR (c), anti-PLA2R (d) in the two groups at baseline and during follow-up. The two groups were compared at different time points (ns, no significant difference, *$P < 0.05$, **$P < 0.01$, $P < 0.05$ indicates significant difference).

TABLE 2. Comparison of Laboratory Indices in the Two Groups for the 12 Months Follow-up.

	RTX + TAC	RTX	P
	N = 34	N = 57	
Rituximab dose (g)	2.77 ± 0.31	2.62 ± 0.45	0.072
Systolic blood pressure (mmHg)	120.25 ± 7.68	119.85 ± 12.04	0.276
Diastolic blood pressure (mmHg)	80.02 ± 5.77	76.37 ± 6.81	0.513
Proteinuria (g/24 h)	1.45 (0.18, 3.62)	3.36 (0.58, 4.61)	0.033
Albumin (g/l)	38.57 ± 7.86	33.98 ± 8.89	**0.018**
eGFR (ml/min/1.73 m^2)	99.91 ± 33.26	89.31 ± 34.64	**0.319**
Uric acid (μmol/l)	342.09 ± 96.85	327.69 ± 104.79	0.434
Cholesterol (mmol/l)	5.31 ± 1.02	5.17 ± 0.94	0.709
Triglyceride (mmol/l)	1.54 ± 0.09	1.87 ± 0.56	0.068
Hemoglobin (g/l)	133.36 ± 20.16	127.58 ± 21.95	0.737
Anti-PLA2R (RU/ml)	30.01 (10.19,73.25)	49.87 (18.21, 98.62)	0.682
Patients positive for anti-PLA2R, n (%)	6 (17.65%)	13 (22.81%)	0.709

eGFR, estimated glomerular filtration rate.

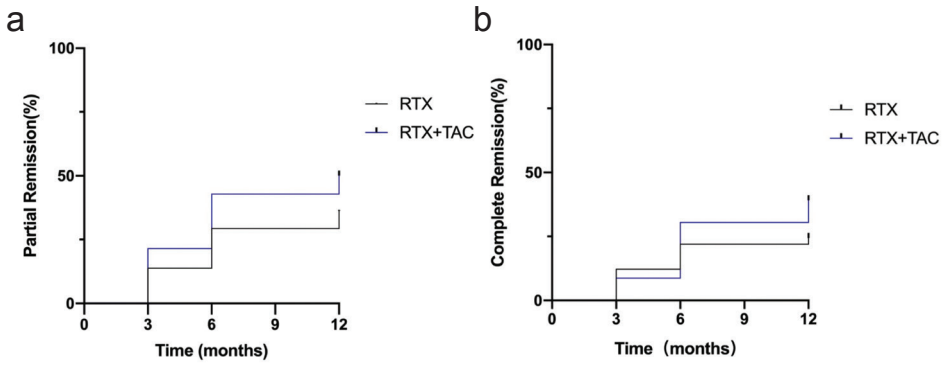

FIG. 3. Partial remission rate and complete remission rate of the RTX and RTX + TAC groups during the follow-up. (a) Partial remission rates of the two groups. The partial remission rates of the RTX + TAC and RTX groups were 50.01% and 39.48%, respectively, at 12 months (P = 0.019). (b) Complete remission rates of the two groups. The complete remission rates of RTX + TAC and RTX groups were 37.13% and 26.39%, respectively, at 12 months (P = 0.037).

TABLE 3. Non-remission Risk Factors in Patients with IMN by Multivariate Analysis (Cox Regression).

	HR	95% CI
Age	0.74	0.38, 1.21
Gender	0.52	0.04, 3.75
Rituximab dose	0.34	0.16, 0.89
Proteinuria	1.15	1.02, 2.03
Albumin	0.58	0.35, 0.98
eGFR	0.96	0.90, 1.36
Uric acid	1.97	0.46, 3.98
Hemoglobin	0.77	0.52, 2.22
Baseline levels of anti-PLA2R antibodies	1.04	1.01, 1.73

CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; IMN, idiopathic membranous nephropathy.

TABLE 4. Comparison of Adverse Events in RTX + TAC and RTX Groups.

	RTX + TAC	RTX	P
Adverse events, n (%)	N = 34	N = 57	
Total adverse events	6 (17.65%)	11 (19.30%)	0.473
Infusion reaction	2 (5.88%)	4 (7.02%)	0.791
Infection	1 (2.94%)	2 (3.51%)	0.392
Pneumonia	0	1 (1.75%)	0.510
Upper respiratory infection	1 (2.94%)	0 (3.51%)	0.104
Other infectious events	0 (2.94%)	1 (1.75%)	0.510
Palpitations	1 (2.94%)	2 (3.51%)	0.392
Headache	1 (2.94%)	1 (1.75%)	0.089
Myalgia	0	1 (1.75%)	0.510
Gastrointestinal complain	1 (2.94%)	0	0.104
Leukopenia	0	1 (1.75%)	0.510

extremely high-risk patients with membranous nephropathy.[7] The use of RTX in the treatment of IMN, particularly refractory IMN, maybe a new option for clinicians.

RTX monotherapy is effective in the treatment of membranous nephropathy; however, the clinical effect is slow, and the complete remission rate is relatively low. Some studies have found that the antibody titer does not decrease when CD20-positive B cells are eliminated during RTX treatment, which implied that non-CD20-positive B-cells may be involved in producing pathogenic antibodies.[15] Antibodies against RTX may be produced after the RTX administration.[16] Long-lived plasma cells in vivo may continuously secrete pathogenic antibodies of membranous nephropathy, and RTX cannot block the production of plasma cell antibodies.[17] The change in the CD20 epitope of B-cells leads to a decrease in the binding ability of RTX to specific sites,[18] which may lead to a therapeutic effect of RTX lower than expected. The addition of other immunosuppressive agents based on RTX may achieve better therapeutic effects, accelerate disease remission, and delay the progression of kidney disease. Therefore, some scholars began to try to treat IMN with RTX combined with immunosuppressive agents. At present, few comparative studies have analyzed RTX in combination with other immunosuppressive agents and RTX monotherapy in the treatment of refractory IMN.

Waldman et al.[19] combined RTX with cyclosporine A to treat 13 IMN cases, in which conservative treatment failed. After the treatment, the mean protein levels decreased by 65% and 80% at 3 and 6 months, respectively, 92% of patients achieved partial or complete remission at 9 months, and 54% achieved complete remission at 12 months. Renal function was stable, and the combination was well tolerated. Zonozi et al.[20] reported outcomes of 60 patients with IMN treated with RTX combined with low-dose cyclophosphamide and glucocorticoids. After a median treatment time of 3.4 months, 100% and 83% of the patients achieved partial and complete remission at 2 years. No patients had a relapse during the B-cell clearance phase, and 10% had a relapse 2 years after the last RTX dose. This study showed that RTX combined with low-dose cyclophosphamide and glucocorticoids led to partial remission in all patients and sustained complete remission in most patients with acceptable safety. According to Zhu et al.,[21] ultralow-dose RTX plus low-dose TAC in non-responsive IMN had a higher remission rate and a lower side effect than standard TAC monotherapy. The

STARMEN trial[22] is a multicenter RCT comparing the efficacy of RTX combined with TAC with that of glucocorticoid combined with cyclophosphamide. In this protocol, the initial TAC dose was 0.05 mg/kg/day, and the dosage was adjusted until the blood concentration reached 5-7 ng/ml for 6 months. A single dose of RTX 1 g was used after 6 months of TAC treatment. The remission rate, recurrence rate, renal function maintenance rate, and adverse reactions were observed after 2 years of follow-up. The results of the 24-month follow-up showed that the complete remission rate of TAC combined with RTX was 26%, which was lower than that of glucocorticoid combined with cyclophosphamide with 60%. The STARMEN study was a sequential clinical trial with RTX added after TAC application for 6 months, and the lower RTX dosage may not have shown its actual effect and the treatment effect of the combination with TAC. Therefore, the efficacy of RTX and TAC should be further studied.

The present study compared the efficacy and side effects of a titrated dose of RTX combined with a lower TAC dose with those of RTX alone in the treatment of refractory IMN. For refractory IMN, the remission rate of the combined therapy was better than that of RTX monotherapy, and the adverse reactions were not higher than that of RTX monotherapy. RTX + TAC is a more effective treatment for refractory membranous nephropathy, which provides a new idea for the treatment of membranous nephropathy. In this study, RTX differs slightly between the two groups, but it is not statistically significant, which may be related to the different body surface areas of the patients.

This study still had some limitations. This is a retrospective cohort study, with a small sample size derived from a single center; thus, the case representation is slightly poor. Further RCTs are necessary to obtain more meaningful conclusions. In the future, the sample size should be expanded to further clarify the efficacy and adverse reactions of RTX + TAC through multicenter RCT studies.

In conclusion, the complete and partial remission rates of RTX combined with low-dose TAC in the treatment of refractory IMN were higher than those of RTX alone, and no significant increase in adverse events was noted.

Acknowledgements: The authors declare that there is no conflict of interest. This paper was supported by S&T Program of Hebei (20377755D, 21377753D), Hebei Provincial Medical Science Project Research (20221078). The funding body plays an important role in the analysis, and interpretation of data.

Ethics Committee Approval: The study received favorable opinion from the Ethics Committee of Second Hospital of Hebei Medical University. The decision number is 2020-R306. The date of the approval is February 12th in 2020.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authorship Contributions: Design- Z.Y.; Data Collection and Processing- S.J., S.L., P.L., J.L., F.S.; Analysis or Interpretation- S.J., S.L.; Literature Search- Z.Y.; Writing- X.C.

Conflict of Interest: No conflict of interest was declared by the authors.

Funding: The authors declared that this study received no financial support.

REFERENCES

1. Keri KC, Blumenthal S, Kulkarni V, Beck L, Chongkrairatanakul T. Primary membranous nephropathy: comprehensive review and historical perspective. *Postgrad Med J.* 2019;95:23-31. [CrossRef]
2. Tomas NM, Huber TB, Hoxha E. Perspectives in membranous nephropathy. *Cell Tissue Res.* 2021;385:405-422. [CrossRef]
3. Cattran D, Brenchley P. Membranous nephropathy: thinking through the therapeutic options. *Nephrol Dial Transplant.* 2017;32(Suppl 1):22-29. [CrossRef]
4. Caravaca-Fontán F, Fernández-Juárez GM, Floege J, et al. The management of membranous nephropathy-an update. *Nephrol Dial Transplant.* 2022;37:1033-1042. [CrossRef]
5. Roccatello D, Sciascia S, Di Simone D, et al. New insights into immune mechanisms underlying response to Rituximab in patients with membranous nephropathy: A prospective study and a review of the literature. *Autoimmun Rev.* 2016;15:529-538. [CrossRef]
6. Gauckler P, Shin JI, Alberici F, et al. Rituximab in Membranous Nephropathy. *Kidney Int Rep.* 2021;6:881-893. [CrossRef]
7. Rovin BH, Adler SG, Barratt J, et al. Executive summary of the KDIGO 2021 Guideline for the Management of Glomerular Diseases. *Kidney Int.* 2021;100:753-779. [CrossRef]
8. Alsharhan L, Beck LH Jr. Membranous Nephropathy: Core Curriculum 2021. *Am J Kidney Dis.* 2021;77:440-453. [CrossRef]
9. Teisseyre M, Cremoni M, Boyer-Suavet S, et al. Advances in the Management of Primary Membranous Nephropathy and Rituximab-Refractory Membranous Nephropathy. *Front Immunol.* 2022;13:859419. [CrossRef]
10. Del Vecchio L, Allinovi M, Rocco P, Brando B. Rituximab Therapy for Adults with Nephrotic Syndromes: Standard Schedules or B Cell-Targeted Therapy? *J Clin Med.* 2021;10:5847. [CrossRef]
11. Furuta S, Nakagomi D, Kobayashi Y, et al. Effect of Reduced-Dose vs High-Dose Glucocorticoids Added to Rituximab on Remission Induction in ANCA-Associated Vasculitis: A Randomized Clinical Trial. *JAMA.* 2021;325:2178-2787. [CrossRef]
12. Yuan Z, Xie Q, Wu X, Tan B, Zhang X. Rituximab treatment for lupus nephritis: A systematic review. *Clin Invest Med.* 2020;43:47-54. [CrossRef]
13. Fervenza FC, Appel GB, Barbour SJ, et al. Rituximab or Cyclosporine in the Treatment of Membranous Nephropathy. *N Engl J Med.* 2019;381:36-46. [CrossRef]
14. Hanset N, Esteve E, Plaisier E, et al. Rituximab in Patients With Phospholipase A2 Receptor-Associated Membranous Nephropathy and Severe CKD. *Kidney Int Rep.* 2020;5:331-388. [CrossRef]
15. Teisseyre M, Boyer-Suavet S, Crémoni M, Brglez V, Esnault V, Seitz-Polski B. Analysis and Management of Rituximab Resistance in PLA2R1-Associated Membranous Nephropathy. *Kidney Int Rep.* 2021;6:1183-1188. [CrossRef]
16. Boyer-Suavet S, Andreani M, Lateb M, et al. Neutralizing Anti-Rituximab Antibodies and Relapse in Membranous Nephropathy Treated With Rituximab. *Front Immunol.* 2019;10:3069. [CrossRef]
17. Schrezenmeier E, Jayne D, Dörner T. Targeting B Cells and Plasma Cells in Glomerular Diseases: Translational Perspectives. *J Am Soc Nephrol.* 2018;29:741-758. [CrossRef]
18. Sethi S, Kumar S, Lim K, Jordan SC. Obinutuzumab is Effective for the Treatment of Refractory Membranous Nephropathy. *Kidney Int Rep.* 2020;5:1515-1518. [CrossRef]
19. Waldman M, Beck LH Jr, Braun M, Wilkins K, Balow JE, Austin HA 3rd. Membranous nephropathy: Pilot study of a novel regimen combining cyclosporine and Rituximab. *Kidney Int Rep.* 2016;1:73-84. [CrossRef]
20. Zonozi R, Laliberte K, Huizenga NR, et al. Combination of Rituximab, Low-Dose Cyclophosphamide, and Prednisone for Primary Membranous Nephropathy: A Case Series With Extended Follow Up. *Am J Kidney Dis.* 2021;78:793-803. [CrossRef]
21. Zhu F, Chu X, Guo Y, et al. Combination of ultra-low dose rituximab and low dose tacrolimus versus tacrolimus alone in the treatment of non-responsive idiopathic membranous nephropathy: a Chinese retrospective cohort study. *Am J Transl Res.* 2021;13:7622-7631. [CrossRef]
22. Fernandez-Juarez G, Rojas-Rivera J, Logt AV, Justino J, Sevillano A, Caravaca-Fontan F, et al. The STARMEN trial indicates that alternating treatment with corticosteroids and cyclophosphamide is superior to sequential treatment with tacrolimus and rituximab in primary membranous nephropathy. *Kidney Int.* 2021;99:986-998. [CrossRef]