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Treatment of Membranous Nephropathy in Chinese Patients: Comparison of Rituximab and Intravenous Cyclophosphamide with Steroids

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Keywords
Primary membranous nephropathy · Rituximab · Cyclophosphamide · Remission

Abstract

Introduction: Previous studies have shown that rituximab (RTX) and cyclic oral corticosteroid-cyclophosphamide (CTX) regimens have similar effects on primary membranous nephropathy (PMN). However, no studies have compared RTX with an intravenous CTX regimen, which is more commonly used in China and requires fewer cumulative CTX doses. ***Methods:*** We prospectively assigned 141 PMN patients with baseline proteinuria ≥4 g/24 h, serum albumin <30 g/L, and eGFR ≥30 mL/min × 1.73 m^2 despite at least 3 months of treatment with ACEI and/or ARB to the RTX group (375 mg/m^2 per injection per week × 4 injections) or to the CTX group (prednisone 0.8 mg/kg/day and intravenous CTX 500 mg/m^2 per month until the total dose reached 6–8 g). The primary endpoint was defined as a combination of partial remission or complete remission at 12 months. ***Results:*** By the end of 12 months, 43 of 70 patients (61.43%) in the RTX group and 54 of 71 patients (76.06%) in the CTX group reached the primary endpoint ($p = 0.06$). Significantly fewer patients in the RTX group achieved complete remission than the CTX group (14.29% vs. 33.80%, $p = 0.01$). The adverse events rate was similar between the RTX group and the CTX group (28.57% vs. 40.85%, $p = 0.13$). In subgroup analysis, we found that fewer patients from the RTX group achieved the primary endpoint than the CTX group (48.65% vs. 74.29%, $p = 0.03$) among patients with massive proteinuria (urine protein ≥8 g/24 h). During the observational phase, 61 patients in the RTX group and 58 in the CTX group completed 24 months of follow-up, exhibiting similar remission rates (RTX vs. CTX: 75.41% vs. 68.97%, $p = 0.54$). ***Conclusions:*** Our results show that the intravenous CTX regimen has similar safety and efficacy with higher rates of early complete remission than RTX in the treatment of PMN patients.

Introduction

Primary membranous nephropathy (PMN) is one of the most common types of adult-onset nephrotic syndrome worldwide [1–4]. Although the pathogenic

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mechanism has not been fully elucidated, the discovery of an increasing number of PMN-related antigens such as PLA2R, THSD7A, and EXT1/2 [5–7] has significantly improved our understanding of the mechanism of PMN. It is now well accepted that PMN is an immune complex-mediated glomerular disease in which B cells are vital for autoantibody production.

Previous studies [8–10] on the natural course of PMN showed that some PMN patients may accomplish spontaneous remission, but others may develop renal progression in the long term. With the widespread use of immunosuppressive therapies in patients with PMN, the prognosis has significantly improved. Cyclophosphamide (CTX) combined with corticosteroid was long considered the gold standard therapy in PMN with a remission rate of around 72–93% [11–13]. However, following the extensive use of rituximab (RTX) and its great success in treating PMN, whether RTX can replace CTX combined with a corticosteroid regimen as the first-line treatment for PMN remains a contentious topic in the field. Van den Brand et al. [10] performed a head-to-head comparison of two retrospective non-randomized studies that investigated the efficacy and safety profiles of RTX and CTX (oral CTX 1.5 mg/kg daily for 6–12 months with steroid) in a retrospective cohort of 203 patients with PMN. The study showed that CTX was superior to RTX in inducing partial remission, but the combined endpoint (defined as doubling serum creatinine, ESRD, need for chronic RRT, or death from any cause) was similar between the two groups. Considering that RTX caused fewer adverse events than CTX, the authors suggested that RTX may replace the CTX regimen as the first-line treatment for PMN owing to its superior safety profile. However, the RI-CYCLO randomized clinical trial [13] found patients with PMN treated by RTX or cyclic CTX (cyclical corticosteroid/CTX therapy, consisting of three consecutive cycles of 2-month duration each for a total of 6 months) had similar remission rates (16% vs. 32%, OR: 0.4, 95% CI: 0.13–1.23) as defined by CR at 12 months, but also similar severe adverse events (19% vs. 14%, p = 0.75). The study concluded that there was no evidence of greater benefit or less harm associated with RTX versus a cyclic CTX regimen in the treatment of PMN. The results of 2 studies were controversial with 2 different CTX regimens applied and two different study designs. More head-to-head RCT studies should be performed to further explore the issue.

Furthermore, previous studies [14] have mainly focused on the oral cyclic regimen of CTX. No studies have compared RTX with intravenous CTX combined with a low-dose corticosteroid regimen, which is more commonly used in China and elsewhere and usually requires fewer CTX cumulative doses than an oral CTX regimen. Thus, the effect of intravenous CTX regimen on PMN remains to be determined.

To address this research gap, we conducted a study that enrolled and assigned 141 patients with PMN to receive either RTX (375 mg/m^2 × 4 injections) or intravenous CTX combined with an oral corticosteroid regimen to compare the efficacy and safety of the two treatments, which may help elucidate the optimal treatment strategy for patients with PMN.

Methods

Study Population

This prospective study included 141 patients with PMN diagnosed at Shanghai Ruijin Hospital, Shanghai Ruijin Hospital Northern branch, and Shanghai East Hospital from January 2016 to January 2020. The inclusion criteria were as follows: (1) patients biopsied and diagnosed with PMN; (2) aged 18–70 years; (3) baseline proteinuria ≥4 g/24 h and serum albumin <30 g/L despite at least 3 months treatment with maximum tolerated doses of ACEI and/or ARB; (4) EPI-eGFR ≥30 mL/min × 1.73 m^2; and (5) informed consent was signed. The exclusion criteria were as follows: (1) patients who were treated with RTX prior to the study; (2) patients allergic to the investigational drug; (3) patients who had a recent operation plan; (4) patients with severe acute or chronic infection (sepsis, respiratory or urinary or digestive infection), or receiving antibiotics; (5) patients with severe cardiac failure (NYHA III-IV); 6) patients with WBC <4 × 10^9/L, or Hb <10 g/dL, or PLT <100 × 10^9/L; (7) patients who were pregnant or in lactation phase; (8) patients with uncontrolled diabetes; (9) patients with severe hepatic lesion (persistent GPT or GOT > twice the normal range) or HBV-DNA positive; (10) patients with newly diagnosed malignant tumor or receiving radiotherapy/chemotherapy; and (11) patients who refused to participate in the study. This study was approved by the Institutional Review Board of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, and was conducted in accordance with the principles of the Declaration of Helsinki, with Approval No. DLY201510.

Study Design

Randomization was performed using sequentially numbered opaque sealed envelopes. The sequence of interventions was obtained from computer-generated random numbers. Experimental group received RTX

treatment. RTX was administered at a dose of 375 mg/m^2 every week for a total of 4 doses. Methylprednisolone 40 mg i.v. will be given before the first dose. Chlorpheniramine (10 mg) and acetaminophen (500 mg) or other similar drugs will be given orally before each infusion to prevent allergic reactions.

Control group received steroids + CTX. oral prednisone starting at 0.8 mg/kg/24 h combined with intravenous CTX at a dose of 500 mg/m^2 every 4 weeks until the total amount administered reached 6–8 g. Oral prednisone was maintained for 8 weeks and then tapered gradually to 5–10 mg every 4 weeks and may be stopped at 1 year. Anticoagulation agents and lipid-lowering drugs were administered to all patients without any contraindications. Entecavir was administered to patients with antibodies against HBV core protein, and isoniazid was administered to patients with a medical history of tuberculosis (flowchart shown in Fig. 1). The primary endpoint was CR or partial remission (PR) at 12 months. CR was defined as proteinuria <0.3 g/24 h in the absence of renal function deterioration. Partial remission was defined as proteinuria <3.5 g/24 h and a urine protein reduction of at least 50% compared to baseline, with stable renal function. Renal progression was defined as a 50% decrease in eGFR compared to the baseline eGFR.

Data Collection

Baseline clinical data and patient characteristics were collected from medical records. eGFR was calculated using the EPI-GFR formula [15]. All patients were regularly followed up. Urinary protein, serum albumin, serum creatinine levels, treatment, and adverse events were recorded during each follow-up period. Baseline (time of renal biopsy) serum PLA2R antibodies were measured using the ELISA test kit (EUROIMMUN, Lubeck, Germany) by a standard protocol. Serum PLA2R antibody levels >20 RU/mL were considered positive.

Statistical Analysis

Statistical analysis was mainly performed based on intention-to-treat analysis and included all patients who did not withdraw consent. Per-protocol analysis was also performed to compare remission rates and complete remission rates between 2 regimens. Continuous variables that were normally distributed were expressed as the mean ± standard deviation and compared with each other using Student's *t* test. Continuous variables with a skewed distribution were presented as median (range) and compared using the Mann-Whitney U test. Categorical variables were compared using the χ^2 test. A logistic regression model was used to compare the efficacy of RTX with that of CTX in different subgroups. Statistical significance was defined as a two-tailed p value of <0.05. Statistical analyses were performed using IBM SPSS software (version 21.0; IBM Corp., Armonk, NY, USA).

Results

Study Participants

A total of 141 patients with PMN were enrolled in this study. Seventy patients were assigned to the RTX group and 71 to the CTX group. The baseline characteristics of the enrolled patients are presented in Table 1. The median age was 53.5 years (range, 18–70) in the RTX group and 55 years (range, 27–69) in the CTX group, with male predominance in both groups. The median proteinuria (8.13 [4–21.14] vs. 7.94 [4.11–20.1] g/24 h, p = 0.62), albumin (19.73 ± 4.99 vs. 18.51 ± 4.26 g/L, p = 0.12), eGFR (93.72 ± 27.19 vs. 87.95 ± 22.17 mL/min × 1.73 m^2, p = 0.17), and PLA2R antibody (63.79 [0.40–1,049.90] vs. 47.10 [0.80–1,316.70], p = 0.57) were similar in the RTX and CTX groups at baseline (Table 1).

Primary Endpoints

By the end of 12 months, 43 of 70 patients in the RTX group and 54 of 71 patients in the CTX group reached the primary endpoint (ITT: 61.43% vs. 76.06%, p = 0.06; per-protocol: 67.27% vs. 88.64%, p = 0.02). Fewer patients in the RTX group achieved CR than the CTX group (ITT: 14.29 vs. 33.80%, p = 0.01; per-protocol: 12.73% vs. 36.36%, p = 0.01) (Table 2; online suppl. Fig. S1; for all online suppl. material, see https://doi.org/10.1159/000540548). The urine protein level at 12 months was higher in patients from the RTX group than that of the CTX group (1.82 [0.05–26.02] vs. 0.72 [0.07–15.79], p = 0.01). The serum albumin (RTX vs. CTX: 33.52 ± 9.55 vs. 32.55 ± 8.18, p = 0.52) and eGFR (RTX vs. CTX: 94.72 ± 26.03 vs. 89.11 ± 22.27, p = 0.17) at 12 months were similar between the two groups (Fig. 2; online suppl. Table S1). The median cumulative dose of CTX at 12 months was 7.4 g (range, 6–8 g). A total of 27 patients received dynamic surveillance for PLA2R antibodies at 12 months. The PLA2R antibody depletion rates were identical at 12 months between the two groups (RTX vs. CTX: 50% vs. 63.64%, p = 0.48, PLA2R ab titer: RTX vs. CTX: 15.15 [0.6–154.6] versus 4.70 [0.8–75.60] RU/mL, p = 0.37). By the end of 12 months, 6 of 70 patients (8.57%) in the RTX group and 4 of 71 patients (5.63%) in the CTX group had a relapse (p = 0.53).

The patients were then divided into subgroups based on age, sex, baseline urine protein level, baseline eGFR, and PLA2R antibody. We performed a subgroup analysis

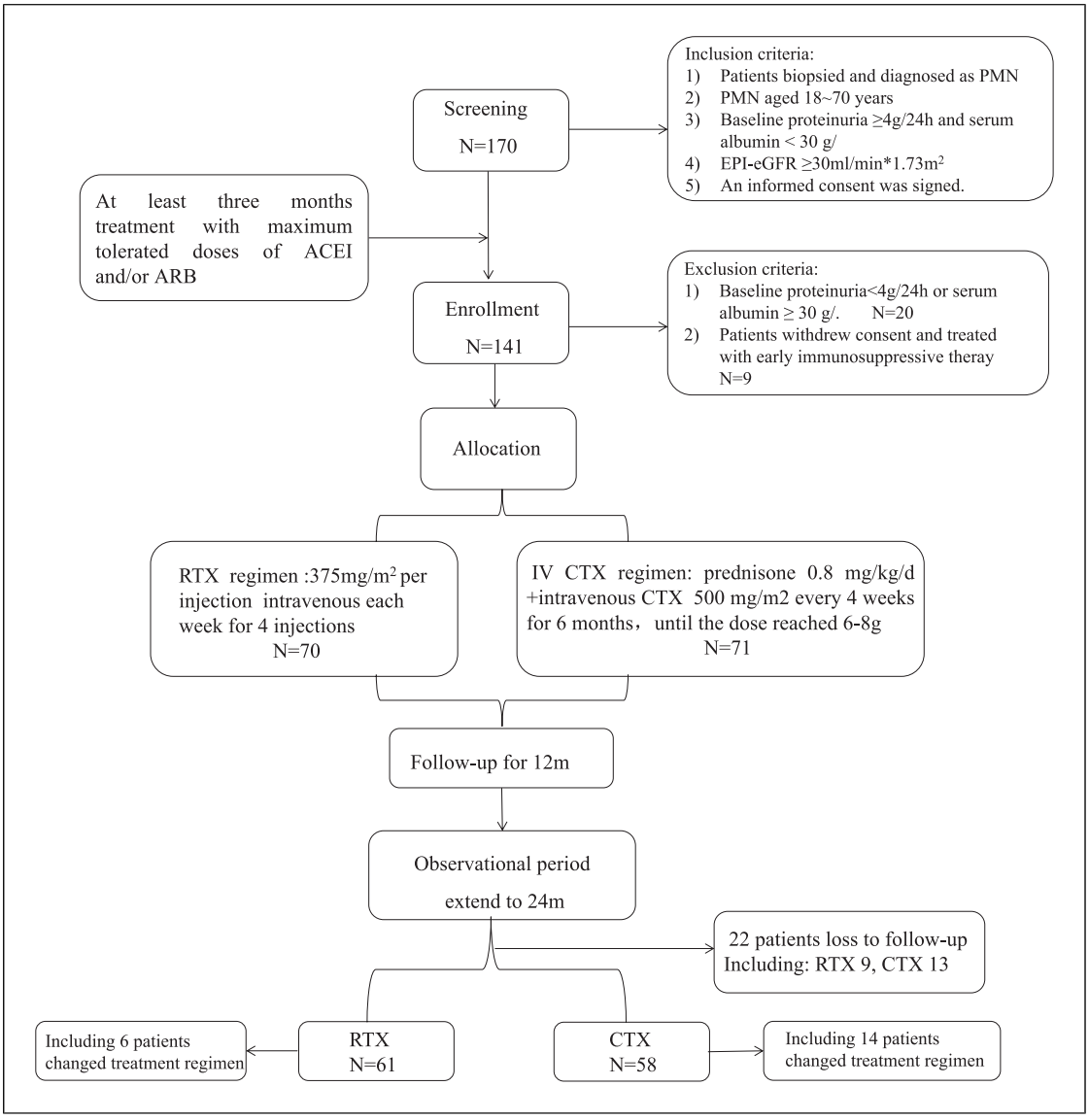

Fig. 1. Flowchart of the study.

to determine which patients would benefit more from RTX or CTX treatment. CTX was superior to RTX in inducing primary endpoints in patients with urine protein >8 g/24 h at baseline (RTX as reference, OR: 3.05, 95% CI: 1.13–8.25, p = 0.03). For the other subgroup categories, the two groups showed similar efficacy (Fig. 3; online suppl. Table S2).

Adverse Events and Serious Adverse Events

Adverse events occurred in 49 participants during the study period: 20 (28.57%) occurred in the RTX group and 29 (40.85%) in the CTX group (p = 0.13). The main adverse events in the RTX group were infections (8.57%), rashes (8.57%), and hepatic dysfunction (7.14%). Moreover, in the CTX group, adverse events included infections (15.49%), hyperglycemia (8.45%), and hepatic dysfunction (7.04%) (Table 3). Serious adverse events (SAEs) occurred in 2 patients receiving RTX and in 6 patients receiving CTX combined with a corticosteroid regimen (2.86 vs. 8.45%, p = 0.28). The two SAEs in the RTX group were cerebral hemorrhage and epilepsy crisis of unknown etiology and both recovered after 1 month of treatment. In the CTX group, the SAEs were ischemic cerebral stroke, hepatic dysfunction, and rhabdomyolysis, which quickly improved after hydration and discontinuation of statins; femoral head necrosis; referral to an

Table 1. Clinical parameters of enrolled PMN patients at baseline

	RTX (n = 70)	CTX (n = 71)	p value
Male, n (%)	46 (65.71)	57 (78.87)	0.08
Age, years	53.5 (18~70)	55 (27~69)	0.16
High risk, % (n)	88.57 (62)	94.37 (67)	0.22
Proteinuria, g/24 h	8.13 (4~21.14)	7.94 (4.11~20.1)	0.62
Albumin, g/L	19.73±4.99	18.51±4.26	0.12
eGFR, mL/min×1.73 m^2	93.72±27.19	87.95±22.17	0.17
Creatinine, μmol/L	72 (40~171)	82 (52~177)	0.15
Uric acid, mmol/L	346.41±82.47	355.07±86.4	0.54
Triglyceride, mmol/L	2.19 (0.68–8.19)	2.44 (1.03–13.4)	0.19
Cholesterol, mmol/L	7.07±2.17	7.58±2.34	0.20
PLA2R ab pos, n (%)	33/49 (67.35)	34/54 (62.96)	0.68
PLA2R ab, RU/mL	63.79 (0.40–1,049.90)	47.10 (0.80–1,316.70)	0.57
Systolic tension, mm Hg	128.5 (101–175)	137 (91–205)	<0.01
Diastolic tension, mm Hg	77 (51–100)	82 (57–124)	0.01

Table 2. Composite outcome of complete or partial remission of PMN patients at 3–12 months

	ITT analysis			Per-protocol analysis		
	RTX (n = 70)	CTX (n = 71)	p value	RTX (n = 55)	CTX (n = 44)	p value
3 months						
CR + PR, n (%)	24 (34.29)	29 (40.85)	0.42	19 (34.55)	21 (47.73)	0.18
CR, n (%)	2 (2.86)	1 (1.41)	0.62	0 (0)	2 (3.64)	–
6 months						
CR + PR, n (%)	43 (61.43)	44 (61.97)	0.95	34 (61.82)	34 (77.27)	0.10
CR, n (%)	3 (4.29)	8 (11.27)	0.12	2 (3.64)	5 (11.36)	0.24
12 months						
CR + PR, n (%)	43 (61.43)	54 (76.06)	0.06	37 (67.27)	39 (88.64)	0.02
CR, n (%)	10 (14.29)	24 (33.80)	0.01	7 (12.73)	16 (36.36)	0.01
18 months						
CR + PR, n (%)	42/59 (71.19)	44/64 (68.75)	0.77	40/50 (80)	36/42 (85.71)	0.47
CR, n (%)	15/59 (25.42)	21/64 (32.81)	0.37	14/50 (70)	18/42 (42.86)	0.14
24 months						
CR + PR, n (%)	46/61 (75.41)	40/58 (68.97)	0.54	46 (83.64)	40 (90.91)	0.29
CR, n (%)	22/61 (36.07)	22/58 (37.93)	0.83	22 (40)	22 (50)	0.42

orthopedic surgeon; and three infections, including pneumonia, erysipelas, and recovery after treatment (Table 3).

Comparisons of total adverse events and infection between 2 regimens were then performed in different subgroups (online suppl. Fig. S2). Among patients with 30< eGFR ≤90 mL/min×1.73 m^2, CTX seemed to be associated with a higher incidence of side effects compared to RTX (odds ratio: 4.14, 95% confidence interval: 1.26–13.57, p = 0.02). However, in other subgroups, the adverse rates were similar. Additionally, the infection rates were similar between 2 regimens in subgroup analysis.

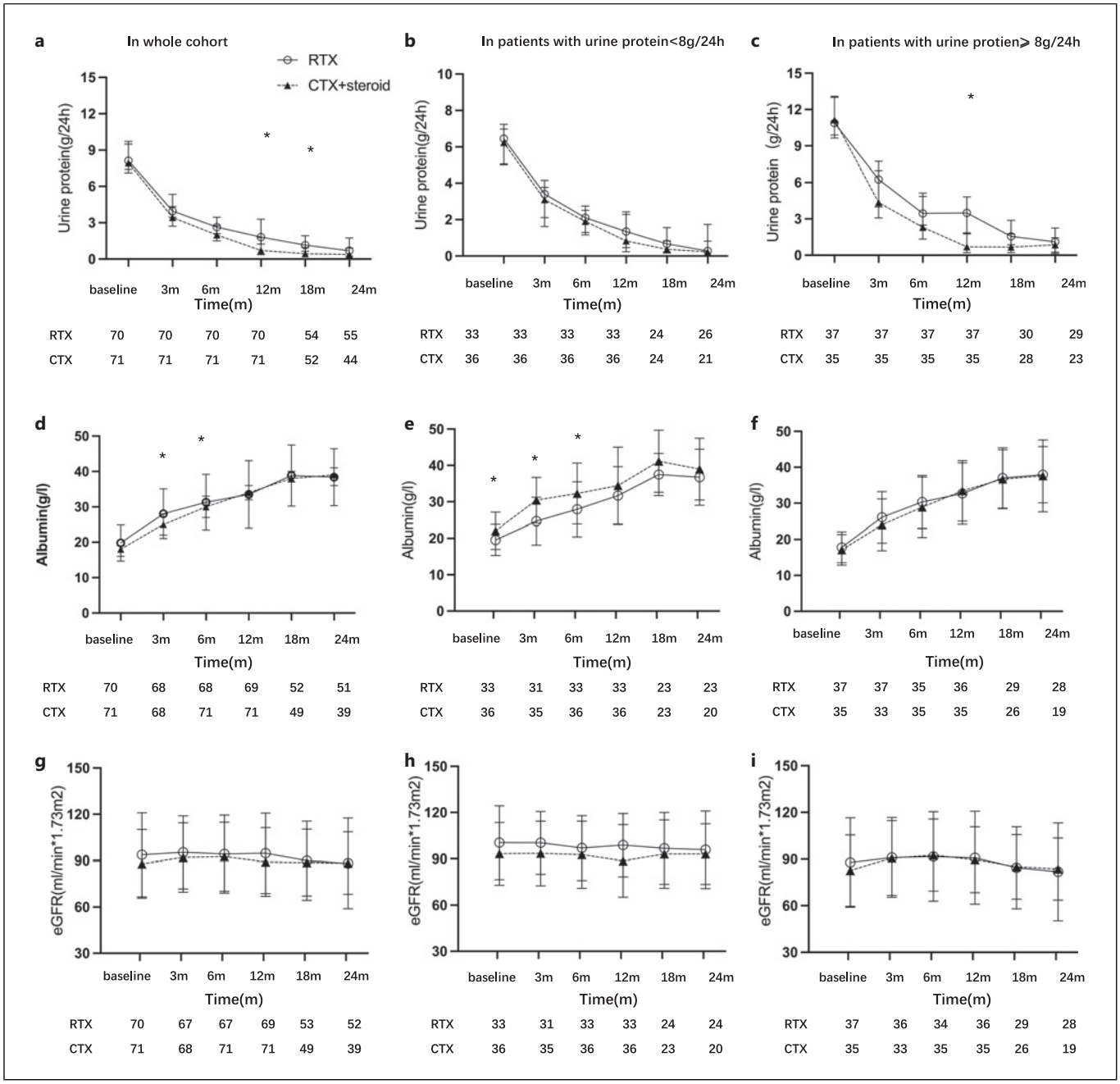

Fig. 2. Comparison of urine protein, serum albumin, and eGFR between the RTX and CTX group in the whole cohort, in patients with baseline urine protein ≥8 g/24 h and in patients with baseline urine protein <8 g/24 h. **a** Comparison of urine protein between RTX and CTX in the whole cohort. **b** Comparison of urine protein between RTX and CTX in patients with urine protein <8 g/24 h. **c** Comparison of urine protein between RTX and CTX in patients with urine protein ≥8 g/24 h. **d** Comparison of serum albumin between RTX and CTX in the whole cohort. **e** Comparison of serum albumin between RTX and CTX in patients with urine protein <8 g/24 h. **f** Comparison of serum albumin between RTX and CTX in patients with urine protein ≥8 g/24 h. **g** Comparison of eGFR between RTX and CTX in the whole cohort. **h** Comparison of eGFR between RTX and CTX in patients with urine protein <8 g/24 h. **i** Comparison of eGFR between RTX and CTX in patients with urine protein ≥8 g/24 h. Dashed lines with triangle refer to the CTX group. Solid lines with circle refer to the RTX group.

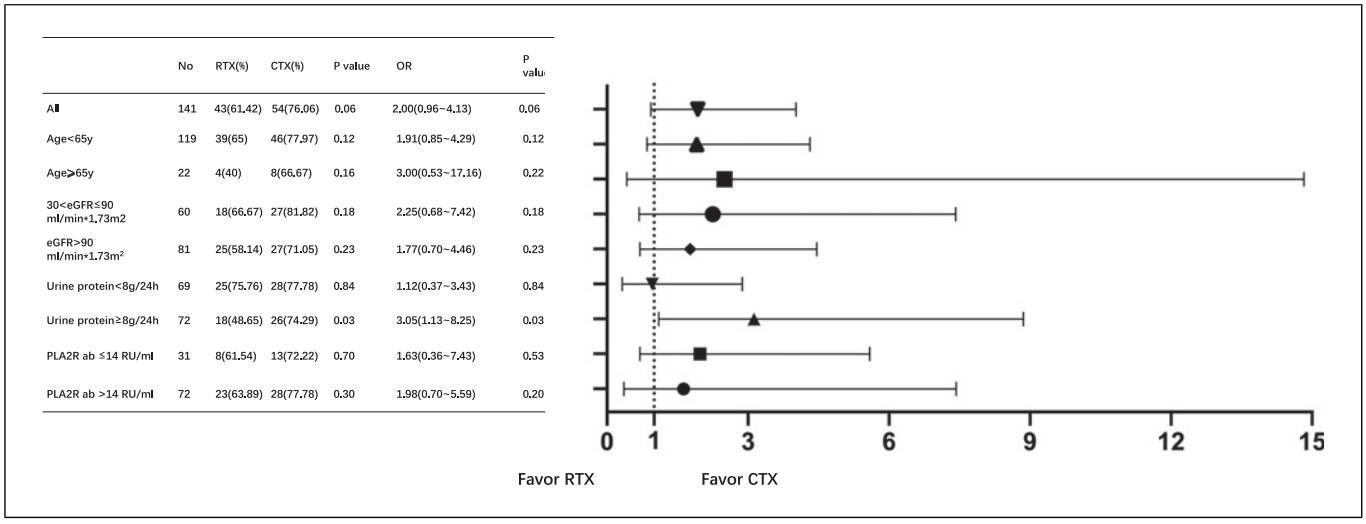

Fig. 3. Comparison of RTX and CTX regimen in inducing remission in different subgroups in 12 months: steroid + CTX as reference. In patients with urine protein ≥8 g/24, CTX was more effective than RTX in inducing remission (OR: 3.05 [1.13–8.25], $p = 0.03$). In other subgroups, RTX and CTX showed similar efficacy.

Post hoc Observational Period

Sixty-one patients in the RTX group and 58 patients in the CTX group completed the 24-month follow-ups. There were 6 (9.84%) patients from the RTX group and 14 (24.14%) patients from the CTX group who changed the treatment regimen (CTX vs. RTX: 14/58 [24.14%] versus 6/61 [9.84%], $p = 0.04$), due to no remission. The remission rate (ITT: 75.41% vs. 68.97%, $p = 0.54$; per-protocol: 83.64% vs. 90.91%, $p = 0.29$) and CR rate (ITT: 36.07% vs. 37.93%, $p = 0.83$; per-protocol: 40% vs. 50%, $p = 0.42$) between the RTX and CTX groups were similar (Table 2). There were 2 (4.17%) patients in the RTX group and 2 (4.76%) patients in the CTX group who had a relapse (RTX vs. CTX: 4.17% vs. 4.76%, $p = 0.89$) at 24 months. The renal progression rate was 3.28% in the RTX group, whereas all patients in the CTX group had stable renal function (Table 2). In subgroup analysis at 18 m and 24 m, the two groups showed similar efficacy (online suppl. Fig. S3).

Discussion

With the extensive use of RTX and the success of RTX in treating PMN, both RTX and cyclic oral corticosteroid-CTX regimens are the first-line treatments for PMN based on the most recent update of the KDIGO glomerulonephritis guidelines [16]. To determine which of the 2 regimens was superior, only a randomized controlled trial investigated the efficacy and safety of these 2 regimens [13]. Moreover, most of these studies [11–13] were performed in Western populations and mainly focused on the oral cyclic CTX regimen, with few analyzing the intravenous CTX regimen. Intravenous administration is more commonly used in patients with PMN from China and other countries because of its potentially better safety profile due to its relatively lower cumulative dose. Therefore, our study compared the efficacy and safety of CTX combined with prednisone and RTX and found that the intravenous CTX regimen had a higher early response rate and similar safety to RTX for treating patients with PMN.

Oral cyclic CTX alternated with corticosteroids is a classic regimen that has been frequently used in previous studies [11–13]. The remission rate was around 72–93% with a CTX cumulative dose of approximately 12–20 g [11–13]. In our study, the remission rate at 12 months was 76.06% with a median CTX cumulative dose of 7.4 g, significantly lower than that of an oral cyclic regimen. Li et al. [17] also reported an intravenous CTX combined with a corticosteroid regimen for PMN, in which CTX was given 0.50–0.75 g/m^2 by intravenous drip once or twice a month for 6 months. During a median follow-up period of 15 months, the remission rate was 82.4% with a CTX cumulative dose of around 7.2–10 g over 6 months, consistent with our study. The intravenous CTX regimens showed a similar remission rate to the oral cyclic regimen, while the cumulative CTX dose was much lower, which may have

Table 3. Adverse events and SAEs at 12 months

	RTX (n = 70)	CTX (n = 71)			p value*
	patients, n (%)	events, n (rate per 100 patients)	patients, n (%)	events, n (rate per 100 patients)	
Adverse events	20 (28.57)	26 (37.14)	29 (40.85)	41 (57.75)	0.13
Hyperglycemia	1 (1.43)	1 (1.43)	6 (8.45)	8 (11.26)	0.12
Infection	6 (8.57)	12 (17.14)	11 (15.49)	21 (26.58)	0.21
Respiratory tract infection	4 (5.71)	9 (12.86)	5 (7.04)	10 (14.08)	1.00
Urinary tract infection	2 (2.86)	3 (4.29)	4 (5.63)	9 (12.68)	0.68
Erysipelas	0 (0)	0 (0)	2 (2.82)	2 (2.82)	0.50
Hepatic dysfunction	5 (7.14)	5 (7.14)	5 (7.04)	5 (7.04)	1.00
Hyperkalemia	0 (0)	0 (0)	1 (1.41)	1 (1.41)	1.00
Infusion-related reaction	6 (8.57)	6 (8.57)	0 (0)	0 (0)	<0.01
Severe adverse events	2 (2.86)	2 (2.86)	6 (8.45)	6 (8.45)	0.28
Cerebral hemorrhage	1 (1.43)	1 (1.43)	0 (0)	0 (0)	0.50
Cerebral infarcts	0 (0)	0 (0)	1 (1.41)	1 (1.41)	1.00
Hepatic dysfunction and rhabdomyolysis	0 (0)	0 (0)	1 (1.41)	1 (1.41)	1.00
Epilepsy	1 (1.43)	1 (1.43)	0 (0)	0 (0)	0.50
Femoral head necrosis	0 (0)	0 (0)	1 (1.41)	1 (1.41)	1.00
Infection	0 (0)	0 (0)	3 (4.23)	3 (4.23)	0.25
Erysipelas with thrombosis	0 (0)	0 (0)	1 (1.41)	1 (1.41)	1.00
Pneumonia	0 (0)	0 (0)	2 (2.82)	2 (2.82)	0.50

*p values are for the differences in proportions of patients having a specific type of event.

caused fewer side effects. Thus, we suggest that intravenous CTX combined with a corticosteroid regimen may be a safe and effective alternative treatment strategy for patients with PMN.

Compared to the RTX regimen, our study showed that the intravenous CTX regimen had a higher early CR rate and a similar short-term safety profile. The main side effects of the intravenous CTX regimen were infection, hyperglycemia, and hepatic dysfunction, which were similar to the findings of previous studies [14]. Both groups showed similar rates of remission and relapse when the follow-up time was extended to 24 months, probably due to the delayed effect of RTX. In the RI-CYCLO study [13], although not statistically significant, RTX was shown to have a trend toward lower remission rates than oral CTX at 12 months. Our study and the RI-CYCLO study showed that the early response rate (at 12 months) to the CTX regimen, either orally or intravenously, was higher than that of RTX. However, probably because of the delayed effect of RTX, the response rates to the two treatments were similar at 24 months. In the subgroup analysis, our study showed that CTX was superior to RTX in patients with baseline proteinuria >8 g/24 h, indicating that the prior choice of CTX over RTX in treating patients with PMN at high risk for progression was in line with KDIGO 2021 [16]. In addition, although we found that the incidence of infection in the CTX group was slightly higher than that of the RTX group, the difference was not statistically significant. Both our study and the RI-CYCLO study determined similar safety profiles of the CTX regimen compared to RTX. Considering that the risk of adverse reactions to CTX is associated with its cumulative dose, intravenous CTX has potential safety advantages over oral CTX owing to its lower cumulative dose.

Our study had several limitations. First, it was a small-scale study with limited patient diversity; thus, the conclusions of our study need to be further confirmed by subsequent studies with sufficient research power that include more ethnically diverse patients with PMN. Second, only a portion of the patients in this study received dynamic PLA2R antibody testing. Therefore, the effects of these 2 treatment regimens on the immunological remission of patients with PMN still need to be clarified in future studies. In conclusion, our results show that the intravenous CTX regimen has similar safety and efficacy to RTX with higher rates of early complete remission in the treatment of patients with PMN.

Acknowledgment

The authors would like to thank their colleagues and all the patients participating in the study.

Statement of Ethics

This study was approved by the Institutional Review Board of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, and was conducted in accordance with the principles of the Declaration of Helsinki, with Approval No. DLY201510. Written informed consent was obtained from the parent/legal guardian of participants prior to the study.

Conflict of Interest Statement

All the authors declared no competing interests.

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Author Contributions

Chen Nan and Xie Jingyuan designed the research, provided substantial guidance, and revised the manuscript. Ren Hong and Hu Xiaofan contributed to the document, data collection, analysis, and drafting of the manuscript. Hu Xiaofan, Gao Chenni, and Ouyang Yan participated in data collection and patients' follow-up. Wu Yifan assisted in data analysis and manuscript revision. Lin Li assisted in specimen collection and the acquisition of clinical data. Ren Hong, Li Xiao, Wang Weiming, Liu Na, Xie Jingyuan, and Chen Nan were responsible for follow-up. Xu Jing was responsible for kidney biopsy readings. All authors read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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