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Editorial Board Member of *World Journal of Clinical Cases*, Baharudin Abdullah, MMed, Professor, Surgeon, Department of Otorhinolaryngology-Head and Neck Surgery, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian 16150, Kelantan, Malaysia. profbaha@gmail.com

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The primary aim of *World Journal of Clinical Cases* (WJCC, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

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Retrospective Study

Successful treatment of patients with refractory idiopathic membranous nephropathy with low-dose Rituximab: A single-center experience

Yao-Wei Wang, Xin-Hui Wang, Hong-Xia Wang, Ren-Huan Yu

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Yao-Wei Wang, Xin-Hui Wang, Hong-Xia Wang, Ren-Huan Yu, China Department of Nephrology, Xiyuan Hospital of China Academy of Chinese Medical Sciences, Beijing 100091, China

Corresponding author: Ren-Huan Yu, PhD, Professor, China Department of Nephrology, Xiyuan Hospital of China Academy of Chinese Medical Sciences, No. 1 Xiyuan Playground, Haidian District, Beijing 100091, China. tezhonggeyu@vip.sina.com

Abstract

BACKGROUND

The recognition of idiopathic membranous nephropathy (IMN) as an autoimmune disease has paved the way for the use of B-cell-depleting agents, such as Rituximab (RTX), which is now a first-line drug for treating IMN with proven safety and efficacy. Nevertheless, the usage of RTX for the treatment of refractory IMN remains controversial and challenging.

AIM

To evaluate the efficacy and safety of a new low-dose RTX regimen for the treatment of patients with refractory IMN.

METHODS

A retrospective study was performed on refractory IMN patients that accepted a low-dose RTX regimen (RTX, 200 mg, once a month for five months) in the Xiyuan Hospital of Chinese Academy of Chinese Medical Sciences' Department of Nephrology from October 2019 to December 2021. To assess the clinical and immune remission data, we performed a 24 h urinary protein quantification (UTP) test and measured the serum albumin (ALB) and serum creatinine (SCr) levels, phospholipase A2 receptor (PLA2R) antibody titer, and CD19⁺ B-cell count every three months.

RESULTS

A total of nine refractory IMN patients were analyzed. During follow-up conducted twelve months later, the results from the 24 h UTP decreased from baseline [8.14 ± 6.05 g/d to 1.24 ± 1.34 g/d ($P < 0.05$)] and the ALB levels increased from baseline [28.06 ± 8.42 g/L to 40.93 ± 5.85 g/L ($P < 0.01$)]. Notably, after administering RTX for six months, the SCr decreased from 78.13 ± 16.49 μ mol/L to 109.67 ± 40.87 μ mol/L ($P < 0.05$). All of the nine patients were positive

for serum anti-PLA2R at the beginning, and four patients had normal anti-PLA2R titer levels at six months. The level of CD19⁺B-cells decreased to 0 at three months, and CD19⁺B-cell count remained at 0 up until six months of follow-up.

CONCLUSION

Our low-dose RTX regimen appears to be a promising treatment strategy for refractory IMN.

Key Words: Refractory nephrotic syndrome; Idiopathic membranous nephropathy; Low-dose rituximab

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Core Tip: According to the Kidney Disease Improving Global Outcomes 2021 guidelines, Rituximab (RTX) is now the first-line therapy for patients with idiopathic membranous nephropathy (IMN). However, the use of RTX for the treatment of patients with refractory IMN remains challenging. We conducted a retrospective study on nine patients with refractory IMN to explore the efficacy and safety of a new low-dose RTX regimen (RTX, 200 mg, once a month for five months), and conclude that our low-dose RTX regimen is a promising treatment strategy for refractory IMN.

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INTRODUCTION

Idiopathic membranous nephropathy (IMN) is a common pathological type of glomerular disease, and its incidence rate has been continuously increasing yearly[1]. In the past 10 years, the proportion of adult patients with IMN with renal puncture has risen from 12.2%–24.9%, ranking second among those with primary glomerular diseases[2]. Currently, IMN is considered to be an autoimmune disease[3]. The M-type phospholipase A2 receptor (PLA2R) on the cell surface of podocytes is the major target antigen in IMN and can be found in 70%–80% of IMN patients[4]. Additionally, new antigens. Such as thrombospondin type-1 domain-containing 7A, neural epidermal growth factor-like 1 protein, and semaphorin 3b have also been recently discovered[5,6], further rationalizing the use of B-cell-depleting agents.

Rituximab (RTX) is an anti-CD20 monoclonal antibody that is used to treat several autoimmune disorders[7]. Since 2004, some reports have explored the use of RTX in patients with refractory nephrotic syndrome, and the preliminary results showed that RTX may lead to remission and reduce immunosuppressive drug use[8,9]. According to the Kidney Disease Improving Global Outcomes 2021 guidelines, RTX is now the first-line therapy for patients with IMN, and the remission rate can reach 60%–80% at 12 mo[10]. However, 35%–40% of IMN patients still show no response to RTX. Refractory IMN is characterized by recurrence or resistance to RTX-based and other traditional immunosuppressive therapies, including prednisone (Pre), cyclophosphamide (CTX), and calcineurin inhibitors (CNIs)[11]. In Asia, 5%–14% of refractory patients progress to end-stage renal disease (ESRD) within 10–15 years[12]. Therefore, new therapies are urgently needed to treat IMN.

When introduced to IMN treatment, standard doses for RTX (375 mg/m² every week for four weeks or 1 g fixed-dose with a repeat dose in two weeks) were drawn from the preexisting dosages for treating other autoimmune diseases, such as anti-neutrophil cytoplasmic antibody-associated vasculitis, rheumatoid arthritis (RA), autoimmune cytopenia, and focal segmental glomerulosclerosis[13]. Recently, few case series studies have proven the effectiveness of low-dose RTX regimens with repeated injections in treating patients with refractory IMN and showed that low-dose RTX could effectively improve the remission rate and peripheral blood B-cell elimination[14]. Currently, for the treatment of RA, a low-dose RTX regimen (500 mg twice daily) has replaced the original dose (1000 mg twice daily) and become the new standard. Kurosu *et al*[15] reported a case of steroid-resistant Nephrotic syndrome, where the kidney pathology showed minimal changes in glomerulopathy. The patient achieved complete remission (CR) with a single dose of RTX of 375 mg/m². Wang *et al*[16] reported the case of a 51-year-old man diagnosed with refractory IMN. The patient received a single dose of 100 mg RTX, after which the B-cells declined rapidly, and a gradual reduction in proteinuria was also observed. Katsuno *et al*[17] reported three patients with refractory IMN who were treated with single-dose RTX (500–600 mg) where two of the patients achieved complete and incomplete remission.

Based on previous studies, we evaluated the efficacy and safety of low-dose RTX in patients with refractory IMN. The regimen included 200 mg RTX once a month for five months. Compared to traditional regimens, our regimen appears to be a promising treatment strategy for refractory IMN.

MATERIALS AND METHODS

Patients

This was a retrospective case series study that included patients with refractory IMN who were admitted at the Xiyuan Hospital of the Chinese Academy of Chinese Medical Science Department of Nephrology from October 2019 to December 2021 ($n = 9$).

Acceptance and discharge standards

The inclusion criteria were as follows: (1) Patients with histologically proven IMN and a PLA2R antibody-positive status (Anti-PLA2R titer > 20 RU/mL); (2) Patients diagnosed with refractory IMN, broadly defined, who still presented with the nephrotic syndrome after six months of regular corticosteroid and immunosuppressive therapies, including those with Pre, CTX, cyclosporine, tacrolimus, mycophenolate mofetil, and RTX[10]; (3) Patients who signed the informed consent form for the low-dose RTX regimen and fully understood the risks of treatment; and (4) Patients with a follow-up period of > 1 year with an interval of < 3 months or > 4 visits between visits *per year*. The patients had complete clinical data, including routine blood test results, liver and kidney function test results, 24 h urinary protein quantitation (UTP) test results, serum anti-PLA2R antibody titer, and CD19⁺ B-cell counts. The exclusion criteria were as follows: (1) Presence of secondary membranous nephropathy, such as lupus nephritis, hepatitis B virus, hepatitis C, and tumors; (2) Glomerular diseases combined with other types; (3) Severe infections; and (4) Allergic reactions constitution.

Intervention

The low-dose RTX regimen was administered with a dose of 200 mg once a month for five months. Notably, after the patients were treated with RTX, the dosage of the primary therapeutic immunosuppressant was gradually decreased in all patients. If the patient's blood pressure remained $> 130/80$ mmHg, an appropriate angiotensin receptor blocker was added to the regime to stabilize blood pressure.

Every three months, clinical data such as 24 h UTP, serum ALB and serum creatinine (SCr) levels, PLA2R antibody titer, and CD19⁺ B-cell count were evaluated.

Efficacy evaluation criteria

The primary outcome was complete clinical remission. A composite remission was defined either as a complete response (CR) or partial response (PR). Proteinuria of < 0.3 g/d is defined as CR, while PR is defined as a 24 h UTP of 0.3 g-3.5 g/d, or 24 h UTP decreased by more than 50% compared to baseline. No reaction was defined as a decrease in proteinuria of less than 30% or renal function deterioration.

The secondary outcomes were 24 h UTP, ALB and SCr levels, Anti-PLA2R titer, CD19⁺ B-cell count, adverse events, and a composite endpoint of 40% reduction in estimated glomerular filtration rate, doubling of SCr, ESRD, and death.

Statistical methods

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, N.Y., United States). Data is presented as the mean \pm SD unless otherwise indicated. The comparison of each indicator before and after treatment was performed using a paired sample t-test, and unsatisfactory results were expressed as the median. The paired rank-sum test was used to compare before and after the treatment. Qualitative data was expressed as percentages (%). Comparisons between the groups were performed using the chi-square test, and the test level was set to 0.05.

RESULTS

Baseline characteristics

Nine patients with refractory IMN were treated with low-dose RTX at our center between October 2019 and December 2021. The baseline features of the patients are listed in Table 1. There were five men and four women, with an average age of 44.0 ± 11.7 years. Of these, six patients were diagnosed with IMN by kidney biopsy, and the other three patients were diagnosed with a serum anti-PLA2R titer > 100 RU/mL. Furthermore, all nine (100%) patients tested positive for serum anti-PLA2R at the beginning of the trial. Before the administration of RTX, all nine patients had received regular corticosteroid and immunosuppressive therapy for at least six months prior and still presented with the nephrotic

Table 1 Baseline characteristics

Patient No.	Age (yr)	Sex	PLA2R	Duration (mo)	Previous treatment	Effect	Side effect	Current treatment
1	57	M	+	12	(1) RTX 500 mg iv twice in two months; and (2) Pre 40 mg/d + CSA 150 mg/d	SR	Serum glucose up	Pre + TAC
2	28	M	+	54	(1) Pre 20 mg/d + TAC 2 mg/d; and (2) Pre 24 mg/d + TAC 2 mg/d	SR	Cushing's syndrome	Pre + TAC
3	40	M	+	21	(1) CSA 150 mg/d; (2) Pre 20 mg/d + CTX 100 mg/d; and (3) Pre 30 mg + TAC 2 mg/d	SR	Hypertension	Pre + TAC
4	60	F	+	51	(1) TAC 2 mg/d; and (2) Pre 20 mg + CSA 150 mg/d	SR	Steroid-induced diabetes	Non
5	31	M	+	9	(1) CsA 150 mg/d; (2) Pre 48 mg/d + TAC 2 mg/d; and (3) Pre 48 mg/d + CTX 100 mg/d	SD	Steroid-induced diabetes; liver damage; Hypertension	Pre + TAC
6	29	F	+	31	(1) Pre 15 mg/d + CSA 150 mg/d; (2) Pre 40 mg/d + LEF 30 mg/d; and (3) Pre 25 mg/d + TAC 2 mg/d	SD	Cushing's syndrome; Hypertension	Pre
7	49	M	+	44	(1) Pre 40 mg/d + CSA 150 mg/d; and (2) Pre 24 mg/d + TAC 2 mg/d	SD	Cushing's syndrome; Steroid-induced diabetes	Pre + TAC
8	49	F	+	35	(1) Pre 50 mg/d + CTX 1000 mg iv; (2) Pre 30 mg/d + CSA 150 mg/d; and (3) TAC 3 mg/d	SR	Cushing's syndrome; Liver damage; Steroid-induced diabetes	Non
9	36	F	+	18	(1) Pre 24 mg/d + CSA 100 mg/d; and (2) TAC 2 mg/d	SR	Non	Non

M: Male; F: Female; PLA2R: Phospholipase A2 receptor; RTX: Rituximab; Pre: Prednisone; CAS: Cyclosporine; TAC: Tacrolimus; LEF: Leflunomide; SR: Steroid-resistant; SD: Steroid-dependent.

syndrome; therefore, they were diagnosed with refractory IMN. Of these, six patients were steroid-resistant and three patients were steroid-dependent.

Furthermore, at baseline, all nine patients experienced adverse reactions triggered by the above treatment, including two with elevated serum glucose levels, one with hypertension, one with Cushing syndrome; one combined with steroid-induced diabetes, hypertension, and an abnormal liver function; one combined with hypertension and Cushing syndrome; one combined with steroid-induced diabetes and Cushing syndrome; and one combined with steroid-induced diabetes, an abnormal liver function, and an abnormal liver function.

Clinical outcomes during follow-up

The clinical outcomes of the nine patients during the twelve months of follow-up are listed in Table 2 and Supplementary Table 1. The proportion of patients who achieved CR or PR over time, as well as the trends of the remission rate, 24 h UTP, ALB, and SCr levels are shown in Figure 1. The PR and CR rates gradually increased with a lengthened treatment time. The remission rates were 56% (5/9; PR 5) at three months, 67% at six months (6/9; PR 6), 89% at nine and twelve months (8/9; CR 3 and PR 5). One patient did not complete the course of treatment due to adverse infusion reactions.

The comparison of the clinical outcomes at twelve months of follow-up is shown in Table 3. In the eight patients treated with a low dose of RTX for six months, the 24 h UTP and ALB levels showed no significant changes when compared with those before treatment. Nine months later, the 24 h UTP decreased from 8.14 ± 6.05 g/d to 1.74 ± 1.81 g/d ($P < 0.05$), and the ALB level improved from 28.06 ± 8.42 g/L to 36.84 ± 6.74 g/L ($P < 0.05$). At the end of the twelve-month follow-up, 24 h UTP decreased to 1.24 ± 1.34 , and ALB improved to 40.93 ± 5.85 g/L, which are significant differences compared with those before treatment ($P < 0.05$ and $P < 0.01$, respectively). This means that the longer the follow-up period, the higher the remission rate. Notably, after administering RTX, there was a significant difference in the SCr levels when compared with those before treatment ($P < 0.05$).

Immunologic remission during follow-up

We used serum PLA2R antibodies and CD19⁺ B-cells to assess immune remission. As shown in Table 4, all nine patients had elevated serum PLA2R antibody titers at the beginning of the trial. Concerning the anti-PLA2R titers before RTX administration, three patients had low titers of anti-PLA2R (≤ 50 IU/L), two patients had medium titers of anti-PLA2R (50–150 IU/L), and four patients had a high titer of anti-PLA2R (> 150 IU/L). Of them, eight patients were followed up for six months, and the titers of anti-PLA2R decreased after administering RTX. Furthermore, at the three-month follow-up, one patient (No. 6) tested negative for the PLA2R antibody; at the six-month follow-up, four patients (No. 1, 6, 8, and 9)

Table 2 Clinical outcomes

Patient No.	Before administering of RTX (0 mo)			After administering of RTX (6 mo)				Follow-up (12 mo)			
	24 h UTP (g/d)	ALB (g/L)	Scr (μmol/L)	24 h UTP (g/d)	ALB (g/L)	Scr (μmol/L)	Remission	24 h UTP (g/d)	ALB (g/L)	Scr (μmol/L)	Remission
1	15.2	13.9	97	2.3	25.1	64	PR	1.88	44	66	PR
2	7.1	29	78	3.6	36.9	72	NR	2	36.2	83	PR
3	17	16	202	9.9	24.3	93	NR	4	29.9	116	PR
4	6.7	26	142	-	-	-	-	-	-	-	-
5	5.7	35	84	1.03	45.1	64	PR	0.09	49.5	90	CR
6	1.8	37.4	78	1.3	42	82	PR	0.6	40.1	75	PR
7	3.5	32.5	90	1.8	35.1	69	PR	0.27	44.1	88	CR
8	15	26.9	91	6.2	29.4	70	PR	0.9	41.4	82	PR
9	1.3	35.8	125	0.64	39.1	111	PR	0.175	42.2	124	CR

UTP: Urinary protein quantitation; RTX: Rituximab; ALB: Albumin; Scr: Serum creatinine; PR: Partial remission; CR: Complete remission; NR: No remission.

Table 3 Comparison of clinical outcomes during follow-up

Outcome	0 (mo)	3 (mo)	6 (mo)	9 (mo)	12 (mo)
24 h UTP (g/d)	8.14 ± 6.05	5.65 ± 4.99	3.35 ± 3.20	1.74 ± 1.81 ^a	1.24 ± 1.34 ^a
ALB (g/L)	28.06 ± 8.42	32.39 ± 8.7	34.63 ± 7.69	36.84 ± 6.74 ^a	40.93 ± 5.85 ^{b,c}
Scr (μmol/L)	109.67 ± 40.87	97.38 ± 27.34	78.13 ± 16.49 ^a	84.5 ± 16.96	90.5 ± 19.81
Remission rate (%)	—	56% (5/9)	67% (6/9)	89% (8/9)	89% (8/9)

^a*P* < 0.05 vs 0 mo.

^b*P* < 0.01 vs 0 mo.

^c*P* < 0.05 vs 3 mo.

Data were analysed by one-way ANOVA followed by post hoc LSD test (albumin and serum creatinine) and presented as the mean ± SD. Data were analysed by Kruskal Wallis H test (24 h urinary protein quantitation).

UTP: Urinary protein quantitation; ALB: Albumin; Scr: Serum creatinine.

were negative for the PLA2R antibody. The level of CD19⁺ B-cells decreased to 0 at three months, and remained the same until six months of follow-up.

Adverse events

During the median (8.7 ± 3.7 mo) period of follow-up, among the nine patients who experienced adverse reactions, one patient presented with shivering. Shivering occurred during the first infusion of RTX, but no dyspnea or fever occurred simultaneously. Symptoms were relieved 10 min after terminating the RTX treatment, and no RTX was infused afterwards; the patient did not complete the treatment. Two patients had a fever, which occurred within 24 h of RTX infusion. The body temperature was 37.5–38.5 °C, but returned to normal within 48 h without administering antibiotics. The fever did not recur.

DISCUSSION

IMN is the most common cause of primary nephrotic syndrome in adults. The prognosis of patients with IMN varies greatly, with around 1/3 of the patients progressing to ESRD within 10–15 years, and another 1/3 being relieved of symptoms[3]. To date, alkylating agents are the only drugs with a proven efficacy in preventing the development of ESRD[18]. Therefore, corticosteroid therapy combined with alkylating agents has been recognized as the treatment of choice for decades. Other immunosuppressive agents[19], such as CNIs, have been tested only in trials using proteinuria reduction as an alternative

Table 4 Serum anti-phospholipase A2 receptor titer and CD 19⁺ B-cell count during administering of Rituximab

Patient No.	Before administering of RTX (0 mo)		Administering of RTX (3 mo)		After administering of RTX (6 mo)	
	Anti-PLA2R titer (RU/mL)	CD19 ⁺ B (pcs/ μ L)	PLA2R antibody (RU/mL)	CD19 ⁺ B (pcs/ μ L)	PLA2R antibody (RU/mL)	CD19 ⁺ B (pcs/ μ L)
1	1400	418	104	0	Negative	0
2	180	6	96	0	82	0
3	215	169	67	0	48	0
4	500	422	-	-	-	-
5	32	114	27	0	20	0
6	45	28	Negative	0	Negative	0
7	52	460	22	0	17	0
8	130	192	38	0	Negative	0
9	36	258	21	0	Negative	0

RTX: Rituximab; PLA2R: Phospholipase A2 receptor.

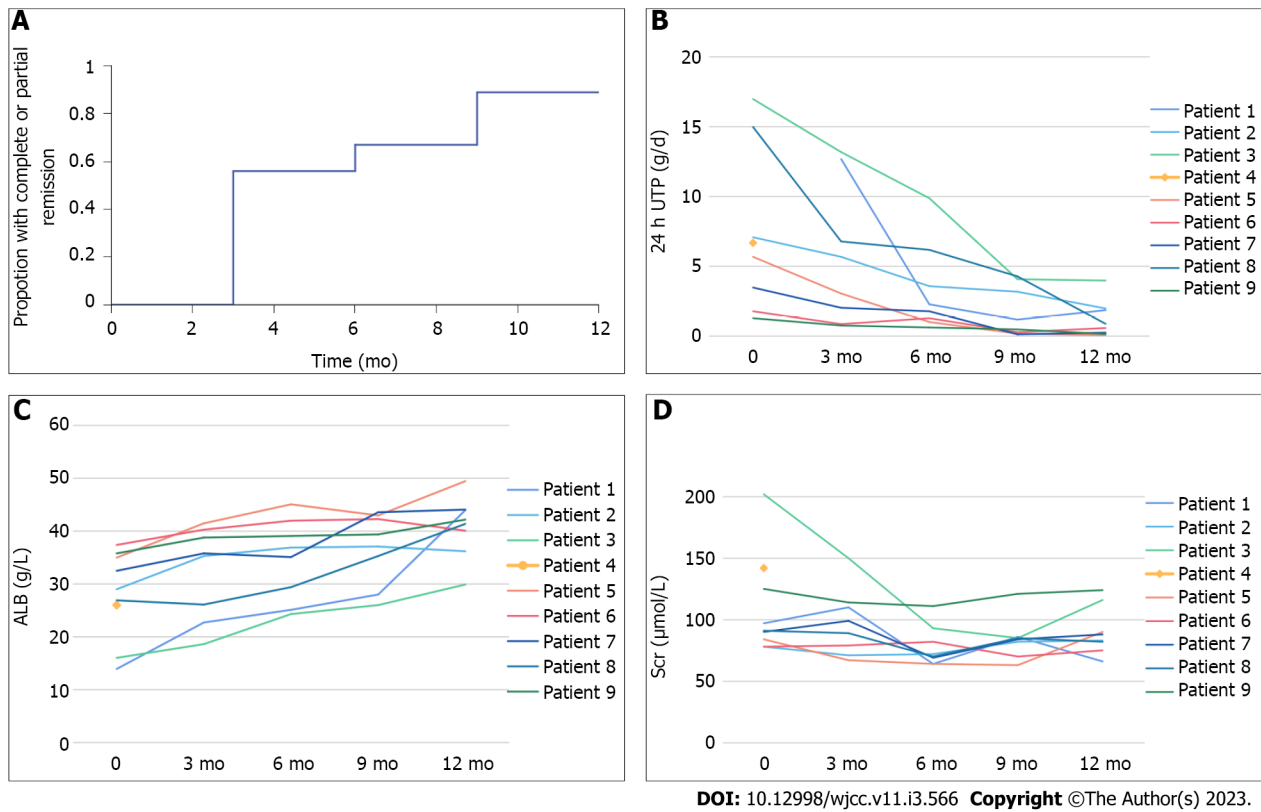


Figure 1 Clinical outcomes. A: Kaplan-Meier curve for complete or partial remission; B: 24 h urinary protein quantification trend after Rituximab (RTX) in 9 patients with refractory idiopathic membranous nephropathy (IMN); C: Albumin trend after RTX in 9 patients with refractory IMN; D: Serum creatinine trend after RTX in 9 patients with refractory IMN. UTP: Urinary protein quantification; ALB: Albumin; SCr: Serum creatinine.

endpoint.

Although an effective immunosuppressive treatment scheme for IMN has been established clinically, 20%–30% of IMN patients are resistant to standard immunosuppressive therapy or often relapse[20]; these patients were diagnosed with refractory IMN. In Asia, 5%–14% of refractory IMN patients will progress to ESRD. Therefore, effective and safe therapeutic strategies for refractory IMN must be explored. In the past decade, significant advances in understanding of IMN have established that it is an autoantibody-driven disease[21,22]. As a result, there is a clear choice for treating B-cell depletion. Currently, RTX is the most important immunosuppressive treatment for IMN. The results of the MENTOR trial provide the basis for RTX being the first-line treatment in patients with IMN[23].

Although the results of RTX are promising, it should be noted that approximately 30%–40% of cases experience treatment failure, which means that other treatment regimens are needed. Currently, some studies have focused on the paradigm shift from RTX to new alternatives or combined drugs in treating patients with refractory IMN to overcome drug resistance. However, the second course of RTX may achieve remission even in the setting of resistant RTX after the first course[24].

The natural course of IMN varies greatly; thus, it is not suitable for all patients to receive a unified treatment and the optimal RTX dose for the treatment of IMN remains controversial. Different RTX application regimens were used across various studies, ranging from a single dose of 375 mg/m² to a repeated dose of 375 mg/m² for four weeks after six months. A prospective clinical study evaluated the low-dose RTX regimen (375 mg/m², once) compared with the standard RTX regimen (375 mg/m², four times)[25]. If the consumption of B-cells is insufficient, the same dose can be used in the low-dose RTX group. The results showed that among the twelve patients who were administered with low-dose RTX, only one needed a second dose to achieve complete B-cell depletion, and at 1 year, the remission rate of the two groups was the same. They also concluded that a single-dose RTX regimen was extremely cost-effective and may limit the production of antichimeric antibodies, lowering the risk of adverse reactions. Similarly, another retrospective study compared forty-two patients administered low-dose RTX (375 mg/m²)[26]. The control group was treated with steroid hormones combined with alkylating agents or a standard RTX regimen (375 mg/m², four times). At twenty-four months, there was no significant difference in clinical outcomes between the two groups. All patients treated with RTX showed complete B-cell depletion in the first month, but B-cell recovery occurred earlier in the low-dose group than in the standard group. Recently, some case reports and case series studies have proven the effectiveness of low dose but RTX regimens with repeated injections in treating patients with refractory IMN. These regimens seem to extend the inhibition of B-cells. We explored a new RTX regimen (200 mg once a month for five months) for treating patients with refractory IMN in our hospital.

Nine patients with refractory PLA2R-associated MN were included in this analysis. In the data provided twelve months after baseline, the remission rate was 56% (5/9; PR 5) at three months, 67% at six months (6/9; PR 6), and 89% at nine and twelve months (8/9; CR 3 and PR 5). Another patient did not complete the treatment because of infusion reactions. In a review of currently available studies, the overall remission rates (complete and partial) of RTX at twelve months of treatment for patients with IMN consistently ranged from 44%–85%. Few studies have reported that among patients with refractory IMN, the efficacy rate of RTX can only reach 40%. The remission rate of the low-dose RTX regimen at our center was significantly higher than that reported in previous studies.

In addition, we observed that clinical remission in patients with refractory IMN was slower than in patients with immune remission. We used serum PLA2R antibody titer and CD19⁺ B-cell counts to assess immune remission. The level of CD19⁺ B-cells decreased to 0 at three months, which was maintained until six months of follow-up. At the beginning of the trial, all nine patients were positive for the PLA2R antibody. The titers of anti-PLA2R decreased after administering low-dose RTX, and one patient (No. 6) had a normal anti-PLA2R titer after three months, while four patients (No. 1, 6, 8, and 9) had a normal anti-PLA2R titer after six months. However, when compared with the previous situation, the 24 h UTP and ALB levels showed no significant changes at six months. Until nine months post-treatment, 24 h UTP decreased from 8.14 ± 6.05 g/d to 1.74 ± 1.81 g/d ($P < 0.05$), while ALB has increased from 28.06 ± 8.42 g/L to 36.84 ± 6.74 g/L ($P < 0.05$). At the end of the twelve-month follow-up period, the clinical outcomes were significantly enhanced when compared to those before treatment. This means that the longer the follow-up time, the higher the remission rate that was observed. Notably, none of the eight patients had a recurrence until the date.

Compared with the standardized dose (375 mg/m² every week for four weeks, or 1 g fixed-dose with a repeat dose in two weeks), our low-dose RTX regimen lasted for a longer time (*i.e.*, B-cell levels remained low for a longer period of time), which meant that the disease was less likely to relapse. Furthermore, when compared to the high-dose RTX and traditional immunosuppressive regimens, our low-dose RTX regimen also has advantages in terms of security. Although effective immunosuppressive regimens for IMN have been established clinically, the preceding therapeutic options have significant disadvantages, which limit their application, especially in patients with renal insufficiency. At the beginning of the trial, eight patients had a side reaction associated with previous immunosuppressive treatment. During the twelve-month follow-up that tracked adverse reactions, there was only one case of shivering. Notably, after administering RTX for six months, the SCr level decreased from 78.13 ± 16.49 μmol/L to 109.67 ± 40.87 μmol/L ($P < 0.05$). In this study, we found that our low-dose RTX regimen for the treatment of refractory IMN significantly improved the clinical outcomes and further increased the remission rate. Moreover, treatment with our low-dose RTX regimen is more cost-effective than that with high-dose RTX.

However, it is worth noting that this research also has few limitations that must be considered. First of all, since our study was retrospective in nature and the sample size was small ($n = 9$), the statistical analysis of data may have biases and inadequacies in terms of generalization. Second, the clinical outcomes were monitored after 1 year; however, the data on immunological indicators, including serum anti-PLA2R titer and CD19⁺ B-cell count, were monitored only after six months. The long-term prognosis of our low-dose RTX regimen in treating refractory IMN patients is still yet to be explored. To confirm these results and deepen our understanding about this treatment option, we need to conduct

large-scale clinical trials and further clarify the mechanism of action of RTX in refractory IMN.

CONCLUSION

The treatment of patients with refractory IMN using RTX remains controversial and challenging. Conventional immunosuppressive treatment strategies have been applied for several years and have clinically established therapeutic efficacy. In conclusion, we found that our low-dose RTX regimen significantly improved clinical outcomes and further increased the remission rate of patients with IMN. Moreover, treatment with our low-dose RTX regimen is more cost-effective than that with high-dose RTX.

ARTICLE HIGHLIGHTS

Research background

The recognition of idiopathic membranous nephropathy (IMN) as an autoimmune disease has paved the way for the use of B-cell depleting agents such as Rituximab (RTX), which is now a first-line drug for IMN patients with proven safety and efficacy.

Research motivation

RTX for the treatment of refractory IMN patients remains controversial and challenging.

Research objectives

To evaluate the efficacy and safety of a new low-dose RTX regimen for the treatment of refractory IMN patients.

Research methods

A retrospective study was performed on refractory IMN patients that accepted Low-dose RTX regimen (RTX, 200 mg, once a month for five months).

Research results

A total of 9 refractory IMN patients were analyzed. At 12 mo of follow-up data from baseline, the 24 h urinary protein quantification was decreased from 8.14 ± 6.05 g/d to 1.24 ± 1.34 g/d ($P < 0.05$), and the albumin was improved from 28.06 ± 8.42 g/L to 40.93 ± 5.85 g/L ($P < 0.01$). Notably, after administering RTX for 6 mo, the serum creatinine decreased from 78.13 ± 16.49 μ mol/L to 109.67 ± 40.87 μ mol/L ($P < 0.05$). All of the 9 patients were serum anti-phospholipase A2 receptor (PLA2R) positive at the beginning, and 4 patients had a normal anti-PLA2R titer at six months. The level of CD19⁺ B-cells decreased to 0 at three months, and the count of CD19⁺ B-cells lasted to 0 until six months of follow-up.

Research conclusions

We found that our low-dose RTX regimen for the treatment of refractory IMN significantly improved clinical outcomes and further increased the remission rate.

Research perspectives

Treatment with our low-dose RTX regimen is more cost-effective than high-dose RTX.

FOOTNOTES

Author contributions: Wang HX and Wang YW contributed to the conception and design of the study; Wang HX, Wang YW, and Wang XH contributed to data collection, analysis, and interpretation; Wang YW and Wang XH wrote the manuscript; Yu RH critically revised the manuscript for important intellectual content; All authors revised the manuscript and approved the submitted version.

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Institutional review board statement: The study protocol was approved by the ethics review board of Xiyuan Hospital, China's Academy of Chinese Medical Sciences (Beijing, China, approved No. 2022XLA130-2). All of the procedures were performed in accordance with the Declaration of Helsinki and relevant policies in China.

Informed consent statement: A written informed consent was obtained from the patient for publication of this case report.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Country/Territory of origin: China

ORCID number: Ren-Huan Yu [0000-0003-0879-5357](https://orcid.org/0000-0003-0879-5357).

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