Therapeutic Efficacy Observation of Rituximab Combined With Low-Dose Glucocorticoids in the Treatment of Idiopathic Membranous Nephropathy

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Abstract
Objective: To compare the clinical efficacy and safety of rituximab (RTX) combined low-dose glucocorticoid for idiopathic membranous nephropathy (IMN).
Methods: A total of 35 IMN patients were recruited from July, 2019 to December, 2023. Control group (n=19): CTX combined glucocorticoid. Experimental group (n=26): rituximab combined low-dose glucocorticoid. The differences of 24-hour urinary protein, serum albumin, blood creatinine, anti-PLA2R antibody titer, disease re-mission rate and adverse reactions were compared between two groups before and at different timepoints post-treatment.
Results: No significant inter-group differences existed in gender, age, body mass index, blood pressure, 24-hour urinary protein, serum albumin, blood creatinine, eGFR or anti-PLA2R antibody count pre-treatment (P>0.05). At Month 6, 24-hour urinary protein declined markedly in 2 groups as compared with pre-treatment (P<0.01); serum level of albumin spiked markedly as compared with pre-treatment (P<0.01). However, no significant inter-group difference existed in reduction of urinary protein and recovery of serum albumin post-treatment (P>0.05). In terms of serum creatinine, total renal function of 2 groups remained stable without statistical significance (P>0.05). Anti-PLA2R-Ab level declined markedly in two groups post-treatment as compared with pre-treatment and the difference was not statistically significant (P>0.05). In terms of disease remission, total effective rate reached 71.43% at Month 6. Meanwhile, recurrence rate was no significant inter-group difference existed in adverse reactions (P>0.05).
Conclusion: With a higher clinical remission rate without a higher incidence of adverse reactions, RTX combined low-dose glucocorticoid is more suitable for treating IMN. However, adverse reactions causing severe hypokalemia deserve greater attention

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1. Introduction

Idiopathic membranous nephropathy (IMN) is an autoimmune disease in humans and a highly prevalent pathological type of adult nephrotic syndrome [1-2]. Without timely intervention and treatment, it poses a significant threat to patients' lives. Conventional therapies such as glucocorticoids and immune suppressants have limited efficacy. Recent molecular pathway studies have confirmed that PLA2R is the primary target antigen in IMN, resulting from the activation and differentiation of B lymphocytes.

Its expression correlates with disease activity, and its antibody titer fluctuates in parallel with proteinuria levels [3-5]. Given the critical role of B cell-derived autoantibodies in the pathogenesis of immune-mediated glomerular diseases, biologic agents have been explored for refractory glomerulopathies. Rituximab (RTX), a monoclonal antibody targeting CD20, binds with high affinity to the CD20 surface antigen on B cells. It eliminates CD20+ B cells through antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), antiproliferative effects, or apoptosis induction, thereby suppressing pathogenic antibody production [6]. Although RTX has been successfully used in IMN in multicenter studies worldwide, reports on rituximab combined with low-dose glucocorticoids remain limited. Whether this combination improves efficacy or prevents adverse effects such as renal function deterioration still requires validation through prospective, randomized controlled trials.

2. Patients and Methods

2.1 Patients A total of 35 patients diagnosed with idiopathic membranous nephropathy (IMN) at Jingmen Central Hospital between July 2022 and December 2023 were enrolled in this study. The study protocol was approved by the Medical Ethics Committee of Jingmen Central Hospital (Approval No.: 202202035), and written informed consent was obtained from all participants. Patients were randomly assigned to either the control or observation group using a random number table.

Inclusion Criteria

1. Diagnosis of IMN confirmed by renal biopsy, including immunohistopathology and light microscopy, with positive serum anti-PLA2R antibodies.
2. No prior treatment with immunosuppressants or cytotoxic drugs.
3. Willingness to comply with the hospital's full-course treatment protocol.
4. Expected survival >6 months.

Exclusion Criteria

1. Coexisting glomerular diseases or severe infections.
2. Long-term use of immunosuppressive therapy.
3. Allergy to any study medications.
4. Incomplete baseline data precluding analysis.

2.2 Methods

The control group received conventional classic treatment: glucocorticoids combined with cyclophosphamide pulse therapy. Specifically, an initial full dose of methylprednisolone (1.0-0.8 mg/kg/d) was administered, with tapering beginning after 8 weeks and reduced every 2 weeks. Cyclophosphamide was administered via intravenous pulse therapy at a dose of 0.5–1.0 g per session, once monthly for 6 consecutive months. The observation group, in addition to symptomatic and basic treatments, received low-dose glucocorticoids combined with rituximab therapy: methylprednisolone (0.5 mg/kg/d), with tapering beginning after 4 weeks and reduced every 2 weeks. Intravenous infusion of rituximab was administered once a month at a dose of 375 mg/m², with observation over 6 months. Both groups of patients received symptomatic and basic treatments, such as antihypertensive and hypoglycemic therapies, renal protection, etc.

Before treatment and monthly after treatment, the following indicators were monitored:

1. 24-hour urinary protein quantification;
2. Serum albumin;
3. Serum creatinine;
4. Serum uric acid;
5. Serum PLA2R antibody (PLA2R-Ab) levels.

After 6 months of treatment, the patients' conditions were assessed as follows

Complete remission

24-hour urinary protein ≤ 0.5 g/24h; Serum albumin ≥ 35 g/L; Serum PLA2R-Ab turned negative; No decline in eGFR; Improvement in blood biochemical markers.

Partial remission

24-hour urinary protein decreased by ≥50% from baseline; Serum albumin increased compared to pre-treatment levels; Serum PLA2R-Ab titer decreased compared to pre-treatment levels; No significant decline in eGFR.

No response (Ineffective)

No significant improvement in observed indicators compared to pre-treatment levels; OR a ≥50% decline in eGFR from baseline.

Relapse

During observation, after achieving complete or partial remission, rebound in the monitored indicators occurred.

2.3 Statistical Methods

Statistical analysis was performed using SPSS. Measurement data were expressed as mean ± standard deviation ($\bar{x} \pm s$) and compared using the t-test. Count data were presented as numbers (percentages) [n (%)] and analyzed using the chi-square test. Ordinal data were compared using the rank-sum test. A P-value < 0.05 was considered statistically significant.

3. Results

3.1 General Information and Baseline Data of Included Patients

A total of 35 patients with membranous nephropathy were enrolled in this study. Among them, 12 cases were diagnosed via renal biopsy, and 23 cases were confirmed by positive serum phospholipase A2 receptor antibody (PLA2R-Ab). The 35 patients were randomly divided into an experimental group (19 patients) and a control group (16 patients), with no statistically significant differences in baseline characteristics. All patients received relevant treatments according to the study protocol. Detections of 24-hour urine protein quantification, serum albumin, blood creatinine, blood uric acid, and serum PLA2R-Ab levels were conducted before and after treatment. Estimated glomerular filtration rate (eGFR) was calculated, and a 6-month treatment period was set as the endpoint to evaluate therapeutic efficacy. Adverse reactions during treatment were also observed.

3.2 Changes in Laboratory Indicators Before and After Treatment

Table 1: Measurement Parameters and Statistical Differences of the Two Groups Pre- and Post-Treatment

	Experimental group（n=19）		Control group（n=16）	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Serum PLA2R-Ab（U/ml）	66.5±31.4	＜20#	71.4±34.9	＜20#
24-hour Urine Protein Quantification（g/24hr）	4.25±1.79	0.31±0.14#	5.11±1.26	0.45±0.22#
Serum Albumin（g/L）	21.3±4.7	35.2±4.1#	24.3±5.3	32.9±6.8#
eGFR（ml/min*1.73m^2）	45.89±9.47	44.21±10.23	49.72±11.24	47.20±12.26
Statistical Differences	Differences（* P＜0.05） Significant Differences（# P＜0.01）			

As shown in Table 1, Changes in indicators including 24-hour urine protein quantification, serum albumin, blood creatinine, estimated glomerular filtration rate (eGFR), and anti-PLA2R-Ab levels were analyzed in both groups before treatment and after 6 months of treatment. Statistically significant differences were observed in anti-PLA2R-Ab levels, 24-hour urine protein quantification, and serum albumin between baseline and 6 months post-treatment in both groups (P < 0.01). However, no statistically significant differences were found in eGFR before and after treatment (P > 0.05).

3.3 Clinical Efficacy Analysis

After 6 months of treatment, the experimental group achieved complete remission in 14 cases and partial remission in 5 cases, while the control group had complete remission in 11 cases, partial remission in 4 cases, and no response in 1 case. The comparison of complete remission rates and partial remission rates between the two groups showed no statistically significant difference (P>0.05). (Table 2)

The time to achieve complete remission was comparable between the two groups, with no statistically significant difference (P>0.05). Among the 5 patients with partial remission in the experimental group, the duration of remission was significantly shorter than that in the control group, showing a statistically significant difference (P<0.05). (Table 3)

Table 2: Comparison of Disease Remission Rates Between the Two Groups

Parameter	Complete Remission Rate (%)	Partial Remission Rate (%)	No Response Rate (%)	Recurrence Rate (%)
Experimental Group	n=19	73.68 (n=15)	26.32 (n=5)	0 (n=0)
Control Group	n=16	68.75 (n=11)	25.00 (n=4)	6.25* (n=1)
Statistical Difference	None	None	Yes (*P≤0.05)	None

Table 3: Comparison of Disease Remission Time Between the Two Groups

Parameter	Complete Remission Time (d)	Partial Remission Time (d)
Experimental Group	62.75 ± 5.72	36.45 ± 9.72
Control Group	64.77 ± 7.49	45.22* ± 11.49
Statistical Difference	None	Yes (*P≤0.05)

3.4 Adverse Reaction Observation

Experimental Group

- Influenza A virus upper respiratory tract infection: 1 case, resolved well following aggressive anti-viral treatment.
- Bacterial pulmonary infection: 1 case, resolved well following aggressive antibacterial treatment.
- Elevated blood glucose: 1 case (not meeting diabetes diagnostic criteria), well-controlled after adjustment of diet and exercise.
- Cushing's syndrome: Not prominent.
- No gastrointestinal ulcers or bleeding.
- No osteoporosis, femoral head necrosis, or glaucoma.

Control Group

- Bacterial pulmonary infection: 1 case, resolved well following aggressive antibacterial treatment.
- Steroid-induced diabetes: 1 case, well-controlled with adjustment of diet, exercise, and hypoglycemic therapy.
- Cushing's syndrome: Prominent.
- Post-medication discomfort: Substernal discomfort and heartburn in 1 case, bone pain in 1 case.
- No gastrointestinal ulcers or bleeding.
- No femoral head necrosis or glaucoma.

4. Discussion

The incidence of idiopathic membranous nephropathy (IMN) has been increasing annually. Extensive molecular pathway studies have confirmed that PLA2R is the primary "target antigen" in IMN, accounting for over 70% of cases. PLA2R arises from the activation and differentiation of B lymphocytes, and its expression titer exhibits a positive correlation with disease progression, directly predicting the occurrence, development, and prognosis of IMN. Given the critical role of B lymphocyte-derived autoantibodies in the pathogenesis of immune-mediated glomerular diseases, biologic agents are being explored as therapeutic options for refractory glomerular diseases, including IMN.

Currently, the traditional treatment for IMN involves glucocorticoids combined with immune suppressants. Glucocorticoids are administered following the principle of adequate dosing and prolonged courses with gradual tapering, while immune suppressants such as cyclophosphamide, calcineurin inhibitors (CNI), or cyclosporine A (CsA) are optional [7-8]. The conventional treatment duration is no less than 12 months, with a 12-month complete/partial remission rate of 60%. However, the adverse effects of glucocorticoid use are prominent, including opportunistic infections, metabolic abnormalities in blood glucose and lipids, osteoporosis, femoral head necrosis, and

Cushing's syndrome. These issues contribute to poor patient compliance and even treatment discontinuation. Therefore, the concept of balancing therapeutic efficacy with rigorous monitoring and minimizing treatment-related complications is gaining increasing recognition.

Rituximab (RTX), a monoclonal antibody targeting CD20, highly binds to CD20 on B cell surfaces. It eliminates CD20+ B cells through mechanisms such as antibody- or complement-dependent cytotoxicity, anti-proliferative effects, or apoptosis induction, thereby inhibiting pathogenic antibody production [9]. Studies applying RTX to IMN have shown that the protein remission rate at 12 months is non-inferior to conventional therapy. Although its onset of action is slightly slower than traditional treatments, RTX offers the potential for reduced or corticosteroid-free regimens.

In this study, a combination therapy of low-dose glucocorticoids and rituximab, administered for 6 months on top of symptomatic and foundational treatment, demonstrated comparable remission rates to the control group. The time to achieve complete remission was not longer than that of the control group, and the time to partial remission was even slightly shorter. However, due to the reduced dosage and duration of glucocorticoid use, the incidence and severity of adverse reactions—such as Cushing's syndrome, metabolic abnormalities in blood glucose and lipids, and osteoporosis—were significantly lower. The infection rate was similar between the two groups, with all cases remaining controllable. Neither group experienced progressive declines in estimated glomerular filtration rate (eGFR).

In conclusion, the combination of low-dose glucocorticoids and rituximab for IMN treatment achieved non-inferior remission rates and remission times compared to traditional regimens, while offering superior safety. This approach improved patient compliance with treatment and holds potential for clinical implementation. Further follow-up is warranted to evaluate long-term maintenance efficacy and relapse rates, which will provide additional evidence-based data to support this therapeutic strategy.

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