

Clinical Observation of Serum Anti-PLA2R Antibody Levels in the Treatment of Idiopathic Membranous Nephropathy with Rituximab

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Abstract: *Objective:* To investigate the efficacy of rituximab in the treatment of idiopathic membranous nephropathy with varying levels of serum phospholipase A2 receptor antibodies. *Methods:* A total of 137 patients with idiopathic membranous nephropathy admitted to Beijing Sixth Hospital were selected. Based on their blood PLA2R antibody levels before rituximab treatment, patients were categorized into the PLA2R antibody positive group ($n = 94$) and the PLA2R antibody negative group ($n = 43$). They were followed up for at least 1 year, during which the efficacy, measured through 24-hour urine protein quantification and serum albumin levels, were compared between the two groups before and after treatment. *Results:* After 3 months of treatment, there was no significant difference in the quantitative levels of 24-hour urine protein between the two groups ($P > 0.05$). However, after 6 and 12 months of treatment, there was a significant difference in the levels of 24-hour urine protein between the two groups ($P < 0.05$). Additionally, after 3 months of treatment, there was a notable difference in the serum albumin levels between the two groups ($P < 0.05$). However, after 6 and 12 months of treatment, there was no significant difference in serum albumin levels between the two groups ($P > 0.05$). Analysis of complications in the two groups revealed that in the positive group, 9 individuals experienced thrombosis, 5 had infections, and 11 developed acute kidney injury (AKI). In contrast, in the negative group, 5 individuals had thrombosis, 2 had infections, and 3 developed AKI. There was no statistically significant difference in complications between the two groups ($P > 0.05$). *Conclusion:* Serum anti-PLA2R antibody levels provide valuable insights into the clinical observation of rituximab treatment for idiopathic membranous nephropathy. They aid in understanding the disease's pathogenesis, evaluating treatment efficacy, and predicting disease prognosis.

Keywords: Serum anti-PLA2R; Rituximab treatment; Idiopathic membranous nephropathy

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1. Introduction

Idiopathic membranous nephropathy (MN) presents as a chronic glomerular disease characterized by subepithelial foot process fusion and immune deposits on the epithelial side of the basement membrane. Despite its clinical significance, the exact pathogenesis of this disease remains incompletely understood, and

the efficacy of various treatment modalities remains ambiguous. Among these treatments, rituximab, a CD20 monoclonal antibody targeting B cells, stands out as a potential therapeutic option due to its ability to modulate immune responses and reduce inflammation.

Renal biopsies of patients diagnosed with idiopathic MN have revealed elevated levels of serum anti-PLA2R antibodies, suggesting a potentially pivotal role in disease pathogenesis [1-5]. Consequently, these antibodies are regarded as valuable biomarkers for monitoring disease progression and evaluating treatment efficacy.

Although numerous studies have investigated rituximab's efficacy in treating idiopathic MN, a comprehensive evaluation of its therapeutic effects remains elusive. Therefore, the primary objective of this study is to monitor changes in serum anti-PLA2R antibody levels during rituximab treatment for idiopathic MN. This investigation aims to provide further insights into the therapeutic efficacy of rituximab and enhance the foundation for managing this challenging disease.

2. Materials and methods

2.1. General information

A retrospective analysis involving 137 patients diagnosed with idiopathic MN admitted to Beijing Sixth Hospital was conducted. Patients were divided into two groups based on their blood PLA2R antibody levels before rituximab treatment. The PLA2R antibody-positive group ($n = 94$) comprised 59 males and 35 females, with an average age of 50.98 ± 13.56 years, while the PLA2R antibody-negative group ($n = 43$) consisted of 26 males and 17 females, with an average age of 48.53 ± 13.11 years. Both groups underwent a minimum 1-year follow-up, during which the 24-hour urine protein quantification and serum albumin levels before and after treatment were compared.

Inclusion criteria comprised patients diagnosed with idiopathic MN, aged between 18 and 70 years, with positive serum anti-PLA2R antibody and urine protein quantity ≥ 3.5 g/d, who consented to participate in the clinical observation study and signed the informed consent form. Exclusion criteria included patients with other types of kidney or serious organ diseases, pregnant or lactating women, individuals who received rituximab treatment in the past 6 months, those allergic to rituximab or its constituents, patients with active infections or other conditions requiring immunomodulatory drugs, individuals with severe mental illness or inability to comply with the study, and those with inadequate follow-up time.

2.2. Research methods

The rituximab regimen involved administering 1 g per session, diluted to 1 mg/mL with 0.9% normal saline, via intravenous infusion. Infusion rates commenced at 25 mL/h, escalating to 150 mg/h after 1.5 h, and were maintained thereafter. Pre-infusion preconditioning involved administering intravenous dexamethasone (5 mg), intramuscular diphenhydramine (20 mg), and oral acetaminophen (650 mg) to mitigate allergic reactions. Electrocardiogram (ECG) monitoring was performed during infusion to detect cardiovascular adverse events. Subsequent rituximab injections and dosing intervals were determined based on B cell depletion extent and associated clinical manifestations. Patients underwent routine follow-up visits at 3-, 6-, and 12-month post-treatment.

All serum samples underwent enzyme-linked immunosorbent assay (ELISA) using kits from the EUROIMMUN (Germany), following manufacturer instructions. Anti-PLA2R antibody concentrations < 2 RU/mL were deemed negative according to reagent company guidelines.

2.3. Observation indicators

Treatment efficacy was assessed and compared between the two groups using 3/6/12-month follow-up indicators, including 24-hour urine protein and serum albumin levels. Complete remission was defined as 24-hour urine protein < 0.3 g and serum albumin > 35 g/L, while partial remission involved 24-hour urine protein of 0.3–3.5 g, with a decrease exceeding 50% from pre-treatment values, and serum albumin > 30 g/L.

2.4. Statistical methods

Data analysis employed SPSS 23.0 statistical software. Measurement data were expressed as mean \pm standard deviation (SD), with intergroup comparisons performed using *t*-tests. Count data were presented as %, and group comparisons were conducted using χ^2 tests. A significance level of $P < 0.05$ indicated statistical significance.

3. Results

3.1. Clinical data analysis

Table 1 shows that there were no significant differences in gender, age, weight, initial treatment, minimum albumin value, or 24-hour urine protein peak between the PLA2R antibody-positive and negative groups, indicating comparability between the two groups ($P > 0.05$).

Table 1. Clinical data

Group	PLA2R antibody positive group	PLA2R antibody negative group	χ^2 / t	<i>P</i>
Gender	Male	59	26	0.07 > 0.05
	Female	35	17	
Age (years)	50.98 \pm 13.56	48.53 \pm 13.11	0.99	> 0.05
Weight (kg)	77.66 \pm 16.99	72.22 \pm 12.97	1.86	> 0.05
Initial treatment	Yes	19	6	0.77 > 0.05
	No	75	37	
Albumin min value	23.72 \pm 4.72	23.12 \pm 4.79	0.69	> 0.05
24h up peak	10.82 \pm 6.14	10.96 \pm 5.96	0.13	> 0.05

3.2. 24-hour urinary protein quantitative level

After 3 months of treatment, no significant difference was observed in the quantitative levels of 24-hour urinary protein between the two groups ($P > 0.05$). However, after 6 and 12 months of treatment, a statistically significant difference emerged ($P < 0.05$), as shown in **Table 2**.

Table 2. Comparison of 24h urine protein quantitative levels (mean \pm SD)

Group	<i>n</i>	3 months	6 months	12 months
PLA2R antibody positive group	94	4.36 \pm 3.26	4.09 \pm 4.53	2.82 \pm 3.31
PLA2R antibody negative group	43	3.30 \pm 3.61	2.02 \pm 2.39	1.65 \pm 2.84
<i>t</i>		1.70	2.82	2.01
<i>P</i>		0.09	0.00	0.04

3.3. Serum albumin level

Following 3 months of treatment, a disparity in blood albumin levels was evident between the two groups ($P < 0.05$). However, no significant difference in blood albumin levels was observed between the groups after 6 and 12 months of treatment ($P > 0.05$), as shown in **Table 3**.

Table 3. Comparison of serum albumin levels (mean \pm SD)

Group	<i>n</i>	3 months	6 months	12 months
PLA2R antibody positive group	94	33.07 \pm 6.15	34.22 \pm 6.99	38.15 \pm 6.37
PLA2R antibody negative group	43	35.33 \pm 6.03	36.73 \pm 7.50	39.68 \pm 7.04
<i>t</i>		2.01	1.91	1.25
<i>P</i>		0.04	0.06	0.21

3.4. Analysis of complications

Analysis of complication (**Table 4**) revealed that in the PLA2R antibody-positive group, 9 individuals experienced thrombosis, 5 had infections, and 11 developed acute kidney injury (AKI), whereas in the PLA2R antibody-negative group, 5 people experienced thrombosis, 2 had infections, and 3 developed AKI. There were no significant differences in complications between the PLA2R antibody-positive and negative groups ($P > 0.05$).

Table 4. Statistical analysis of complications [*n* (%)]

Group	<i>n</i>	Thrombosis	Infections	AKI
PLA2R antibody positive group	94	9 (9.57)	5 (5.32)	11 (11.70)
PLA2R antibody negative group	43	5(11.63)	2 (4.65)	3(6.98)
χ^2		0.00	0.06	0.29
<i>P</i>		0.95	0.80	0.59

4. Discussion

Idiopathic MN represents a chronic glomerular disorder characterized by subepithelial foot process fusion and immune deposits along the epithelial side of the basement membrane. While its pathogenesis remains incompletely understood, factors such as genetics, immunity, and the environment are believed to be closely intertwined [6-15]. Genetic predispositions, including certain human leukocyte antigen (HLA) alleles and mutations in genes like complement factor H (CFH) and complement factor I (CFI), are linked to idiopathic MN susceptibility. Such genetic variations can disrupt self-antigen recognition and immune responses, triggering the disease. Aberrant immune system activation, where the body mistakenly targets self-antigens, serves as the primary pathophysiological mechanism underlying idiopathic MN. This dysregulated immune response leads to immune complex deposition beneath glomerular epithelial cells, complement activation, inflammatory cascades, and subsequent glomerular injury. Moreover, cellular immunity, involving T lymphocytes and macrophages, also contributes to disease pathogenesis. Environmental factors, such as prolonged use of certain drugs (e.g., nonsteroidal anti-inflammatory drugs and diuretics) and exposure to toxins or organic solvents, may heighten idiopathic MN risk [16-18]. Smoking is identified as an independent risk factor, likely due to tobacco's direct impact on kidney cells and function. Additionally, chronic conditions like obesity, hypertension, and

hyperlipidemia^[19,20], alongside social and psychological stressors, may further exacerbate disease development.

24-hour urine protein is one of the important indicators for evaluating kidney filtration function. Under normal circumstances, the protein content in urine is extremely low. However, in the case of idiopathic MN, the glomerular filtration barrier is compromised, causing proteins in the blood to be filtered through the kidneys and appear in the urine. Therefore, elevated 24-hour urinary protein levels are a typical manifestation of idiopathic MN. In this study, the values of 24-hour urinary protein in the PLA2R antibody-positive group after 3, 6, and 12 months of treatment were 4.36 ± 3.26 , 4.09 ± 4.53 , and 2.82 ± 3.31 , respectively. They gradually decreased over time and were 3.30 ± 3.61 , 2.02 ± 2.39 , and 1.65 ± 2.84 at 3, 6, and 12 months, respectively. There was no statistical difference in 24-hour urine protein between the PLA2R antibody-positive negative groups at three months post-treatment ($P > 0.05$), but there was a statistical difference at 6 and 12 months post-treatment ($P < 0.05$). The level of 24-hour urine protein can reflect the severity of idiopathic MN. The higher the urine protein, the more serious the damage to the glomerular filtration barrier. This study's findings underscore the potential of serum anti-PLA2R antibody levels as a biomarker for disease activity and treatment response.

Serum albumin, a vital blood protein, plays essential roles in maintaining blood colloid osmotic pressure and facilitating nutrients and drug transport. In idiopathic MN, glomerular filtration barrier impairment often leads to decreased serum albumin levels. This is because part of the albumin that the glomerulus should have filtered is excreted in the urine, causing the albumin level in the blood to drop. In this study, after 3 months of treatment, the serum albumin level of the PLA2R antibody-positive group was 33.07 ± 6.15 , and the serum albumin level of the PLA2R antibody-negative group was 35.33 ± 6.03 . There was a difference between the two groups after 3 months of treatment ($P < 0.05$), but no difference after 6 and 12 months of treatment ($P > 0.05$). Research results show that during the treatment of idiopathic MN, it is necessary to pay close attention to the changes in the patient's condition to evaluate the treatment effect^[21]. However, how the serum anti-PLA2R antibody levels change after rituximab treatment of idiopathic membranous nephropathy and how to use this change to guide clinical treatment still need further exploration.

In conclusion, serum anti-PLA2R antibody levels hold significant research implications for rituximab's clinical efficacy in idiopathic MN. They offer valuable insights into disease pathogenesis, treatment evaluation, and prognostication. Nonetheless, further investigations are warranted to validate these findings.

Disclosure statement

The author declares no conflict of interest.

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