The Efficacy of an Initial Prednisone Monotherapy Regimen on PLA2R-associated Idiopathic Membranous Nephropathy

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ABSTRACT

The aim of this study was to evaluate the efficacy and safety of prednisone monotherapy for phospholipase A2 receptor (PLA2R)-associated idiopathic membranous nephropathy (IMN). This was a retrospective cohort study involving 32 patients enrolled between January 2017 and June 2019 at Beijing Friendship Hospital, Capital Medical University, Beijing, China. Seventeen patients received prednisone monotherapy, and 15 received the Ponticelli regimen. The primary outcome was nephrotic syndrome remission at 12th month. The secondary outcomes were the incidence of adverse events and recurrence over the 12-month follow-up. At 12th month, 16/17 patients (94.1%) in the prednisone monotherapy group and 14/15 patients (93.3%) in the Ponticelli regimen group achieved remission ($p = 0.19$). The adverse events occurred in 9/17 and 9/15 of the patients receiving prednisone monotherapy and the Ponticelli regimen, respectively ($p = 0.74$). Four and three patients relapsed in the prednisone monotherapy and Ponticelli regimen groups, respectively ($p = 0.99$). Initial prednisone monotherapy had similar efficacy and safety compared with the Ponticelli regimen for PLA2R-associated IMN.

Key Words: PLA2R-associated idiopathic membranous nephropathy, Ponticelli regimen, Prednisone monotherapy.

How to cite this article: Bai Y, Liu J, Duan Y, Liu W, Diao Z. The Efficacy of an Initial Prednisone Monotherapy Regimen on PLA2R-associated Idiopathic Membranous Nephropathy. *J Coll Physicians Surg Pak* 2022; **32(03)**:404-406.

Several retrospective studies showed satisfactory efficacy of first-line steroid monotherapy in Asian patients with idiopathic membranous nephropathy (IMN).¹ However, these analyses may have been confounded by imbalanced baseline data, especially urinary protein and serum albumin concentrations. Furthermore, M-type phospholipase A2 receptor (PLA2R)-associated IMN was not distinguished in previous studies because the value of PLA2R was recognised only in the recent decade. These issues may have affected the results in previous studies. Therefore, a retrospective cohort study was designed to assess the efficacy and safety of prednisone monotherapy for the treatment of PLA2R-associated IMN patients.

This was a retrospective cohort study, conducted at Beijing Friendship Hospital, Capital Medical University, Beijing, China. Patients with IMN confirmed by kidney biopsy between January 2017 and June 2019 were included. The inclusion criteria were age 18–75 years; kidney pathological examination confirming IMN stage I/II; urinary protein >4 g/24 hr; serum albumin ≤25 g/L, and kidney PLA2R antigen-positive and/or serum PLA2R autoantibody-positive.

The exclusion criteria were MN caused by secondary factors, such as autoimmune diseases; any serious complication and patients with fertility requirements. The patients were divided into two groups according to the initial regimen as a prednisone monotherapy group and Ponticelli regimen group. Prednisone was taken orally once a day at an initial dose of 1 mg/Kg/day (maximum dose: 60 mg/day) for 8 weeks and then reduced gradually. The Ponticelli regimen was modified, according to the patient's weight; and the total course of treatment was six months.

The primary outcome was remission of nephrotic syndrome (including complete or partial remission) at 12th month. The secondary outcomes were the incidence of adverse events and relapse of nephrotic syndrome within the 12-month follow-up period.

Complete remission was defined as urinary protein <0.3 g/24 hours and serum albumin >35 g/L, with normal renal function. Partial remission was defined as a reduction in proteinuria of at least 50% from baseline and final proteinuria between 0.3 g and 3.5 g/24 hours. Recurrence of nephrotic syndrome was defined as reappearance of urinary protein of >3.5 g/24 hours.

All statistical tests were performed with SPSS version 26.0 (IBM Corp., Armonk, NY). A value of $p < 0.05$ was considered statistically significant. The categorical variables were expressed as percentages, and normally distributed continuous variables were expressed as mean ± standard deviation (SD). Between the prednisone monotherapy and Ponticelli groups, categorical data

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Received: September 20, 2021; Revised: November 24, 2021;

Accepted: December 20, 2021

DOI: <https://doi.org/10.29271/jcpsp.2022.03.404>

were compared by Fisher's Exact test, and normally distributed continuous variable data were compared by the t-test. Repeated measurement data comprised urinary protein and serum albumin concentrations, and these data were compared by generalised estimating equations. Kaplan-Meier analysis was used to estimate remission rates, and the log-rank test was used to compare the remission rates between the two groups.

A total of 32 patients with IMN were included; 53.1% (17/32) comprised the prednisone monotherapy group and 46.9% (15/32) comprised the Ponticelli regimen group. The follow-up period was 12 months. The demographic data and biochemical parameters of the patients in the two groups were comparable at baseline (Table I). Kidney tissue PLA2R antigen was positive for all patients. Serum anti-PLA2R antibodies were assessed in 25 patients and were detected in 50.0% (5/10) and 53.3% (8/15) of the patients in the prednisone monotherapy and Ponticelli regimen groups, respectively ($p = 0.99$). The therapeutic regimen was adjusted in seven and one patients in the prednisone monotherapy and Ponticelli regimen groups, respectively.

Regarding the primary outcome, nephrotic remission at 12th month was achieved in 94.1% (16/17) of the patients in the prednisone monotherapy group and 93.3% (14/15) of the patients in the Ponticelli regimen group, with no statistical difference in the cumulative incidence of remission ($p = 0.19$; log-rank; Figure 1a). The median remission time in both groups was six months.

Table I: Baseline characteristics of the IMN patients.

Characteristics	Prednisone (n=17)	Ponticelli regimen (n=15)	p-value
Sex (M/F)	12/5	11/4	0.99 ¹
Age (year)	51.9±11	54.4±10.7	0.52 ²
Urinary protein (g/24 hr)	5.4±1.3	6.4±1.8	0.09 ²
Serum albumin (g/L)	22.5±3.4	22.1±3.1	0.73 ²
Serum creatinine (μmol/L)	74.1±18.5	77.3±12.8	0.58 ²
Cholesterol (mmol/L)	8.1±2.3	7.3±3.1	0.40 ²
Triglyceride (mmol/L)	2.0±1.0	2.9±1.3	0.04 ²
History of hypertension No. (%)	8 (47.1%)	9 (60.0%)	0.50 ¹
ACEI or ARB - No. (%)	8 (47.1%)	14 (40.0%)	0.74 ¹
Statins - No. (%)	13 (76.5%)	14 (93.3%)	0.34 ¹
Kidney tissue PLA2R antigen positive	17 (100%)	15 (100%)	NA
Anti-PLA2R - U/mL*	162.4±78.8	107.9±68.2	0.23 ¹
Anti-PLA2R positive - No. (%) ^Δ	8/15 (53.3%)	5/10 (50%)	0.99 ¹

Values represent mean ± standard deviations. *The anti-PLA2R titers were calculated only in patients with positive serum anti-PLA2R. ^ΔPatients were considered anti-PLA2R-positive if the value was > 20 U per milliliter. ¹By Fisher's Exact test, ²By t-test. ACEI: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin receptor blockers; F: Female; IMN: Idiopathic membranous nephropathy; M: Male; PLA2R: Phospholipase A2 receptor.

Regarding the secondary outcome, adverse events occurred in 9/17 and 9/15 of the patients receiving prednisone monotherapy and the Ponticelli regimen, respectively ($p = 0.74$; Fisher's Exact test). Adverse events in the prednisone monotherapy group comprised infection (4 cases), new-onset diabetes (3 cases), liver damage (1 case) and insomnia (1 case). Adverse events in the

Ponticelli regimen group comprised infection (4 cases), new-onset diabetes (4 cases) and new-onset tumor (1 case). Four and three patients relapsed in the prednisone monotherapy and Ponticelli regimen groups, respectively ($p = 0.99$; Fisher's Exact test).

Five patients (29.4%) in the prednisone monotherapy group and 9 patients (60.0%) in the Ponticelli regimen group achieved complete remission at 12th month. Although there was no statistical difference in the cumulative incidence of complete remission ($p = 0.07$; log-rank test; Figure 1b), a clinical difference was considered. Urinary protein decreased, and serum albumin increased gradually in both groups during the follow-up. There were no significant differences in the changes in urinary protein or serum albumin levels between the groups ($p = 0.93$ and 0.12 , prednisone monotherapy and Ponticelli regimen, respectively, using generalised linear models, Figure 1c and d).

Figure 1: Probability of nephrotic syndrome remission during the 12-month follow-up and changes in urinary protein or serum albumin levels.

The previous studies showed that Asian patients with IMN responded well to steroids.^{2,3} Consistent with previous studies,¹⁻³ it was found that the nephrotic syndrome remission rates in patients receiving prednisone monotherapy were similar to those of patients receiving the Ponticelli regimen. In the present study, the baseline characteristics, especially urinary protein and serum albumin, were well-balanced between the two groups, and these markers were important predictors of clinical outcomes in IMN.⁴ The efficacy of the Ponticelli regimen was confirmed in several clinical studies.⁵ However, the safety of the Ponticelli regimen remains controversial.⁶ In the current study, the incidence of adverse events in the prednisone monotherapy group was similar to that in the Ponticelli regimen group. Notably, the authors did not evaluate reproductive toxicity, which was a conclusive and irreversible side effect of cyclophosphamide. The current study showed that the efficacy and safety of prednisone monotherapy were similar to that of the Ponticelli regimen. Therefore, prednisone monotherapy may be an alternative for PLA2R-associated IMN, especially for patients with fertility requirements.

There were several limitations in this study. First, the sample size was relatively small. Second, it was not possible to periodically monitor serum anti-PLA2R antibodies owing to limitations

in the hospital laboratory. In conclusion, prednisone monotherapy showed similar efficacy to that with the Ponticelli regimen in patients with PLA2R-associated IMN.

FUNDING:

This work was supported by the Research Foundation of Beijing Friendship Hospital (yyqdk2019-2).

ETHICAL APPROVAL:

This study was approved by the Hospital (2021-P2-269-01).

CONFLICT OF INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

YB, JL: Contributed equally to this work.

YB, JL, YD: Performed data collection and manuscript writing.

ZD: Designed and performed the statistical analysis.

WL: Reviewed the manuscript and provided final approval of the manuscript.

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