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Relationship Between the Efficacy of Low-Dose Glucocorticoids Combined with Tacrolimus in the Treatment of Adult Idiopathic Membranous Nephropathy and the Level of Serum Anti-PLA2R Antibodies

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Abstract: *Objective:* To further evaluate the efficacy and safety of low-dose glucocorticoids combined with tacrolimus in the treatment of adult idiopathic membranous nephropathy (IMN) in a clinical setting. *Methods:* We carried out a single-center prospective study of 88 patients with IMN who were admitted into the Affiliated Hospital of Hebei University from January 2019 to December 2021, and the participants were divided into two groups based on their serum anti-PLA2R antibody levels: the negative group and the positive group. 46 patients were positive for anti-PLA2R antibodies and 42 were negative. *Results:* After 6 months of treatment, the serum albumin, cholesterol, and 24h urine protein quantification in the anti-PLA2R negative group improved more significantly compared to the positive group ($P < 0.05$); after 6 months of treatment, the remission rate of the positive group was significantly lower than that of the negative group, and ($P < 0.05$); *Conclusion:* After treatment with tacrolimus combined with low-dose glucocorticoids, patients with idiopathic membranous nephropathy who were tested positive for anti-PLA2R antibodies had a higher overall remission rate compared those who were tested negative for serum anti-PLA2R antibodies.

Keywords: Tacrolimus; Idiopathic membranous nephropathy; PLA2R antibody

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1. Introduction

Membranous nephropathy (MN) is a glomerular disease characterized by the deposition of immune complexes on the outer glomerular basement membrane (GBM), subepithelial cells with GBM thickening, which can involve the whole kidney, and its diagnostic criteria are mainly based on renal histopathology, and clinical treatment is more difficult. idiopathic membranous nephropathy (IMN) is the most common type of MN and the most common renal cause of massive proteinuria in adults in China. Recent domestic and international research have shown that IMN shows a diversity of natural course, with about 30% of patients in spontaneous complete remission, about 30% in partial remission, and the remaining 30% to 40% of IMN patients with progressive decompensation of renal function, which then progresses to end-stage renal disease [1-4]. Thus, IMN is not a benign disease, and early diagnosis, prognosis, and effective treatment are major tasks clinical practice. Glucocorticoid (GC) is the main drug for the treatment of MN, but its clinical application is limited due to its severe adverse effects, unclear efficacy, and difficulty in long-term

use. Tacrolimus (FK506) is a novel calcium-regulated phosphatase inhibitor that inhibits the gene transcription of various cytokines (gamma interferon, interleukin-2, etc.) by inhibiting calcium-dependent signaling pathways in T cells and suppressing T cell activation and proliferation, thus suppressing abnormal immune responses to reduce proteinuria. The side effects of FK506 are low, and several studies have shown that low-dose GCs combined with FK506 are effective in MN. The aim of this study is to evaluate the relationship between the efficacy of low-dose GCs combined with tacrolimus in the treatment of adult IMN and the level of serum anti-phospholipase A2 receptor (anti-PLA2R) antibodies, and to provide a basis for the clinical treatment of IMN.

2. Information and methods

2.1. General information

A single-center prospective study was performed using the clinical data of 88 patients with IMN who were admitted into our hospital from January 2019 to December 2021. All 88 patients enrolled in this study were diagnosed with IMN by renal biopsy, and this study complied with the Guidelines for the Treatment of MN and the Guidelines for the Reporting of Kidney Biopsy Pathology by the Ethics Committee of Peking Union Medical College Hospital, Chinese Academy of Medical Sciences.

Among the 88 patients, there were 42 males and 46 females, aged 65.3 ± 14.7 years old. All the 88 patients had different levels of urinary protein at 24h > 3.5g/d, with an average of 6.74 ± 0.15 g/d. The patients were divided according to their serum anti-PLA2R antibody levels: negative and positive. 46 of 88 patients (52.27%) were positive for anti-PLA2R antibodies and 42 (47.73%) were negative for anti-PLA2R antibodies.

Inclusion criteria: (i) meeting the diagnostic criteria of IMN and hospitalized in our hospital and treated with FK506 for at least 6 months; (ii) blood creatinine (Scr) < 132.6 μmol/L; (iii) renal biopsy pathology showed membranous nephropathy and the stage of illness was determined.

Exclusion criteria: (i) secondary membranous nephropathy caused by drugs, infection, hepatitis, systemic lupus erythematosus, etc.; (ii) patients with other serious renal diseases or combined with diseases affecting renal function; (iii) patients with combined oncological diseases; (iv) patients with other systemic diseases, such as leukemia, dry syndrome, etc.; (v) patients with combined active infection; (vi) patients with severe cardiac, pulmonary, hepatic, renal, and other major organ deficiencies.

2.2. Methods

All patients were treated with angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) analogues for blood pressure control and received anticoagulants and statins. The initial dose of tacrolimus was 0.05 mg/kg per day, which was taken after breakfast and 2 h after dinner. The daily dose of tacrolimus was adjusted according to the tacrolimus trough concentration. During the first month of treatment, patients were seen every 2 weeks and their dose was adjusted according to the tacrolimus serum concentration (5–10 ng/ml); a daily dose of 0.5 mg/kg of prednisone acetate was also given.

2.3. Observation indicators

Patients were treated with low-dose glucocorticoids in combination with tacrolimus for at least 6 months. The primary endpoints were 24 h urine protein quantification, serum albumin, cholesterol, and serum anti-PLA2R antibody levels. The secondary endpoint was the overall remission rate.

2.4. Statistical methods

SPSS 20.0 software was used for statistical analysis. The measurement data were expressed as mean ± standard deviation, and *t*-test was used for comparison between groups. Differences were considered

statistically significant at $P < 0.05$.

3. Results

3.1. Comparison of clinical indicators between the two groups of patients

After 6 months of treatment, serum albumin, cholesterol, and 24h urine protein quantification improved more significantly in the anti-PLA2R negative group than in the positive group ($P < 0.05$), as shown in **Table 1**.

Table 1. Comparison of clinical indicators between the two groups of patients

Group	Negative group (n = 42)			Positive group (n = 46)		
	Before treatment	3 months of treatment	6 months of treatment	Before treatment	3 months of treatment	6 months of treatment
Serum albumin (g/L)	20.14 ± 3.45	24.69 ± 3.12	30.11 ± 3.88	20.24 ± 3.05	24.29 ± 3.02	28.11 ± 3.88
Serum ALT (U/L)	30.12 ± 3.21	38.71 ± 4.01	36.12 ± 3.44	30.02 ± 3.41	38.41 ± 4.11	32.12 ± 3.44
Serum creatinine (μmol/L)	76.21 ± 5.69	81.12 ± 4.98	80.11 ± 3.66	76.01 ± 5.49	81.32 ± 4.48	78.11 ± 3.66
Cholesterol (mmol/L)	7.22 ± 0.36	6.24 ± 0.78	4.12 ± 0.69	7.42 ± 0.26	6.34 ± 0.58	5.12 ± 0.69
Urine protein quantification (g/24h)	6.87 ± 0.11	4.69 ± 0.44	1.11 ± 0.24	6.67 ± 0.21	4.19 ± 0.34	2.91 ± 0.24
Tacrolimus (ng/ml)	0	5.41 ± 0.24	7.78 ± 0.21	0	5.11 ± 0.14	6.78 ± 0.21
Hemoglobin (g/L)	124.11 ± 8.01	131.29 ± 8.36	136.11 ± 8.12	124.61 ± 8.11	131.29 ± 8.36	130.11 ± 8.12

Note: $P < 0.05$ compared to the negative group

3.2. Therapeutic efficacy analysis

After 6 months of treatment, the remission rate in the positive group was significantly lower than that in the negative group, and $P < 0.05$ was considered a statistically significant difference, as shown in **Table 2**.

Table 2. Efficacy analysis

Group	Negative group (n = 42)		Positive group (n = 46)	
	3 months of treatment	6 months of treatment	3 months of treatment	6 months of treatment
Complete relief	5	16	4	10
Partial relief	10	18	11	14
No relief	27	8	31	22
Remission rate (%)	35.71	76.19	32.61	52.17

Note: $P < 0.05$ compared to the negative group

4. Discussion

IMN is a common cause of primary glomerular disease in adults, with an incidence of 1/100,000 in China. Its pathogenesis is unclear, and is generally thought to be related to genetic factors, infection, immune system factors, etc. The main treatment for IMN is GCs combined with immunosuppressants, but the adverse effects of GCs are severe, and their long-term effect is unclear. Tacrolimus is a new type of immunosuppressant invented by Professor Satoshi Hirata in Japan in 1975 [5]. It inhibits the production of complement and cytokines, thus achieving anti-inflammatory, antioxidant, and immunomodulatory effects [6]. Tacrolimus can significantly improve the clinical and immunological prognosis of IMN patients.

In this study, we analyzed the relationship between the efficacy of low-dose glucocorticoids combined with tacrolimus in the treatment of adult IMN and the level of serum anti-PLA2R antibodies. The results showed that the overall efficiency of the treatment in serum anti-PLA2R antibody-positive patients was significantly lower than that of serum anti-PLA2R antibody-negative patients ($P < 0.05$). The results of this study suggest that low-dose GCs combined with tacrolimus for the treatment of adult IMN can improve the clinical and immunological prognosis of patients, but there is a correlation between the efficacy and serum anti-PLA2R antibody levels, which may be due to the adverse effects of low-dose GCs combined with tacrolimus for the treatment of IMN in most patients due to the presence of immunosuppression, especially to hormone and tacrolimus allergic individuals [7,8].

In this study, all patients enrolled were examined monthly after starting treatment with low-dose glucocorticoids in combination with tacrolimus. Parameters like routine blood, urine, 24-hour urine protein quantification, liver function, kidney function, blood lipids, and tacrolimus concentration were tested 3 and 6 months after the treatment was initiated. During the course of tacrolimus treatment, the glomerular filtration rate (GFR) was found to have decreased to below 30 ml/min-1.73m^2 in 3 patients (mean decrease of 1.22 ml/min-1.73m^2) during the renal function examination 3 months into the tacrolimus treatment.

There are some limitations to this study, such as the small sample size and the uncertainty of the continuity of tacrolimus treatment for patients with negative serum anti-PLA2R antibodies. However, this study provides a basis for clinical practice in the treatment of IMN and can be used as a first- line treatment option. The feasibility of conducting single-center, large-sample, multicenter clinical trials in patients with IMN can be further explored in the future.

In conclusion, low-dose glucocorticoids combined with tacrolimus have a higher overall remission rate in the treatment of patients with IMN who are serum anti-PLA2R antibody-negative compared to patients who are serum anti-PLA2R antibody-positive.

Disclosure statement

The authors declare no conflict of interest.

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