Association of anti-phospholipase A2 receptor antibody with the efficacy of traditional Chinese medicine (Shenqi particle) for patients with idiopathic membranous nephropathy: a prospective, cohort clinical study

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To the Editor: Membranous nephropathy (MN) is an autoimmune disease and accounts for the most common cause of nephrotic syndrome in adults. In China, the incidence of MN is estimated at approximately 12/million per year, with a mean age between 30 and 60 years and a 2:1 male predominance. MN (29.1%) was the most common pathological disease in a 10-year renal biopsy analysis.[1]

In 2019, the Kidney Diseases: Improving Global Outcomes (KDIGO) guidelines recognized anti-phospholipase A2 receptor (anti-PLA2R) autoantibodies as a valuable molecular risk factor for the pejorative evolution of kidney function and recommended monitoring them for the diagnosis and assessment of MN immune activity. Assessing circulating anti-PLA2R autoantibodies may help in monitoring disease activity and guiding personalized therapy in patients with primary MN.

Traditional Chinese medicine (TCM) such as Shenqi particle has been used to treat idiopathic MN for decades in China. A prospective, multicenter, randomized, controlled, clinical trial conducted in 2008 to 2011 confirmed the efficacy and safety of Shenqi particles in adult patients with primary membranous nephropathy (PMN).[2] However, the association of anti-PLA2R antibody with the efficacy of TCM (Shenqi particle) for patients with idiopathic MN remains unknown.

This prospective study was undertaken at the Longhua Hospital affiliated to Shanghai University of Traditional Chinese Medicine. The protocol was approved by the institutional review boards for human studies of Longhua Hospital (No: 2016LCSY022, Trial registration: www.chictr.org.cn; Registration No: ChiCTR-OOC-16009632). Informed consent was obtained from all patients.

Patients who met the following criteria were included in the study[3]: (1) age between 18 and 75 years, (2) 24-h urinary protein excretion >1 g/day after a minimum observation interval of 6 months, (3) estimated glomerular filtration rate (eGFR) >30 mL·min⁻¹·1.73 m⁻², (4) biopsy-proven MN (stages 1–4), (5) TCM syndrome differentiation belongs to spleen deficiency, damp heat, and blood stasis (according to the “guiding principles for clinical research of new TCM”[4]), (6) Patients were excluded if they had any of the following conditions: (1) other types of MN, such as rapidly progressive MN (defined as rapid loss of kidney function[5]) or secondary MN, which were ruled out by obtaining patients’ medical histories of chronic inflammatory disease, malignancy, drug use, contact with poison, and by performing laboratory tests, such as for kidney function and autoimmune antibodies; (2) diabetes or hemoglobin A1c level >6.2 mmol/L; (3) treatment with steroids and/or immunosuppressive medications in the last 6 months; (4) presence of infection, such as with hepatitis B virus or human immunodeficiency virus, or malignant diseases; or (5) uncontrolled hypertension with blood pressure (BP) >130/80 mmHg; (6) TCM syndrome differentiation does not belong to spleen deficiency, damp heat, and blood stasis.

Of 327 patients screened, 215 patients were excluded based on exclusion criteria [Supplementary Figure 1, Table 1].

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One hundred and twelve patients were divided into two groups according to the baseline anti-PLA2R antibody level. Forty-nine patients with a baseline anti-PLA2R antibody level exceeding the threshold of 20 RU/mL were identified as the “positive group.” In the remaining 63 patients identified as the “negative group,” the baseline anti-PLA2R antibody level was ≤20 RU/mL according to the 2020 KDIGO Clinical Practice Guideline for Glomerulonephritis. The main baseline clinical and laboratory characteristics for all patients and the two groups are given in Supplementary Table 2. The baseline characteristics of those two groups were compared, and no statistically significant differences were observed, except for sex proportion and triglyceride.

All patients were treated with TCM (Shenqi particle) for 48 weeks. Clinical data were collected from all patients and included age, sex, serum creatinine (Scr), serum albumin, 24-h urinary protein excretion, serum cholesterol, triglycerides, and anti-PLA2R antibody quantification. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. All patients were followed up monthly by experienced nephrologists throughout the whole follow-up period.

Of the 49 patients in the positive group, 19 patients had achieved remission at 48 weeks, including three patients who achieved CR. Of the 63 patients in the negative group, 52 patients had achieved remission, including 13 patients who achieved CR. The negative group had a higher remission rate (82.53%) than the positive group (38.77%; \(P < 0.001\)).

After 48 weeks of treatment, 24-h proteinuria was improved significantly in both groups. The negative group had greater improvement in proteinuria than the positive group. Patients in both groups had significantly higher serum albumin levels at 48 weeks than at baseline. However, no difference was observed between the two groups. Kidney function was stable and not different in the two groups according to eGFR. No significant difference was observed in Scr and eGFR in both groups [Figure 1]. For adverse events, only one patient had a mild liver injury in the negative group at the 12th week and achieved spontaneous remission at the 24th week. No severe adverse events were reported in either group.

To conclude, serial evaluation of circulating anti-PLA2R antibodies might help predict the response to TCM in MN. Negative antibodies are associated with better outcomes. Compared with patients with positive anti-PLA2R antibodies, those with negative anti-PLA2R antibody-related MN responded better to TCM.

The limitation of this study is without a control group. The efficacy and safety of Shenqi particles in adult patients with PMN have been confirmed. Some patients in this study...
had been treated with glucocorticoid or immunosuppressant before they were enrolled, but they did not achieve remission; other patients were enrolled because they were not willing to bear the possible side effects caused by glucocorticoid or immunosuppressant. Therefore, this study can no longer use glucocorticoid or immunosuppressive therapy for those patients. But patients still need to receive effective treatment. TCM was also administered as an effective treatment in patients who had previously failed to respond to steroids, alkylating agents, or calcineurin inhibitors in China. Shenqi particle may be a promising alternative therapy for adults with PMN.

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**Conflicts of interest**

None.

**References**


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