

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

Xian-Wen Zhang¹, Xiao-Xia Liu², Jun Yong¹, Li-Feng Wei¹, Chun-Yan Ling¹, Yu Jin³, Yi-Ping Chen¹, Lin Wang¹

¹Longhua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai 200032, China;

²Shanghai Minhang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai 200241, China;

³Engineering Research Center of Pharmaceutical Engineering and Process Chemistry, Ministry of Education, School of Pharmacy, East China University of Science and Technology, Shanghai 200237, China.

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 50 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^[2]: (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”^[3]). 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^[4]) 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,

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DOI:
10.1097/CM9.0000000000001565

Xian-Wen Zhang and Xiao-Xia Liu contributed equally to this work.

Correspondence to: Lin Wang, Longhua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai 200032, China
E-Mail: happytlynn@163.com

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Chinese Medical Journal 2021;134(18)

Received: 20-04-2021 Edited by: Jing Ni

<http://links.lww.com/CM9/A605>], whereas 112 patients were recruited from October 2016 to October 2019. These 112 PMN patients, with a mean age of 49.79 ± 14.64 years, entered the study. The median course of PMN before treatment with TCM was 20 months, ranging from 6 to 156 months. Most patients had MN with histological stage I or II, and their BP was well controlled. The ratio of men to women was 76 to 36, the average proteinuria level was 4.10 ± 2.60 g/24 h, and the average serum albumin level was 28.23 ± 7.04 g/L.

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 on Glomerular Diseases.^[5] The main baseline clinical and laboratory characteristics for all patients and the two groups are given in Supplementary Table 2, <http://links.lww.com/CM9/A605>. The baseline clinical 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 during this 48-week treatment period. Clinical details and laboratory parameters were evaluated every 3 months during the study. Anti-PLA2R was estimated per 6 months of therapy. PLA2R antibody testing was performed by enzyme-linked immunosorbent assay (EUROIMMUN AG, Lubeck, Germany).

Shenqi particles are mainly made of 13 different Chinese herbs described previously.^[2] The decoction was prepared by boiling in water and spray drying. The analysis results of three batches of Shenqi particle showed good reproducibility [Supplementary Figure 2, <http://links.lww.com/CM9/A605>]. Patients received 9.6 g of Shenqi particle 3 times/day. At the same time, Bai'ao Lumbrokinase capsule (600,000 U/time, 3 times/day) or Huoxue Tongmai capsule (4 capsules/time, 3 times/day) was used. For hypertensive patients, the target systolic BP was <130 mmHg, and the target diastolic BP was <80 mmHg. Other antihypertensive drugs were prescribed in addition to angiotensin-converting-enzyme inhibitors/angiotensin receptor blockers at each nephrologist's discretion based on BP.

Adverse events and serious adverse events, and unexpected changes in clinical or laboratory parameters observed throughout the whole follow-up period were reported in patient case report forms and monitored up to complete

resolution. Serious adverse events were defined as serious liver injury, double creatinine, dialysis, and death.

Data are expressed as continuous variables, percentages, means and standard deviation, or medians and interquartile ranges. The Student's *t* test was used to compare means for parametric data, and non-parametric data were analyzed using the Mann-Whitney test. Correlations between the baseline PLA2R antibody levels, the improvement rate of proteinuria, and serum albumin were examined by regression analysis. All *P* values were two-sided, and a *P* value of <0.05 was considered significant. Statistical analyses were carried out using SPSS statistical software (version 19.0; SPSS Inc., Chicago, IL, USA).

Primary outcomes include complete remission (CR) and partial remission (PR). Clinical remission included CR and PR. Using the criteria developed by the 2012 KDIGO Clinical Practice Guideline for Glomerulonephritis; CR was defined as proteinuria <300 mg/d with normal serum albumin and serum creatinine (Scr). PR was defined as proteinuria of >300 g/d or a $<50\%$ decline from baseline with normal serum albumin or increased serum albumin and stable Scr. Non-remission: the previously mentioned mitigation criteria were not met.

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%; $P < 0.001$) [Supplementary Table 3, <http://links.lww.com/CM9/A605>].

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. Patients in both groups had significantly lower serum cholesterol and triglycerides 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.^[2] Some patients in this study

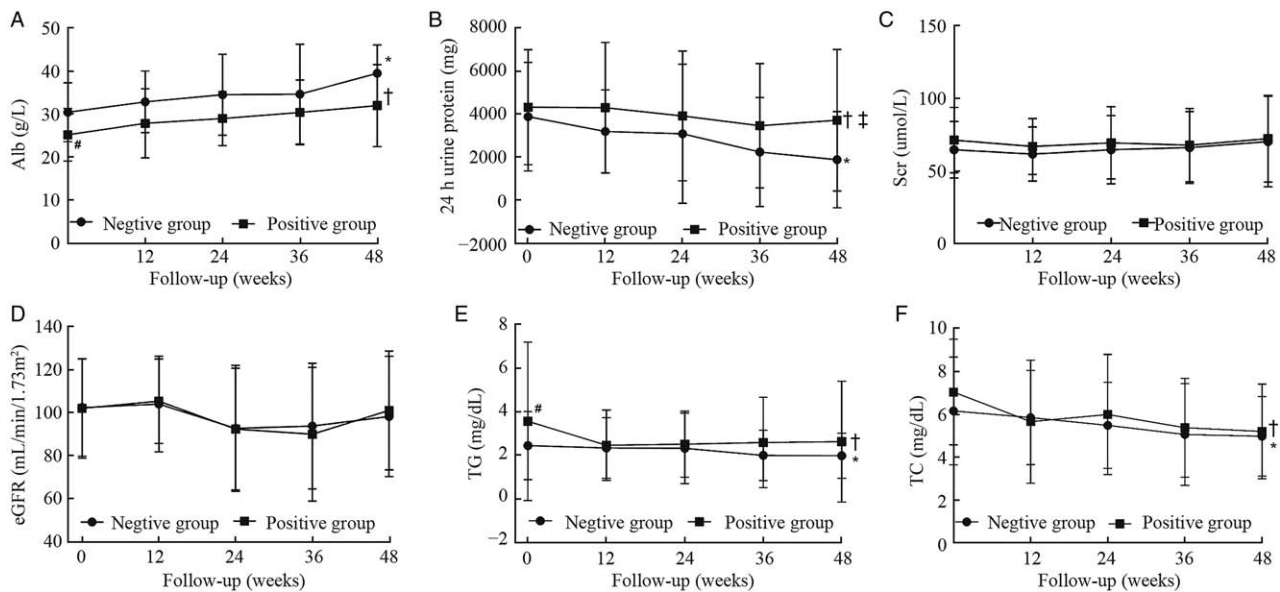


Figure 1: Patients in both groups had significantly higher serum albumin levels at 48 weeks than at baseline. No difference was observed between the two groups at 48 weeks. (A) After 48 weeks of treatment, 24-h proteinuria excretion was improved significantly in both groups. The negative group had greater improvement in proteinuria excretion than the positive group. (B) Kidney function was stable and not different in the two groups according to eGFR. No significant difference was observed in (C) Scr and (D) eGFR in both groups at 48 weeks. Patients in both groups had significantly better (E) triglyceride and (F) total cholesterol levels at 48 weeks than at baseline. *Statistically significant difference between the start and the end of treatment in the negative group. †Statistically significant difference between the start and the end of treatment in the positive group. ‡Statistically significant difference between the negative group and positive group. eGFR: Estimated glomerular filtration rate. Alb: Albumin; Scr: Serum creatinine; TC: Total cholesterol; TG: triglyceride.

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.

Funding

The research is supported by grants from the “3-Year Action Plan of Shanghai to Further Speed Up the Development of Traditional Chinese Medicine” (Nos. ZY [2018-2020]-FWTX-6025; ZY[2018-2020]-ZYBZ-02).

Conflicts of interest

None.

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How to cite this article: Zhang XW, Liu XX, Yong J, Wei LF, Ling CY, Jin Y, Chen YP, Wang L. 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. *Chin Med J* 2021;134:2252–2254. doi: 10.1097/CM9.0000000000001565