JTCM Journal of Traditional Chinese Medicine

Online Submissions: http://www.journaltcm.com
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J Tradit Chin Med 2016 June 15; 36(3): 299-306
ISSN 0255-2922

CLINICAL STUDY

Effect of Astragali and Angelica particle on proteinuria in Chinese patients with primary glomerulonephritis

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Supported by Ministry of Scientific Technology of China Grant (Optimum Proposal of Traditional Chinese Medicine on Proteinuria in Patients with Primary Glomerulonephritis, No. 201007005); Shanghai Science & Technology Commission Grant (Clinical Study of Astragali Xiaobai Particle on Proteinuria in Patients with Primary Chronic Glomerulonephritis, No. 14401972203); Three Years of Development Project for Traditional Chinese Medicine of Shanghai Municipal Commission of Health and Family Planning (Senior Chinese Integrative Medicine Talent Cultivation Project, No. ZYSNXD012-RC-ZXY003); Three Years of Development Project for Traditional Chinese Medicine of Shanghai Municipal Commission of Health and Family Planning (Effect of Astragali Xiaobai Particle on Proteinuria in Patients with Primary Chronic Glomerulonephritis, No. ZY3-JSFC-2-1029), and Innovative Research Team in Universities, Shanghai Municipal Education

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Accepted: December 17, 2015

Abstract

OBJECTIVE: To investigate the effect of the traditional Chinese herbs Astragali and Angelicae Sinensis (A & As) particle [contains Huangqi (*Radix Astragali Mongolica*), Danggui (*Radix Angelicae Sinensis*), Huzhanggeng (*Rhizoma Polygoni Cuspidati*) and Danshen (*Radix Salviae Miltiorrhizae*)] on proteinuria in glomerulonephritis patients with stage 2 chronic kidney disease.

METHODS: A prospective, multi-center, and randomized controlled clinical trial was performed for 24 weeks. From March 2011 to April 2012, 158 patients from nine hospitals in China participated. They were randomized into the A&As group (79 cases, A&As particle 15.2 g/day) and losartan group (79 cases, losartan 50 mg/day). At each follow-up visit, clinical data including blood pressure, urinalysis, 24-h-urinary protein excretion, serum albumin and serum creatinine were collected.

RESULTS: All 158 patients completed the follow-up. Proteinuria in the losartan group exhibited a biphasic time-dependent decline with a significant steady reduction from baseline to week 12 ($P = 0.0014$), and a platform level during the remaining 12-week follow-up ($P > 0.05$). In contrast, there was a continual significant decrease of proteinuria in the A & As group ($P < 0.001$). When compared with the losartan results, proteinuria in the A & As group from week 16 to week 24 was significantly reduced ($P < 0.001$). Stable eGFRs and blood pressure were also observed in both groups. Medication side effects were minimal and non-fatal.

CONCLUSION: For Chinese glomerulonephritis patients with stage 2 chronic kidney disease, therapy with A & As particles may provide effective anti-proteinuria treatment.

Key words: Angelica sinensis; Renal insufficiency, chronic; Glomerulonephritis; Proteinuria; Medicine, Chinese Traditional

INTRODUCTION

Globally, chronic kidney disease (CKD) has been increasing. In China, the prevalence of CKD in adults is

more than 10%,[1,2] and unlike in developed countries, primary glomerulonephritis (GN) rather than hypertensive nephropathy and diabetic nephropathy is the leading cause of end-stage renal disease.[3,4] For CKD, it is critical to slow down the progression of stage 2, because renal disorder could accelerate beyond this stage.[5,6] Therefore, a major challenge for Chinese nephrologist is to delay the progression of GN with stage 2 CKD.

Proteinuria is recognized as an independent risk factor for progression of GN.[7] Corticosteroid and other immunosuppresants are cornerstone therapies for proteinuria. Nevertheless, these drugs are not indicative for many GN patients with stage 2 CKD. Instead, angiotensin Ⅱ type 1 receptor blockers (ARBs) and/or angiotensin converting enzyme (ACE) inhibitors play important roles in the treatment of proteinuria.[8] However, the therapeutic effect of renin-angiotensin system blockade is not always satisfactory for Chinese GN patients with stage 2 CKD. Many of these patients, who are normotensive, cannot tolerate even moderate dosages of ARBs and/or ACE inhibitors because of systemic hypotension.[9] This condition is particularly common in Chinese patients, especially in the early stages of CKD. In addition, a higher dosage of ARBs and/or ACE inhibitors does not exert an incremental nephroprotective response.[9-11] Therefore, it is essential to explore other alternative therapeutic approaches.

In Asian countries including China, Traditional Chinese Medicines (TCM) have long been used to treat proteinuria.[12,13] Based on the personal experiences of experts from different regions in China, patients with GN have been treated with different herb formulations. Although the therapeutic effect of these on proteinuria has been demonstrated in animal studies, only a few small single-center retrospective studies have been published. The formulation of Astragali and Angelicae Sinensis (A & As) particle [contains Huangqi (*Radix Astragali Mongolica*), Danggui (*Radix Angelicae Sinensis*), Huzhanggeng (*Rhizoma Polygoni Cuspidati*) and Danshen (*Radix Salviae Miltiorrhizae*)] was developed for the treatment of GN in the 1990s at Shuguang hospital which is affiliated to Shanghai University of TCM. There are four herbs selected in the A & As particle, which are based on the theory of TCM and on extensive experience from senior physicians over several decades who have used traditional Chinese medicine to treat patients with GN. Of note, the A&As particle contains Astragali and Angelicae Sinensis, which are known to reduce proteinuria.[14,15] Several small clinical studies showed that the A & As particle and its components could improve proteinuria in patients with GN.[16,17] However, none of these individual herbs have been tested in a large clinical trial.

To investigate the effect of A & As particles on proteinuria in Chinese GN patients with stage 2 CKD, we performed a prospective, multi-center and randomized controlled clinical study using identical qualitative and quantitative preparation. Our secondary objectives were to observe A & As particle safety and tolerability.

MATERIALS AND METHODS

Selection and description of participants

The study recruited 158 patients from nine hospitals in China (Shuguang Hospital affiliated to Shanghai University of Traditional Chinese Medicine, Heilongjiang Academy of Traditional Chinese Medicine, Chinese Medicine Hospital of Hubei Province, Putuo Hospital affiliated to Shanghai University of Traditional Chinese Medicine, Zhongshan Hospital affiliated to Fu-Dan University, Yueyang Hospital affiliated to Shanghai University of Traditional Chinese Medicine, the Fifth Hospital Affiliated to Zunyi Medical College, Yangpu Hospital of Traditional Chinese Medicine, and Yinhang Community Health Center). All patients were clinically diagnosed with primary chronic glomerulonephritis.

Inclusion criteria for all recruits included the following: (a) underwent renal biopsy, (b) diagnosed with stage 2 CKD having a mild decrease of estimated glomerular filtration rate (eGFR) from 60 to 89 mL/min per 1.73 m^2 according to The National Kidney Foundation Kidney Disease Outcomes Quality Initiative definition, (c) persistent stable non-nephrotic proteinuria (0.5 to 2.5 g/day), (d) not taking ACE inhibitors and/or ARBs, or having taken these drugs but after a washout period, (e) normal blood pressure (an office blood pressure of ≤ 130/80 mm Hg in the sitting position), and (f) age between 18 and 70 years.

Exclusion criteria included: (a) secondary etiology including lupus, diabetes, and hypertension, (b) women in pregnancy or lactation, (c) serious complications including hematologic diseases, malignancy and infection, (d) acute kidney failure or renal allografts, (e) known allergy to the study drugs, (f) psychosis or uncooperative, (g) enrolled in other clinical trials in the previous 3 months, and 8) treatment with steroids and/or other immunosuppresants.

The study followed evidence-based principles and used a prospective, multi-center and randomized controlled design. Ethical guidelines were strictly conducted in accordance with the Declaration of Helsinki and with local regulations. The protocol was approved by the research ethics committee of Shuguang Hospital.

Two assessors monitored the study and were blinded to the treatment groups. All participants were clearly informed and provided written informed consent for participation. The study sponsors provided the first available allocation number, which were assigned in consecutive order, to the enrolled patients from the nine hospitals. The numbers of patients from each hospital were 18 each from Shuguang Hospital, Heilongjiang Academy of Traditional Chinese Medicine, Chinese Medicine Hospital of Hubei Province, Putuo Hospital, and Zhongshan Hospital, and 17 each from Yueyang Hospital, Fifth Hospital Affiliated to Zunyi Medical College, Yangpu Hospital of Traditional Chinese Medicine, and Yinhang Community Health Center.

Drug preparation

The formulation of A & As particle consisted of Huangqi (*Radix Astragali Mongolici*) 15 g, Danggui (*Radix Angelicae Sinensis*) 15 g, Huzhanggeng (*Rhizoma Polygoni Cuspidati*) 15 g , and Danshen (*Radix Salviae Miltiorrhizae*) 15 g. These traditional Chinese herbs were processed into particles by Jiangyin Tianjiang Pharmaceutical Co., Ltd., (Jiangyin, China). The particles were prepared by decoction, concentration, and spray drying. The quality of A&As particles were controlled rigorously according to good manufacturing practice standards. The active constituents of traditional Chinese herbs were analyzed by HPLC (Table 1). Losartan tablets were purchased from MSD Pharmaceutical Co., Ltd., (Hangzhou, China). Besides, placebo tablets and placebo particles were also produced in the two companies.

Interventions

Eligible patients were enrolled in a screening and washout period (weeks -4 to 0) , then were assigned numbers consecutively. The study sponsors then dispensed the study medications in sequentially numbered containers to the patients according to their assigned number. The patients had an equal probability of being assigned to A & As particle (A & As group) or to losartan (losartan group). In addition, placebo tablets were given to both groups of patients. All the patients and observers were blinded to the assigned medication and placebo interventions. Patients were instructed to take the study medication (A & As particle 15.2 g/bag or losartan 50 mg/tablet) orally once daily in the morning. Besides, placebo tablets were given to the patients in A & As group, and placebo particles were also given to the patients in losartan group.

Study sponsors monitored basic treatments between groups, which were the same including diet and nutrition consisting of daily protein intake (0.8 g/kg) with high biological value protein > 50%, and daily calorie intake (30-35 kcal/kg).

Measurements

All enrolled patients undertook follow-up visits once every 4 weeks from week 4 to 24. After week 24, all patients continued to be followed up for another 8 weeks but without their initial treatment plan. Clinical and laboratory data were assessed at each visit. The clinical data observed was blood pressure and laboratory data including urinalysis, 24-h urinary protein excretion, serum albumin, blood urea nitrogen, serum creatinine, electrocardiogram and liver function test. At each visit, adverse events were recorded. Drug consumption and adherence were checked by counting pills. Patients were considered adherent if at least 95% of the study drug had been taken.

Urinary protein excretion was determined using 20% sulfosalicylic acid at individual hospital laboratory. Serum data were measured by standard laboratory techniques and eGFR was calculated by using a modified Modification of Diet in Renal Disease (MDRD) Study equation based on data from Chinese CKD patients [eGFR ($mL \cdot min^{-1} \cdot 1.73\ m^{-2}$) = 175 × Scr $[mg/dl]^{-1.234}$ × age $[year]^{-0.179}$ (female × 0.79)].[18]

Statistical analysis

All statistical analysis was done by SPSS software program v13.0 (SPSS Inc., Chicago, IL, USA). All data were expressed as mean ± standard deviation ($\bar{x} \pm s$). The significance of differences between groups was examined using Student's *t*-test for unpaired data. Changes from baseline to the last follow-up were compared between the losartan and A & As groups using the *t*-test. When differences could be demonstrated, values were compared with the baseline using a paired-sample *t*-test. Discrete data were examined using the *Chi*-squared analysis. Clinical parameters were analyzed in both groups by repeated-measures analysis of variance (ANOVA). Two-way repeated-measures ANOVA were used to compare the proteinuria variation between baseline and follow-up visits in each group and the differences in proteinuria between groups. Values of $P < 0.05$ were considered to indicate statistical significance.

Table 1 Active constituents of the traditional Chinese herbs used in the Astragali and Angelica (A & As) particle

Active constituent	Astragaloside Ⅳ	Ferulic acid	Emodin	Salvianolic acid B
Molecular formula	$C_{41}H_{68}O_{14}$	$C_{10}H_{10}O_4$	$C_{15}H_{10}O_5$	$C_{36}H_{30}O_{16}$
Extract from traditional Chinese herb	*Radix Astragali*	*Radix Angelicae Sinensis*	*Rhizoma Polygoni Cuspidati*	*Radix Salviae Miltiorrhizae*
Chromatography column (mm×mm, μm)	Shim-pack octadecyl silane (150 × 4.6, 5)	Dionex Acclaim120 C18 (250 × 4.6, 5)	Thermo octadecyl silane Hypersil C_(18) (250 × 4.6, 5)	Kinetex core-shell technology (100 × 4.6, 2.6)
Mobile phase	Acetonitrile -water	1.5% glacial acetic acid-methanol	0.1%aqueous acetic acid-methanol	0.1% trifluoroacetic acid aqueous solution-acetonitrile
Column temperature (℃)	20	35	35	30
Detection wavelength (nm)	203	320	254	286
Number of theoretical plates (peak calculation, *n*)	4000	5000	3000	2000
Content per bag (mg)	1.5	2	13.5	30

RESULTS

Baseline characteristics

From March 2011 to April 2012, 158 screened patients satisfied the study criteria and were enrolled. All patients were ethnic Chinese. Patients were randomly allocated to either the A & As or losartan groups with 79 in each. All patients completed the study (Figure 1). The mean age at baseline was (49.8 ± 10.5) years (range 20 to 65 years). Baseline characteristics did not significantly differ between the two groups (Table 2).

The primary histological type of all patients was IgA nephropathy (IgAN, 57 cases). The remaining types included mesangial proliferative glomerulonephritis (MsPGN, 31 cases), focal segmental glomerular sclerosis (FSGS, 25 cases), minimal change disease (MCD, 17 cases), membranous nephropathy (MN, 15 cases), IgM nephropathy (IgMN, 7 cases), and membranoproliferative glomerulonephritis (MPGN, 6 cases).

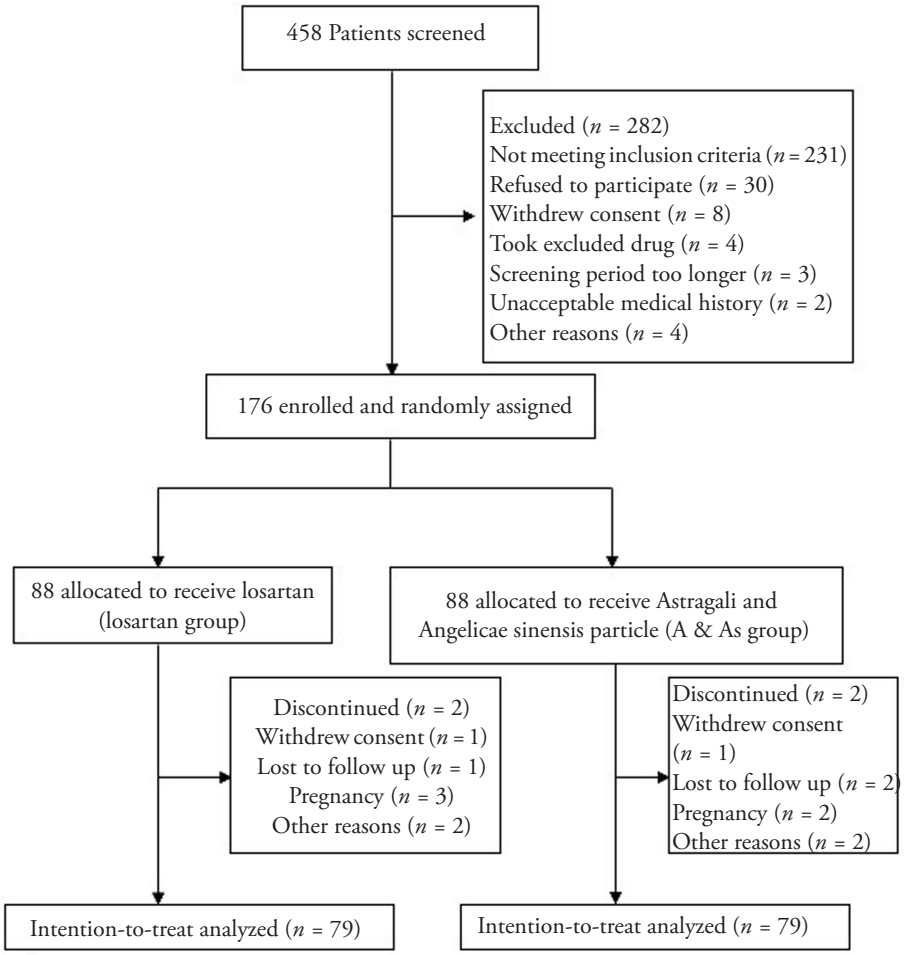

Figure 1 Enrollment and randomization of patients

Table 2 Baseline characteristics in the Losartan and A & As groups ($\bar{x} \pm s$)

Parameter	Losartan (*n*=79)	A & As (*n*=79)	*P* value
Age (years)	50.82±10.33	49.86±10.85	0.89
Female/Male (*n*)	37/42	36/43	0.79
Body weight (kg)	61.67±11.21	62.44±10.74	0.71
SBP (mm Hg)	119.64±10.75	118.93±9.64	0.66
DBP (mm Hg)	78.38±9.89	77.55±9.96	0.61
Proteinuria (g/day)	1.37±0.52	1.38±0.55	0.93
Serum albumin (g/L)	39.11±4.26	38.69±3.87	0.43
Serum creatinine (mg/dL)	1.09±0.27	1.08±0.31	0.83
eGFR ($mL \cdot min^{-1} \cdot 1.73m^{-2}$)	73.88±8.17	72.63±8.52	0.37
Hemoglobin (g/L)	115.92±13.39	113.58±12.71	0.25

Notes: A & As: Astragali and Angelica; SBP: systolic blood pressure; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate.

Table 3 Changes in clinical parameters in the Losartan and A & As groups ($\bar{x} \pm s$)

Parameter	Losartan group		[a]*P* value	A & As group		[b]*P* value	[c]*P* value
	Baseline	Week 24		Baseline	Week 24		
SBP (mm Hg)	119.64±10.75	118.53±11.22	0.53	118.93±9.64	117.97±10.35	0.53	0.73
DBP (mm Hg)	78.38±9.89	77.54±8.83	0.59	77.55±9.96	78.22±8.04	0.62	0.60
Proteinuria (g/day)	1.37±0.52	0.98±0.75	< 0.001	1.38±0.55	0.52±0.51	< 0.001	< 0.001
Serum albumin (g/L)	39.11±4.26	38.94±3.91	0.76	38.69±3.87	38.06±4.18	0.34	0.16
Serum creatinine (mg/dL)	1.09±0.27	1.12±0.29	0.50	1.08±0.31	1.10±0.25	0.65	0.64
EGFR ($mL \cdot min^{-1} \cdot 1.73m^{-2}$)	73.88±8.17	71.94±9.26	0.17	72.63±8.52	73.93±7.79	0.31	0.14
Hemoglobin (g/L)	115.92±13.39	112.65±12.17	0.11	113.58±12.71	111.24±12.31	0.25	0.47
Serum potassium (mmol/L)	4.22±0.09	4.24±0.12	0.32	4.23±0.08	4.25±0.09	0.21	0.62

Notes: Losartan group treated with losartan; A & As group treated with A & As particle. A & As: Astragali and Angelica; SBP: systolic blood pressure; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate. [a]*P*: losartan, week 24 *vs* baseline; [b]*P*: A & As, week 24 *vs* baseline; [c]*P*: A & As *vs* losartan at week 24.

Effect on proteinuria

The proteinuria profile throughout the study period is presented in Table 3 and Figure 2. There was a steady decrease in the A & As group, while the losartan group, in contrast, exhibited a biphasic time-dependent decline from baseline to week 12 (P = 0.0014) and a platform level during the remaining weeks 16 to 24 period (P > 0.05). The proteinuria in the A & As group from week 16 to week 24 was significantly reduced compared with the losartan group (P < 0.05). After treatment with A & As particles, 18 patients (22.5%) achieved a reduction in proteinuria to the normal range (< 0.15 g/day). Conversely, in the losartan group, the minimum proteinuria was 0.21 g/day.

With regard to the pathological types of GN, the anti-proteinuria efficacy of A & As particles were ordered as follows from the best to the worst: MCD and IgAN without focal segmental sclerosis, MsPGN, MN, FSGS, MPGN and IgAN with crescents.

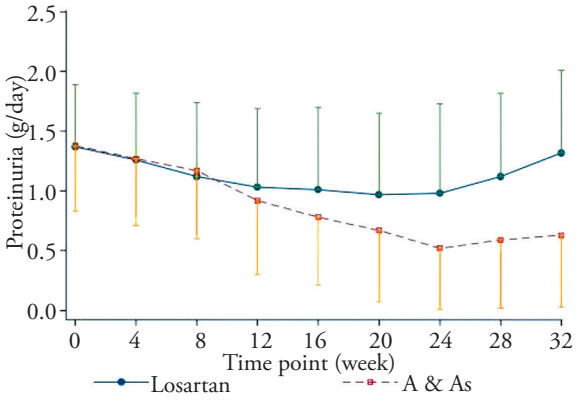

Figure 2 Changes in proteinuria in two groups

Losartan group treated with losartan; A & As group treated with A & As particle. A & As: Astragali and Angelica. Proteinuria decreased significantly during the administration of Astragali and Angelica particles (1.38 ± 0.55 g/day to 0.52 ± 0.51 g/day, P < 0.001) and losartan (1.37 ± 0.52 g/day to 0.98 ± 0.75 g/day, P < 0.001). Conversely, the proteinuria from week 16 to week 24 between the two groups was found to differ significantly.

Additionally, A & As and losartan therapies were withdrawn after week 24 in the two groups until week 32. An obvious increase in proteinuria occurred in 53 losartan patients [67.9%, (1.3 ± 0.7) g/day] and in 30 A & As patients [37.5%, (0.6 ± 0.6) g/day].

As shown in Table 3 and Figure 3, eGFR had a reduction trend in the losartan group (P = 0.173), but remained constant in the A & As group (P = 0.31). Also, the results of eGFR in the losartan group compared with the A & As group were not significantly reduced at each visit during the study period (P > 0.05).

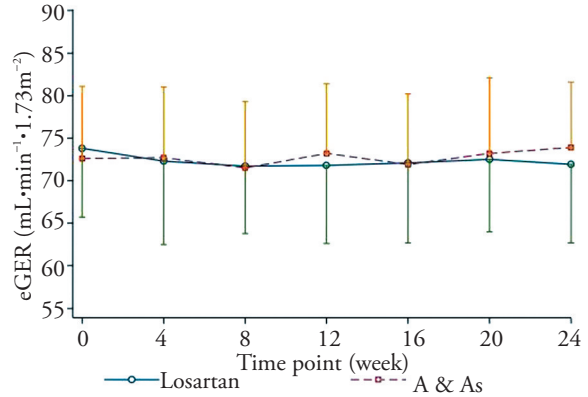

Figure 3 Changes in estimated glomerular filtration rate in the two groups

Losartan group treated with losartan; A & As group treated with A & As particle. A & As: Astragali and Angelica.

Effects on other parameters

The blood pressure measurements for the two groups are shown in Figure 4. During the 24-week period, no patient was instructed to take additional antihypertensive agents. Blood pressure was usually maintained at normal levels in both the A & As and losartan groups (Table 3). No difference in mean blood pressure reduction was observed between the two groups. A correlation analysis was conducted between the changes in blood pressure and the changes in proteinuria in the losartan group (P = 0.18, r = 0.15) and the A & As group (P = 0.09, r = 0.27). The changes in blood pressure did not significantly correlate.

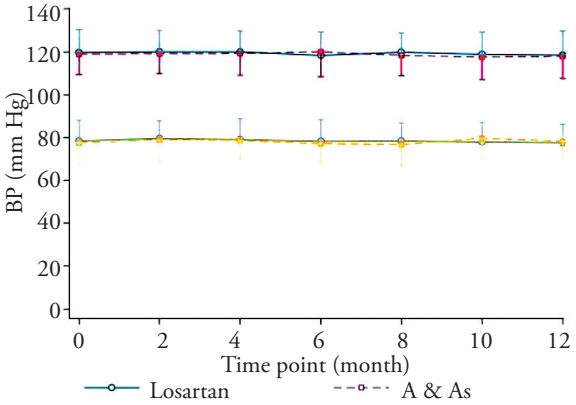

Figure 4 Changes in blood pressure in the losartan group and A & As group

Losartan group treated with losartan; A & As group treated with A & As particle. A & As: Astragali and Angelica. Systolic blood pressure and diastolic blood pressure did not change significantly in the two groups during the study period.

No significant changes were observed in the other laboratory parameters in both groups during the study period (Table 4). Patients treated with either A & As particles or losartan had no difference in serum albumin levels from baseline levels to the study end. Neither losartan nor A & As particles affected serum potassium or hemoglobin levels.

Adherence, tolerability and safety

There were no patients who dropped out or died during the research period. Overall, the incidence of side effects in the A & As group was lower than that in the losartan group (losartan group, 9 events and A & As group, 2 events; $P = 0.03$). The side effects in the losartan group included dry cough (5 cases), hypotension (2 cases), and liver function disorder (1 case). For the two hypotensive patients, the losartan tablet of 50 mg was divided into two equal dosages of 25 mg each and given 12 h apart after which improvement was reported in their symptoms. One case of gastrointestinal symptoms occurred in A & As group and one case of upper respiratory tract infection was reported in each group.

DISCUSSION

Currently, the main treatments for proteinuria for GN patients with stage 2 CKD are immunosuppresants and/or ARBs/ACE inhibitors. However, they are associated with side effects, which offset the beneficial renoprotective effects, and are usually restricted.[19-21] As a result, patients may be intolerant and discontinue the therapy, and thus lose valuable therapy time. In this study, proteinuria was significantly decreased, and the proteinuria in the A & As particle group was markedly reduced from week 16 to week 24, as compared with losartan ($P < 0.05$). As regards the magnitude of the decrease in proteinuria, nearly one-quarter of A & As patients achieved a complete remission (24-h urinary protein excretion < 0.15 g/day). Thus, A & As particles appear to have a comparatively good anti-proteinuria effect.

The anti-proteinuria effect of A & As particles persisted throughout the study protocol and increased with time. However, losartan was associated with a biphasic time-dependent reduction, i.e. a sustained decrease during the early phase followed by a platform level during the later phase. Additionally, after stopping the therapies, proteinuria in more than two-thirds of the losartan patients had nearly achieved their baseline levels, but approximately 60% of the A & As patients remained stable. Indications suggest that the anti-proteinuria efficacy of A & As particle may be sustainable,not only initially but persistently for some time. Patients with consecutive mild proteinuria during treatment are more liable to renal function deterioration than those with substantial proteinuria at the beginning.[7,22,23] Also, when the reduction of proteinuria is greater during the course of the disease, the likelihood of progression is less. Although traditional Chinese herbs are relatively safe at therapeutic doses, some can cause severe side effects including liver toxicity. In this study, there were relatively few side effects and no liver injury occurred in the A & As group, implying that it's safe and tolerable.

Therapeutic efficacy of TCM in treating CKD is mainly supported by the cumulative empiric experience, but most of clinical TCM studies cannot be widely accepted. In this study, only one unified predefined protocol was applied at each center. According to our knowledge, it is the first attempt to treat Chinese GN patients in CKD stage 2 in a multi-center, randomized controlled, clinical study with a traditional Chinese herbal formulation (A & As particle). The results of this study indicate that in such patients, treatment with TCM possesses the pronounced anti-proteinuria efficacy, as well as good safety and tolerability.

The formulation of A & As particles contains four traditional Chinese herbs. Basic practice of TCM generally consists of multiple drug therapy. It is generally believed that multiple herbal formulas are more effective than a single herbal agent. The underlying anti-proteinuria mechanism of A & As particles has not been exactly clarified, but a series of relevant clinical and experimental studies have been reported. Astragalus is reported to improve proteinuria in CKD.[14,24] It could attenuate podocyte injury by regulating the expression and distribution of nephrin and podocin. [25,26] In addition, Huangqi (*Radix Astragali Mongolici*) and Danggui (*Radix Angelicae Sinensis*) are associated with fewer infiltration of macrophages and limitation of renal intrinsic cell activation, which may lead to earlier and persistent reduction of proteinuria.[15,27] Dangshen (*Radix Codonopsis*) can alleviate glomerular injury by decreasing Ang Ⅱ-induced PAI-1 and TGF-β1 secretion.[28] Recently, many promising active ingredients have been purified from herbal extracts, which provide increased understanding of TCMs for targeting different pathways to improve proteinuria. Astragaloside Ⅳ from Huangqi (*Radix Astragali Mongolici*) exhibits regulation of the

immune system and anti-inflammation.[29-32] Ferulic acid, an active compound of Danggui (*Radix Angelicae Sinensis*), has been confirmed to ameliorate adenine-induced kidney damage in rats.[33] Emodin, an active compound of Huzhanggen (*Rhixoma Polygoni Cuspidati*), has a major role in inhibiting the differentiation and maturation of dendritic cells, and increases the number of regulatory T cells.[34,35] These results indicate that A & As particles have multiple mechanisms of action that may contribute to its anti-proteinuria effect. More thorough molecular mechanistic studies using modern scientific methodology and approaches are needed.

In the present study, there was no clinical effect observed on blood pressure, because the enrolled patients were normotensive at study entry and during the study. Therefore, we did not have to add extra antihypertensive agents. These findings confirm that the anti-proteinuria benefit observed in the A & As-treated group might be attributed to a direct action, rather than based on a reduction of systemic blood pressure. Although the study period was relatively short, there was no observed deterioration of renal function in the two groups during the 24 week study period. This indicates that the anti-proteinuric process was independent of changes in eGFR. In addition, we collected data on the level of serum albumin in these patients, to exclude this parameter as the reason for the observed differences in proteinuria in both groups. The levels of serum albumin were similar during the observational period, so we could verify that the lower proteinuria in the patients who received A&As was not due to lower serum albumin, i.e. lower albumin clearance.

Of the 158 biopsy-proven patients, the anti-proteinuria efficacies of the A & As particles were positive in MCD, IgAN without focal segmental sclerosis, and MsPGN, but disappointing in FSGS, MPGN and IgAN with crescents. However, this is consistent with the clinical observation that MCD and MsPGN may usually have an optimistic prognosis, while FSGS, MPGN and severe IgAN imply worse progression. Hence, early establishment of diagnosis and timely appropriate therapeutic intervention for CKD should be considered in order to improve prognosis.

There are several limitations to our research. First, the study was of relatively short duration. Given the lack of long-term data, the study could have been strengthened by a longer follow-up period to confirm whether the superior renoprotective effect of the A & As particle could be sustainable. Second, because this study only involved Chinese patients, we do not know whether this TCM therapy could also be applied to other ethnic patients.

In summary, this study is the first prospective, multi-center, and randomized controlled clinical study of TCM for treating Chinese proteinuric GN patients with stage 2 CKD. The results indicated that A & As particles can improve proteinuria and notably without significant side effects. Further investigations with longer follow-up are necessary to improve our understanding that A & As particles may be a more effective substitute therapy for CKD.

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