ORIGINAL ARTICLE

Beneficial effect of *Astragalus membranaceus* on estimated glomerular filtration rate in patients with progressive chronic kidney disease

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Available online 22 February 2012

**KEYWORDS**

CKD stages 4 and 5; Controlled before-and-after trial; Herbal medicine; Progressive kidney disease; Renoprotective effect

**Summary**

**Background/Purpose:** Several types of herbal preparations have been used as supplementary therapies for the treatment of progressive chronic kidney disease (CKD), but the scientific evidence for their use is scarce. The aim of the present study was to determine the effects of *Astragalus membranaceus* on renal outcome in patients with progressive CKD.

**Methods and Results:** The study population consisted of 35 patients with CKD stages 4 and 5 whose estimated glomerular filtration rate (eGFR) decreased over a 3-month period before the start of *A membranaceus* treatment despite the use of conventional therapy (from 14.6±6.28 mL/min/1.73 m² to 11.6±5.24; mean±SD, p<0.05). Similarly, the eGFR of 15 patients with CKD stage 4 decreased over the same period despite conventional therapy (from 20.8±4.59 to 16.7±4.17; r=−1.298; p<0.05), but increased after the initial period of 3 months of supplementary treatment with *A membranaceus* (to 18.6±5.67; r=0.973; p<0.05) and remained at that level at 6 months (17.8±5.60) and 12 months (16.3±5.89).

However, in 20 patients with CKD stage 5, the beneficial effect of *A membranaceus* was limited to the first 3 months only (−3 months: 10.5±2.7, baseline: 8.0±2.75, 3 months: 8.4±2.96, 6 months: 6.8±2.45). *A membranaceus* had no significant effects on other laboratory parameters.

Only seven patients (1 in stage 4 and 6 in stage 5) required dialysis within 12 months of *A membranaceus* treatment, whose eGFR at baseline was relatively low (7.4±1.06).

**Conclusion:** The results suggest that *A membranaceus* can maintain stable levels of eGFR and delay the initiation of renal replacement therapy in patients with progressive CKD stage 4.
Introduction

With increasing numbers of patients undergoing renal replacement therapy, the cost of chronic kidney disease (CKD) is rising worldwide. The number of patients requiring dialysis therapy in Japan has also increased almost linearly, about 10,000 a year, since surveys began in 1983, reaching 297,126 at the end of 2010. Therefore, it is important to establish strategies to delay the progression to end-stage kidney disease in CKD patients. However, despite significant advances in conventional medicine, no specific treatment is available for patients with stages 4 and 5 CKD. There was no prohibited combination of drugs. The primary outcome measurement was retardation of CKD progression as assessed by the slope of eGFR. The study population eventually consisted of 35 patients (15 with CKD stage 4 and 20 with CKD stage 5) who were treated with A membranaceus daily for more than 3 months.

Study design

Outpatients with progressive CKD stage 4 to 5 who consented to undergo treatment with A membranaceus were enrolled in this study. Progressive CKD in this study was defined as reduction in the estimated glomerular filtration rate (eGFR) over a period of 3 months preceding enrollment in the study despite the use of conventional therapy. We compared the slope of eGFR decline before and after treatment with A membranaceus. All enrolled patients were already being treated for CKD-related complications such as hypertension, renal anemia, metabolic acidosis, and mineral bone disease with antihypertensive drugs, erythropoietin, xanthine oxidase inhibitors, sodium bicarbonate, vitamin D analogs, and absorbent AST120. During the study, the patients were advised to continue to take all their medications wherever possible. The trial protocol was approved by the institutional review board of Juntendo University Hospital, and all patients gave written informed consent. Whenever a patient demanded a revocation of consent, we excluded that patient’s information from our study.

The A membranaceus used in this study was inspected and certified according to the regulations established by the Japanese Pharmacopeia. Participants were treated with 2.5 g A membranaceus twice a day, together with conventional therapy. There was no prohibited combination of drugs. The primary outcome measurement was retardation of CKD progression as assessed by the slope of eGFR. The eGFR for each patient was estimated using the four-variable Modification of Diet in Renal Disease study equation.

The following information was recorded every 4 weeks at each visit to Juntendo University Hospital: body weight, blood pressure, hemoglobin (Hb), serum creatinine, blood urea nitrogen (BUN), uric acid (UA), Na, K, Cl, albumin, low-density lipoprotein cholesterol, e-GFR, and urinary protein excretion (mg/g-Cr).

Statistical analyses

Data are expressed as mean ± SD. Statistical comparison of data before and after treatment with A membranaceus was performed using the Mann–Whitney U-test, and the analysis of changes in eGFR was performed using the paired
t-test (StatView version 5.0; SAS Institute Inc., Tokyo, Japan). A p value <0.05 was considered statistically significant. The correlation coefficient between before and after treatment with Astragalus membranaceus was expressed as r = .

Results

Demographic and clinical characteristics of the patients

In these patients, the primary kidney diseases were nephrosclerosis (n = 13), chronic glomerulonephritis (n = 10), diabetic nephropathy (n = 5), autosomal dominant polycystic kidney disease (n = 4), chronic interstitial nephritis (n = 2), and vesicoureteral reflux (n = 1). This group consisted of 22 (63%) males and 13 (47%) females aged 40–94 years (64.1 ± 13.1). Table 1 lists the demographic and clinical characteristics, blood pressure, laboratory findings, and drug usage of these patients.

Changes in eGFR and proteinuria

For the entire group of 35 patients, the mean eGFR at 3 months before the administration of Astragalus membranaceus...
Table 3

<table>
<thead>
<tr>
<th>CKD stage 4</th>
<th>0 mo</th>
<th>3 mo</th>
<th>6 mo</th>
<th>9 mo</th>
<th>12 mo</th>
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<tr>
<td><strong>n</strong></td>
<td>3</td>
<td>3</td>
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<tr>
<td>Systolic BP (mmHg)</td>
<td>134 ± 14.1</td>
<td>131 ± 17.1</td>
<td>130 ± 14.3</td>
<td>131 ± 15.8</td>
<td>125 ± 10.7</td>
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<tr>
<td>Diastolic BP (mmHg)</td>
<td>82 ± 6.9</td>
<td>81 ± 11.9</td>
<td>86 ± 14.5</td>
<td>81 ± 11.5</td>
<td>81 ± 13.8</td>
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<td>Hemoglobin (g/dL)</td>
<td>12.9 ± 1.5</td>
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<tr>
<td>BUN (mg/dL)</td>
<td>10.6 ± 5.5</td>
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<td>10.6 ± 5.5</td>
<td>10.6 ± 5.5</td>
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<td>creatinine (mg/dL)</td>
<td>2.0 ± 0.5</td>
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<td>eGFR (mL/min/1.73 m²)</td>
<td>62 ± 9.3</td>
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<td>Urine acid (mg/dL)</td>
<td>43.2 ± 11.5</td>
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<td>LDL-C (mg/dL)</td>
<td>7.9 ± 1.7</td>
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<td>K (mmol/L)</td>
<td>4.7 ± 0.6</td>
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<td>Albumin (g/dL)</td>
<td>3.8 ± 0.7</td>
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<td>Proteinuria (g/24 h)</td>
<td>0.9 ± 0.3</td>
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The clinical courses of eGFR in each patient of 3 months before to 3 months after treatment with A membranaceus are shown in Fig. 1A. Although they already underwent treatment with conventional therapy, the slope of eGFR started to decline (r = −1.232) even before treatment. After A membranaceus treatment for 3 months, the slope of eGFR was significantly improved (r = 0.89). However, this effect did not continue after 6 months. The mean values of eGFR of 3 months before to 12 months after treatment with A membranaceus are shown in Fig. 1B. The improved eGFR reverted to the level of 3 months after the treatment, for 6 months. The amount of proteinuria tended to decrease after treatment with A membranaceus for 3 months, but it was not statistically significant. On the other hand, increment of eGFR and decrement of proteinuria for 3 months were well correlated (r = 0.802, Fig. 1C).

**Adverse events**

Twelve adverse events in 10 patients were reported. They included skin eruptions (n = 5, 12.2%), digestive symptoms...
(n = 3, 7.3%), anemia (n = 2, 4.9%), and stomatitis (n = 2, 4.9%). All events were mild to moderate in severity. Two patients discontinued A membranaceus treatment temporarily due to skin rashes on the legs and gastritis, but they resumed and continued treatment without any further adverse events, suggesting that these adverse events were rather associated with the uremic state.

Discussion

Since there are no specific therapies for recovery of renal function after reaching the end stage of CKD, multidisciplinary treatment and diet therapy including protein restriction are considered to delay the progression of CKD.2 In Japan, not only herbalists but general practitioners also sometimes use Chinese herbal preparations as complementary therapies to reduce the rate of progression of CKD. In general and traditional medicine, the prescribed herbs are often polyherbal formulas, because it is generally believed that herbs have synergistic effects. Among several herbs, A membranaceus is often present in polyherbal formulas prescribed for renal diseases because of its anti-inflammatory and diuretic actions. For this reason, we chose A membranaceus to study the effects of a single herbal therapy in patients with CKD stages 4 and 5 whose eGFR was decreasing in the previous 3 months, in place of a multidisciplinary therapy. Since A membranaceus has been inspected and certified by the Japanese government health authorities and included in the health insurance system, the cost of treatment is less than that with other medicines such as oral adsorbent AST120,19 which is sometimes used for the same purpose.

In this study, A membranaceus significantly increased eGFR in patients with progressive CKD stage 4, but the effectiveness period was limited to about 1 year, because otherwise A membranaceus might prolong the initiation of renal replacement therapy for at least 1 year.

Progressive CKD was defined as a reduction in the eGFR value over a period of 3 months preceding enrollment in this study despite conventional therapy. We classified the stage of CKD by eGFR at the start of A membranaceus treatment. What is the underlying mechanism(s) of action of A membranaceus on renal function? Previous studies reported that the combination of two herbs, A membranaceus and Angelica sinensis, increased the densities of aminopeptidase P-positive glomerular and peritubular capillaries, similar to enalapril treatment in five of six nephrectomized rats.21 The authors concluded that up-regulation of renal cortical vascular endothelial growth factor in the treatment group reduced capillary loss and improved microstructural dysfunction.21 In another study, the same herbal combination also enhanced nitric oxide production via activation of endothelial NO synthase and scavenging reactive oxygen species in a mouse UUO model.22 Based on a histopathological examination, the enhanced production of NO was considered to explain the improvement observed in ischemic microvasculature and attenuation of interstitial fibrosis.22 Since A membranaceus contains a relatively high amount of flavonoids which have strong antioxidative action, it may exert these positive effects on eGFR. In another study using the rat UUO model, treatment with A membranaceus reduced the mRNA expression levels of TGF-β1 and smooth muscle actin, which rectified the decrease in fibronectin and type I collagen depositions, suggesting that the renoprotective effects of the two herbal medicines might be related to inhibition of myofibroblast action.16 Motomura et al23 demonstrated that astragalosides, especially astragaloside V isolated from the root of Astragalus radix, inhibited the formation of advanced glycation end products (including both N-carboxymethyl-lysine and pentosidine) in vitro. In rats with streptozotocin-induced diabetes, treatment with A membranaceus improved renal function by reducing nuclear factor-kappa B and increasing IκB mRNA levels in the renal cortex.44 Although we could not investigate the mechanisms of action of A membranaceus in our clinical study, the results confirmed that A membranaceus was able to maintain the eGFR during the study period. The effects of A membranaceus were similar regardless of the underlying mechanism of CKD. The significant temporal increment of eGFR was not recognized in patients with CKD stage 5, suggesting that the number of residual nephrons is critical for the effect of A membranaceus. The beneficial effects of A membranaceus allowed a delay in the initiation of renal replacement therapy in patients with progressive CKD stage 4. Hence, early commencement of A membranaceus treatment might enhance the beneficial effects with a clearer impact on the disease process. The reason why A membranaceus improved eGFR but had no effect on BUN and UA was not clear. Since most patients took loop diuretics, the use of diuretics may be one of the reasons.

Several adverse events of A membranaceus were observed within the first month of treatment. However, these side effects were mild, and recovery was noted following discontinuation of the herbal preparation. Accordingly, daily treatment with A membranaceus for up to 24 months seems to be safe.

In conclusion, A membranaceus should be effective in the treatment of progressive CKD, but a randomized control
Figure 1  (A) Estimated glomerular filtration rate (eGFR)-time plot for 35 patients 3 months before, at the start of, and 3 months after treatment with Astragalus membranaceus. (B) The mean eGFR values of patients from 3 months before to 12 months after treatment with A membranaceus. Asterisk indicates significance (<0.05) compared with the value at 3 months before treatment with A membranaceus. (C) Proteonuria-time plot for patients from 3 months before to 12 months after treatment with A membranaceus.
study is needed to confirm the exact effects of this herbal preparation.

Acknowledgments

The work was supported in part by grants-in-aid from the Tokyo Metropolitan Government, Program for Intractable Disease Studies.

References