KAMPO MEDICINE

Successfully Reducing Serum Creatinine and Increasing eGFR in a CKD Patient Treated with Orally Administered *Astragalus membranaceus* Powder: A Case Report

Takaaki Kinoue[1)], Makoto Arai[2)], Kagemasa Kajiwara[3)]

ABSTRACT

Introduction: **Currently, no medicine directly improves renal function. Administration of *Astragalus membranaceus* (AM), however, could decrease serum creatinine (SCr) concentration and increase estimated glomerular filtration rate (eGFR), although whether it improves renal function is unclear. Here we report a case in which SCr decreased and eGFR increased with administration of this powder.**

Case Presentation: **A 58-year-old male received a diagnosis of stage G3b chronic kidney disease (CKD), whose pathological etiology had not been determined. His SCr and eGFR before AM administration were 1.4 mg/dl and 41 ml/min/1.73 m^2, respectively. One month after the administration of 1.5 g of AM powder twice a day together with conventional Kampo therapies, they were 1.09 mg/dl and 53.8 ml/min/1.73 m^2. For more than 1 year since the commencement of AM administration, SCr and eGFR remained at 1.0-1.1 mg/dl and 52-57 ml/min/1.73 m^2, respectively. On the other hand, blood urea nitrogen (BUN) remained almost unchanged within normal limits from before AM commencement to the present. Throughout the clinical course, no other medication beside AM was added.**

Discussion: **In China successful cases were reported, in which AM was injected intravenously, on the contrary we could ameliorate renal dysfunction by oral AM administration.**

Conclusion: **AM administration to a CKD patient successfully decreased SCr and increased eGFR. As a future target, the mechanism should be elucidated. Furthermore, whether AM is an effective medicine for renal disease, i.e., whether it really ameliorates renal function, should also be explored. (242words)**

KEY WORDS

chronic kidney disease (CKD), *Astragalus membranaceus* (AM), creatinine

INTRODUCTION

The chief purposes of treatment for chronic kidney disease (CKD) are definitely preserving residual renal function and reducing complications. The current CKD interventions affect lifestyle factors (i.e., the amount of sodium and protein intake, smoking habit, and exercise among other lifestyle factors) and the values of blood pressure, blood glucose, cholesterol, hemoglobin, uric acid, and so on. For appropriately achieving values within the clinical test reference range in CKD patients, supportive symptomatic medicines, e.g., antihypertensive drugs, antidiabetic medicines, cholesterol lowering drugs among others are administered. Furthermore, complications of the disease, e.g., hyperkalemia, metabolic acidosis, and hyperphosphatemia, should be properly controlled (Japanese Society of Nephrology, 2018).

Astragalus membranaceus (AM) is one of the crude drugs widely used in oriental medicine and an important constituent in Kampo formulas. In China, AM therapy is also widely used for treating kidney diseases and reported to be effective for reducing serum creatinine (SCr) (Li. Wang, Xue, Gu, Lin, 2011; Zhang, Lin, Xu, Leung, Chan, 2014; Zhang, Shergis, Yang, Zhang, Guo, Zhang, Zhou, Zeng, Mao, Xue, 2019) and increasing creatinine clearance (CrCl) (Li *et al*., 2011; Zhang *et al*., 2014) in meta-analyses. In such positive reports, however, the route of AM administration is surprisingly intravenous. Definitely, this method of administration cannot be used in most countries outside of China due to its safety risk. Certainly, in Japan, Kampo formulas and crude drugs are orally administered, whether as powder, pill, or decoction. Although there are few reports of AM treatment for CKD in Japan and they indicate its effectiveness (Nagasaka, Fukuda, Watanabe, Nagata, 2012; Fushimi, Yamaoka, Nagata, Kano, Iguchi, 2017; Tsujimoto, Wada, Achiwa, Yuhki, Goto, Fukuzawa, Harada, 2017), and a few reports from China deny AM's effectiveness for CKD when administered orally (Zhang *et al*., 2014; Zhang *et al*., 2019).

Here we would like to report that orally administered AM powder successfully reduced SCr and increased estimated glomerular filtration rate (eGFR) in a CKD patient whom we treated.

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1) Department of Community Health, Tokai University, School of Medicine
2) Department of Kampo Medicine, Tokai University, School of Medicine
3) Division of Basic Molecular Science and Molecular Medicine, Tokai University, School of Medicine
Correspondence to: Takaaki Kinoue
(e-mail: clubmed0001@yahoo.co.jp)

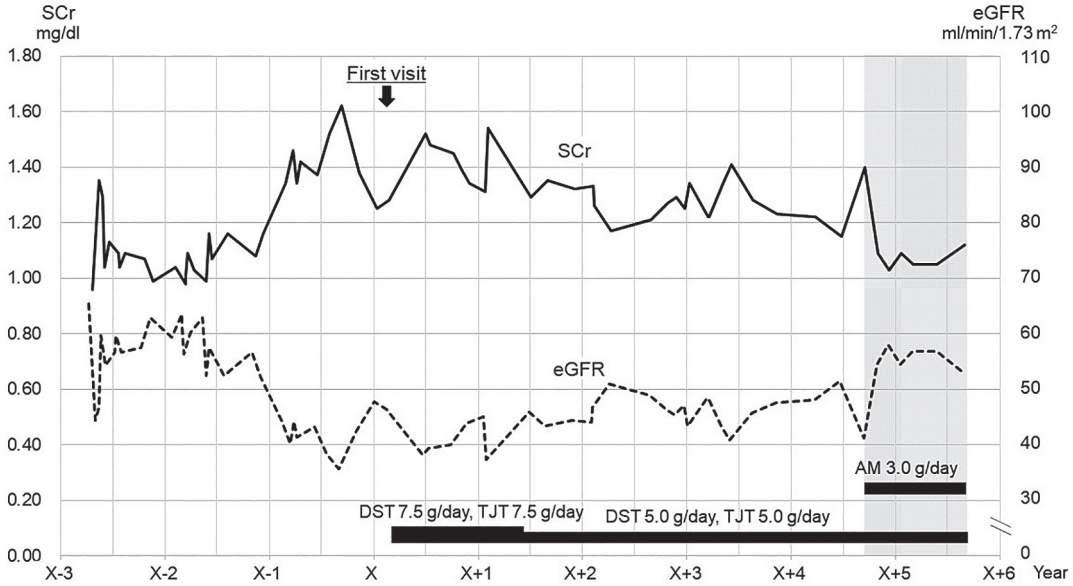

Figure 1: Clinical course of the patient

CASE PRESENTATION

A 58-year-old male who complained of cold sensation in his left arm presented to the outpatient clinic of the Department of Kampo Medicine in Tokai University Hospital in March of the year X. He suffered from left hemiplegia accompanied by cold sensation in the left arm due to cerebral hemorrhage and complained of insomnia and vertigo. Past medical history revealed angina pectoris, hypertension, hyperlipidemia, impaired glucose tolerance, functional dyspepsia, and constipation. For this reason, clopidogrel sulfate 75 mg, carvedilol 15 mg, telmisartan 40 mg, hydrochlorothiazide 12.5 mg, atorvastatin calcium 10 mg, and sodium picosulfate hydrate were regularly administered. Furthermore, he also was diagnosed with renal dysfunction, whose pathological etiology had not been determined at our hospital in year X-3. He received only dietary counselling without drug treatment, since his SCr and eGFR remained 1.2-1.5 mg/dl and 40-50 ml/min/1.73 m^2, respectively, for several years without urinary protein or occult blood; that is to say, his renal function had no tendency to deteriorate.

Physical examination revealed that his height and weight were 183 cm and 80 kg. Besides, his body temperature, pulse, and blood pressure were 36.1 degrees Celsius, regular 68 beats/min, and 142/90 mmHg, respectively. No edema or skin lesions, no pale or icteric conjunctivas, and no swelling of the tonsils and thyroid were noted. The heart sounds were normal, and no murmur was heard. The liver, spleen, and kidneys were not palpable. The patient had left hemiparesis and walked wearing a brace on the left leg. Kampo medical examination revealed that he had strong tension in the upper abdominal region and tenderness in the lower abdominal region, which were indications for a saiko (Bupleurum Root) -containing medication and suggested a diagnosis of blood stasis, respectively. Therefore daisaikoto (DST; extract: TJ-8, Tsumura Co., Tokyo, Japan) 7.5 g/day and tokakujokito (TJT; extract: TJ-61, Tsumura) 7.5 g/day were prescribed, with effects of early amelioration of constipation and gradual improvement of insomnia and vertigo. One year later, both Kampo medicines were reduced in dose to 5.0 g/day due to symptoms stabilization. The left arm hemiplegia, however, remained unchanged throughout the course.

Eventually, SCr increased to 1.4 mg/dl and eGFR fell to 41 ml/min/1.73 m^2 in September of year X+4. Abdominal ultrasonography of the kidneys at that point revealed that they had normal size and were free of tumors or stones, however in the renal parenchyma, the brightness was slightly elevated and the margin was irregular. In addition, urinalysis showed no protein, sugar, or occult blood, and complete blood count (CBC) revealed no anemia. The stage of CKD was diagnosed as G3b. To improve renal function, 1.5 g of AM powder twice a day was administered, together with his conventional Kampo therapies. One month after the commencement of AM treatment, SCr decreased to 1.09 mg/dl and eGFR recovered to 53.8 ml/min/1.73 m^2. For more than one year since the commencement of the AM prescription, SCr and eGFR has been maintained at 1.0-1.1 mg/dl and 52-57 ml/min/1.73 m^2, respectively. On the other hand, blood urea nitrogen (BUN) was almost within the normal range before AM commencement and thereafter. No amelioration of diabetes or hypertension was observed. Throughout the clinical course, no medication other than AM was added (Clinical course is shown in Figure 1).

DISCUSSION

In this paper, oral administration of AM powder successfully reduced SCr and increased eGFR in a CKD patient.

According to three meta-analyses (one in non-diabetic patients and the others in diabetic patients), AM therapy is an effective, widely administered treatment for kidney diseases in China (Li *et al*., 2011; Zhang *et al*., 2014; Zhang *et al*., 2019). All these meta-analyses concluded that SCr level and the amount of urine protein were decreased in patients given AM therapy. Intravenous injection was the route of administration in all but four reports; however oral administration did not ameliorate SCr. The most common adverse effects of intravenously administered AM were dry cough, SCr elevation more than 30% from baseline, dizziness, angioedema, and hyperkalemia (Zhang *et al*., 2019); however adverse effects were not mentioned in many reports or were not identified in the rest of reports. On the other hand, in Japan, case reports of AM therapy for CKD are scarce, and in these reports AM was orally administered as a decoction or was in powdered form for safety and ethical reasons (Nagasaka *et al*., 2012; Fushimi *et al*., 2017; Tsujimoto *et al*., 2017). All these reports indicated SCr reduction and 1/Cr-time slope improvement without incidence of major adverse effects, although BUN level did not change. Whether the mechanisms of SCr reduction and prolonged prognosis really indicate amelioration of renal function with AM treatment, i.e., longer time to renal replacement therapy and improved mortality rate and quality of life, have not been sufficiently elucidated so far. To elucidate the latter issue, long term study of AM treatment should be carried out. On the other hand, for the former issue, although some reports show protection of kidneys with AM administration in animal experiments, the matter is still unresolved (Kajiwara, Arai, Nakada, Kinoue, 2019). For example, extract of *Astragali radix* reduced oxidative stress (You, Lu, Gui, Peng, Chen, Gu, 2011; Gao , Zhang, Li, Ren, Ren, Shi, Pan, Ren, 2012) and suppressed renal fibrosis (Zuo, Xie, Qiu, Deng, Zhu, Fan, 2009) in rats' kidneys. Furthermore, it remains unclear whether this SCr reduction is due to renal protection by AM or just interference with the biochemical test for SCr by components of AM.

As a limitation, this study was a one-patient case report so that the mechanism of reducing SCr remains unknown at the moment and is not elucidated. Therefore, future research should address whether this outcome of AM administration is brought about by renal function improve-

ment, change in creatinine metabolism, or mere interference with creatinine measurement.

CONCLUSION

We reported here that AM administration to our CKD patient decreased SCr and increased eGFR. However, the mechanisms underlying this phenomenon were undetermined and should be elucidated in the future. Furthermore and more importantly, whether AM is a treatment for renal disease, or really ameliorates renal function, should also be explored.

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