Effects of Oral Adsorbent AST-120 (Kremezin®) on the Progression of Chronic Kidney Disease

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Purpose: AST-120 is known to delay progression of chronic kidney disease (CKD) when combined with other proven therapy. AST-120 is an oral adsorbent for uremic toxin, such as indoxyl sulfate from the gastrointestinal tract. There have been a lot of studies to show its effect in other countries, but there are few studies done in Korea yet.

Methods: 195 patients were included in the study (mean age, 64±14 years; diabetes mellitus (DM), 104 patients; male, 130 patients). The patients with CKD who started AST-120 and maintained the medication for at least 6 months were enrolled. The patients' laboratory results for 6 months before and after administrating AST-120 was surveyed. Then the rate of patients' renal functional deterioration was compared before and after AST-120. In addition, adverse effects during the medication were surveyed.

Results: There were no statistically significant differences in laboratory data between before and after AST-120 administration. But, after administrating AST-120, the renal deterioration slope has blunted significantly from -0.0123±0.0318 to -0.0013±0.0184 dL/mg/month (p<0.01) in 1/sCr and from -1.1423± 2.3906 to 0.0639±1.3825 ml/min/1.73m^2/month (p<0.01) in estimated glomerular filtration rate (eGFR). There were no differences between DM and non-DM patients in the effect of AST-120, as well as ages over 70 and below 70. There were no serious adverse effects during medication.

Conclusion: This study showed that AST-120 had additive effect on retarding the CKD progression when combined with established therapy regardless of DM and ages without serious adverse effects.

Key Words: AST-120, Chronic renal failure, Glomerular filtration rate

INTRODUCTION

AST-120 (Kremezin®, Kureha, Tokyo, Japan) is an oral carbonaceous adsorbent used in pre-dialysis renal failure patients to adsorb uremic toxin such as indoxyl sulfate, indoxyl-D-glucuronide and p-cresol.

When tryptophan is introduced to the body, it is metabolized into indole in gastrointestinal tract by bacteria. Indole is then absorbed into the body and change into a potent uremic toxin, indoxyl sulfate in liver[1]. Serum indoxyl sulfate level is correlated with CKD progression. In uremic rat model, administration of indoxyl sulfate decreases renal function and induces glomerular sclerosis by stimulating transforming growth factor-ß1 (TGF-ß1), tissue inhibitor of metalloproteinase-1, and pro-α 1 collagen[2].

There have been many overseas studies showing the effect of AST-120 in delaying progression to end-stage renal disease (ESRD), hence prolonging

the interval to inception of dialysis[3−12]. However, there were few studies done in Korea.

In this study, the effect of AST−120 on delaying the progression from CKD to ESRD was examined in relation to DM and age[5].

PATIENTS AND METHODS

1. Subjects

Clinical records of 310 patients with CKD who started AST−120 between September 2005 and September 2009 in outpatient department of Gangnam Severance hospital were reviewed retrospectively. The patients who met following inclusion criteria were enrolled in the study: (1) CKD (serum creatinine: 1.5−6.0 mg/dL; eGFR: 15−60 mL/min/1.73m^2) patients otherwise stable hemodynamically and metabolically; (2) no recent history of comorbidity as mentioned below at exclusion criteria. The patients who met the following criteria were excluded: (1) patients who failed to visit outpatients department or refuse to blood sampling for 2 consecutive session (for 4 months); (2) malnutrition or a serum albumin ≤3.0 g/dL[13]; (3) major cardiovascular event (acute myocardial infarction, angina undergone coronary angioplasty); (4) hemoglobin A1c >8.1% in diabetics[14]; (5) acute kidney injury; (6) use of systemic immunosuppressive therapy; (7) cancer; (8) alcoholics or drug abuse; (9) inflammatory bowel disease, chronic diarrhea, malabsorption; (10) hepatic disease (hepatitis, cirrhosis, hepatic failure, viral carrier, OT/PT elevation above normal range); (11) non−compliance.

Out of 310 patients screened, 195 patients met the above criteria. The most common reasons for exclusion were non−compliance (n=35; 30.7%), starting renal replacement therapy (n=22; 19.3%).

The patients were encouraged to have low protein diet (0.8−1.0 g protein/kg body weight/day) and salt restriction (<7−8 g/day). Strict blood sugar control was supplemented for those with DM. The patients

were taking angiotensin−converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) if not contraindicated. And the blood pressure was strictly controlled to maintain below 130/80 mmHg in patient without proteinuria or proteinuria under 1 g/day, and 125/75 mmHg in patient with proteinuria over 1 g/day.

2. Administration of AST−120

The patients received 2 g of AST−120 between meals 3 times a day for at least 24 weeks. The patients who refused to take the medicine even a bit due to various reasons were excluded. Since AST−120 is an adsorbent, simultaneous drug administration was carefully avoided.

3. Clinical parameter

During the study periods, CBC with differential count, blood urea nitrogen (BUN)/creatinine, total cholesterol, albumin, HbA1c, blood pressure, pulse rate, body weight were measured every 2 months.

4. Evaluation of the effect of AST−120 on deterioration of renal function

The gradient of renal functional deterioration was evaluated as the slope of the reciprocal serum creatinine level (1/sCr)[15], and by eGFR obtained from modified MDRD (Modification of Diet in Renal Disease) equation[16] before and after administration of AST−120 preferably every 2 months. And, subgroup analyses according to the presence of DM, age of 70 were conducted. In addition, adverse effects were surveyed during medication.

5. Statistical analysis

The analyses were performed using SPSS for window version 17.0 (SPSS Inc., Chicago, IL, USA)

and data are expressed as the mean±SD.

Patient backgrounds were analyzed by the Student's t-test and the χ^2-test for continuous and categorical data, respectively. P-values less than 0.05 were considered to be statistically significant.

RESULTS

1. Clinical and biochemical characteristics

Clinical and biochemical characteristics of 195 selected patients are shown in Table 1. The ages of the group were 64±14 years, and 130 patients were male (66.7%), and 104 patients had DM (53.3%). The eGFR of the patients at the point when AST-120 was administered was 25.82±7.58 ml/min/1.73m^2, compatible to CKD stage 3 and 4 according to the GFR staging in the Kidney Disease Outcome Quality Initiative (K/DOQI) guidelines proposed by the US National Kidney Foundation[17]. Mean Hemoglobin level was 11.7±1.6 mg/dL and hematocrit was 35.0±4.9%. Blood pressure was controlled with at least 1 anti-hypertensive medication to target systolic pressure of 130 mmHg and diastolic pressure of 75 mmHg (beta bloc-

ker, 60 pts; ACEi 92 pts; ARB, 107 pts; calcium channel blocker, 76 pts). Mean HbA1c of DM patients were 7.9%. Underlying renal diseases were shown in Table 2. DM nephropathy was the most common etiology of CKD (104 pts; 53.3%) and hypertensive nephropathy was the second most common etiology (58 pts; 29.7%).

The mean values of biochemical parameter for 6 months before and after AST-120 administration were calculated. There were no statistically significant differences in biochemical parameters between before and after taking AST-120 (Table 3). And there were no statistically significant differences in clinical and biochemical characteristics between DM group and non-DM group or between ages over and below 70s (Table not included).

2. Changes in reciprocal serum creatinine and eGFR slope with AST-120

Table 2. Etiology of Chronic Kidney Disease

Etiology	N (%)
DM nephropathy	104 (53.3)
Hypertensive nephropathy	58 (29.7)
Glomerulonephropathy	13 (6.7)
Others	4 (2.1)
Etiology unknown	16 (8.2)

Abbreviation: DM, diabetes mellitus.

Table 1. Baseline Characteristics of Selected Patients (N= 195)

Male	66.7% (n=130)
Age (yrs)	64±14
Height (cm)	163.2±8.3
Weight (kg)	64.5±14.2
SBP (mmHg)	131±18
DBP (mmHg)	74±11
Hemoglobin (g/dL)	11.7±1.6
Hematocrit (%)	35.0±4.9
T. Cholesterol (mg/dL)	161.8±40.7
Albumin (g/dL)	4.1±0.5
BUN (mg/dL)	38.9±14.1
sCr at starting AST-120 (serum creatinine; mg/dL)	2.65±0.67
eGFR at starting AST-120 (ml/min/1.73m^2)	25.82±7.58

Abbreviations: BUN, blood urea nitrogen; Cr, creatinine; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; T, total.

Table 3. Comparison of Baseline Characteristics Before and After AST-120

	Before AST-120	After AST-120
SBP (mmHg)	132±17	129±19
DBP (mmHg)	75±11	74±11
Hemoglobin (g/dL)	12.1±1.9	11.4±1.8
Hematocrit (%)	36.2±5.0	34.1±4.9
T. Cholesterol (mg/dL)	152.0±44.2	155.5±44.0
Albumin (g/dL)	4.0±0.6	3.8±0.6
BUN (mg/dL)	40.4±14.6	
sCr (serum creatinine; mg/dL)[*]	2.64±0.77	42.57±15.6 2.32±0.64
eGFR (ml/min/1.73m^2)[*]	30.62±10.06	26.22±9.04

[*]p<0.05, significantly different between before AST-120 and after AST-120.

The gradient of 1/sCr before and after administrating AST-120 was -0.0123 ± 0.0318 and -0.0013 ± 0.0184 dL/mg/month ($p<0.01$), respectively. The gradient of eGFR before and after AST-120 was -1.1423 ± 2.3906 and 0.0639 ± 1.3825 mL/min/1.73m^2/month ($p<0.01$), respectively (Fig. 1A, 1B). After the patients started taking AST-120, the slope of 1/sCr and eGFR has been alleviated. There were statistically significant differences in estimated GFR and 1/sCr of pati ents between before and after administrating AST-120.

3. The difference in effects of AST-120 in DM vs. non-DM patients

The subgroups of DM and non-DM patients were comprised of 104 patients and 91 patients, respec-

tively. In DM subgroup, the slope of 1/sCr has blunted from -0.0186 ± 0.0230 to -0.0017 ± 0.0152 dL/mg/month ($p<0.01$), and that of eGFR has blunted from -1.2793 ± 2.1370 to -0.0628 ± 1.2171 mL/min/1.73m^2/month ($p<0.01$). On the other hand, in non-DM group, the slope of 1/sCr has been alleviated from -0.0132 ± 0.03118 to 0.0037 ± 0.0193 dL/mg/month ($p<0.01$), and that of eGFR has blunted from -0.9940 ± 2.6182 to 0.2541 ± 1.5472 mL/min/1.73m^2/month ($p<0.01$). Both subgroups showed statistically significant blunting of the slope of 1/sCr and eGFR between before and after AST-120 administration. There were no statistically significant differences between DM vs. non-DM subgroups in the effects of AST-120. (Fig. 2A, B)
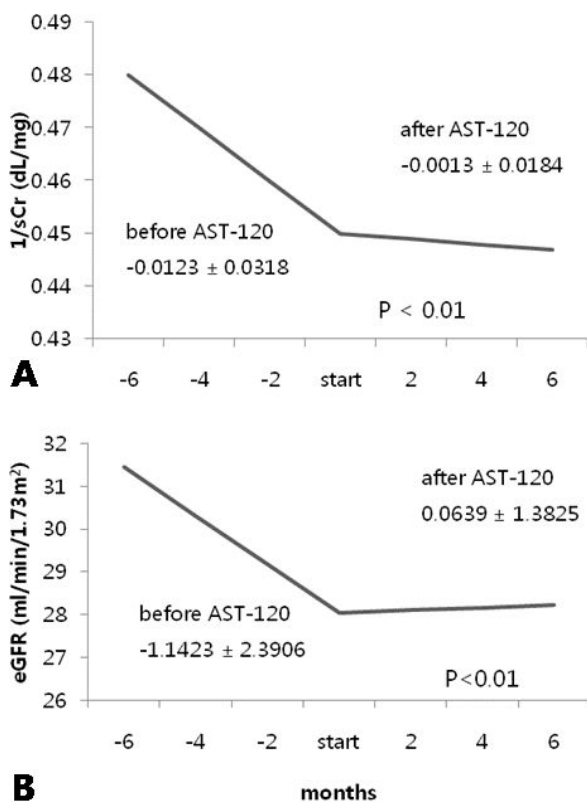

Fig. 1. (A), (B) pre- vs. post-treatment slope on reciprocal of serum creatinine (1/sCr) and estimated GFR (eGFR) in total patients. The figures show that the renal deterioration gradient has blunted after administrating AST-120, which means AST-120 is effective in delaying the progression of CKD.
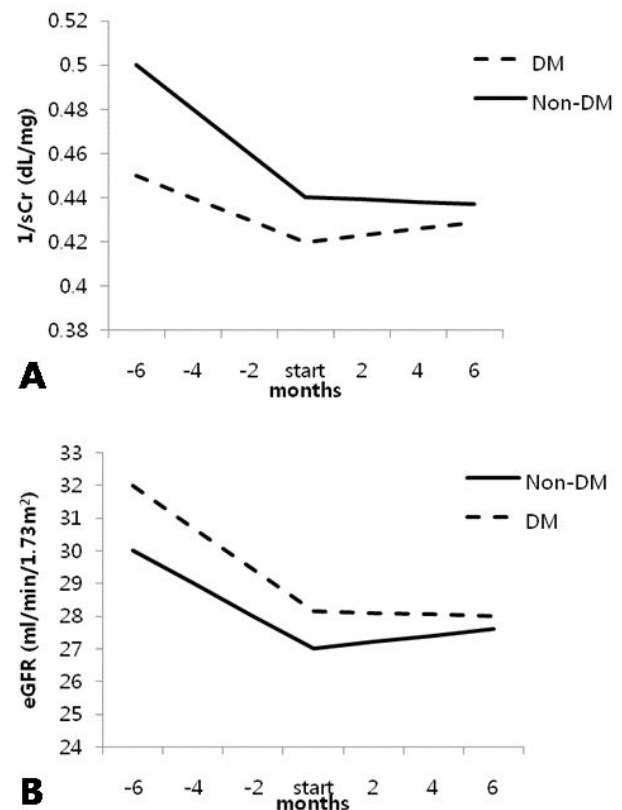

Fig. 2. (A), (B) pre- vs. post-treatment slope on reciprocal of serum creatinine (1/sCr) and estimated GFR (eGFR) in DM and non-DM patients. There are no statistically significant differences between DM and non-DM patients in blunting the slope of 1/sCr or eGFR, and both groups show delays in the CKD progression.

4. The difference in effects of AST-120 by age

The subgroups of patients aged over 70 and below 70 were comprised of 69 patients and 126 patients, respectively. In subgroup of age over 70, the slope of 1/sCr has blunted from −0.0078±0.0392 to −0.0030±0.0161 dL/mg/month (p<0.01), and that of eGFR has blunted from −1.0513±1.9740 to 0.2339± 1.2405 mL/min/1.73m^2/month (p<0.01). On the other hand, in subgroup of age below 70, the slope of 1/sCr has blunted from −0.0148±0.0264 to −0.0004± 0.0197 dL/mg/month (p<0.01), and that of eGFR has blunted from −1.1960±2.5662 to −0.0131±1.4035 mL/min/1.73m^2/month (p<0.01). Both subgroups showed statistically significant alleviation of the slope of 1/sCr and eGFR between before and after AST- 120 administration. There were no statistically significant differences between subgroups of aged over 70 vs. below 70 in the effect of AST-120 (Fig. 3A, B).

5. Adverse effects of AST-120

Out of 195 patients who were surveyed in this study, 6 patients (3.1%) suffered from constipation, 2 patients (1.0%) showed serum creatinine elevation, 2 patients (1.0%) showed poor oral intake and 1 patient (0.5%) suffered from nausea and vomiting. There were no serious or life-threatening adverse effects that need discontinuation of AST-120 (Table 4).

DISCUSSION

The population with CKD is expanding worldwide. In USA, approximately 470,000 people were diagnosed with ESRD in 2004 and around 10,000 patients start dialysis every year[18]. In Korea, 96,008 patients are being treated for CKD according to national health insurance corporation (NHIC)[19].

Managing CKD is becoming more and more important because CKD not only leads to ESRD, but also increases risk of cardiovascular events and deaths[20-24]. Furthermore, the financial benefit by delaying the progression of CKD cannot be ignored[25, 26].

In CKD, renal functional deterioration leads to accumulation of uremic toxin which induces renal inflammation and fibrosis and further deteriorates renal function in vicious cycle[22, 27]. AST-120 is an oral adsorbent to adsorb uremic byproduct in gastro-

Table 4. Adverse Effects of AST-120

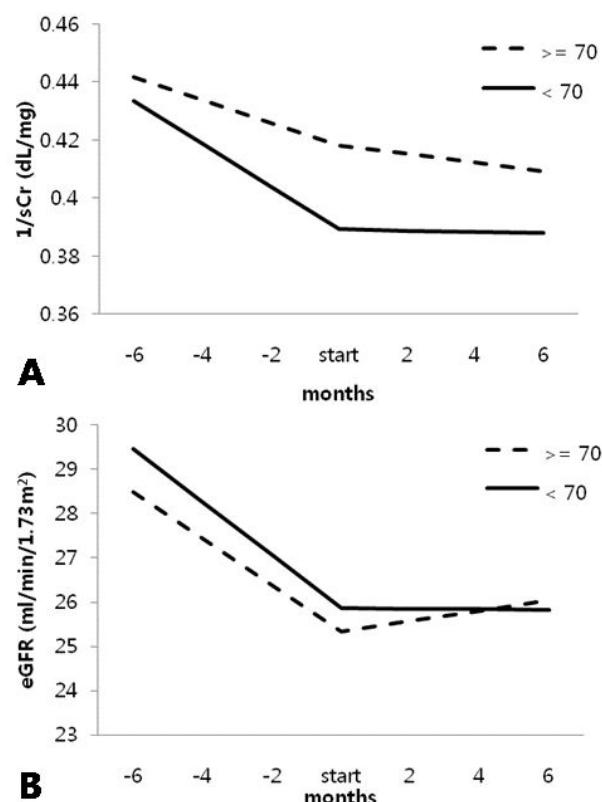| Adverse effect	N (%)
Constipation	6 (3.1)
Cr elevation	2 (1.0)
Poor oral intake	2 (1.0)
Nausea/Vomiting	1 (0.5)

Abbreviation: Cr, creatinine.

Fig. 3. (A), (B) pre- vs. post-treatment slope on reciprocal of serum creatinine (1/sCr) and estimated GFR (eGFR) in patients over age of 70 and under age of 70. There are no statistically significant differences in patients aged over 70 and below 70 in blunting the slope of 1/sCr or eGFR, and both groups show delays in the CKD progression.

intestinal tract in the effort to break out of this vicious cycle and has been available on the market since 1991. The mechanism of AST-120 is still not fully understood but there had been many studies on the mechanism of AST-120 on prevention of CKD progression. It is now proven that AST-120 can adsorb indole derived from tryptophan by gastrointestinal bacteria[28]. Since indole is a precursor of indoxyl sulfate, AST-120 may reduce serum indoxyl sulfate level[29]. Indoxyl sulfate can cause tubular hypertrophy following glomerular sclerosis by stimulating the synthesis of transforming growth factor-ß (TGF-ß)[30]. Glomerular sclerosis and interstitial fibrosis are irreversible changes in CKD. Consequently, blocking indoxyl sulfate synthesis by AST-120 may reduce the progression to ESRD.

Studies on the effect of AST-120 to delay the progression of CKD were mostly done in Japan. There are several studies showing that AST-120 can retard the progression of CKD when added to conventional treatments. Sanaka et al. showed that AST-120 has protective effect over renal function in diabetic nephropathy with good control of blood pressure and hematocrit over 30%[31]. In Korea, there have been few studies that showed the effect of AST-120 on clinical basis.

This study was focused on whether additional treatment of oral AST-120 with conventional treatment for CKD is effective in delaying progression to ESRD in Korea. The result shows that administration of AST-120 can delay the progression of CKD based on the statistically significant blunting of the 1/sCr and eGFR slope after AST-120 administration. The subgroup analysis showed no significant difference in the effect of AST-120 between both DM and non-DM groups.

Ueda et al. showed that long term treatment with AST-120 is effective in delaying the progression of CKD, regardless of whether the patients had DM or not[32], which is consistent with this study.

Maeda et al. demonstrated that the patients aged over 70 showed more blunting of reciprocal serum creatinine slope than younger patients[5], but the result was not consistent with this study. Maeda et al. suggested that the difference might be caused by that older patients tends to comply to the prescription better than younger patients or since elderly patients tend to eat less, and it might be easier to maintain a better life style, especially a low protein diet. However, in this study, the compliance of AST-120 and low protein diet was strictly checked.

On the contrary to these positive reports, Akizawa et al reported that AST-120 did not substantially slow the progression of kidney disease in patients with moderate to severe CKD during 1 year. But, as it was mentioned in the report, primary end-point events occurred infrequently, and life style modification was not strictly educated as this report[33].

As shown in table 4, only 11 out of 195 patients experienced adverse effects which were not serious. The most common adverse effects of AST-120 were gastrointestinal symptom, such as constipation, abdominal discomfort, nausea/vomiting.

The limitation of this study is that it is retrospective and in small scale, so there is no control group to compare the effect of AST-120. To further evaluate the effect of AST-120, prospective study should be carried on in a larger scale. And more studies are needed to be done to elucidate the association between pathophysiology of CKD and effect of AST-120 on CKD.

In conclusion, treatment of CKD patients by AST-120 along with conventional treatments appears to be beneficial in retarding the deterioration of renal function and delaying the initiation of renal replacement therapy without serious adverse effects.

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