Effect of AST-120 in Chronic Kidney Disease Treatment: Still a Controversy?

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Key Words

Indoxyl sulfate · Uremia · AST-120 · Chronic kidney disease · Cardiovascular disease · Glomerular filtration rate

Abstract

AST-120 (kremezin; Kureha Chemical, Tokyo, Japan) is an oral spherical carbonaceous adsorbent, which was approved for clinical use in Japanese chronic kidney disease (CKD) patients in 1991. It adsorbs indole, the precursor of indoxyl sulfate, in the intestines and prevents indoxyl sulfate production. Indoxyl sulfate, initially identified as a major uremic toxin that causes uremic symptoms, contributes to CKD progression. Since AST-120 decreases serum indoxyl sulfate in a dose-dependent manner, multicenter prospective trials have been conducted in Japan in the 1980s; these trials were mostly in favor of the efficacy of AST-120 in delaying the initiation of dialysis in patients with advanced stage CKD. Many animal studies support the effects of AST-120 on renal outcomes as well as on cardiovascular complications. However, there are yet no reports that unequivocally demonstrate the improvement of hard renal endpoints and/or cardiovascular endpoints. This commentary briefly reviews the major outcomes of the recent clinical trials on AST-120.

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Indoxyl Sulfate, AST-120, and Evidence in Animal Studies

Chronic kidney disease (CKD) results in the accumulation of metabolic wastes that are normally cleared by the kidney. Accumulation of uremic toxins, such as indoxyl sulfate and p-cresyl sulfate, in plasma and tissues is implicated in the progression of CKD and cardiovascular disease, which is supported both by animal and human studies [1, 2]. Indoxyl sulfate is synthesized in the liver from indole, which is a tryptophan metabolite by intestinal bacteria (Fig. 1). CKD patients with serum creatinine (sCr) levels of 3.0 mg/dL or greater present with increased serum indoxyl sulfate levels, generally exceeding 0.8–1.0 mg/dL [1]. A pathogenic role of indoxyl sulfate is experimentally demonstrated in rats with subtotal nephrectomy; oral administration of indoxyl sulfate accelerated the progression of glomerular sclerosis, which was associated with the deterioration in the renal function. The following multiple mechanisms are thought to be implicated: oxidative stress, stimulation of pro-inflammatory, and/or pro-fibrotic factors, endoplasmic reticulum stress, suppression of erythropoietin production, an increase in oxygen consumption in proximal tubules, and perturbation of tubular hypoxic response [3–7].

Fig. 1. Expected modes of action of AST-120. Indole is metabolized to indoxyl sulfate in liver and excreted from the kidney. Accumulated indoxyl sulfate due to renal function decline causes kidney injury and cardiovascular complications. AST-120 absorbs indole in the gut and prevents serum indoxyl sulfate accumulation.

Although AST-120 can bind many low-molecular-weight compounds (100–10,000 kDa), it has superior adsorption ability for certain small-molecular weight organic compounds including indoxyl sulfate. The phase II study in the United States has evaluated the effect of 3 doses of AST-120 (2.7, 6.3, and 9 g) versus placebo on changes in serum indoxyl sulfate levels from baseline in CKD patients with sCr 3.0–6.0 mg/dL [8]. AST-120 showed dose-dependent reduction of serum indoxyl sulfate, in which 9.0- and 6.3-g AST-120 treatment groups reached statistically significant reduction compared with the placebo group. Importantly, this study showed minor changes in urinary creatinine excretion by AST-120 treatment. sCr under AST-120 treatment is thus expected to authentically reflect the renal function. A recent animal study of a rat CKD model even demonstrated reductions in indoxyl sulfate accumulation in organs such as the kidney, heart, and liver [9]. In multiple animal CKD studies, AST-120 prevented proteinuria, glomerular hypertrophy, interstitial fibrosis, and CKD progression by interfering with the above-described mechanisms. Some studies even showed the amelioration of cardiovascular complications associated with uremia [3–7, 10, 11].

Clinical Use in Japan and Other Countries

AST-120 (6 g/day) is approved for progressive CKD patients in Japan, Korea, and the Philippines. In order to delay incident renal replacement therapy (RRT), it is best

prescribed in patients in whom an increase in sCr is more than moderate (1/sCr change greater than 0.01 dL/mg per month) before starting treatment [12]. It is better to validate the effect of AST-120 by the change in either sCr or uremic symptoms after the treatment for 6 months. The most frequent adverse events, which are reported in about 5% of the treated patients, are gastrointestinal symptoms such as constipation, appetite loss, and nausea.

Clinical Evidence to Support the Use of AST-120

A multi-center, double-blind placebo-controlled phase III study on AST-120 performed in Japan (244 progressive CKD patients, 124 in the AST-120 group and 120 in the placebo group; sCr 5–8 mg/dL) showed significant improvement in 1/sCr slope after 24 weeks of treatment (-0.0329 ± 0.0245 to -0.0222 ± 0.0378 dL/mg · week in AST-120 group vs. -0.0293 ± 0.0184 to -0.0274 ± 0.0279 dL/mg · week in placebo group), and improvement of uremic symptoms (nausea, anorexia, pruritus, and halitosis) from 2 weeks after the initiation of treatment (22% of patients in the AST-120 group vs. 8% in the placebo group; Table 1) [13]. The study duration was, however, too short to assess the renal hard endpoint, which is the time to renal death.

Another trial in Japan (sCr 5.8 ± 1.1 mg/dL, mean $\pm$ SD; 27 in the AST-120 group and 24 in the control group) evaluated the 1/sCr slope, the time for half of the patients to start RRT, and hematology [14]. AST-120 improved

Table 1. Outcomes of major clinical studies of AST-120

Author, year, Country	N analyzed	Inclusion criteria of sCr, mg/dL	Use of RAS inhibitor, %	Mean duration of treatment, months	Arm 1/arm 2	Main clinical outcomes	Limitation
Phase III, 1987, Japan	241	sCr: 5–8, Δ sCr 24 weeks ≥ 1.2	–	6	AST-120 6 g/day* Placebo 6 g/day*	1/sCr slope (10^{-5} dL/mg-week) before and after trial (-329 ± 245 to 222 ± 378 vs. -293 ± 184 to -274 ± 279 ; $p < 0.001$)	Short study duration to evaluate the hard end point
CAP-KD, 2009, Japan	460	sCr < 5 , $\Delta 1/\text{sCr} < 0$	100	14	AST-120 6 g/day + conventional therapy** Conventional therapy**	– Primary end point events 42 vs. 43 – Estimated creatinine clearance decrease – 0.12 vs. 0.15 mL/min/year; $p = 0.001$)	Infrequent primary end points than expected
EPPIC, 2014, multi (13 countries)	1,999	sCr: 2–5 (male), sCr: 1.5–5 (female), UP/Ucr ≥ 0.5	84.3	23.1 22.6	AST-120 9 g/day Placebo 9 g/day	Primary and end point 350 vs. 360 (HR 0.97, 95% CI 0.83–1.12)	Slower disease progression than expected (1/sCr slope -0.006 dL/mg per month instead of -0.01 dL/mg per month)
K-STAR, 2016, Korea	538	sCr 2–5, Expected Δ eGFR 6 months ≥ 2.5 or 12 months ≥ 5.0	90.5	36	AST-120 6 g/day Conventional therapy	Primary and end point 100 vs. 100 (HR 1.12; 95% CI 0.85–1.48; $p = 0.45$)	– Improvement of eGFR decline rate in both arms ← Possible effects of the detailed medical care – High exclusion rate (20%) – Potential inclusion of non-progressive CKD patients

* 4.2 g for the first 2 weeks; ** ACEI and/or ARB + low protein diet (0.8 g/day). UP/Ucr, Urinary creatinine ratio.

the 1/sCr slope in nondialysis CKD patients (-0.01004 ± 0.01012 to -0.00347 ± 0.0509 dL/mg/month in AST-120 group vs. -0.01251 ± 0.0856 dL/mg/month in control group) and the times for half of the patients to start RRT (14.3 months in AST-120 group vs. 5.0 months in control group). AST-120 also prevented anemia progression; RBC counts 360.6 ± 53.2 to $354.5 \pm 65.8 \times 10^4/\mu\text{L}$ during 6 months after AST-120 treatment, while 395.2 ± 61.7 to $360.6 \pm 53.2 \times 10^4/\mu\text{L}$ during 6 months before AST-120 treatment.

Multiple postmarketing physician-led prospective clinical trials have been performed on AST-120 and showed some beneficial effects [15–18]. The largest multicenter, randomized, controlled trial in Japan is the Carbonaceous Oral Absorbent's Effects on Progression of CKD (CAP-KD) study [19] (Table 1). After 48 weeks of

run-in period, 479 progressive CKD patients (sCr < 5.0 mg/dL) were randomized to AST-120 (6 g/day) plus conventional therapy (low-protein diet with an ACE inhibitor and/or ARB) or conventional therapy alone. The primary composite endpoint was sCr doubling, an increase in sCr ≥ 6.0 mg/dL, ESKD that requires RRT, or death. During the follow-up period of 56 weeks, there was no difference in composite primary endpoint between the 2 groups (42 for AST-120 group vs. 43 for control group). A decrease in estimated creatinine clearance, one of the secondary endpoints, was significantly less in the AST-120 group (-0.12 mL/min/year) than in control group (0.15 mL/min/year). The difference between the 2 groups spreads toward the end of the study. Other secondary outcomes including quality of life (QOL) score (SF-36) and proteinuria did not differ between the 2 groups. The lim-

itation of the study was that the primary end-point event rate was much less frequent than expected, partly due to an insufficient number of patients and a relatively a short period of treatment.

In the United States, the previously described randomized, double-blind, placebo-controlled phase II trial showed a decrease in uremia-related malaise by AST-120 (6 or 9 g/day) [8]. Other uremic symptoms, however, did not differ among the groups. The subsequent phase III trial, the Evaluating Prevention of Progression in CKD (EPPIC) trials, consisted of 2 double-blind, placebo-controlled trials performed in North America/Latin America and Europe in order to evaluate the efficacy of AST-120 (9 g/day) for retarding the progression of CKD [20] (Table 1). The primary end-point was a composite of RRT initiation and sCr doubling. A total of 2,035 moderate to severe CKD patients (sCr 2.0–5.0 mg/dL for men and 1.5–5.0 mg/dL for women) were randomly assigned (1,020 in EPPIC-1 and 1,015 in EPPIC-2). In both trials, most patients were white (80%), male (60%), stage 4 CKD patients on either ACE inhibitor or ARB. Forty percent of the patients had a history of diabetes. Each trial continued until 291 primary end points accrued. The time to primary end point did not reach any significant difference value (EPPIC-1: hazard ratio [HR] 1.03; 95% CI 0.84–1.27; $p = 0.78$; EPPIC-2: HR 0.91; 95% CI 0.74–1.12; $p = 0.37$). The actual median times to primary end points for the placebo groups were much longer (189.0 weeks for EPPIC-1 and 170.3 weeks for EPPIC-2) than the projected median time (124 weeks), which suggested unintended selection of patients leading to difficulty in detecting a difference. The differences in the estimated glomerular filtration rate (eGFR) changes from baseline between the 2 groups did not reach statistically significant values ($p = 0.93$) in EPPIC-1. However, they were significantly different in EPPIC-2 ($p = 0.004$) and in the pooled analysis ($p = 0.04$). It should be noted, however, that the difference is very small, and the difference becomes smaller toward the end of the study. In addition, regional differences in the initiation of dialysis were notable, which may have accounted for the results. In fact, in EPPIC-2, significant covariate-based differences were observed in the subgroup of the United States, in the time to the occurrence of the primary endpoint (HR 0.67; 95% CI 0.46–0.99; $p = 0.04$). The speculated reason for this to happen was that the event rate of the primary endpoint for placebo-treated US patients was similar to the projected rate. Whatever be the underlying reasons, the study did not support the benefit of AST-120 in addition to conventional therapy in moderate to severe CKD patients.

Recently, as reported in this issue by Cha et al. [21], the Kremezin Study Against Renal Disease Progression in Korea (K-STAR), a multi-center, randomized, open-label, controlled trial, was performed in patients with advanced CKD in Korea, to evaluate the long-term effect of AST-120 on CKD progression (Table 1). A total of 579 progressive CKD patients (sCr 2.0–5.0 mg/dL; measured or expected eGFR decline of ≥ 2.5 mL/min/1.73 m² over 6 months) were randomized after 2–6 months screening period to receive AST-120 (6 g/day) plus conventional therapy or conventional therapy alone. The primary outcome, which was a composite of sCr doubling, 50% reduction in eGFR, or the initiation of RRT, did not show any significant difference in the 2 arms during the 36-month follow-up study period (100 events in 272 patients in AST-120 arm and 100 events in 266 patients in control arm; HR 1.12; 95% CI 0.85–1.48; $p = 0.45$). None of the secondary outcomes including the decline in eGFR, changes in proteinuria, all-cause mortality, unplanned hospitalization, or changes in health-related QOL scores (SF-36) were significantly different between the 2 arms. In this study, the overall slope of eGFR decline in the AST-120 group compared to that of the control group was -1.47 (95% CI -6.55 to 3.61 ; $p = 0.57$). Limitations of the study include (1) the recruitment of some patients without an actual measurement of continuous eGFR decline over 6–12 months before the enrollment, and (2) a high drop rate (20% of the participants) from the study, both of which may have accounted for the lower event rate than expected in the study.

Limitation of Clinical Studies to Demonstrate the Benefits of AST-120 on CKD

Multiple prospective randomized clinical studies have been performed to demonstrate the benefits of AST-120 to slow CKD progression. Overall, results from recent large-scale studies have not proven unequivocal beneficial effects of AST-120. There seem to be some caveats, however, in interpreting the results of these studies. While some are specific to each clinical trial, others are shared; of particular note is that the actual decline of renal function during the study period was milder than expected from power calculation, thus rendering these studies underpowered. These studies clearly highlight the difficulty of calculating the sample size and/or the study duration to adequately evaluate the effect of a drug on renal hard endpoint. It is noteworthy that in some studies, a subset of patients seems to benefit from the AST-120 treatment;

a post hoc analysis of the EPPIC trials demonstrated that in patients with hematuria and proteinuria (more than 0.5 g/gCr in the presence of ACE inhibitors and/or ARB), AST-120 significantly reduced the event rate [22]. This suggests that the therapeutic benefits may derive from a distinct mechanism of action, including lowering levels of uremic solutes, such as indoxyl sulfate. It will be of great interest to identify AST-120 responders in patients with progressive CKD.

Conclusions

Uremic toxins have drawn great attention in the last couple of years based on the latest studies on the gut-microbiota-kidney axis. Tryptophan, which is abundantly present in a protein-rich diet, contributes to the accumulation of indole and its metabolite, indoxyl sulfate, in CKD patients. Animal studies support the therapeutic concept that the removal of indoxyl sulfate by AST-120 has beneficial effects in preventing the kidney

damage as well as systemic complications associated with uremia. A final proof of a therapeutic role for AST-120 requires large, prospective, randomized clinical trials, which have been unable to demonstrate unequivocal advantage so far, partly because of lower-than-expected event rates of preceding studies. Meanwhile, technology advances in metabolomics and next-generation sequencing may give some unbiased approaches to evaluate its effects on the CKD patients particularly susceptible to AST-120. Taken together, the treatment effect of AST-120 in CKD still remains a controversy, and physicians are required to carry out an individualized treatment plan for each CKD patient, in order to provide an optimal treatment to retard the progression of CKD and uremia-related complications, including cardiovascular disease.

Disclosure Statement

All authors declare no competing interests.

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