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Editorial

Prediction of Patients Who Can Benefit from Oral Intestinal Sorbent AST-120

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▸ See the article "Predictive Factors for Efficacy of AST-120 Treatment in Diabetic Nephropathy: a Prospective Single-Arm, Open-Label, Multi-Center Study" in volume 34, number 15, e117.

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Indoxyl sulfate (IS) increases the expression of fibrogenic genes while it impairs anti-oxidative systems and down-regulates Klotho expression in the kidney. AST-120, which adsorbs uremic toxins and precursors including indole, can decrease serum and urinary levels of IS, the levels of advanced glycation end products (AGEs), and 8-hydroxydeoxyguanosine while it increases the renal expression of Klotho. In addition to the improvement of glomerular sclerosis, serum creatinine levels, and the survival in chronic kidney disease (CKD) animal models, AST-120 alleviated uremic symptoms and slowed the progression of renal dysfunction through small clinical investigations. There have been large clinical studies using AST-120.[1-3] But they only recruited patients with advanced renal dysfunction and failed to prove the effectiveness of AST-120 except that Carbonaceous oral Adsorbent's effectiveness on Progression of CKD study showed less decrease of the estimated glomerular filtration rate (eGFR) in the AST-120 group.[1]

In this issue of the journal, Hwang et al.[4] reported the delay of renal dysfunction in the vast majority (80.3%) of participating patients with less advanced diabetic nephropathy (mean eGFR 35 mL/min/1.73 m^2) after 24 weeks of AST-120 treatment and suggested initial low diastolic blood pressure and the decrease of serum lipid peroxidation level as surrogate markers of the responsiveness to AST-120.

Per-protocol group analysis of Kremezin study against renal disease progression in Korea study showed that long-term use of AST-120 has potential for renal protection, especially in diabetic patients, as well as cardiovascular benefits.[5] In addition, reduction of the serum IS level showed the possibility of being used to identify patients who would benefit from AST-120 administration. As mentioned above, AST-120 treatment decreases serum and urinary levels of AGEs in CKD patients which induce cellular responses that include up-regulation of profibrogenic and proinflammatory cytokines leading to progressive nephropathies. The formation of AGEs is increased when there is hyperglycemia and oxidative stress, such as in uremic conditions. Furthermore, renal dysfunction increases the level of circulating AGEs due to both reduced clearance and increased formation. Since those effects are prominent in diabetic nephropathy, the responsiveness to AST-120 could be the favorable in patients with that condition, i.e., diabetic nephropathy. The post-hoc analysis also suggested that the alleviation of inflammation and oxidative stress via IS reduction reduces the urinary protein excretion and improves the prognosis.[5] Because AST-120 compliance was not different among

several serum IS change groups, patients' condition related to the serum IS responsiveness to AST-120 including inflammation and oxidative stress may have importance beyond the AST-120 compliance itself.

Evaluating Prevention of Progression In CKD (EPPIC) trial also indicated that the higher proteinuria and hematuria were more prevalent in patients with fast eGFR decline than in patients with slow eGFR decline.[2] And the post-hoc analysis of EPPIC study, recently released,[6] showed that additional treatment with AST-120 reduced the risk of achieving the primary endpoint in the hematuria-positive group taking angiotensin converting enzyme inhibitor (ACEi)/angiotensin receptor blockers (ARBs) at baseline. And patients with extremely rapid disease progression, who were hematuria positive with proteinuria > 1.0 g/day and taking ACEi/ARBs at baseline, also showed similar result.

Another small clinical trial showed that AST-120 treatment in CKD patients tended to be more effective in delaying the progression of renal dysfunction in the high eGFR (≥ 31.4 mL/min) group than in the low eGFR (< 31.4 mL/min) group.[7] And another study showed the greatest preservation of renal function in patients who had been receiving AST-120 the longest (> 30 months).[8] The time interval for AST-120 efficacy was 33 months in the per-protocol analysis of K-STAR trial, suggesting that the long-term AST-120 treatment may be beneficial for pre-dialysis CKD patients.[5] In addition, the actual median time to primary end points in EPPIC-1/-2 trials were 189.0 and 170.3 weeks which were much longer than the estimated median time (124 weeks).[2]

In conclusion, longer period of AST-120 treatment added to standard managements in patients at earlier stages of kidney disease, especially diabetic nephropathy, with the potential of rapid progression could be effective in delaying the progression of renal dysfunction. And the serum IS concentration change may have clinical significance as a marker for predicting renal disease progression while ingesting AST-120. Further prospective studies recruiting patients with CKD progression risk factors of diabetic nephropathy, higher proteinuria, and hematuria are required to confirm the effectiveness of AST-120.

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