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Authors
Kovesdy, CP
Lerma, E
Kalantar-Zadeh, K

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Guest Editorial

AST-120 for Preventing Progression of Chronic Kidney Disease: What Can We Conclude From the Available Evidence?

Csaba P. Kovesdy, MD; Edgar Lerma, MD; Kamyar Kalantar-Zadeh, MD, PhD

Dr. Kovesdy is with the Division of Nephrology, Salem Veterans Affairs Medical Center, Salem, and the Division of Nephrology, University of Virginia, Charlottesville, Virginia; Dr. Lerma is with the Department of Medicine, University of Illinois at Chicago College of Medicine, Chicago, Illinois; and Dr. Kalantar-Zadeh is with the Harold Simmons Center for Chronic Disease Research and Epidemiology, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, California and the David Geffen School of Medicine at UCLA, Los Angeles, California. Dr. Lerma is also a member of D&T's Editorial Advisory Board.

Treatment of chronic kidney disease (CKD) and its complications remains largely unresolved. Currently applied measures include blood pressure control and the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ACEIs/ARBs), which can slow down progression of CKD, but are unable to halt or reverse it, nor can they oppose uremic toxicity. There is hence an unmet need to find additional therapies for CKD and progressive uremia.

An additional treatment measure to slow the progression of CKD and mitigate azotemia is dietary protein restriction. The putative mechanisms of action responsible for its therapeutic effects include beneficial hemodynamic effects (lowering intraglomerular pressure similar to ACEIs/ARBs)[1] and the limitation of absorbable protein breakdown products, which could lead to the accumulation of uremic waste and consequent various deleterious effects. The down side of protein restriction is of course that it could also involve limiting the intake of useful or even essential nutrients and thus lead to protein-energy wasting, which in itself is associated with poor outcomes.[2] Hence the proper application of protein restriction needs concerted efforts both from a well-trained team of professionals and from highly dedicated patients.

An alternative dietary approach is to selectively prevent the gastrointestinal absorption of only certain components that are responsible for dietary protein-related harmful effects in patients with CKD. Several such components have been suggested, with various mechanisms of action responsible for their deleterious effect. Phosphorus has numerous adverse effects including direct vascular toxicity and an association with increased mortality and progression of CKD. Disappointingly, even though phosphorus is a plausible uremic toxin and treatment regimens have been established to treat its elevated levels, the mortality and morbidity benefits of lowering phosphorus have not yet been tested in clinical trials.

Potassium is also introduced through intestinal absorption, and the abnormally high or low levels that are common in patients with CKD have been linked to increased mortality. Similar to phosphorus, there are also no clinical trials proving the benefits of strategies to normalize serum potassium levels. Other potential uremic toxins linked directly or indirectly to intestinal absorption are advanced glycation end products, indoles and phenols, which have been linked to deleterious processes such as increased oxidative stress,[3] inflammation,[4] vascular[5] and renal[6] toxicity, and increased mortality.[5]

Of the various uremic toxins resulting from intestinal absorption and/or abnormal metabolism and excretion, indoxyl sulfate (IS) is one of the most frequently studied; the consequences of its elevated levels have been examined in a variety of in vitro, in vivo animal, and human observational and interventional studies. Increased levels of IS have been shown to induce oxidative stress, enhanced leukocyte adhesion and inflammation, endothelial toxicity and abnormal wound healing, parathyroid hormone resistance, inhibition of nitric oxide production, stimulation of vascular smooth muscle proliferation, reduction in klotho expression, and induction of cell senescence. Higher IS levels also promote kidney damage and progression of CKD.[7] In addition, higher IS levels have also been associated with vascular calcification and increased mortality in patients with CKD including ESRD.[5] The plethora of adverse effects that abnormally elevated IS levels have been linked to have increased interest to find interventions that lower IS levels.

Oral administration of the substance known as AST-120 (Kremezin, Kureha, Tokyo, Japan) has been shown to effectively lower IS levels,[8] and in animal models has resulted in amelioration of renal interstitial fibrosis, glomerular sclerosis, proteinuria, and endothelial dysfunction, as well as increased urinary nitric oxide levels; these effects tended to be proportionate to the lowering of IS.[7] Given the foregoing promising effects, AST-120 has been examined as a potential organ-protective treatment for patients with CKD; in Japan it has been approved as a remedy for uremic toxicity in patients with non-dialysis-dependent (NDD) CKD since 1991, and it is currently being examined for an indication to reduce progression of CKD in the United States (see clinicaltrial.gov, study numbers: NCT00500682 and NCT00501046).

Until the results of these latter clinical trials are available, it remains unclear whether the large-scale clinical application of AST-120 can indeed be beneficial in preventing progression to end-stage renal disease (ESRD) and/or mortality in CKD patients. Previous randomized controlled trials that showed benefits in this regard[8-13] have been too small to be used as unequivocal proof for the drug's efficacy and safety. A larger clinical trial examined 460 patients with advanced NDD CKD (mean creatinine clearance 22 mL/min) and failed to find a significant benefit in lowering a composite outcome of death, ESRD

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or doubling of serum creatinine,[14] but the event rates were relatively small, and hence the study could have been underpowered for the detection of smaller differences.

Another way to gain insight into the clinical benefits of a medication besides performing lengthy and expensive randomized controlled trials is by pharmacoepidemiologic methods, utilizing data accumulated in the course of routine clinical practice. Since AST-120 has been used in the treatment of NDD CKD in Japan for almost two decades, observational studies have described beneficial effects on delaying progression of kidney disease[15,16] and on mortality after the initiation of dialysis.[17] In a similar study in the current issue of *D&T*, Maeda et al. examined cumulative dialysis initiation rates and changes in estimated glomerular filtration rate (GFR) before and after treatment in a case cohort of patients who were matched according to propensity scores.[18] Fifty-six patients took AST-120 and 56 did not. Both end points indicated a significantly favorable effect associated with AST-120 use, in concordance with the previous observational studies.[15-17]

While the study by Maeda et al.[18] strengthens the knowledge gained from other observational studies, it also has a number of limitations. The small number of patients and the single-center nature of the study limit its generalizability. The patients were not randomly assigned to AST-120 vs. placebo; hence the better outcomes seen in the former group may be due to selection bias. The use of propensity scores mitigates this limitation somewhat, but only to the extent that factors influencing physicians' choice to initiate treatment with AST-120 are fully known and are included in the propensity score; the presence of both of these prerequisites is uncertain at best in the study by Maeda et al.[18] Consequently, these results should be greeted with cautious optimism. The introduction of an effective treatment to lower progression of CKD and/or mortality in CKD is long overdue, but one needs to consider the shortcomings of observational studies (see above), which do not allow us to conclude that the results reported by Maeda et al.[18] are proof of AST-120's clinical efficacy. Such proof can only come from clinical trials, and the negative results of one such trial[14] should make us pause before we jump to premature conclusions. The debate about the efficacy of AST-120 will likely conclude after the publication of the clinical trials that are currently still in progress. Until then, we should regard this therapy as promising, but not yet proved. D&T

References

1. King AJ, Levey AS. Dietary protein and renal function. *J Am Soc Nephrol.* 1993;3:1723-1737.
2. Kovesdy CP, George SM, Anderson JE, Kalantar-Zadeh K. Outcome predictability of biomarkers of protein-energy wasting and inflammation in moderate and advanced chronic kidney disease. *Am J Clin Nutr.* 2009;90:407-414.
3. Schepers E, Meert N, Glorieux G, Goeman J, Van der Eycken J, Vanholder R. P-cresylsulphate, the main in vivo metabolite of p-cresol, activates leucocyte free radical production. *Nephrol Dial Transplant.* 2007;22:592-596.
4. Witko-Sarsat V, Friedlander M, Nguyen KT, et al. Advanced oxidation protein products as novel mediators of inflammation and monocyte activation in chronic renal failure. *J Immunol.* 1998;161:2524-2532.
5. Barreto FC, Barreto DV, Liabeuf S, et al. Serum indoxyl sulfate is associated with vascular disease and mortality in chronic kidney disease patients. *Clin J Am Soc Nephrol.* 2009;4:1551-1558.
6. Motojima M, Nishijima F, Ikoma M, et al. Role for "uremic toxin" in the progressive loss of intact nephrons in chronic renal failure. *Kidney Int.* 1991;40:461-469.
7. Niwa T. Indoxyl sulfate is a nephro-vascular toxin. *J Ren Nutr.* 2010;20:S2-S6.
8. Niwa T, Nomura T, Sugiyama S, Miyazaki T, Tsukushi S, Tsutsui S. The protein metabolite hypothesis, a model for the progression of renal failure: an oral adsorbent lowers indoxyl sulfate levels in undialyzed uremic patients. *Kidney Int Suppl.* 1997;62:S23-S28.
9. Konishi K, Nakano S, Tsuda S, Nakagawa A, Kigoshi T, Koya D. AST-120 (Kremezin) initiated in early stage chronic kidney disease stunts the progression of renal dysfunction in type 2 diabetic subjects. *Diabetes Res Clin Pract.* 2008;81:310-315.
10. Nakamura T, Kawagoe Y, Matsuda T, et al. Oral ADSORBENT AST-120 decreases carotid intima-media thickness and arterial stiffness in patients with chronic renal failure. *Kidney Blood Press Res.* 2004;27:121-126.
11. Owada A, Shiigai T. Effects of oral adsorbent AST-120 concurrent with a low-protein diet on the progression of chronic renal failure. *Am J Nephrol.* 1996;16:124-127.
12. Shoji T, Wada A, Inoue K, et al. Prospective randomized study evaluating the efficacy of the spherical adsorptive carbon AST-120 in chronic kidney disease patients with moderate decrease in renal function. *Nephron Clin Pract.* 2007;105:c99-107.
13. Yorioka N, Ito T, Masaki T, et al. Dose-dependent effect of an oral adsorbent, AST-120, in patients with early chronic renal failure. *J Int Med Res.* 2002;30:467-475.
14. Akizawa T, Asano Y, Morita S, et al. Effect of a carbonaceous oral adsorbent on the progression of CKD: a multicenter, randomized, controlled trial. *Am J Kidney Dis.* 2009;54:459-467.
15. Sanaka T, Fujimoto K, Niwayama J, et al. Effect of combined treatment of oral sorbent with protein-restricted diet on change of reciprocal creatinine slope in patients with CRF. *Am J Kidney Dis.* 2003;41:S35-S37.
16. Ueda H, Shibahara N, Takagi S, Inoue T, Katsuoka Y. AST-120, an oral adsorbent, delays the initiation of dialysis in patients with chronic kidney diseases. *Ther Apher Dial.* 2007;11:189-195.
17. Ueda H, Shibahara N, Takagi S, Inoue T, Katsuoka Y. AST-120 treatment in pre-dialysis period affects the prognosis in patients on hemodialysis. *Ren Fail.* 2008;30:856-860.
18. Maeda K, Hamada C, Hayashi T, et al. Efficacy of adsorbent in delaying dialysis initiation among chronic kidney disease patients. *Dial Transplant.* 2011;40:212-216.