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Case Report

Importance of AST-120 (Kremezin®) Adherence in a Chronic Kidney Disease Patient with Diabetes

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Keywords
Chronic kidney disease · Diabetic kidney disease · AST-120

Abstract
We report herein an adult case of chronic kidney disease (CKD) associated with diabetes. The patient had been treated with insulin injection for diabetes 10 years ago. At the time of his first visit to our division for further examinations, we diagnosed him as CKD: cause (C) diabetes; glomerular filtration rate (GFR) (G) G5 (estimated [e] GFR, 10.2 mL/min/1.73 m^2; serum creatinine of 4.90 mg/dL); and albuminuria (A) A3 (2.62 g/gCr) by the Japanese Society of Nephrology (JSN) CGA classification. Because he had complained of severe constipation and kidney function, i.e., eGFR was not improved by previous medications, we added on a minimal dosage (2 g/day) of AST-120 (Kremezin®; ordinary dose 6 g/day). After 3 months of AST-120 therapy, eGFR was increased to 17.8 mL/min/1.73 m^2 (serum creatinine of 2.90–2.72 mg/dL). Although the patient used some laxative products, he could not continue to take Kremezin and completely stopped 8 months after starting this drug. Kidney function then abruptly declined and progressed to end-stage kidney disease (ESKD). In June 2017, he was introduced to hemodialysis. It appears that the adherence of Kremezin is very important for inhibiting the progression to ESKD for patients with CKD with diabetes.

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Case Report

We report the case of a 67-year-old male with kidney dysfunction. His past medical history included thyroidectomy due to hyperthyroidism at the age of 30 years. In 2006, the patient was admitted to our hospital for cerebral infarction, diabetes, hypertension, hyperuricemia, and dyslipidemia. Since that time, the patient had been prescribed the following medicines: levothyroxine sodium hydrate, 25 μg/day; amlodipine basilate OD, 5 mg/day; valsartan, 160 mg/day; feburostat, 10 mg/day; and atorvastatin calcium hydrate, 5 mg/day. Rapid types of insulin, such as the 16-unit Novo RapidN and the 10-unit Novolin RN had been used. The levels of uric acid are 4.90 mg/dL, and blood pressure was 140/70 mm Hg. The levels of FT3, FT4, TSH, and total cholesterol and triglyceride were within normal limits. An ophthalmologist diagnosed him with diabetic proliferative retinopathy and performed photocoagulation therapy. In November 2015, a serum urea nitrogen level of 56.0 mg/dL, a serum creatinine (s-Cr) level of 3.9 mg/dL and an estimated glomerular filtration rate (eGFR) of 13.4 mL/min indicated renal dysfunction at another division.

Due to a recent increase in frothy urine, the patient was transferred to our nephrology division for a further treatment. At the time of the first visit to our division, body height was 160 cm and weight was 68 kg (BMI: 26.6). He showed slight obesity (obesity criteria in Japan: a BMI of more than 25.0). Laboratory data from the time of his first visit to our division in March 2016 showed a fasting plasma glucose level of 121 mg/dL and a HbA1c (national and glycohemoglobin standardization program: NGSP) of 6.9%. Thus, we moved him to a DPP-4 inhibitor, i.e., saxagliptin hydrate of 5 mg/day. High-density urine and a strongly positive proteinuria quantified at 2.62 g/gCr were found. Urine ketone bodies were negative, and there was a negative urine occult blood reaction, which resulted in a clinical diagnosis of diabetic nephropathy. The frothy (with small bubbles) urine meant that there was a high dose of protein in the urine. A serum urea nitrogen level of 60.7 mg/dL, a s-Cr level of 4.9 mg/dL, and an eGFR of 10.2 mL/min showed a progressive renal dysfunction. Antiglutamic acid decarboxylase antibodies in sera were negative (normal value: <1.5 U/mL).

In the Japanese Society of Nephrology (JSN) classification, the causal disease, eGFR, and albuminuria (proteinuria) levels have to be determined. eGFR is divided into 5 stages, from GFR 1 to 5, and albuminuria (proteinuria) is divided into 3 stages, from A1 to 3, as shown in Figure 1. According to this classification, he was diagnosed as follows; chronic kidney disease (CKD); cause diabetes (type 2); GFR G5, (eGFR range: <15 min/mL); and albuminuria, A3 (albuminuria range: >300 mg/gCr). A definite diagnosis of diabetic nephropathy could not be made without renal biopsy. Kidney function, i.e., eGFR, was not improved by previous medications. We added on a minimal dosage of AST-120 (Kremezin®) of 2 g/day because of his severe constipation. After 3 months of AST-120 therapy, eGFR increased to 18.1 mL/min/1.73m^2 (with a s-Cr of 2.90–2.72 mg/dL). Although he used some laxative products (senna 1 g/day and sennnoside 12 mg/day), he could not continue to take AST-120 and then completely stopped the drug 8 months after starting. Kidney function then abruptly declined (eGFR of 7.3 mL/min/1.73 m^2; s-Cr of 6.7 mg/dL) and progressed to end-stage kidney disease (ESKD), as shown in Figure 2. In June 2017, he was introduced to hemodialysis (HD).

Discussion

In 1982, an oral carbonaceous adsorbent (AST-120, Kremezin) for the gastrointestinal tract was developed by the Kureha Company in Japan. It consists of black spherical particles

0.2–0.4 mm in diameter. Composed mainly of carbon (approximately 96%), AST-120 exhibits a superior adsorption ability for certain acidic and basic organic compounds that are known to be increased in ESKD patients. AST-120 is an orally administered adsorbent that was approved for prolonging the time to initiation of HD and improving uremic symptoms in CKD patients [1, 2]. Long-term use and early treatment of AST-120 has the potential for renal protection, especially in diabetic patients, as well as cardiovascular benefits [3]. Reduction of the serum indoxyl sulfate (small-molecules <500 D: protein-bound) level may be used to identify patients who would benefit from AST-120 administration. A marked improvement was observed in patients with chronic glomerulonephritis (mainly IgA nephropathy), diabetic nephropathy, or hypertensive nephrosclerosis [2]. Results from a subgroup analysis of the EPPIC-pooled ITT (intention-to-treat) population demonstrated the effect of AST-120 on the prolongation of the time to the event in CKD patients. These results suggest that AST-120 has an effect when added to current standard care, including treatment with renin angiotensin system inhibitors. It is indicated that a greater effect was observed with good drug compliance in a subanalysis of EPPIC 1 and 2 trials [4–6]. However, the drug adherence of Kremezin is generally low in Japan. About 70% of the patients in Japan have adherence problems with AST-120, the resolution of which is a big issue. Thus, we performed a Kremezin Adherence Supporting Program for hundred days (KRASP-study) for CKD patients in the Juntendo University Hospital, Tokyo, Japan [7]. It is suggested that a long-term AST-120 medication in outpatient clinic as well as better responders for the support program were related to the drug adherence [7]. There are some side effects of this drug, such as constipation, appetite loss, nausea, and vomiting. Oblate-coated AST-120 or orally disintegrated (newly developed rapid collapse) AST-120 tablet with a lot of water may improve some adherence problems. Among them, a major severe side effect of this drug is constipation. Although this patient used some laxative products for a long time (about 10 years), he could not continue to take AST-120 due to severe constipation and then completely stopped the drug 8 months after starting. Thereafter, kidney function abruptly declined and then progressed to ESKD when he was introduced to HD. It appears that the adherence of AST-120 (Kremezin) is very important to inhibit the progression to ESKD for patients with CKD, such as diabetic nephropathy.

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Statement of Ethics

The authors have no ethical conflicts to declare

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

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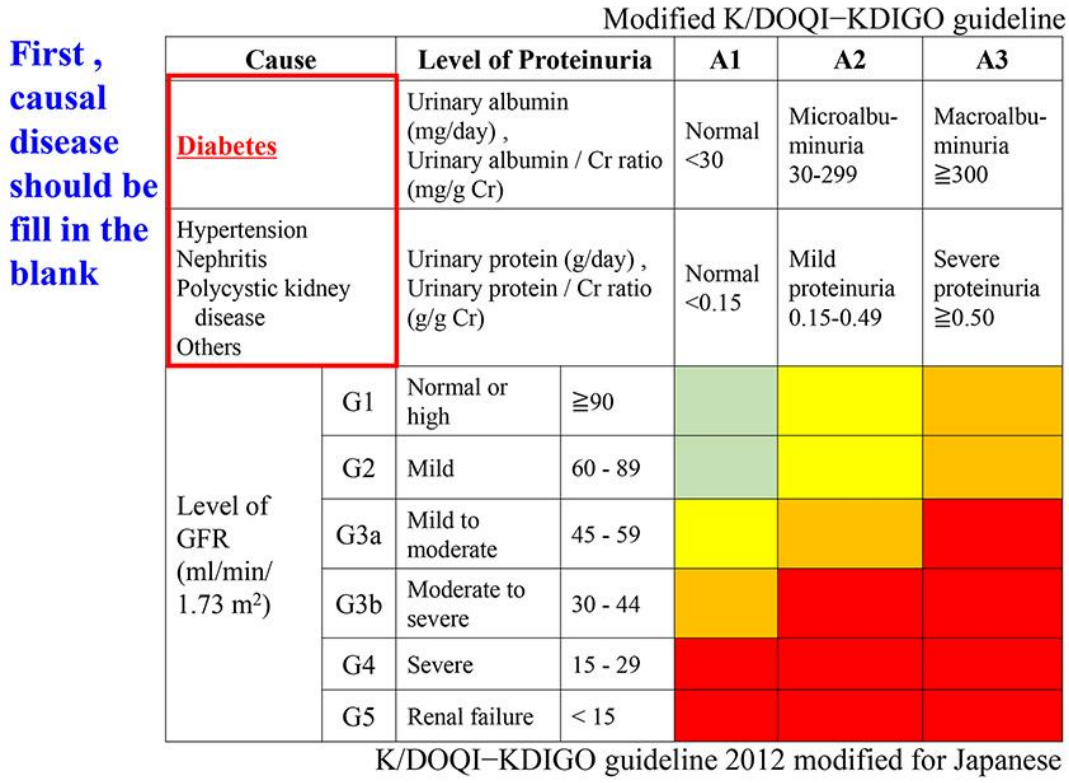

Fig. 1. New CKD (CGA) classification in Japan.

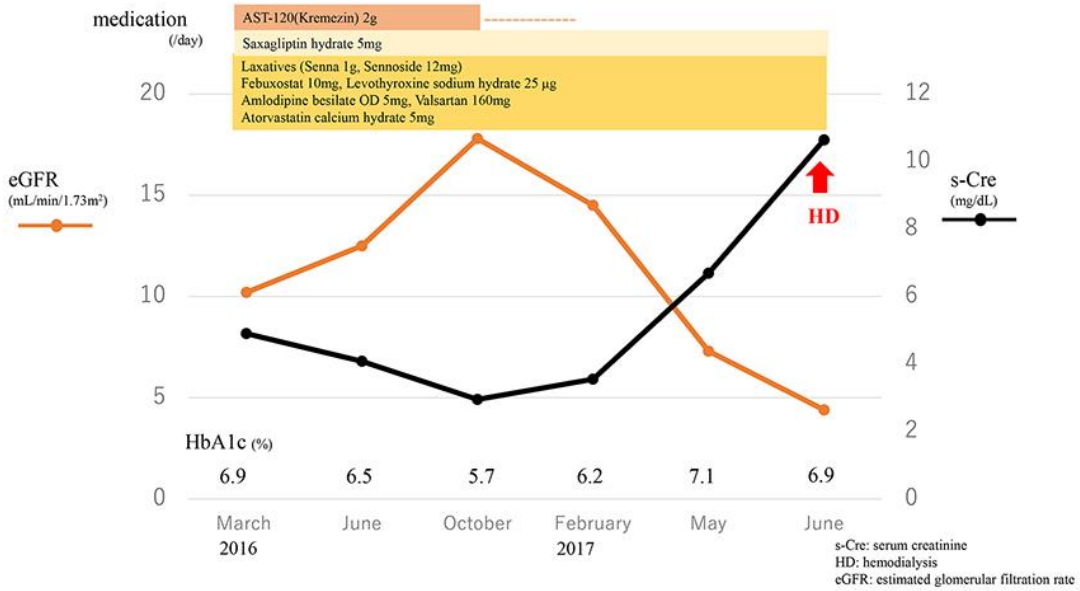

Fig. 2. Clinical course of this patient after starting AST-120 treatment.