Original Article
Yonsei Med J 2021 Jan;62(1):41-49
https://doi.org/10.3349/ymj.2021.62.1.41
Yonsei Medical Journal
YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

Comparison of Different Types of Oral Adsorbent Therapy in Patients with Chronic Kidney Disease: A Multicenter, Randomized, Phase IV Clinical Trial

Youn Kyung Kee[1], Sang Youb Han[2], Duk-Hee Kang[3], Jung Woo Noh[4], Kyung Hwan Jeong[5], Gheun-Ho Kim[6], Yang Wook Kim[7], and Beom Seok Kim[8]

[1]Department of Internal Medicine, Kangdong Sacred Heart Hospital, Seoul;
[2]Department of Internal Medicine, Ilsan-Paik Hospital, Inje University College of Medicine, Goyang;
[3]Division of Nephrology, Department of Internal Medicine, Ewha Womans University School of Medicine, Ewha Medical Research Center, Seoul;
[4]Department of Internal Medicine, Kangnam Sacred Heart Hospital, Hallym University College of Medicine, Seoul;
[5]Division of Nephrology, Department of Internal Medicine, Kyunghee University, Seoul;
[6]Division of Nephrology, Department of Internal Medicine, Hanyang University College of Medicine, Seoul;
[7]Department of Internal Medicine, Haeundae Paik Hospital, Inje University College of Medicine, Busan;
[8]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea.

Purpose: Oral adsorbents delay disease progression and improve uremic symptoms in patients with chronic kidney disease (CKD). DW-7202 is a newly developed oral adsorbent with high adsorptive selectivity for uremic toxins. We evaluated patient preference for and adherence to DW-7202 versus AST-120 therapy and compared treatment efficacy and safety in patients with pre-dialysis CKD.

Materials and Methods: A seven-center, randomized, open-label, two-way crossover, active-controlled, phase IV clinical trial was conducted. Patients with stable CKD were randomly assigned to receive DW-7202 (capsule type) or AST-120 (granule type) for 12 weeks. The groups then switched to the other adsorbent and took it for the next 12 weeks. Patient preference was the primary outcome. Secondary outcomes included changes in estimated glomerular filtration rate (eGFR) and serum creatinine, cystatin C, and indoxyl sulfate (IS) levels.

Results: Significantly more patients preferred DW-7202 than AST-120 (p<0.001). Patient adherence improved after switching from AST-120 to DW-7202; there was no apparent change in adherence after switching from DW-7202 to AST-120. Changes in eGFR and serum creatinine, cystatin C, and IS levels were not significantly different according to adsorbent type. There was also no significant difference in the incidences of adverse events during treatment with DW-7202 and AST-120.

Conclusion: DW-7202 can be considered as an alternative to AST-120 in patients who cannot tolerate or show poor adherence to granule type adsorbents. Further studies to evaluate factors affecting patient preferences and improved adherence are warranted (Clinical trial registration No. NCT02681952).

Key Words: Chronic kidney disease, AST-120, DW-7202, preference, adherence

INTRODUCTION

Chronic kidney disease (CKD) is an increasing global health problem.[1] In Korea, the prevalence of CKD was 8.2% from 2011 to 2013 according to the Korean National Health and Nutrition Examination Survey, and it is steadily growing.[2] As CKD has be-

Received: March 23, 2020 **Revised:** July 23, 2020 **Accepted:** August 3, 2020
Corresponding author: Beom Seok Kim, MD, PhD, Department of Internal Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemoon-gu, Seoul 03722, Korea. Tel: 82-2-2228-1969, Fax: 82-2-393-6884, E-mail: DOCBSK@yuhs.ac

•The authors have no potential conflicts of interest to disclose.

come more common, the number of patients with end-stage renal disease (ESRD) has also rapidly increased.[3,4] Because the cost of ESRD treatment, including dialysis and kidney transplantation, is quite high and constantly rising, it has become a serious social problem in many countries.[5] Therefore, preventing or slowing disease progression at the earliest stage possible is important in the treatment of patients with CKD.

Previous studies have shown that management of factors associated with renal deterioration, such as high blood pressure (BP), uncontrolled diabetes, and proteinuria, could delay disease progression.[6-8] Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are considered important agents that slow disease exacerbation through their renoprotective effects.[9,10] However, disease progression is not completely prevented, and many patients with CKD develop ESRD. Therefore, a new therapeutic option with a different mechanism is needed in this population.

Serum levels of indoxyl sulfate (IS), a uremic toxin, are elevated in patients with CKD and appear to be correlated with disease progression.[11] Oral carbon adsorbents may reduce circulating uremic toxins including IS and delay renal deterioration.[12] AST-120 (Kremezin®, Kureha Chemical Industry Co., Ltd., Tokyo, Japan), a granule type adsorbent, was approved in 1991 for delaying the initiation of dialysis and improving uremic symptoms in patients with CKD.[13-17] Despite its potential effects, the clinical use of AST-120 has some limitations: many patients find AST-120 difficult to tolerate because of its unpleasant texture and taste. It is also difficult to take the exact prescribed amount because of granule retention in the oral cavity and because of drug loss that occurs when packing the granules in a wrapper. Further, there is an additional cost for purchasing the wrapper used to assist consumption of the granules. These limitations could reduce patient adherence to granule adsorbent treatment, which could, in turn, reduce drug efficacy.

DW-7202 (Renamezin®, Daewon Pharmaceutical Co., Ltd., Seoul, Korea) is a new oral adsorbent developed using a furan resin-based formula, unlike the phenol-based formula used in existing oral adsorbents. We conducted a phase IV clinical trial to evaluate patient preference for and adherence to DW-7202 versus AST-120 therapy and to compare the efficacy and safety of the two oral adsorbents in patients with pre-dialysis CKD.

MATERIALS AND METHODS

Study design

We performed a prospective, randomized, open-label, active-controlled, two-way crossover study in patients aged 20–75 years with pre-dialysis CKD in seven medical facilities in Korea between December 2015 and December 2016. All subjects provided written consent before participating. The trial was registered on Clinical Trials.gov (NCT02681952), and the study start date was February 15, 2016. Sample size calculation was conducted to determine the number of participants who would prefer a capsule type adsorbent to a granule type adsorbent. Assuming a preference for the capsule type of 65%, we selected 114 subjects under the following conditions: 5% α error (two-sided) and 90% statistical power. We finally set the number of subjects at 152 (76 patients per group) to compensate for a dropout rate of 25%.

Fig. 1 shows the study design. After a 4-week screening period, we used a computer-generated randomization process (SAS 9.4 software; SAS Institute, Cary, NC, USA) to randomly allocate subjects who satisfied the final selection criteria into two groups (1:1 ratio). One group received the capsule type adsorbent, DW-7202 (capsule to granule group), and the other received the granule type adsorbent, AST-120 (granule to capsule group). After 12 weeks, participants switched to the other type of adsorbent for the next 12 weeks. The dose of the capsule type adsorbent was seven capsules (2 g) three times daily (21 capsules/day). The dose of the granule type adsorbent was one pack (2 g) three times daily. Written informed consent was obtained from all enrolled individuals in line with the Declaration of Helsinki. The study's protocol was reviewed and approved by the Institutional Review Boards of the clinical trial centers of each participating institution (Hallym University, Ilsan-Paik Hospital of Inje University, Ewha Womans University, Kyunghee University, Hanyang University, Haeundae-Paik Hospital of Inje University, and Yonsei University). The methods were carried out in accordance with the approved guidelines.

Study drugs

DW-7202 consists of black spherical carbon particles approximately 0.2 to 0.5 mm in diameter. The particles are produced from a furan resin-based formula and have a porous structure, which determines the adsorption properties. The DW-7202 used in this study was provided as a capsule containing 285.7 mg per capsule. Patients took seven capsules to achieve a dose of 2 g. AST-120 also consists of black spherical carbon particles; however, it is produced from a phenol-based formula. The AST-120 used in this study was provided as a granule pack containing 2 g. Patients consumed the entire granule pack (2 g) for one dose. The same dosage was used for both adsorbents because previous in vivo experiments showed that the adsorption capacity of DW-7202 was equivalent to that of AST-120 (Supplementary Table 1, only online) and that the ability of DW-7202 to reduce serum levels of IS was also equivalent to that of AST-120 (Supplementary Fig. 1, only online) (unpublished data).

Participants

We reviewed outpatient medical records at participating facilities to identify eligible patients. Eligibility criteria included a stable serum creatinine level (2.0–5.0 mg/dL) and estimated glomerular filtration rate (eGFR, 15–60 mL/min/1.73 m^2) in

https://doi.org/10.3349/ymj.2021.62.1.41

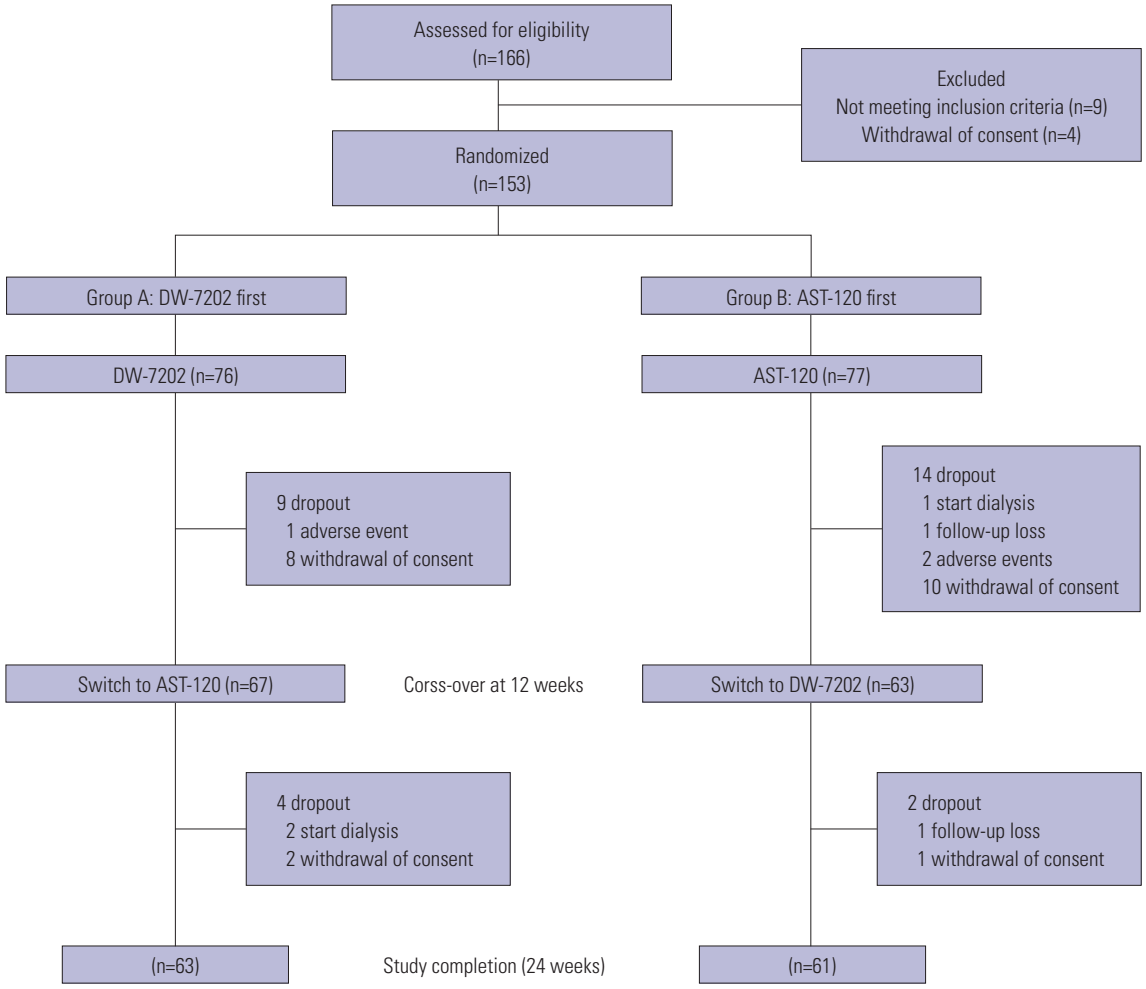

Fig. 1. Study design and subject disposition: 153 patients were randomly assigned.

the 3-month pre-screening period, no change in CKD treatment in the 4-week pre-screening interval, and no expected care plan change during the study. Eligible patients were excluded if they met any of the following conditions during the subsequent 4-week screening period: 1) uncontrolled diabetes [hemoglobin A1c (HbA1c) >10% or fasting glucose >180 mg/dL]; 2) uncontrolled hypertension (systolic BP ≥170 mm Hg or diastolic BP ≥100 mm Hg); 3) current infection; 4) hepatic impairment (2.5 times greater than the upper limit of normal aspartate aminotransferase or alanine aminotransferase levels); 5) required immunosuppressive agents or kidney transplant; 6) hospitalized with cardiovascular disease within 3 months before screening; 7) inadequate CKD treatment before screening; 8) malignant tumor; 9) pregnant, lactating, or had a chance of becoming pregnant during the study; 10) drug or alcohol dependency; 11) taking an oral adsorbent for 3 months before screening; 12) participation in another clinical study or receiving another study drug; 13) expected to start dialysis within 3 months; 14) uncontrolled constipation, peptic ulcer disease, or esophageal varix; and 15) gastrointestinal tract obstruction.

Preference, efficacy, safety, and adherence assessments

Patient preference was the primary outcome and was assessed using a questionnaire after the two 12-week periods of drug administration. Participants were asked, "Which of the two types of adsorbents do you prefer?" They selected one of the following answers, taking their overall satisfaction into account: no difference, capsule type of adsorbent, or granule type of adsorbent. We evaluated drug efficacy by analyzing changes in clinical variables (serum creatinine, IS, cystatin C, and eGFR) after the first 12-week period. Overall treatment satisfaction was determined using a patient global assessment (PGA) scale, which included five categories: very bad, bad, neutral, good, and very good. Changes in subjective symptoms (anorexia, halitosis, nausea, itching, and edema) and PGA scale ratings at the end of the first and second 12-week periods were also evaluated as efficacy parameters (secondary outcomes). The results were summarized according to whether the subjective symptoms and PGA scale ratings were better or worse after the second 12-week period, compared to those after the first 12-week period.

Safety was evaluated by investigating the incidence and types

of adverse events associated with the administration of each adsorbent. Additionally, vital sign measurements, laboratory tests, and physical examinations were conducted at the end of both 12-week periods to evaluate medication safety. Patient adherence to drug treatment was assessed by using the pill count technique and estimated by comparing the expected amount of drug remaining with the actual amount participants brought to the evaluation at the end of each 12-week period.

Data collection

Baseline demographic data, including age, sex, BP, medical history, and current medications, were obtained at the start of the first 12-week period. Laboratory tests for hemoglobin, electrolytes, uric acid, albumin, total cholesterol, triglycerides, high-density lipoprotein cholesterol, HbA1c, serum creatinine, cystatin C, and IS were also carried out at that time. We calculated eGFR using the Modification of Diet in Renal Disease equation.[18] Serum creatinine, cystatin C, IS, and eGFR were re-checked after the first and second 12-week periods to assess drug efficacy. The four serum variables were analyzed by an outside laboratory (Seoul Central Laboratory, Seoul, Korea) to minimize measurement bias.

Statistical analyses

We performed our safety analysis in the group of participants who took a study medication at least once after group allocation (the safety population). Inter-group comparisons of baseline demographic and laboratory data were conducted using Student's t-test for numerical variables and Fisher's exact test or a chi-squared test for categorical variables. Patient preference was analyzed using the Cochran-Mantel-Haenszel test to control for institutional differences in patient preference. In analyses of efficacy using clinical variables, the treatment effect of each type of adsorbent was compared using the Wilcoxon-signed rank test. For other efficacy analyses, McNemar's test or Prescott's test was used to evaluate the significance of differences in changes in subjective symptoms or PGA scale ratings in both groups. Statistical significance was defined as a two-tailed p value less than 0.05. All analyses were performed using SAS version 9.4 software.

RESULTS

Baseline characteristics

Recruitment began in December 2015, and the study ended in December 2016 (the last day on which a participant was seen). Of the 166 patients screened at seven study centers, 153 (male, 65%; mean age, 57.1 years) met the inclusion criteria and were randomly assigned to group A (n=76, administration of DW-7202 followed AST-120) and group B (n=77, administration of AST-120 followed DW-7202). Twenty-three patients (group A, n=9; group B, n=14) dropped out during the first 12-week period, and 6 (group A, n=4; group B, n=2) dropped out during the second. One hundred twenty-four patients completed the study (81.0%; group A, n=63; group B, n=61). Baseline characteristics and laboratory data of the study subjects are shown in Table 1 and Table 2, respectively. There were no significant differences in demographic and clinical characteristics between the two groups. Stage 3 or 4 CKD was present in 96% of all subjects, and there was no significant difference between the two groups in terms of CKD stage distribution. There were also no significant differences in baseline laboratory data between the two groups.

Preference

Results of the preference analyses are presented in Fig. 2. Preference analyses were conducted in the full analysis set (FAS, the group of patients who received at least one dose of the assigned drug and whose data on the primary outcome could be obtained). One hundred and nineteen patients expressed a drug preference, and the group that preferred DW-7202 (65.5%) was significantly larger than the group that preferred AST-120 (34.5%) (p<0.001).

Efficacy

Fig. 3 shows the results of our efficacy analyses. Due to the limitations of a crossover study, we evaluated the changes in clinical variables between 0 and 12 weeks. After the first 12-

Table 1. Baseline Characteristics of the Study Subjects

Variables	Total (n=153)	Group A (n=76)	Group B (n=77)	p value
Age (yr)	57.1±11.4	57.8±10.0	56.4±12.6	0.453
Male sex	100 (65.4)	53 (69.7)	47 (61.0)	0.258
SBP (mm Hg)	129.2±13.2	129.5±13.1	128.9±13.4	0.816
DBP (mm Hg)	74.8±9.1	74.4±9.7	75.2±8.6	0.583
Hypertension	128 (84.8)	67 (88.2)	61 (81.3)	0.174
Diabetes	67 (44.4)	33 (43.4)	34 (45.3)	0.471
Medications				
RAS blocker	127 (83.0)	66 (86.8)	61 (79.2)	0.149
CCB	53 (34.6)	26 (34.2)	27 (35.1)	0.523
β-blocker	45 (29.4)	23 (30.3)	22 (28.6)	0.479
Diuretics	28 (18.3)	12 (15.8)	16 (20.8)	0.278
Statin	93 (60.8)	50 (65.8)	43 (55.8)	0.137
CKD stage				0.502
Stage 2	1 (0.7)	0 (0.0)	1 (1.3)	
Stage 3	94 (61.4)	48 (63.2)	46 (59.7)	
Stage 4	53 (34.6)	27 (35.5)	26 (33.8)	
Stage 5	5 (3.3)	1 (1.3)	4 (5.2)	

SBP, systolic blood pressure; DBP, diastolic blood pressure; RAS blockers, renin-angiotensin system blocker; CCB, calcium channel blocker; CKD, chronic kidney disease.
Data are presented as a mean±standard deviation or number (%). Group A: administration of DW-7202 followed AST-120, group B: administration of AST-120 followed DW-7202.

https://doi.org/10.3349/ymj.2021.62.1.41

week period, the changes in serum creatinine, cystatin C, and eGFR were not significantly different between group A and group B. Serum IS levels were significantly lower after the first 12-week period in both groups, and there was no significant between-group difference in the magnitude of this change (25.8% decrease in group A and 24.2% decrease in group B). Table 3 shows the change in subjective symptoms and PGA scale ratings in each group. Subjective symptoms evaluated after 12 and 24 weeks were unchanged in most patients, and there were no significant between-group differences in the proportion of patients who showed subjective symptom improvement or worsening. PGA scale ratings assessed after 12 and 24 weeks were also unchanged in most patients in both groups. Furthermore, the proportion of patients whose PGA scale ratings changed was not significantly different between the groups. All of the above efficacy analyses were also performed in the per protocol set that included only subjects without major protocol violations (n=111), and the results were the same as those in the FAS cohort.

Table 2. Laboratory Data of Study Subjects

Variables	Total (n=153)	Group A (n=76)	Group B (n=77)	*p* value
Hemoglobin (g/dL)	12.5±1.9	12.6±1.9	12.3±1.9	0.245
Sodium (mEq/L)	140.3±2.2	140.4±2.1	140.3±2.4	0.821
Potassium (mEq/L)	4.8±0.5	4.7±0.5	4.8±0.5	0.466
Uric acid (mg/dL)	6.9±1.9	6.9±1.9	6.9±1.8	0.788
Albumin (g/dL)	4.1±0.4	4.1±0.4	4.0±0.4	0.791
Total cholesterol (mg/dL)	175.7±37.0	175.7±39.5	175.7±34.7	0.999
Triglyceride (mg/dL)	161.3±103.6	151.8±79.6	170.7±122.6	0.259
HDL-cholesterol (mg/dL)	47.6±13.8	47.8±14.6	47.5±12.9	0.876
HbA1c (%)	6.2±1.1	6.3±1.1	6.2±1.0	0.668
Cystatin C (mg/dL)	2.1±0.6	2.1± 0.6	2.1±0.7	0.840
Indoxyl sulfate (mg/dL)	0.33±0.25	0.32± 0.21	0.34± 0.28	0.549
Creatinine (mg/dL)	2.14±0.70	2.18± 0.75	2.10± 0.66	0.493
eGFR (mL/min/1.73 m^2)	37.6±13.4	36.9±13.7	38.3±13.1	0.550

HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate.
Data are presented as a mean±standard deviation, Group A: administration of DW-7202 followed AST-120, group B: administration of AST-120 followed DW-7202.

Adherence

During the first 12-week period, drug adherence was similar

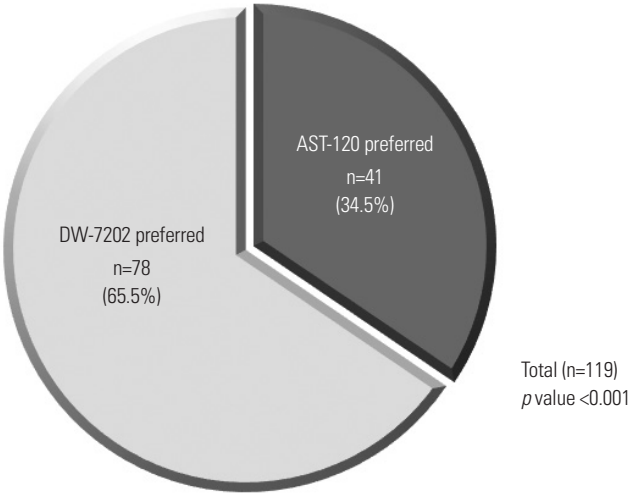

Fig. 2. Preferences of study subjects for the types of oral adsorbent.

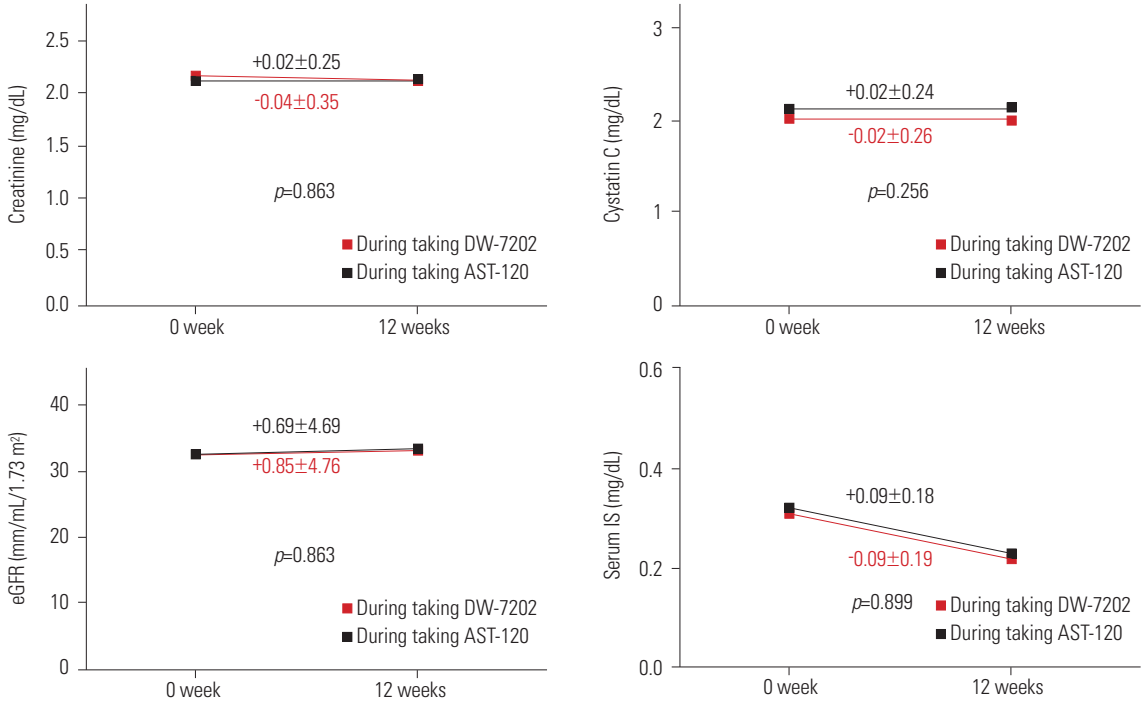

Fig. 3. Changes in variables of the secondary efficacy. eGFR, estimated glomerular filtration rate; IS, indoxyl sulfate.

between group A (85.8±3.6%) and group B (83.4±22.9%) (Fig. 4). During this period, 14 patients (18.2%) in group B dropped out, compared to 9 (11.8%) in group A During the first 12-week period, drug adherence was similar between group A (85.8±3.6%) and group B (83.4±22.9%). Although there was no statistically significant change in adherence in either group, group B showed clinically greater improvement in adherence after medication crossover (83.4±22.9% to 90.0±15.1%, p=0.057) than group A (85.8±23.6% to 87.7±19.2%, p=0.333).

Table 3. Changes in Subjective Symptoms and PGA Scales

Change	Group A (n=61)	Group B (n=58)	*p* value
Anorexia			0.954
Improved	6 (9.8)	9 (15.5)	
No change	54 (88.5)	45 (77.6)	
Worsened	1 (1.6)	4 (6.9)	
Halitosis			0.052
Improved	7 (11.5)	5 (8.6)	
No change	53 (86.9)	45 (77.6)	
Worsened	1 (1.6)	8 (13.8)	
Nausea			0.733
Improved	2 (3.3)	3 (5.2)	
No change	57 (93.4)	53 (91.4)	
Worsened	2 (3.3)	2 (3.4)	
Itching sense			0.199
Improved	7 (11.5)	3 (5.2)	
No change	49 (80.3)	48 (82.8)	
Worsened	5 (8.2)	7 (12.1)	
Edema			0.167
Improved	8 (13.1)	6 (10.3)	
No change	50 (82.0)	44 (75.9)	
Worsened	3 (4.9)	8 (13.8)	
PGA scales			0.523
Improved	8 (13.1)	8 (13.8)	
No change	47 (77.0)	47 (81.0)	
Worsened	6 (9.8)	3 (5.2)	

PGA, patient global assessment.
Data are presented as a number (%). Group A: administration of DW-7202 followed AST-120, group B: administration of AST-120 followed DW-7202.

Safety

Table 4 shows the incidence of adverse drug events (ADEs) and serious adverse events (SAEs) in patients taking each type of adsorbent, respectively. During the entire study period, 15 ADEs were reported in 13 patients taking DW-7202, while 15 were reported in 14 patients receiving AST-120. The most frequent ADE involved gastrointestinal symptoms after the administration of both adsorbent types, including constipation, diarrhea, nausea, abdominal discomfort, dyspepsia, abdominal pain, and abdominal distension. Two SAEs were reported in two patients taking DW-7202, and seven were reported in five subjects receiving AST-120. No deaths occurred during the study period. In our results, the incident rates of ADEs and SAEs were similar during treatment with DW-7202 and AST-120.

DISCUSSION

We compared two types of oral adsorbents and found that the new capsule type, DW-7202, showed efficacy and safety similar to those of the granule type, AST-120, in patients with predialysis CKD. DW-7202 was preferred by more patients than AST-120, and medication adherence was improved in patients who switched from AST-120 to DW-7202.

CKD is characterized by renal function deterioration that causes a progressive retention of a large amount of various uremic toxins.[19] A representative uremic toxin, IS, accumulates in the blood and tissue in patients with reduced renal function.[20] Elevated circulating IS contributes to the loss of renal function in patients with CKD and plays an important role in their increased

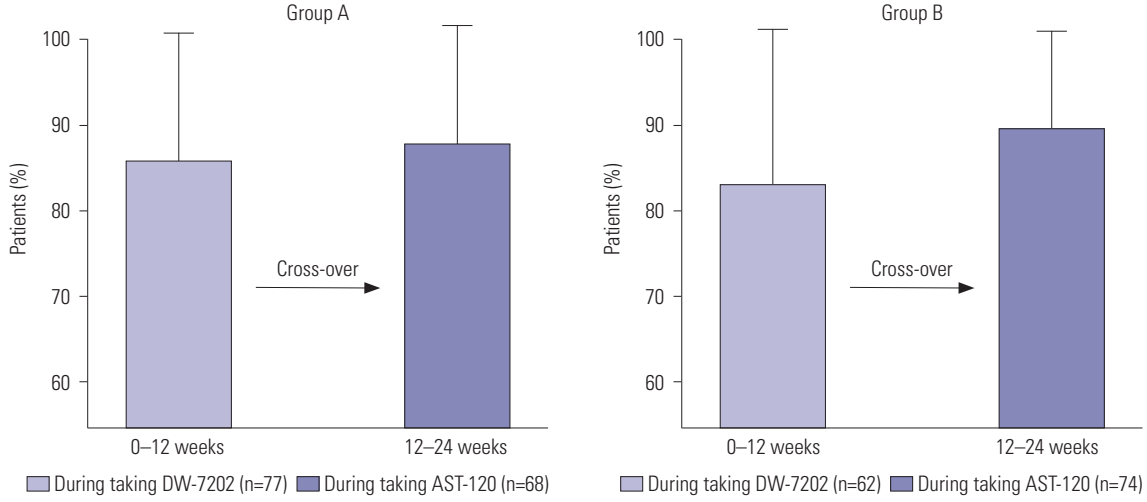

Fig. 4. Adherence of subjects according to type of oral adsorbent.

https://doi.org/10.3349/ymj.2021.62.1.41

Table 4. ADEs and SAE While Taking Each Type of Oral Absorbent

	During treatment with DW-7202	During treatment with AST-120
ADEs		
Total	15 cases, 13 patients	15 cases, 14 patients
Constipation	4 cases, 4 patients	4 cases, 4 patients
Abdominal discomfort	3 cases, 3 patients	3 cases, 3 patients
Dyspepsia	1 case, 1 patient	4 cases, 4 patients
Abdominal pain upper	2 cases, 2 patients	0
Diabetic gastropathy	0	1 case, 1 patient
Nausea	1 case, 1 patient	0
Abdominal distension	1 case, 1 patient	0
Diarrhea	1 case, 1 patient	0
Drug eruption	1 case, 1 patient	0
Pruritus	1 case, 1 patient	0
Dizziness	0	1 case, 1 patient
SAE		
Total	2 cases, 2 patients	7 cases, 5 patients
Diabetic gastropathy	0	1 case, 1 patient
Nausea	0	1 case, 1 patient
Vomiting	0	1 case, 1 patient
Cellulitis	0	1 case, 1 patient
Pyelonephritis	0	1 case, 1 patient
Dacryostenosis	1 case, 1 patient	0
Hyperkalemia	0	1 case, 1 patient
Transient ischemic attack	1 case, 1 patient	0
Cerebrovascular accident	0	1 case, 1 patient

ADEs, adverse drug events; SAE, severe adverse events.

cardiovascular disease risk.[21-26] Thus, a drug capable of adsorbing IS was developed and introduced to treat pre-dialysis CKD.

Previous studies have shown that adsorbents decrease serum IS in a dose-dependent manner and that high medication adherence is associated with positive effects including the prevention of IS accumulation and delayed disease progression.[27-29] Therefore, it is important for patients to comply with treatment and to take the correct dose. DW-7202 is provided in a form that is convenient for patients. Compared to adsorbents that are delivered as granules, the capsule type is easier for patients to swallow and allows for more exact dosing. Additionally, because the granules are sealed within a capsule, patients do not experience the unique and unpleasant taste of the medication. Further, materials (e.g., wrappers) that add to the cost and effort of treatment are not required to facilitate consumption of DW-7202 capsules. Our patients preferred DW-7202 to AST-120, and treatment adherence was improved when participants switched from AST-120 to DW-7202; however, it was difficult to identify the factors that influenced patient preference in this study using only our simple questionnaire. Despite the possibility of the pill burden, the preference for DW-7202 may be a positive finding of our study. Therefore, our results suggest that DW-7202, a capsule type adsorbent, could be an effective treatment option for patients who cannot tolerate or show poor adherence to granule type adsorbent therapy.

DW-7202 is a new type of adsorbent developed to have high adsorption selectivity for uremic toxins, and the compound strength is enhanced by a furan resin-based formula. Our study showed that there were no significant differences in treatment efficacy between the two types of adsorbent. Safety analyses showed that the incident rates of ADEs and SAEs were similar during treatment with DW-7202 and AST-120. Nevertheless, the total incidence of SAEs was lower during treatment with DW-7202 than during treatment with AST-120. The most frequently occurring ADEs during DW-7202 treatment were gastrointestinal disorders, a finding similar to the results of previous studies of AST-120.[30,31] Therefore, our results indicate that DW-7202 could be considered an alternative to granule adsorbents for the treatment of patients with CKD.

This study had some limitations. First, we used an open-label design. One of our goals was to evaluate patient preference for two different types of adsorbent. Therefore, a double-blind study was not feasible. Although the primary outcome results could be considered as just confirmatory results, this study is significant because it is the first clinical study to compare the preference and adherence of two adsorbents. Second, since we employed a crossover design that did not have a washout period, our ability to evaluate the efficacy and safety of the adsorbents was limited. At the beginning of the first 12-week period, the results were fairly reliable because the subjects were evenly assigned to both groups. Due to drop out and loss to follow-up, the two groups were no longer similar when entering the second 12-week period, which could have introduced selection bias. Additionally, patients who dropped out after beginning dialysis were not included in the analysis, which also limited our efficacy and safety assessments. Therefore, further studies with an adequate washout period are needed to compare the efficacy and safety of these adsorbents independently under equal conditions. Third, the study period was not long enough to adequately explore the results of slow CKD progression and to fully compare the efficacy and safety of the two adsorbents. Furthermore, it is difficult to draw conclusions regarding the efficacy and safety of the two adsorbents because of the study design, which did not include patients with CKD who did not take any adsorbent. Thus, in the future, a longer study conducted in a larger population that includes non-medicated patients with CKD will be necessary to assess the usefulness of DW-7202 in comparison to AST-120. Finally, it was difficult to objectively assess patient preference through the simple questionnaire used in this study. To assess preference more objectively, the relative desirability of factors affecting patient choices should be investigated. Further studies using more objective methods, such as some established rating scales, are required to overcome subjective bias in assessing patient preference.

Nevertheless, this study is significant because it is the first clinical trial to compare the efficacy and safety of the new adsorbent DW-7202 with one that is currently prescribed. Although some investigations demonstrated equivalent effects of DW-7202 and AST-120 in reducing IS concentrations, there are few published clinical studies reporting the effects of DW-7202 on disease progression in patients with CKD. Therefore, this study provides an important basis for future DW-7202 trials.

In conclusion, this study shows the new oral adsorbent DW-7202 is preferred to AST-120 in patients with pre-dialysis CKD. DW-7202 can be considered an alternative to AST-120 for patients who cannot tolerate or show poor adherence to granule type adsorbent therapy. A future clinical trial aimed at showing that higher preference and improved adherence positively influence clinical outcomes in patients with CKD is warranted to assess the clinical usefulness of DW-7202.

ACKNOWLEDGEMENTS

The authors thank the clinical trial participants and the physicians involved in the study. We are also grateful to the anonymous reviewers for their helpful suggestions and comments. This study was sponsored by Daewon Pharmaceutical Company.

AUTHOR CONTRIBUTIONS

Conceptualization: Beom Seok Kim and Jung Woo Noh. Data curation: Sang Youb Han, Duk-Hee Kang, Jung Woo Noh, Kyung Hwan Jeong, Gheun-Ho Kim, Yang Wook Kim, and Beom Seok Kim. Formal analysis: Youn Kyung Kee. Funding acquisition: Beom Seok Kim. Investigation: Sang Youb Han, Duk-Hee Kang, Jung Woo Noh, Kyung Hwan Jeong, Gheun-Ho Kim, Yang Wook Kim, and Beom Seok Kim. Methodology: Gheun-Ho Kim, Yang Wook Kim, and Beom Seok Kim. Project administration: Beom Seok Kim, Duk-Hee Kang, and Jung Woo Noh. Supervision: Beom Seok Kim, Duk-Hee Kang, and Jung Woo Noh. Validation: Youn Kyung Kee, Sang Youb Han, and Gheun-Ho Kim. Visualization: Youn Kyung Kee and Sang Youb Han. Writing—original draft: Youn Kyung Kee. Writing—review & editing: Sang Youb Han, Gheun-Ho Kim, and Beom Seok Kim. Approval of final manuscript: all authors.

ORCID iDs

Youn Kyung Kee https://orcid.org/0000-0002-0555-9909
Sang Youb Han https://orcid.org/0000-0003-3312-0597
Duk-Hee Kang https://orcid.org/0000-0001-8475-8932
Jung Woo Noh https://orcid.org/0000-0002-1743-4695
Kyung Hwan Jeong https://orcid.org/0000-0003-1492-8021
Gheun-Ho Kim https://orcid.org/0000-0002-8445-9892
Yang Wook Kim https://orcid.org/0000-0001-9676-5320
Beom Seok Kim https://orcid.org/0000-0002-5732-2583

REFERENCES

1. Mills KT, Xu Y, Zhang W, Bundy JD, Chen CS, Kelly TN, et al. A systematic analysis of worldwide population-based data on the global burden of chronic kidney disease in 2010. Kidney Int 2015;88:950-7.
2. Park JI, Baek H, Jung HH. Prevalence of chronic kidney disease in Korea: the Korean National Health and Nutritional Examination Survey 2011-2013. J Korean Med Sci 2016;31:915-23.
3. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet 2010;375:2073-81.
4. Jin DC. Major changes and improvements of dialysis therapy in Korea: review of end-stage renal disease registry. Korean J Intern Med 2015;30:17-22.
5. Trivedi H. Cost implications of caring for chronic kidney disease: are interventions cost-effective? Adv Chronic Kidney Dis 2010;17:265-70.
6. National Kidney Foundation. KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 Update. Am J Kidney Dis 2012;60:850-86.
7. Andrassy KM. Comments on 'KDIGO 2012 Clinical Practice Guideline for the evaluation and management of chronic kidney disease.' Kidney Int 2013;84:622-3.
8. Sarnak MJ, Astor BC. Implications of proteinuria: CKD progression and cardiovascular outcomes. Adv Chronic Kidney Dis 2011;18:258-66.
9. Agodoa LY, Appel L, Bakris GL, Beck G, Bourgoignie J, Briggs JP, et al. Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomized controlled trial. JAMA 2001;285:2719-28.
10. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345:861-9.
11. Motojima M, Nishijima F, Ikoma M, Kawamura T, Yoshioka T, Fogo AB, et al. Role for "uremic toxin" in the progressive loss of intact nephrons in chronic renal failure. Kidney Int 1991;40:461-9.
12. 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:S23-8.
13. Owada A, Nakao M, Koike J, Ujiie K, Tomita K, Shiigai T. Effects of oral adsorbent AST-120 on the progression of chronic renal failure: a randomized controlled study. Kidney Int Suppl 1997;63:S188-90.
14. Akizawa T, Asano Y, Morita S, Wakita T, Onishi Y, Fukuhara S, et al. Effect of a carbonaceous oral adsorbent on the progression of CKD: a multicenter, randomized, controlled trial. Am J Kidney Dis 2009;54:459-67.
15. Shoji T, Wada A, Inoue K, Hayashi D, Tomida K, Furumatsu Y, 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.
16. Sanaka T, Akizawa T, Koide K, Koshikawa S. Protective effect of an oral adsorbent on renal function in chronic renal failure: determinants of its efficacy in diabetic nephropathy. Ther Apher Dial 2004;8:232-40.
17. Takahashi N, Kawaguchi T, Suzuki T. Therapeutic effects of long-term administration of an oral adsorbent in patients with chronic renal failure: two-year study. Int J Urol. 2005;12:7-11.
18. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006;145:247-54.

https://doi.org/10.3349/ymj.2021.62.1.41

19. Vanholder R, De Smet R, Glorieux G, Argilés A, Baurmeister U, Brunet P, et al. Review on uremic toxins: classification, concentration, and interindividual variability. Kidney Int 2003;63:1934-43.
20. Lekawanvijit S, Kompa AR, Wang BH, Kelly DJ, Krum H. Cardiorenal syndrome: the emerging role of protein-bound uremic toxins. Circ Res 2012;111:1470-83.
21. Niwa T, Ise M, Miyazaki T. Progression of glomerular sclerosis in experimental uremic rats by administration of indole, a precursor of indoxyl sulfate. Am J Nephrol 1994;14:207-12.
22. Niwa T, Ise M. Indoxyl sulfate, a circulating uremic toxin, stimulates the progression of glomerular sclerosis. J Lab Clin Med 1994;124:96-104.
23. Lin CJ, Liu HL, Pan CF, Chuang CK, Jayakumar T, Wang TJ, et al. Indoxyl sulfate predicts cardiovascular disease and renal function deterioration in advanced chronic kidney disease. Arch Med Res 2012;43:451-6.
24. Yu M, Kim YJ, Kang DH. Indoxyl sulfate-induced endothelial dysfunction in patients with chronic kidney disease via an induction of oxidative stress. Clin J Am Soc Nephrol 2011;6:30-9.
25. Barreto FC, Barreto DV, Liabeuf S, Meert N, Glorieux G, Temmar M, et al. Serum indoxyl sulfate is associated with vascular disease and mortality in chronic kidney disease patients. Clin J Am Soc Nephrol 2009;4:1551-8.
26. Gao H, Liu S. Role of uremic toxin indoxyl sulfate in the progression of cardiovascular disease. Life Sci 2017;185:23-9.
27. Schulman G, Agarwal R, Acharya M, Berl T, Blumenthal S, Kopyt N. A multicenter, randomized, double-blind, placebo-controlled, dose-ranging study of AST-120 (Kremezin) in patients with moderate to severe CKD. Am J Kidney Dis 2006;47:565-77.
28. Schulman G, Berl T, Beck GJ, Remuzzi G, Ritz E, Shimizu M, et al. The effects of AST-120 on chronic kidney disease progression in the United States of America: a post hoc subgroup analysis of randomized controlled trials. BMC Nephrol 2016;17:141.
29. Cha RH, Kang SW, Park CW, Cha DR, Na KY, Kim SG, et al. Sustained uremic toxin control improves renal and cardiovascular outcomes in patients with advanced renal dysfunction: post-hoc analysis of the Kremezin Study against renal disease progression in Korea. Kidney Res Clin Pract 2017;36:68-78.
30. 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;11:189-95.
31. Schulman G, Vanholder R, Niwa T. AST-120 for the management of progression of chronic kidney disease. Int J Nephrol Renovasc Dis 2014;7:49-56.