Effects and Safety of Sodium Glucose Cotransporter 2 Inhibitors in Diabetes Patients With Drug-Refractory Advanced Heart Failure

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Background: This study aimed to investigate the effect and safety of sodium glucose cotransporter 2 inhibitors (SGLT2-Is) in patients with drug-refractory heart failure (HF).

Methods and Results: In 12 diabetic patients with advanced HF, SGLT2-Is were added to the treatment regimen. At 6 months after administration, improvements in New York Heart Association class and reduction in B-type natriuretic peptide levels were observed, in particular in patients with high right atrial pressure. During follow-up, they had neither cardiac events nor adverse side effects.

Conclusions: SGLT2-Is may be useful and safe in diabetic patients with drug-refractory HF, in particular accompanied by right-sided HF.

Key Words: Diabetes; Heart failure; SGLT2 inhibitors

The EMPA-REG OUTCOME® trial and CANVAS Program® have shown that the sodium glucose cotransporter 2 inhibitors (SGLT2-Is) significantly reduce cardiovascular events; in particular, heart failure (HF) hospitalizations.^{1,2} Therefore, SGLT2-Is are expected to be a novel treatment of HF, because diabetes is highly prevalent in HF patients. In this study, we sought to investigate the effect and safety of SGLT2-Is in patients with drug-refractory advanced HF in New York Heart Association (NYHA) class III or IV.

Methods

We retrospectively enrolled diabetic patients treated with SGLT2 inhibitors and who were complicated by HF of NYHA class III or ambulatory IV even with the use of evidence-based medicine for HF including β -blockers, angiotensin-converting inhibitor or angiotensin II receptor blocker and aldosterone inhibitor, and diuretics.³ The hospital's ethics committee approved the research protocol, and we provided online information about opting (http://www.md.tsukuba.ac.jp/clinical-med/cardiology/01_jyunnai/01_16.html).

Each patient's status was checked at baseline, 1 month (1 mo), and then every month after administration of the SGLT2-I. Each patient received guidance about checking for symptoms, and the presence of edema and measuring body weight, blood pressure and heart rate every day. Chest X-ray, laboratory tests including B-type natriuretic

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peptide (BNP) and comprehensive echocardiographic studies performed at baseline, 1 mo, and 6 mo after administration of SGLT2-Is. Based on the American Society of Echocardiography recommendations,⁴ left ventricular (LV) end-diastolic volume and ejection fraction (LVEF) were calculated by modified Simpson's equation. The LV out-tract velocity-time integral (LVOT-VTI) was measured as an assessment of cardiac output. The ratio of the peak velocity of the early wave (E) of transmitral flow to the peak early diastolic mitral annular velocity (E/E') was measured. Mitral regurgitation (MR) was graded as A, B, C or D.⁵ The maximum inferior vena cava diameter and the percentage decrease in the diameter during inspiration were used to classify right atrial pressure (RAP) into 3 grades of 3, 8, and 15 mmHg.⁶

Statistical Analysis

Means are expressed with SD for continuous variables, and medians are presented with the interquartile range for skewed variables. Comparisons of continuous variables were made using a linear mixed model analysis with post-hoc Bonferroni test. A chi-square test was used for comparison of categorical variables. $P < 0.05$ was considered to be statistically significant. All statistical analyses were performed using SPSS software (version 25.0, SPSS Inc., Chicago, IL, USA).

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Table. Clinical Characteristics and Echocardiographic Data of the Diabetic Patients Administered Sodium Glucose Cotransporter 2 Inhibitors				
	Baseline	1 month after	6 months after	P value
Age, years	60.1±7.2			
Male	7			
Cardiac disease				
DCM	5			
ICM	3			
Sarcoidosis	2			
AR post AVR	1			
AS post AVR	1			
Medications				
ACEI/ARB	12	12	12	—
β-blocker	12	12	12	—
Loop diuretics				
No. of users	12	12	11	<0.001
Dose, median (min., max. mg)	50 (40, 80)	40 (20, 80)*	20 (0, 40)*	
Trichlormethiazide				
No. of users	7	6	2	
Dose, 0/1/2 mg	—/4/3	1/4/2	5/2 0*/#	0.002
Spironolactone (dose, mg)				
No. of users	9	9	9	
Dose, 25/50 mg	6/3	6/3	6/3	—
Tolvaptan (dose, mg)				
No. of users	10	10	10	
Dose, 3.75/7.5/15 mg	2/3/5	4/3/3	7/3/0*	0.001
Height, cm	165.1±8.0			
Body weight, kg	66.5±7.2	65.6±7.0	67.5±9.0	0.10
Systolic BP, mmHg	109±16	108±15	110±18	0.77
Heart rate, beats/min	72±10	72±8	68±9*	0.02
NYHA class				0.02
I/II	—	3	7	
III	8	8	5	
IV	4	1	—	
Chest X-ray				
CTR, %	57.1±6.4	54.9±6.6*	54.0±7.1*	0.001
Pulmonary congestion	8	1	1	<0.001
Laboratory data				
HbA1c, %	7.1±0.4	6.6±0.4*	6.7±0.3*	<0.001
Hematocrit, %	42.4±4.3	43.4±4.7	44.6±4.6*	0.01
eGFR, mL/min/1.73 m ²	55.3±17.2	54.1±15.6	55.3±14.3	0.75
Sodium, mEq/L	139.5±2.0	139.8±1.7	139.3±1.4	0.60
BNP, pg/mL	438 (371, 783)	358 (272, 430)*	307 (198, 375)*	0.002
Echocardiography				
LVEDV, mL	233±89	221±92	209±104*	0.03
LVEF, %	31±12	32±12	34±14	0.06
LVOT-VTI, cm	10.6±4.4	11.6±4.8	12.3±6.2*	0.02
E/E'	20±6.3	17±7.5	17±7.6	0.06
MR grade (A/B/C/D)	5/7/—/—	9/3/—/—	9/3/—/—	0.15
TRPG, mmHg	34±17	27±13	26±12*	0.03
RAP grade, mmHg				0.007
3	5	8	10	
8	2	4	2	
15	5	0	0	

Values are mean±SD or numbers, or median (interquartile range). *P<0.05 vs. baseline, #P<0.05 vs. 1 month after. ACEI, angiotensin-converting enzyme inhibitor; AR, aortic regurgitation; ARB, angiotensin II receptor blocker; AS, aortic stenosis; AVR, aortic valve replacement; BNP, B-type natriuretic peptide; CTR, cardiothoracic ratio; DCM, dilated cardiomyopathy; E/E', ratio of early diastolic peak velocity of Doppler transmitral flow to early diastolic mitral annular velocity; eGFR, estimated glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; ICM, ischemic cardiomyopathy; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular EF; LVOT-VTI, velocity-time integral at left ventricular out-tract; MR, mitral regurgitation; RAP, right atrial pressure; TRPG, pressure gradient of tricuspid regurgitation.

Results

Consecutive patients in whom SGLT2-I administration was started from February 2016 to January 2017 were enrolled (n=12). All patients tolerated the SGLT2-Is and were followed until August 31, 2017 (11±3 months, range 8–19 months).

The baseline characteristics of the patients and changes in their data are shown in the **Table**. The details are summarized in **Table S1A–C**. Empagliflozin was used in 6 patients, canagliflozin in 4 patients, and dapagliflozin in 2 patients. Furosemide, trichlormethiazide, and tolvaptanin doses were reduced after SGLT2-I administration. Body weight and systolic blood pressure did not change, but heart rate was reduced at 6 mo. Of the 12 patients, NYHA class at 6 mo improved in 9 patients, among whom 2 class improvements occurred in 4 patients. Chest X-ray revealed improvement in pulmonary congestion. Hematocrit increased, and the BNP level decreased. LV end-diastolic volume (LVEDV) decreased and the LVOT-VTI increased, although LVEF, E/E', and MR grades were statistically unchanged. In 3 patients, there was LV functional improvement with LV reverse remodeling and reduced MR grade (patients 2, 8, and 12). The pressure gradient of tricuspid regurgitation (TRPG) and estimated RAP grades were also reduced. In particular, almost all patients in whom the BNP reduction was >200 pg/mL had an estimated RAP grade of 15 mmHg at baseline, which was reduced to 3 mmHg at 6 mo.

During the follow-up period, none of the patients had major cardiovascular events (cardiovascular death, unplanned HF hospitalization, myocardial infarction, or stroke), and none had adverse side effects, including hypotension, dehydration and urinary tract or genital infections.

Discussion

This study showed favorable effects of SGLT2-Is for diabetic patients with drug-refractory advanced HF, showing adequate safety even with the use of multiple diuretics combined with renin-angiotensin-aldosterone system (RAAS) blockers.

The effects of SGLT2-Is may depend on right-sided congestion, because changes in the RAP grade were more apparent in patients with favorable effects of SGLT2-Is. Interestingly, the effects of SGLT2-Is were observed even in patients with tolvaptan. Osmotic diuresis and natriuresis may contribute to improving the volume expansion of the extracellular fluid.⁷ Furthermore, increased substrate availability in the distal nephron works synergistically with diuretics to increase natriuresis under conditions refractory to natriuresis,⁸ and decreases the activation of the macula densa system, inhibiting activation of both the RAAS and sympathetic nerve system (SNS).⁷ These effects may counterbalance activation by plasma volume reduction. The heart rate reduction at 6 mo may also support SAS improvements.^{9,10}

Despite the decreased RAP, cardiac output was preserved, which supported the safety of SGLT2-Is in diabetic patients with drug-refractory HF. Meanwhile, we reduced the dose of diuretics, which may inhibit volume depletion, and decrease RAS and SNS activation.^{11,12} In addition, RAP reduction improves organ congestion; renal congestion in particular has been a focus in HF patients.¹³

The improvement in the LV function of some patients may have multiple mechanisms. Because SGLT2s are not expressed in the human myocardium, it is difficult to explain how they have direct effects on LV function. The metabolic/myocardial fuel supply hypothesis with increased ketone body production may contribute to the mechanism of action.¹⁴ However, we think the main mechanism is plasma volume reduction, which leads to reductions in LV volume and MR. In addition, a reduced RAP improves the LV filling property.¹⁵ Therefore, pulmonary hypertension improved as the TRPG decreased.

Furthermore, increases in the hematocrit might be related not only to plasma volume reduction, but also tubulointerstitial recovery with erythropoietin production, possibly resulting in better oxygen transport.¹⁰

In our series, adverse side effects were not experienced, but as this preliminary study was very small, more large-scale studies are needed to confirm our results.

Conclusions

Our preliminary study suggests SGLT2-I has a potential as a novel feasible option in the treatment of patients with drug-refractory advanced HF with diabetes.

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None.

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Supplementary Files

Supplementary File 1

Table S1. Sequential data of clinical characteristics and echocardiography in each patient

Please find supplementary file(s);
<http://dx.doi.org/10.1253/circj.CJ-18-0171>