Effects of Additional Administration of a Selective Inhibitor of Sodium Glucose co-transporter-2 Inhibitor on the Glycemic Control in Japanese Type 2 Diabetes Mellitus Patients Receiving Treatment with a Dipeptidyl Peptidase-4 Inhibitor

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Keywords

sodium-glucose co-transporter 2 inhibitor, dipeptidyl peptidase-4 inhibitor, type 2 diabetes, hemoglobin A1c

received 30.09.2019
accepted 17.11.2019

Bibliography

DOI https://doi.org/10.1055/a-1070-8783
Published online: 12.3.2020
Drug Res 2020; 70: 131–136

ISSN 2194-9379

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ABSTRACT

We conducted this study to determine whether additional administration sodium-glucose co-transporter 2 (SGLT2) inhibitor might provide further improvement of glycemic control and also to explore any advantages in Japanese type 2 diabetes patients showing relatively good glycemic control under treatment dipeptidyl peptidase-4 (DPP-4) inhibitors. We divided the patients in two groups, MT group and CT group. The MT group were continued on the DPP-4 inhibitor treatment for 6-months, and CT group were additionally administered an SGLT2 inhibitor treatment for 6-months. The MT group showed a significant decrease of hemoglobin A1c (HbA1c), but a significant increase of body weight, body mass index and serum uric acid, compared to the baseline values, while the CT group showed a significant decrease of HbA1c, body weight, BMI, and serum uric acid, and also a significant increase of serum HDL-cholesterol and decrease of serum triglyceride levels. Furthermore, this group showed a significant decrease of serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyl transpeptidase (γ-GTP), which are markers of liver function. These results suggest that the combination therapy is useful, in particular, for the treatment of type 2 diabetes mellitus patients with hyperlipidemia and liver dysfunction. Among the SGLT2 inhibitors added to the DPP-4 inhibitor treatment, the decreases of serum levels of AST, ALT and γ-GTP were particularly significant in the group receiving luseogliflozin, suggesting that the combination of a DPP-4 inhibitor with luseogliflozin is particularly effective for the treatment of type 2 diabetes mellitus patients with liver dysfunction.

Introduction

Combination therapy with 2 or more hypoglycemic agents with different mechanisms of action is sometimes used in patients with type 2 diabetes mellitus not showing sufficient glycemic control. While many combination therapy options are available for patients showing poor glycemic control and elevated hemoglobin A1c (HbA1c) levels because these patients do not easily develop hypoglycemia episodes, the options are more limited in patients showing relatively good glycemic control, because drugs that do not easily cause hypoglycemia need to be used in these patients.

Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted by the gastrointestinal tract in response to fool intake, and active GLP-1, when it reaches the pancreas, stimulates insulin secretion in response to elevated blood glucose levels, resulting in a lowering of the blood glucose levels. However, GLP-1 is rapidly degraded by the degrading enzyme dipeptidyl peptidase-4 (DPP-4). Therefore, DPP-4 inhibitors, which inhibit DPP-4 activity and suppress rapid degradation of active GLP-1, are useful hypoglycemic agents that are effective for lowering the blood glucose levels in patients with type 2 diabetes mellitus [1, 2].

Sodium-glucose co-transporter2 (SGLT2) is a transporter expressed in the proximal tubules of the kidney and is responsible for reabsorption of approximately 90 % of the glucose filtered via the glomeruli [3, 4]. SGLT2 inhibitors are thought to exert hypoglycemic effect by selectively inhibiting SGLT2 and increasing the urinary glucose excretion [5]. In addition, treatment with an SGLT2 inhibitor is thought to be associated with a low risk of hypoglycemia, because drugs of this class are not known to stimulate insulin secretion. Thus, DPP-4 inhibitors and SGLT2 inhibitor are hypoglycemic agents with different mechanisms of action.

The purpose of this study is to study the DPP-4 inhibitor treatment in Japanese patients additionally administered an SGLT2 inhibitor. In the study, we investigated whether the additional treatment might improve the glycemic control further without causing hypoglycemic episodes, and explore any novel advantages compared to the DPP-4 inhibitor monotherapy group. We also investigated which combination of agents of two drug classes might be the most effective.

Materials and Methods

Study patients

Investigators explained the purpose of the study to all the patients who participated in the study and obtained their informed consent for participation in the study. This clinical study was officially registered as an open-label study (ID: UMIN000021584).

The study was conducted in 199 registered Japanese outpatients with type 2 diabetes mellitus (142 males and 57 females) whose HbA1c levels were 6.5 % or higher. The study subjects were divided into a DPP-4 inhibitor MT group (n = 66, 46 males and 20 females), in which patients who were receiving a DPP-4 inhibitor were continued on the DPP-4 inhibitor during the 6-month study period, and a group in which patients who were receiving a DPP-4 inhibitor additionally received an SGLT2 inhibitor during the 6-month study period (CT group) (n = 133, 96 males and 37 females).

Administration methods

Both groups received a DPP-4 inhibitor for 6 months; then, the DPP-4 inhibitor MT group continued to receive the same DPP-4 inhibitor for an additional 6 months. On the other hand, the CT group additionally received an SGLT2 inhibitor during the 6-month study period while the DPP-4 inhibitor was also continued.

The patients of this study received any one of 5 DPP-4 inhibitors: sitagliptin, vildagliptin, alogliptin, anagliptin, or linagliptin.

The CT group, which additionally received an SGLT2 inhibitor, received one of the three following drugs of this class: luseogliflozin, dapagliflozin or empagliflozin. These DPP-4 inhibitors and SGLT2 inhibitors were administered orally once daily before or after breakfast. The doses of all the drugs are shown in ▶**Table 1**. In the MT group, each patient received one of the DPP-4 inhibitors. In the CT group, each patient received one of the DPP-4 inhibitors plus one of the SGLT2 inhibitors.

Measurement of the HbA1c level, body weight, body mass index (BMI), blood lipid profile and other biochemical parameters

In both groups, after 6 months of DPP-4 inhibitor treatment, the baseline body weight was measured and blood samples were collected for the measurements to be conducted at the baseline (baseline values in both groups). Subsequently, the MT group continued to receive a DPP-4 inhibitor for another 6 months; and then, the post-treatment body weight was measured and blood samples were collected for the post-treatment measurements (values after 6 months of treatment). The CT group additionally received an SGLT2 inhibitor for 6 months while the DPP-4 inhibitor was continued; then, after 6 months of treatment with the SGLT2 inhibitor, the post-treatment body weight was measured and blood samples were collected for the post-treatment measurements (values after 6 months of treatment). Non-fasting blood samples were collected, and serum for measurement of the blood biochemical parameters was separated from the samples and stored frozen at −80 ℃ until the assays. Measurement of the serum levels of HbA1c, lipid profile, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (γ-GTP) and uric acid using an autoanalyzer (JCA-BM8000 series, JAOL, Tokyo, Japan) was entrusted to Handa Medical Association Health Center (Aichi, Japan). HbA1c was measured using an automated high-performance liq-

▶ **Table 1** Dose levels of drugs.

	Name of drug	Dose level
DPP-4 inhibitor	Sitagliptin	100 mg/day
	Vildagliptin	100 mg/day (50mg × 2)
	Alogliptin	25 mg/day
	Anagliptin	200 mg/day (100mg × 2)
	Linagliptin	5 mg/day
SGLT2 inhibitor	Luseogliflozin	2.5 mg/day
	Dapagliflozin	5 mg/day
	Empagliflozin	10 mg/day

uid chromatography (HPLC) system (HLC-723GX, Tosoh Corporation, Tokyo, Japan).

Statistical analysis

Data are shown as the means ± standard deviation. The comparison of pre- vs. post-treatment data was conducted using the two-way ANOVA and Student's t-test. Statistical significance was set at $p < 0.05$.

Results

DPP-4 inhibitor monotherapy (MT group)

▶ **Table 2** summarizes the data of patients who received one of the 5 DPP-4 inhibitors. DPP-4 inhibitor administration significantly decreased the HbA1c value. It also significantly increased the body weight, BMI and serum uric acid.

Administration of an SGLT2 inhibitor in addition to a DPP-4 inhibitor (CT group)

▶ **Table 2** summarizes the data of patients who received one of the 3 SGLT2 inhibitors for 6 months in addition to one of the 5 DPP-4 inhibitors. The combination therapy significantly decreased the HbA1c. There were no reports of hypoglycemia episodes. In addition, the treatment also significantly reduced the body weight and BMI. In regard to the effect of the treatment on the blood lipid profile, significant increase of the serum high-density lipoprotein cholesterol (HDL-C) and decrease of the serum triglyceride levels were observed; however, the serum low-density lipoprotein cholesterol (LDL-C) and total cholesterol levels increased significantly. Furthermore, the serum AST, ALT, γ-GTP, and uric acid levels decreased significantly.

Comparison of treatment outcomes between the MT group and CT group

▶ **Table 3** shows the effect of additional treatment with an SGLT2 inhibitor in the patients who were receiving one of the DPP-4 inhibitors.

Combination therapy with a DPP-4 inhibitor and luseogliflozin was associated with a significant decrease of the HbA1c, body weight and BMI. In addition, the serum AST, ALT, γ-GTP, and uric acid levels decreased significantly. Among the components of the blood lipid profile, the serum HDL-C level increased significantly.

Combination therapy with a DPP-4 inhibitor and dapagliflozin was associated with a significant decrease of the HbA1c, body weight and BMI. The serum ALT, γ-GTP and uric acid levels also decreased significantly. Among the components of the blood lipid profile, the serum HDL-C level increased and the serum triglyceride level decreased.

Combination therapy with a DPP-4 inhibitor and empagliflozin was associated with a significant decrease of the HbA1c, body weight and BMI. In addition, serum γ-GTP and uric acid levels also decreased significantly. Among the components of the blood lipid profile, the serum HDL-C level increased significantly.

Discussion

Type 2 diabetes patients not showing sufficient glycemic control sometimes receive additional hypoglycemic agents that act through a different mechanism(s) to exert their hypoglycemic effect (combination therapy).

DPP-4 inhibitors are considered to stimulate insulin secretion through suppressing the rapid metabolism of GLP-1, which is one of the incretins, and increasing the availability of active GLP-1, and not via any effect on the pancreatic beta cells; in addition, it has been suggested that inhibition of DPP-4 may also yield other ef-

▶ **Table 2** Responses to combined DPP-4 inhibitor plus SGLT2 inhibitor therapy in Japanese patients with type 2 diabetes mellitus.

	DPP-4 inhibitor monotherapy		**Combined DPP-4 inhibitor + SGLT2 inhibitor therapy**	
	n = 66 (male: 46; female: 20)		**n = 133 (male: 96; female: 37)**	
Age (yrs.)	**57 ± 11**		**55 ± 11**	
Duration of illness (yrs.)	**10 ± 7**		**12 ± 7**	
	Before	**6 months of therapy**	**Before**	**6 months of therapy**
Body Weight (kg)	71.8 ± 15.3	72.5 ± 15.9 *	75.8 ± 15.1	73.7 ± 14.7 * *
BMI (kg/m2)	26.0 ± 4.5	26.2 ± 4.7 *	27.7 ± 5.5	26.7 ± 4.4 * *
HbA1c (%)	7.1 ± 0.5	6.8 ± 0.8 * *	7.3 ± 0.9	7.0 ± 0.8 * *
AST (U/L)	23 ± 1	23 ± 11	27 ± 18	23 ± 12 * *
ALT (U/L)	28 ± 24	26 ± 17	33 ± 29	25 ± 17 * *
γ-GTP (U/L)	36 ± 26	40 ± 38	45 ± 51	37 ± 36 * *
Uric acid (mg/dL)	5.1 ± 1.4	5.4 ± 1.5 *	5.3 ± 1.4	4.7 ± 1.2 * *
Total-cholesterol (mg/dL)	179 ± 36	180 ± 33	177 ± 28	182 ± 33 *
HDL-C (mg/dL)	58 ± 16	58 ± 16	58 ± 13	61 ± 15 * *
LDL-C (mg/dL)	100 ± 29	100 ± 29	98 ± 23	101 ± 27 *
Triglycerides (mg/dL)	165 ± 115	167 ± 90	156 ± 91	144 ± 89 *

SGLT2 inhibitors: luseogliflozin, dapagliflozin, and empagliflozin DPP-4 inhibitors: sitagliptin, vildagliptin, alogliptin, anagliptin, and linagliptin. Data are expressed as means ± SD. * : P < 0.05, * * : P < 0.01.

▶ **Table 3** By-drug comparison of the responses to combined DPP-4 inhibitor plus SGLT2 inhibitor therapy in Japanese patients with type 2 diabetes mellitus.

	DPP-4 inhibitor monotherapy		Combined DPP-4 inhibitor + SGLT2 inhibitor therapy					
	Sitagliptin, Vildagliptin, Alogliptin, Anagliptin, Linagliptin		Luseogliflozin		Dapagliflozin		Empagliflozin	
	n = 66 (male: 46; female: 20)		n = 66 (male: 40, female: 26)		n = 36 (male: 31, female: 5)		n = 31 (male: 25, female: 6)	
Age (yrs.)	**57 ± 11**		**55 ± 11**		**55 ± 10**		**57 ± 13**	
Duration of illness (yrs.)	**10 ± 7**		**12 ± 7**		**13 ± 6**		**11 ± 7**	
	Before	**6 months of therapy**	**Before**	**6 months of therapy**	**Before**	**6 months of therapy**	**Before**	**6 months of therapy**
Body Weight (kg)	71.8 ± 15.3	72.5 ± 15.9 *	76.3 ± 15.1	74.6 ± 14.6 * *	78.8 ± 15.2	76.4 ± 15.0 * *	71.1 ± 14.3	68.7 ± 14.0 * *
BMI (kg/m2)	26.0 ± 4.5	26.2 ± 4.7 *	28.2 ± 4.5	27.5 ± 4.3 * *	27.8 ± 4.3	26.9 ± 4.2 * *	25.4 ± 4.4	24.5 ± 4.4 * *
HbA1c (%)	7.1 ± 0.5	6.8 ± 0.8 * *	7.3 ± 0.9	7.1 ± 0.9 * *	7.2 ± 0.8	6.9 ± 0.7 * *	7.4 ± 0.8	6.9 ± 0.7 * *
AST (U/L)	23 ± 1	23 ± 11	28 ± 16	23 ± 9 * *	26 ± 15	25 ± 16	25 ± 24	21 ± 10
ALT (U/L)	28 ± 24	26 ± 17	36 ± 28	26 ± 16 * *	35 ± 30	27 ± 22 * *	27 ± 27	22 ± 14
γ-GTP (U/L)	36 ± 26	40 ± 38	43 ± 54	36 ± 40 * *	46 ± 44	38 ± 30 *	48 ± 53	37 ± 33 *
Uric acid (mg/dL)	5.1 ± 1.4	5.4 ± 1.5 *	5.2 ± 1.5	4.6 ± 1.3 * *	5.4 ± 1.3	4.8 ± 1.4 * *	5.1 ± 1.1	4.6 ± 0.9 * *
Total-cholesterol (mg/dL)	179 ± 36	180 ± 33	177 ± 31	182 ± 34	169 ± 24	173 ± 34	187 ± 25	193 ± 23
HDL-C (mg/dL)	58 ± 16	58 ± 16	57 ± 13	60 ± 16 *	56 ± 12	59 ± 13 *	62 ± 15	67 ± 14 * *
LDL-C (mg/dL)	100 ± 29	100 ± 29	98 ± 25	101 ± 30	92 ± 20	96 ± 27	105 ± 20	107 ± 19
Triglycerides (mg/dL)	165 ± 115	167 ± 90	156 ± 83	153 ± 90	160 ± 89	132 ± 75 * *	150 ± 113	142 ± 102

Data are expressed as means ± SD. *: P < 0.05, * *: P < 0.01.

fects than that on the blood glucose levels, i. e., extrapancreatic effects [6, 7].

SGLT2 inhibitors are thought to selectively inhibit SGLT2, which is the transporter mainly responsible for reabsorption of the glucose filtered via the glomeruli [3, 4]; therefore, they exert their hypoglycemic effect by increasing urinary glucose excretion [5]. In addition to exerting a hypoglycemic effect, SGLT2 inhibitors have been reported to decrease the body weight, lower the blood pressure and improve lipid and uric acid metabolism [8]. Due to these pleiotropic effects, SGLT2 inhibitors have been reported to also significantly suppress the risk of cardiovascular death and cardiac failure as compared to placebo in patients at a high risk of development of cardiovascular disease [9].

In this study, to Japanese patients with type 2 diabetes mellitus who were receiving treatment with a DPP-4 inhibitor, we additionally administered a SGLT2 inhibitor and investigated whether the additional treatment might improve the glycemic control further. In addition, we compared the outcomes in this CT group with those in the DPP-4 inhibitor monotherapy group to explore any new advantages of this combination regimen. We also investigated which combination of agents of these two drug classes might be the most effective.

▶ **Table 2** shows a comparison of the outcomes in the MT group and CT group. In the MT group, which had already received a DPP-4 inhibitor for 6 months and was continued on the same drug for another 6 months, during this study period, the HbA1c decreased by a further 4.2 % after the latter 6 months of treatment. That is, extension of the DPP-4 inhibitor treatment period by 6 months yielded a further decrease of the HbA1c value. On the other hand, in the CT group, which had received a DPP-4 inhibitor for 6 months prior to the start of the study and a combination of DPP-4 inhibitor and SGLT2 inhibitor for 6 months after the start of the study, decrease of the HbA1c value by a further 4.1 %, as compared to the baseline, was observed at the end of 6 months of the combined drug therapy. There were no hypoglycemia episodes reported during the study period. There was no difference in the rate of decrease of the HbA1c, as compared to the value at the study baseline, between the groups, suggesting that additional SGLT2 inhibitor administration in patients already receiving a DPP-4 inhibitor exerted no additional beneficial effect on the degree of glycemic control.

The body weight and BMI increased significantly in the MT group. In contrast, the body weight and BMI decreased significantly in the CT group. SGLT2 inhibitor treatment has been reported to result in a decrease of the body weight and BMI [8], suggesting that in the CT group, the SGLT2 inhibitor suppressed the increase in the body weight and BMI that were observed in the patients receiving the DPP-4 inhibitor treatment.

Parameters of liver function, namely, the serum levels of AST, ALT and γ-GTP, were not affected in the MT group, while significant decreases of the serum AST, ALT and γ-GTP were observed in the CT group. Kusunoki et al. [10] reported that SGLT2 inhibitor treatment was associated with a significant decrease of the serum AST, ALT and γ-GTP levels, that is, with improvement of the liver function. Therefore, the results of the present study suggest that combination therapy with a DPP-4 inhibitor and SGLT2 inhibitor is particularly useful for the treatment of type 2 diabetes mellitus patients with liver dysfunction.

In regard to the effects on the blood lipid profile, no effects of the treatment on the blood lipid profile was observed in the MT group. On the other hand, significant increase of the serum HDL-C and decrease of the serum triglyceride level was observed in the CT group. The combination therapy also significantly increased the serum total cholesterol and LDL-C levels. Inagaki et al. also reported that SGLT2 inhibitor treatment increased not only the serum HDL-C level, but also the serum total cholesterol and LDL-C levels, although the underlying mechanism remain unknown [11].

In regard to the treatment effect on the serum uric acid, the serum uric acid level increased in the MT group, while it decreased significantly in the CT group. SGLT2 inhibitors are thought to increase the excretion of uric acid in the urine by osmotic diuresis associated with the increase in the urinary glucose excretion, thereby decreasing the blood uric acid levels. Elevated blood uric acid is known as an independent risk factor for heart disease [12], and decrease of the serum uric acid level may suppress the risk of heart disease, suggesting that combination therapy with a DPP-4 inhibitor and SGLT2 inhibitor might be useful in the treatment of type 2 diabetes mellitus patients who are at a high risk for the development of heart disease.

Merovci A et al. pointed out that since SGLT2 inhibitors stimulate glucagon secretion and increase endogenous glucose production, administration of an SGLT2 inhibitor in combination with a DPP-4 inhibitor, which stimulates insulin secretion, would be effective in the treatment of diabetes mellitus [13].

The present study revealed that additional SGLT2 inhibitor administration to patients who were receiving DPP-4 treatment had no additional beneficial effect, as compared to continued DPP-4 treatment, on the HbA1c. According to previous studies, combination therapy with a DPP-4 inhibitor and an SGLT2 inhibitor proved more effective for lowering the HbA1c than monotherapy with an SGLT2 inhibitor or DPP-4 inhibitor [14, 15]. However, the patients in these studies had HbA1c levels of 8–9 %, with poor glycemic control prior to the treatment.

In the present study, the HbA1c levels of the study patients ranged from 6.8–7.5 %, suggestive of relatively good glycemic control. The results of the present study suggested that additional administration of a SGLT2 inhibitor over a DPP-4 inhibitor had no additive effect on the HbA1c in the patients with HbA1c values of approximately 7 % showing relatively good glycemic control. However, combined administration of the 2 drugs was associated with beneficial effects on the body weight, BMI, serum uric acid, serum lipid profile and parameters of liver function.

In the present study, one of 3 SGLT2 inhibitors, luseogliflozin, dapagliflozin and empagliflozin, was used in the patients. Combined use of a DPP-4 inhibitor plus luseogliflozin significantly improved all the parameters of liver function, namely, the serum AST, ALT and γ-GTP, suggesting that the combination of a DPP-4 inhibitor with luseogliflozin is particularly effective for the treatment of type 2 diabetes mellitus patients with liver dysfunction.

Conclusion

The results of this study revealed no difference in the effect on the HbA1c between continued administration of a DPP-4 inhibitor and additional administration of an SGLT2 inhibitor in patients who

were receiving treatment with a DPP-4 inhibitor at the study baseline. However, significant beneficial effect of addition of an SGLT2 inhibitor was observed on the body weight, BMI and serum uric acid (decrease of all), serum HDL-C (increase), and serum triglycerides (decrease). In addition, significant improvement of the parameters of liver function, namely, the serum AST, ALT and γ-GTP , was also observed. These results suggested that combination therapy with a DPP-4 inhibitor and SGLT2 inhibitor is particularly useful in the treatment of type 2 diabetes mellitus patients with hyperlipidemia and liver dysfunction. Of the three SGLT2 inhibitors, luseogliflozin, dapagliflozin and empagliflozin, used in the study, addition of luseogliflozin, in particular, to DPP-4 inhibitor treatment, was associated with a significant improvement of the liver function, namely, decrease of the serum levels of AST, ALT and γ-GTP, which are indicators of liver function. The above findings suggest that the combination of a DPP-4 inhibitor and luseogliflozin is particularly effective for the treatment of type 2 diabetes mellitus patients with liver dysfunction.

Conflict of Interest

The authors report no conflict of interest.

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