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Pharmacokinetics and Pharmacodynamics of Luseogliflozin, a Selective SGLT2 Inhibitor, in Japanese Patients With Type 2 Diabetes With Mild to Severe Renal Impairment

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Abstract

This open-label, parallel-group, multicenter study aimed to assess the effects of renal impairment on the pharmacokinetics, pharmacodynamics, and safety of luseogliflozin. A single 5-mg dose of luseogliflozin was administered to Japanese patients with type 2 diabetes mellitus in the following groups: G1, normal renal function; G2, mild renal impairment; G3a, mild to moderate impairment; G3b, moderate to severe impairment; G4, severe impairment, based on estimated glomerular filtration rate (eGFR; $\geq$90, 60–89, 45–59, 30–44, 15–29 mL/min/1.73 m^2, respectively). While luseogliflozin pharmacokinetics were similar for patients across all renal function groups, the increase in plasma concentration was slightly slower and maximum concentration was slightly reduced in the lower eGFR groups compared with the other groups. However, luseogliflozin pharmacodynamics were affected by the severity of renal impairment. Urinary glucose excretion (UGE) increased in all groups relative to baseline levels, but the degree of UGE increase was smaller in the lower eGFR groups. Moreover, plasma glucose AUC changes from baseline tended to be smaller in the lower eGFR groups. No clear trends were observed between eGFR and incidence, type, or severity of adverse events. Thus, luseogliflozin administration should be carefully considered, as patients with renal impairment may show an insufficient response to treatment.

Keywords

luseogliflozin, T2DM patients, renal impairment, pharmacokinetics, pharmacodynamics

Diabetes is a metabolic disease that is rapidly emerging as a global health care concern. The number of patients with diabetes worldwide is predicted to increase from 415 million in 2015 to 642 million by 2040.[1] Chronic hyperglycemia is a contributing factor in various diseases such as nephropathy, retinopathy, neuropathy, hypertension, dyslipidemia, premature atherosclerosis, diabetic foot ulcers, obesity, and cardiovascular disease. It is therefore important to control blood glucose levels in patients with diabetes.[2]

Although the mechanisms of currently available antidiabetic drugs used in clinical practice include stimulation of insulin secretion, attenuation of glucose absorption, acceleration of glucose utilization, and inhibition of gluconeogenesis, increase in urinary glucose excretion (UGE) from the body can also improve hyperglycemia. Usually, sodium glucose cotransporter 2 (SGLT2) in the proximal tubules reabsorbs 90% of the filtered glucose, and SGLT2 inhibitors block glucose reabsorption, which consequently lowers

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plasma glucose levels.[3,4] Phlorizin, which is extracted from the root bark of apple trees, is the first nonselective SGLT inhibitor, and luseogliflozin, an orally bioavailable and highly selective SGLT2 inhibitor, is a derivative of phlorizin. The half-maximal inhibitory concentration (IC_{50}) of luseogliflozin for SGLT2 is 2.26 nmol/L, and its selectivity for SGLT2 is 1770-fold higher than that for SGLT1.[5] According to a preclinical study, luseogliflozin is metabolized by multiple enzymes: cytochrome P450 (CYP) 3A4/5, 4A11, 4F2, and 4F3B and uridine diphosphate-glucuronosyltransferase (UGT) 1A1.[6] The main metabolites of luseogliflozin in humans are M2, M8, M12, and M17.[6] M2 is the most abundant human metabolite among the various metabolites in plasma.[6]

It has been reported that luseogliflozin effectively controls hyperglycemia in rat models of both type 1 and type 2 diabetes.[7] In addition, luseogliflozin is expected to be effective without inducing hypoglycemia or weight gain in patients with type 2 diabetes mellitus (T2DM) because it improves hyperglycemia without inducing insulin secretion in rats.[7] Furthermore, luseogliflozin can be used in combination with other oral antihyperglycemic drugs such as sulfonylureas, biguanides, α-glucosidase inhibitors, thiazolidinedione, dipeptidyl peptidase-4 inhibitors, and glinides for T2DM management because its mechanism of action is different from that of traditional oral hypoglycemic drugs.[8]

The glycated hemoglobin (HbA1c)-lowering effects of luseogliflozin when administered as monotherapy or as combined therapy with other oral hypoglycemic agents have been confirmed in more than 1300 Japanese T2DM patients in phase 3 trials.[8–11] No significant safety issues were identified in these trials. Luseogliflozin was well tolerated and significantly increased UGE.[12] However, in patients with renal impairment, the pharmacodynamics of luseogliflozin may be affected because the drug acts on the urinary tubules. Moreover, the pharmacokinetics of SGLT2 inhibitors may be affected by the severity of renal impairment. Therefore, the present study was conducted to evaluate the effects of luseogliflozin on UGE and to determine plasma glucose levels, pharmacokinetics, and safety in Japanese T2DM patients with normal renal function or various degrees of renal impairment.

Subjects and Methods
Patients and Study Design
This open-label, parallel-group comparative study was conducted at 6 sites in Japan (Naka Memorial Clinic, Ibaraki; Keioukai Medical Corp., P-one Clinic, Tokyo; Maruko Central General Hospital, Nagano; Komatsu Hospital, Osaka; Minamiosaka Hospital, Osaka; and AMC Nishiumeda Clinic, Osaka) in compliance with

the principles of the Declaration of Helsinki and the standards of the Japanese Pharmaceutical Affairs Law and Good Clinical Practice and was approved by an institutional review board at each participating clinical site. Eligible subjects comprised Japanese T2DM patients with HbA1c values ranging from 6.5% to 10.5%, estimated glomerular filtration rate (eGFR; calculated using the Japanese GFR estimation equation recommended by the Japanese Society of Nephrology[13]) $\geq$ 15 mL/min/1.73 m^2, and body mass index (BMI) $\geq$ 18.5 and <30.0 kg/m^2. Patient age ranged from 20 to 79 years, and all patients were on a stable diet. Patients were hospitalized after screening and classified into the following groups based on eGFR level before luseogliflozin administration (day 2 of hospitalization): G1, normal renal function (eGFR $\geq$90 mL/min/1.73 m^2); G2, mild renal impairment (eGFR, 60–89 mL/min/1.73 m^2); G3a, mild to moderate renal impairment (eGFR, 45–59 mL/min/1.73 m^2); G3b, moderate to severe renal impairment (eGFR, 30–44 mL/min/1.73 m^2); and G4, severe renal impairment (eGFR, 15–29 mL/min/1.73 m^2). All subjects provided informed consent in writing prior to their participation in the study.

The duration of hospitalization was 6 days and 5 nights, and luseogliflozin was administered as a single oral dose of 5 mg (the maximum approved dose) before breakfast on day 3 of hospitalization. The follow-up examination was performed 3–5 days after discharge from the hospital. Concomitant use of antidiabetic drugs was prohibited. Although continuous use of antihypertensive and antidyslipidemic drugs was allowed (except diuretics and drugs for renal disease), drug type and daily dosage were not changed. In addition, continuous administration of diuretics was allowed only if the same dosage of the same drug had been used for >1 week before screening and if the drug type and dose were not changed during the entire study. Patients were instructed to maintain a consistent diet therapy for >1 week before screening and to maintain consistent exercise therapy from the time of screening until leaving the clinical site.

End Points
Pharmacokinetic end points comprised plasma concentrations of luseogliflozin and its metabolites (M1, M2, M3, and M17), which were measured at 0 hour (before administration) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, and 72 hours after administration. Urinary excretion rates of luseogliflozin and its metabolites were estimated from the concentrations in 24-hour urine samples collected before dosing and from 0 to 24, 24 to 48, and 48 to 72 hours after dosing. Concentrations of luseogliflozin and its metabolites in plasma and urine were determined by validated high-performance

liquid chromatography–tandem mass spectrometry (HPLC-MS/MS) assays as previously described.[6] For the determination of luseogliflozin, 150 μL of plasma or 50 μL of urine was spiked with luseogliflozin-d_5 as an internal standard. After solid-phase extraction (OASIS HLB, Waters, Milford, Massachusetts), the reconstituted sample was injected into a LC-MS/MS system. Chromatographic separation was performed on an Inertsil ODS-3 column (2.1-mm inner diameter $\times$ 50 mm, 5 μm; GL Sciences, Tokyo, Japan) with 1 mM ammonium acetate and acetonitrile under a gradient condition. An API4000 mass spectrometer (AB Sciex, Framingham, Massachusetts) with a TurboIonSpray interface in a negative ionization mode was used for mass spectrometry determination. Multiple reaction monitoring transitions were m/z $433 \rightarrow 104$ for luseogliflozin and m/z $438 \rightarrow 104$ for luseogliflozin-d_5. The lower limits of quantification for luseogliflozin in plasma and urine were 0.05 and 0.1 ng/mL, respectively. Within-day variability (% coefficient of variation) was $\leq 9.4\%$ for plasma and $\leq 7.8\%$ for urine. Between-day variability was $\leq 8.8\%$ for plasma and $\leq 6.1\%$ for urine.

For the simultaneous determination of metabolites (M1, M2, M3, and M17), plasma (150-μL) or urine (50-μL) samples were spiked with M1-d_5, M2-d_5, M3-d_5, and M17-d_5 as internal standards and were subjected to solid-phase extraction. Chromatographic separation was performed on a YMC-Pack Pro C18 analytical column (2.0-mm inner diameter $\times$ 50 mm, 3 μm; YMC, Tokyo, Japan) with 0.1% acetic acid (by volume) in water and acetonitrile under a gradient condition. An API4000 mass spectrometer with a TurboIonSpray interface in a negative ionization mode was used. Multiple reaction monitoring transitions were m/z $419 \rightarrow 225$ or 295 for M1, m/z $405 \rightarrow 315$ for M2, m/z $449 \rightarrow 104$ for M3, m/z $463 \rightarrow 315$ for M17, m/z $424 \rightarrow 225$ or 300 for M1-d_5, m/z $410 \rightarrow 320$ for M2-d_5, m/z $454 \rightarrow 104$ for M3-d_5, and m/z $468 \rightarrow 320$ for M17-d_5. The lower limits of quantification for all metabolites in plasma and urine were 0.1 and 1 ng/mL, respectively. Within- and between-day variability for all metabolites was $\leq 7.8\%$ for plasma and $\leq 9.3\%$ for urine.

Pharmacodynamic end points were glucose levels in urine and plasma samples. Urinary glucose was measured in 24-hour pooled urine samples collected before and after dosing. Plasma glucose was measured at 0 hour (before administration) and 0.5, 1, 2, 4, 6, 8, 12, and 24 hours after administration and was used to calculate plasma glucose area under the concentration-time curve (AUC) by the linear trapezoidal rule. The glucose concentration of each sample was determined using a Hitachi 7180 autoanalyzer (Hitachi High-Technologies Corp., Tokyo, Japan). The effects of impaired renal function on these parameters were evaluated.

The safety of luseogliflozin was evaluated on the basis of the types and incidence rates of adverse events (AEs) by monitoring clinical laboratory test results, body weight, vital signs, and electrocardiogram findings.

Statistical Analysis

Pharmacokinetic parameters were estimated by performing a noncompartmental analysis of the plasma concentrations of luseogliflozin and its metabolites, and descriptive statistics were calculated for each patient group. The effects of renal impairment on the pharmacokinetic parameters of plasma luseogliflozin were analyzed by analysis of variance and calculating the ratio to G1 for each group (estimates and 90% confidence intervals [CIs]).

The change from baseline in the AUC of glucose was estimated for each patient, and descriptive statistics were calculated for each group. The change from baseline in the area under the concentration-time curve from 0 to 4 hours (AUC_{0-4}) of glucose was analyzed using a 1-sample *t* test.

Results

Patient Characteristics

In total, 57 Japanese T2DM patients were enrolled, and all patients completed the study. Table 1 presents the demographic and clinical characteristics of each group. Male patients outnumbered female patients (43 men and 14 women) in the total study population. Similar ratios were observed in the eGFR groups, except for G4, which consisted of all men. Mean patient age in G1 was 50.8 years, which was lower than that in the other groups (range, 64.5–68.1 years). In addition, duration of T2DM tended to be longer in the lower eGFR groups. Mean body weight and BMI in the total study population were 65.7 kg (range, 48.8–95.5 kg) and 24.6 kg/m^2 (range, 18.3–30.8 kg/m^2), respectively.

Mean HbA1c level in the total study population was 7.6% (range, 6.6%–10.1%). HbA1c tended to be reduced in the lower eGFR groups, with a particularly low mean of 7.2% in G4. The mean fasting plasma glucose (FPG) was 151.1 mg/dL (range, 98–278 mg/dL) in the total study population: 167.1 mg/dL in G1, 149.4–151.4 mg/dL in G2-G3b, and 123.7 mg/dL in G4. In addition, glucose level tended to be reduced in the lower eGFR groups (similar to the trend for HbA1c), with particularly low values in G4. Mean eGFR was 61.4 mL/min/1.73 m^2 (range, 13–111 mL/min/1.73 m^2) in the total study population. One patient each in G1 and G2 had a BMI of 18.3 kg/m^2, and 1 patient in G4 had an eGFR of 13 mL/min/1.73 m^2 at baseline. These patients were not excluded from the study, as their BMI

Table 1. Demographic and Clinical Characteristics of Patients

Group eGFR (mL/min/1.73 m^2)	G1 ≥90 (n = 11)	G2 60–89 (n = 17)	G3a 45–59 (n = 10)	G3b 30–44 (n = 13)	G4 <30 (n = 6)
Sex (n)					
Male	8	13	8	8	6
Female	3	4	2	5	0
Age (years), mean ± SD	50.8 ± 10.3	64.5 ± 9.1	68.1 ± 7.0	67.3 ± 7.3	67.0 ± 8.1
Body weight (kg), mean ± SD	69.0 ± 14.6	63.9 ± 9.0	68.1 ± 8.0	64.4 ± 8.5	63.2 ± 8.2
BMI (kg/m^2), mean ± SD	24.6 ± 2.8	24.5 ± 2.6	25.6 ± 1.6	25.0 ± 3.1	22.7 ± 2.3
HbA1c (%), mean ± SD	7.9 ± 1.2	7.6 ± 0.8	7.4 ± 0.8	7.5 ± 0.8	7.2 ± 0.2
FPG (mg/dL), mean ± SD	167.1 ± 42.5	151.4 ± 39.7	149.4 ± 36.1	151.0 ± 43.9	123.7 ± 26.0
Duration of DM (years), mean ± SD	6.2 ± 5.9	6.3 ± 4.4	10.9 ± 8.4	8.8 ± 7.7	13.0 ± 6.3
eGFR (mL/min/1.73 m^2), mean ± SD	100.0 ± 7.8	74.1 ± 10.2	52.9 ± 4.6	35.6 ± 4.1	24.3 ± 5.9

BMI, body mass index; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; SD, standard deviation.
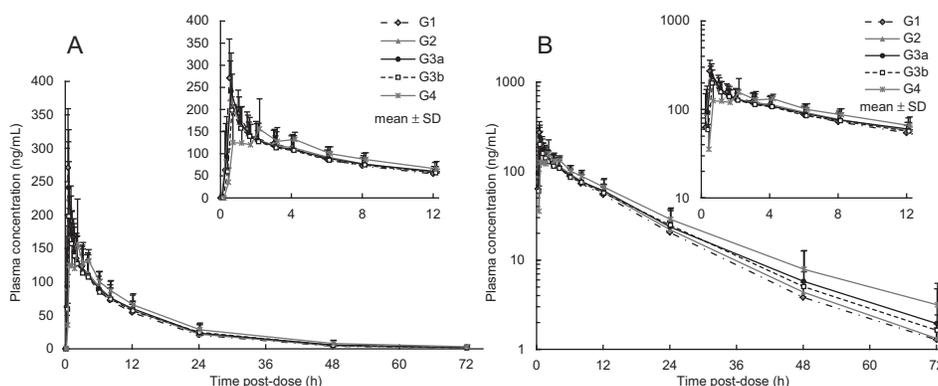

Figure 1. Plasma concentration-time profiles of luseogliflozin after a single 5-mg dose in patients with type 2 diabetes and renal impairment on a (A) linear scale and (B) logarithmic scale. Upper right inset shows 0-12 hours on an expanded time scale. SD, standard deviation.

and eGFR values met inclusion criteria at the time of enrollment.

Pharmacokinetic Analysis

Figure 1 presents the time course of plasma luseogliflozin concentrations in each group. A single 5-mg dose of luseogliflozin was absorbed rapidly, and the median time to reach maximum concentration (t_{max}) ranged from 0.5 to 1.5 hours across all groups (Table 2). The ratios of the geometric mean (90%CI) of each group's maximum concentration (C_{max}) to the C_{max} of G1 were 0.922 (0.756–1.13) in G2, 0.939 (0.720–1.22) in G3a, 0.781 (0.607–1.01) in G3b, and 0.724 (0.525–0.999) in G4. Plasma concentrations in all groups decreased to a range of 1.28–3.15 ng/mL 72 hours after administration, with no obvious differences among the groups. Even in G4, the group with the highest concentration, the concentration 72 hours after administration decreased to approximately one-fiftieth of the C_{max}. The area under the concentration-time

curve from 0 to infinity (AUC_{inf}) after administration of luseogliflozin was not related to eGFR level (Table 2 and Figure 2). Ratios of the geometric mean of AUC_{inf} (90%CI) of each group to that of G1 were 1.05 (0.900–1.21) in G2, 1.05 (0.842–1.32) in G3a, 1.04 (0.879–1.23) in G3b, and 1.21 (0.947–1.53) in G4.

Increases in the time course of changes in plasma concentrations of the metabolites in each group were slower than that of luseogliflozin and reached C_{max} within 1.18-10.0 hours after administration (data not shown). Concentrations of all metabolites tended to be higher in the lower eGFR groups, whereas concentrations of M1 and M3 in most patients were below detectable limits (<0.100 ng/mL) until 48 and 72 hours after administration, respectively. On the other hand, concentrations of M2 and M17 in G4 72 hours after administration were higher than those in G1-G3b but decreased to approximately one-sixth and one-twentieth of the C_{max}, respectively.

Table 2. Pharmacokinetic Parameters and Pharmacodynamic Properties of Luseogliflozin

Group eGFR (mL/min/1.73 m²)	G1 ≥90 (n = 11)	G2 60–89 (n = 17)	G3a 45–59 (n = 10)	G3b 30–44 (n = 13)	G4 <30 (n = 6)
Pharmacokinetic parameters					
C_{max} (ng/mL)	272 ± 86.4	244 ± 53.4	252 ± 67.5	211 ± 62.5	195 ± 63.1
t_{max} (h)[a]	0.5 (0.5–1.0)	0.5 (0.3–6.0)	0.5 (0.5–1.5)	0.5 (0.5–12)	1.5 (0.5–4.0)
AUC_{last} (ng·h/mL)	1990 ± 499	2050 ± 390	2120 ± 804	2030 ± 403	2350 ± 601
AUC_{inf} (ng·h/mL)	2010 ± 508	2070 ± 395	2160 ± 878	2060 ± 414	2420 ± 657
$t_{1/2}$ (h)	10.4 ± 0.832	10.9 ± 0.752	11.2 ± 2.68	11.0 ± 1.49	13.1 ± 3.62
Pharmacodynamic properties					
UGE_{0-24} (g/day)					
Baseline	22.4 ± 25.8	12.9 ± 15.4	7.11 ± 11.9[b]	4.08 ± 4.76[c]	1.95 ± 2.42
Postdose	111 ± 36.0	82.6 ± 23.8	64.4 ± 24.4[b]	39.4 ± 12.9[c]	23.7 ± 8.83
Change from baseline	88.3 ± 36.9	69.7 ± 19.1	57.3 ± 14.9[b]	35.3 ± 10.8[c]	21.8 ± 7.10
FPG (mg/dL)					
Baseline	167.1 ± 42.5	151.4 ± 39.7	151.4 ± 37.7[b]	140.4 ± 22.6[c]	123.7 ± 26.0
Postdose	139.7 ± 25.2	136.4 ± 37.0	140.1 ± 26.6[b]	135.7 ± 24.3[c]	125.8 ± 21.1
Change from baseline	−27.4 ± 23.5	−15.1 ± 13.6	−11.3 ± 13.5[b]	−4.8 ± 11.8[c]	2.2 ± 7.9

AUC_{last}, area under the concentration-time curve from zero to the last interval; AUC_{inf}, area under the concentration-time curve from zero to infinity; C_{max}, maximum concentration; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; t_{max}, time to reach maximum concentration; $t_{1/2}$, half-life; UGE_{0-24}, 24-hour urinary glucose excretion.
Data are expressed as mean ± standard deviation.
[a]Data are expressed as median and range.
[b]n = 9 (male, 8; female, 1).
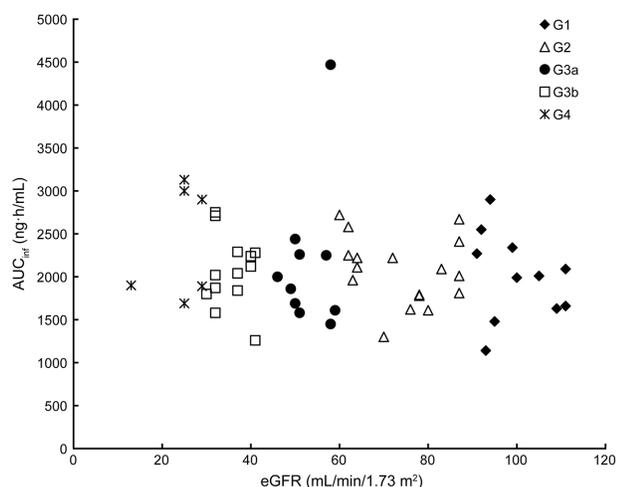[c]n = 12 (male, 8; female, 4).

Figure 2. Estimated glomerular filtration rate (eGFR) versus area under the concentration-time curve from zero to infinity (AUC_{inf}) after administration of luseogliflozin.

With regard to excretion in urine, 4.68%, 4.15%, 3.25%, 2.90%, and 2.15% of luseogliflozin and 9.92%, 8.64%, 7.04%, 4.17%, and 2.77% of M2, the main urinary metabolite, were excreted up to 72 hours after administration in G1, G2, G3a, G3b, and G4, respectively. The excretion rates for luseogliflozin and M2 tended to be reduced in the lower eGFR groups, and a similar tendency was also observed for M3 and M17. The

concentration of M1 in urine was below detectable limit (<0.100 ng/mL).

Pharmacodynamic Analysis
Table 2 shows the variation in 24-hour UGE from baseline. The mean ± standard deviation of 24-hour UGE increased significantly from baseline in all groups. The changes from baseline were 88.3 ± 36.9, 69.7 ± 19.1, 57.3 ± 14.9, 35.3 ± 10.8, and 21.8 ± 7.10 g/day in G1, G2, G3a, G3b, and G4, respectively. A scatterplot showed a correlation between the changes in UGE from baseline and baseline eGFR ($r = 0.716$, $P < .001$; Figure 3).

Figure 4 shows the changes in plasma glucose AUC_{0-4} from baseline. The changes in groups G1, G2, G3a, G3b, and G4 were −135, −104, −108, −30.2, and −32.6 mg·h/dL, respectively, and the levels in groups G1, G2, and G3a were significantly decreased ($P < .05$). A comparison of plasma glucose AUC_{0-4} between G1 and G2-G4 showed 90%CIs for the differences between G1 and G2, G3a, G3b, and G4 of 32.3 (−22.8–87.5), 26.7 (−38.6 to 91.9), 92.2 (21.9–163), and 72.6 (−1.29 to 146), respectively.

Figure 5 shows the relationship between FPG and changes in UGE from baseline. Although the increase in UGE correlated with an increase in FPG, the fitted regression lines show that the degree of increase in the lower eGFR groups was smaller than that in G1.
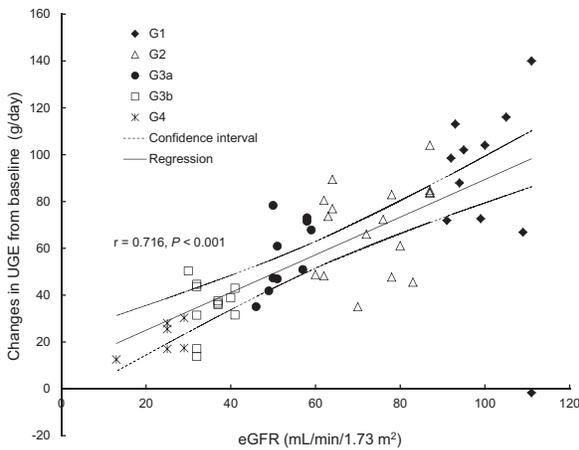
Figure 3. Estimated glomerular filtration rate (eGFR) versus changes in urinary glucose excretion (UGE) from baseline.

Safety Profile and Tolerability

Table 3 lists the AEs observed in the study. Twelve AEs, of mild to moderate severity, occurred in 8 of the 57 patients. AEs judged as moderate involved increased blood glucose in 2 patients and syncope in 1 patient. AEs judged to be related to luseogliflozin administration included rash in the G1 group and dizziness in the G3b group; both were judged to be mild. No tendency was observed of increased incidence rates of AEs or increases in specific AEs in the lower eGFR groups. In addition, no deaths or serious AEs were observed in any group. There were no clinically relevant changes in laboratory parameters or vital signs during the study (data not shown).

Discussion

One of the greatest challenges in the treatment of patients with diabetes is the limited availability of suitable glucose-lowering agents for patients with comorbid chronic kidney disease. In addition, patients with diabetes may develop diabetic nephropathy in the long term. Therefore, effective treatment options are needed for diabetic patients with renal impairment, with a particular emphasis on the effects of renal impairment on the pharmacokinetics and pharmacodynamics of antidiabetic drugs in T2DM patients.

In this study, we investigated the effects of mild to severe renal impairment on the pharmacokinetics, pharmacodynamics, and safety of luseogliflozin in Japanese T2DM patients. The values for C_{max}, AUC_{last}, AUC_{inf}, and t_{max} of luseogliflozin were similar in patients across all renal function groups. On the other hand, the half-life ($t_{1/2}$) tended to be prolonged in the G4 group; this tendency in patients with severe renal impairment could be a result of the slight lowering of urinary excretion in addition to metabolic enzyme activity in the kidneys (including CYP3A5, CYP4A11, CYP4F2, and CYP4F3B). However, for all other parameters, no differences were observed between patients with normal renal function and those with impaired renal function. Consequently, it appears that renal impairment has no significant effect on the pharmacokinetics of luseogliflozin.

In terms of the pharmacokinetics of the metabolites M1, M2, M3, and M17, C_{max} tended to be higher, AUC_{last} and AUC_{inf} tended to increase, and $t_{1/2}$ and t_{max} tended to be prolonged in the lower eGFR groups. However, because the plasma concentrations of the metabolites were much lower than those of luseogliflozin, renal impairment was thought to have no effect on the pharmacokinetic profile of luseogliflozin. In contrast, the AUCs of other SGLT2 inhibitors have been reported to increase in patients with renal impairment, particularly in those with severe impairment.[14–19] This characteristic appears to be
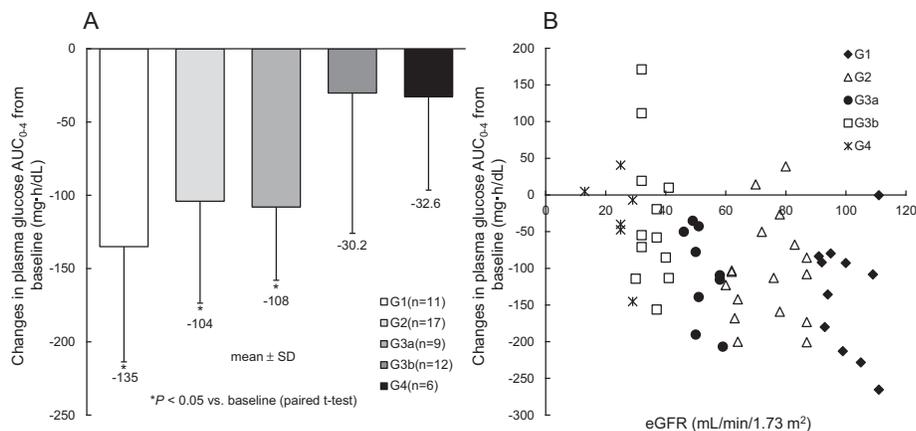

Figure 4. Changes in plasma glucose area under the concentration-time curve (AUC) from baseline for all eGFR groups (A) and scatterplot of changes in plasma glucose AUC and eGFR (B). AUC_{0-4}, area under the concentration-time curve from 0 to 4 hours; SD, standard deviation.
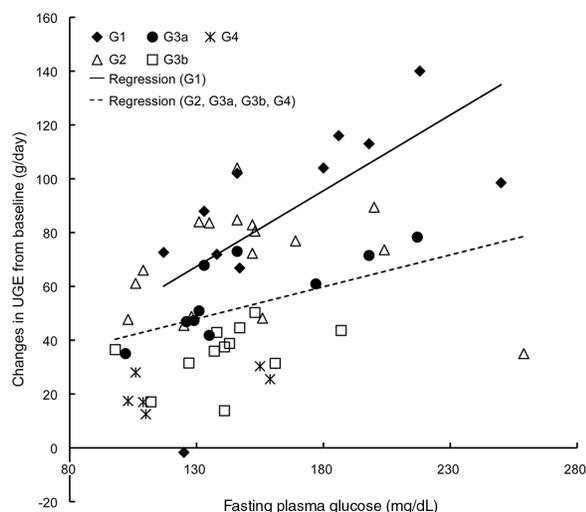
Figure 5. Fasting plasma glucose versus changes in urinary glucose excretion (UGE) from baseline. For the regression relationship in the G1 group (solid line), $r^2 = 0.42$. For the G2, G3a, G3b, and G4 groups combined (dashed line), $r^2 = 0.12$.

because of the decreased renal excretion of SGLT2 inhibitors as well as reduced metabolic enzyme activity in the kidneys resulting from decreased renal function. On the other hand, pharmacokinetic profiles of luseogliflozin are unaffected even in patients with renal impairment. Moreover, in addition to metabolism by CYPs in the kidney, luseogliflozin is also metabolized by CYP3A4/5 and UGT1A1 in the liver; this pathway may play a role in luseogliflozin's stable pharmacokinetic profile despite the presence of renal impairment.

With regard to the pharmacodynamic profile of luseogliflozin, 24-hour UGE values increased in all groups compared with baseline. The degree of increase was smaller in the lower eGFR groups, and the extent of change in UGE decreased in the lower eGFR groups relative to G1 (those with baseline eGFR $\geq$90 mL/min/1.73 m^2). In patients with renal impairment, the filtration capacity for glucose in the kidney decreases, and therefore, the inhibitory action of glucose reabsorption by luseogliflozin appeared to decline. In addition, the amount of filtration of luseogliflozin itself is thought to decline in patients with renal impairment. Because SGLT2 inhibitors appear to act from the luminal side of the renal tubule,[20] the effect of luseogliflozin is thought to be attenuated.

With respect to plasma glucose AUC, decreases from the day before administration tended to be smaller in the lower eGFR groups, and decreases in G3b (eGFR, 30–44 mL/min/1.73 m^2) 0-4 hours after administration were smaller than those in G1 (eGFR, $\geq$90 mL/min/1.73 m^2). In addition, decreases in glucose AUC were smaller in G4 than in G1. This is thought to be from attenuation of the effect of the drug in patients with renal impairment, as discussed above. We also found a positive correlation between FPG and UGE, with smaller UGE increases in the lower eGFR groups compared with the G1 group.

These results are consistent with those reported for other SGLT2 inhibitors.[14–19] As described above, in all groups, UGE increased and plasma glucose decreased after administration of 5 mg luseogliflozin, with the magnitude of the change decreasing with decreasing eGFR levels.

Table 3. List of Adverse Events in All Groups

System Organ Class[a]	Preferred Term	G1 (n = 11)	G2 (n = 17)	G3a (n = 10)	G3b (n = 13)	G4 (n = 6)
All events						
Number of patients		1	2	2	3	0
Number of events		1	3	2	6	0
Cardiac disorders	Bundle branch block, right	—	1	—	—	—
Gastrointestinal disorders	Abdominal discomfort	—	—	—	1	—
	Constipation	—	—	1	—	—
	Vomiting	—	—	1	—	—
General disorders and administration-site conditions	Vessel puncture-site hematoma	—	1	—	—	—
Investigations	Blood glucose increased	—	1	—	1	—
Nervous system disorders	Dizziness	—	—	—	1	—
	Syncope	—	—	—	1	—
Skin and subcutaneous tissue disorders	Pruritus	—	—	—	1	—
	Rash	1	—	—	—	—

[a]Medical Dictionary for Regulatory Activities (Japanese) version 13.1.

In this study, 12 AEs occurred in 8 of the 57 patients; however, all were of mild to moderate severity, and no severe AEs were observed. Although some patients had renal impairment, no AEs related to the renal and urinary systems were observed. In addition, no tendencies toward increased incidence rates of AEs or increases in specific AEs in the lower eGFR groups were observed. No deaths or serious AEs were observed in any group.

There were no clinically relevant changes in laboratory parameters or vital signs during the study. Taken together, the results demonstrate no clinically relevant issues related to the safety of luseogliflozin regardless of the degree of renal impairment.

Conclusion

The pharmacokinetics of luseogliflozin were similar for patients across all renal function groups. Therefore, regardless of the degree of renal impairment, it is not necessary to consider dose reductions or an increased risk of AEs related to increased drug exposure. However, in terms of the pharmacodynamic profile, the efficacy of luseogliflozin decreased depending on the degree of renal impairment. These results indicate that luseogliflozin administration should be carefully considered, as patients with moderate to severe and severe renal impairment may show an insufficient response to treatment.

Declaration of Conflicting Interests

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Supporting Information

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