Effect of Renal Impairment on the Pharmacokinetics, Pharmacodynamics, and Safety of Empagliflozin, a Sodium Glucose Cotransporter 2 Inhibitor, in Japanese Patients With Type 2 Diabetes Mellitus

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ABSTRACT

Purpose: The purpose of this study was to assess the effect of renal impairment on the pharmacokinetic, pharmacodynamic, and safety profiles of empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, in Japanese patients with type 2 diabetes mellitus (T2DM).

Methods: In an open-label, parallel-group study, 32 Japanese patients with T2DM and different degrees of renal function (n = 8 per renal function category: normal renal function, estimated glomerular filtration rate [eGFR; Japanese equation] ≥90 mL/min/1.73 m^2; mild renal impairment, eGFR of 60–<90 mL/min/1.73 m^2; moderate renal impairment, eGFR of 30–<60 mL/min/1.73 m^2; and severe renal impairment, eGFR of 15–<30 mL/min/1.73 m^2) received a single 25 mg dose of empagliflozin.

Findings: Empagliflozin exposure increased with increasing renal impairment. Maximum empagliflozin plasma concentrations were similar among all renal function groups. Adjusted geometric mean ratios for extent of exposure ($AUC_{0-\infty}$) to empagliflozin versus normal renal function were 128.8% (95% CI, 106.0–156.6%), 143.8% (95% CI, 118.3–174.8%), and 152.3% (95% CI, 125.3–185.2%) for patients with mild, moderate, and severe renal impairment, respectively. Decreases in renal clearance of empagliflozin correlated with eGFR. Urinary glucose excretion decreased with increasing renal impairment and correlated with eGFR (adjusted mean [SE] change from baseline: 75.0 [4.84] g, 62.6 [5.75] g, 57.9 [4.86] g, and 23.7 [5.24] g for patients with normal renal function and mild, moderate, and severe renal impairment, respectively). Only 2 patients (6%) had adverse events; both were mild.

Implications: Pharmacokinetic data suggest that no dose adjustment of empagliflozin is necessary in Japanese patients with T2DM and renal impairment because increases in exposure were <2-fold. Urinary glucose excretion decreased with increasing renal impairment. ClinicalTrials.gov identifier: NCT01581658. (*Clin Ther*. 2014;36:1606–1615)

Key words: empagliflozin, Japanese patients, pharmacodynamics, pharmacokinetics, renal impairment, SGLT2 inhibitor.

INTRODUCTION

The number of patients with diabetes worldwide continues to increase, with Japan having the 10th

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highest incidence of the disease at an estimated 7.2 million cases of diabetes.[1] Because most of these patients have type 2 diabetes mellitus (T2DM), the Japan Ministry of Health, Labour and Welfare has identified T2DM as a healthcare priority.[2]

Up to 67% of Japanese patients with T2DM also have impaired renal function[3,4] or chronic kidney disease (CKD) stages 2 to 5 according to the recent Kidney Disease: Improving Global Outcomes guidelines.[5] Indeed, 10% to 15% of patients with T2DM have moderate renal impairment or worse (CKD stages 3–5).[3,4] Diabetic nephropathy in patients with T2DM is the leading cause of end-stage renal disease.[6] The number of patients with diabetic nephropathy in Japan has increased yearly from 1983 to 2010, with 44% of patients starting dialysis in Japan in 2010 having diabetic nephropathy.[7] Impaired renal function can affect the pharmacokinetic properties of drugs that are eliminated primarily through renal excretory mechanisms, which can affect their safety and pharmacodynamic profiles and necessitate dose adjustments.[8]

Empagliflozin, a potent and selective sodium glucose cotransporter 2 (SGLT2) inhibitor,[9] has been approved in the US and Europe for the treatment of T2DM. SGLT2 is responsible for reabsorption of most glucose filtered daily by the glomerulus back into the circulation.[10] By blocking SGLT2, empagliflozin increases urinary glucose excretion (UGE) and improves plasma glucose levels, as seen in both white and Japanese patients with T2DM.[11–13] Empagliflozin is rapidly absorbed with dose-proportional increases in exposure in healthy individuals (both white and Japanese).[14,15] Single oral doses of empagliflozin (0.5–800 mg) exhibit linear pharmacokinetic properties in healthy individuals.[14] Empagliflozin undergoes limited metabolism; no major metabolites of empagliflozin have been detected in plasma (data on file). Empagliflozin is primarily excreted unchanged in urine and feces. In healthy Japanese subjects, approximately 20% to 30% of the dose of empagliflozin is excreted unchanged in the urine.[15] Thus, renal impairment is unlikely to affect the metabolism of empagliflozin but may affect its excretion. Because the mechanism of action of empagliflozin is dependent on the filtered glucose load in the glomeruli, and hence on the glomerular filtration rate (GFR), the increase in UGE is inversely associated with the degree of renal function in white patients with renal impairment.[16] This study was undertaken to assess the effect of renal impairment on the pharmacokinetic, pharmacodynamic, and safety profiles of a single dose of empagliflozin 25 mg, the maximum dose being investigated in Phase III studies, in Japanese patients with T2DM.

PATIENTS AND METHODS

Patients

Japanese patients (male or female) with T2DM and an estimated GFR (eGFR; using the Japanese GFR estimation equation recommended by the Japanese Society of Nephrology[17]) of $\geq$90 mL/min/1.73 m^2 (normal renal function; CKD stage 1), 60 to $<$90 mL/min/1.73 m^2 (mild renal impairment; CKD stage 2), 30 to $<$60 mL/min/1.73 m^2 (moderate renal impairment; CKD stage 3), or 15 to $<$30 mL/min/1.73 m^2 (severe renal impairment; CKD stage 4) were eligible for inclusion in this study. Patients were required to be $\geq$20 and $\leq$75 years of age, have a body mass index (BMI) $\geq$18 and $\leq$34 kg/m^2, body weight $\geq$45 kg, and a glycosylated hemoglobin (HbA1c) $\geq$6.5% at screening. Concomitant medication for the treatment of T2DM, including insulin, or for the treatment of concomitant diseases was permitted, except for medications known to induce P-glycoprotein. The regimen for concomitant medications had to have been unchanged for $\geq$4 weeks before study drug administration. Patients were excluded from the study if they had significant disease other than T2DM and renal impairment, including moderate or severe hepatic impairment. Other key exclusion criteria included gastrointestinal tract surgery; diseases of the central nervous system; psychiatric or neurologic disorders; chronic or relevant acute infections; history of relevant orthostatic hypotension, fainting spells, blackouts, or allergy or hypersensitivity; clinically relevant laboratory abnormalities (except parameters related to renal impairment); intake of drugs known to induce P-glycoprotein within 3 weeks before study drug administration; or participation in another clinical trial within 30 days before study drug administration. Women of childbearing potential were required to use adequate contraception. Dialysis was not an exclusion criterion.

Study Design

This was an open-label, parallel-group study conducted in a single center in Japan. Patients were screened within 21 days of study drug administration. If the interval between screening and study drug administration was $>$7 days, eGFR was recalculated.