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ORIGINAL ARTICLE

Efficacy and safety of empagliflozin in combination with other oral hypoglycemic agents in patients with type 2 diabetes mellitus☆

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KEYWORDS
Empagliflozin;
Type 2 diabetes mellitus;
SGLT-2 inhibitors

Abstract
Introduction: To analyze the efficacy and safety of empagliflozin combined with other oral hypoglycemic agents in patients with type 2 diabetes mellitus.
Methods: Pooled analysis of three phase III trials in patients with type 2 diabetes mellitus (n = 1801) who received placebo or empagliflozin 10 or 25 mg once daily for 24 weeks, in combination with metformin, metformin + sulphonylurea or pioglitazone ± metformin.
Results: Empagliflozin significantly decreased HbA1c (adjusted mean reduction vs placebo with empagliflozin 10 mg: −0.58% [95% CI: −0.66; −0.49]; $p < 0.0001$, and with empagliflozin 25 mg: −0.62% [95% CI: −0.70; −0.53], $p < 0.0001$), weight (adjusted mean reduction vs placebo with empagliflozin 10 mg: −1.77 kg [95% CI: −2.05; −1.48]; $p < 0.0001$, and with empagliflozin 25 mg: −1.96 kg [95% CI: −2.24; −1.67], $p < 0.0001$), and systolic and diastolic blood pressure (SBP/DBP). Adverse effect rates were 64% with placebo, 63.9% with empagliflozin 10 mg, and 60.9% with empagliflozin 25 mg. Documented episodes of hypoglycemia (≤70 mg/dL and/or requiring care) occurred in 3.9% of patients with placebo, 6.9% of patients with empagliflozin

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10 mg, and 5.3% of patients with empagliflozin 25 mg. Urinary tract infections developed in 9.4% of patients with placebo, 10.2% of patients with empagliflozin 10 mg, and 8.3% of patients with empagliflozin 25 mg. Genital infections were reported in 1.0% of patients with placebo, 4.6% of patients with empagliflozin 10 mg, and 3.5% of patients with empagliflozin 25 mg.
Conclusions: Empagliflozin combined with other oral treatments decreased HbA1c, body weight, and SBP/DBP as compared to placebo, with a good safety and tolerability profile.

PALABRAS CLAVE
Empagliflozina;
Diabetes mellitus tipo 2;
Inhibidores de transportador sodio glucosa tipo 2

Eficacia y seguridad de empagliflozina en combinación con otros hipoglucemiantes orales en pacientes con diabetes mellitus tipo 2

Resumen
Introducción: Analizar la eficacia y la seguridad de empagliflozina en combinación con otros hipoglucemiantes orales en pacientes con diabetes mellitus tipo 2.
Métodos: Análisis de 3 ensayos fase III en pacientes con diabetes mellitus tipo 2 (n = 1.801) que recibieron placebo, empagliflozina 10 o 25 mg, una vez al día, durante 24 semanas, en combinación con metformina, metformina + sulfonilurea o pioglitazona ± metformina.
Resultados: Empagliflozina redujo significativamente la HbA1c (reducción media ajustada vs placebo con empagliflozina 10 mg: −0.58% [IC 95%: −0,66; −0,49]; p < 0,0001 y con empagliflozina 25 mg −0,62% [IC 95%: −0,70; −0,53], p < 0,0001), el peso (reducción media ajustada vs placebo con empagliflozina 10 mg: −1,77 kg [IC 95%: −2,05; −1,48]; p < 0,0001 y con empagliflozina 25 mg: −1,96 kg [IC 95%: −2,24; −1,67], p < 0,0001) y la presión arterial sistólica y diastólica. La frecuencia de efectos adversos fue del 64% con placebo, del 63,9% con empagliflozina 10 mg y del 60,9% con empagliflozina 25 mg. Las hipoglucemias confirmadas (≤ 70 mg/dl y/o requiriendo asistencia) ocurrieron en un 3,9% de los pacientes con placebo, un 6,9% con empagliflozina 10 mg y un 5,3% con empagliflozina 25 mg. Las infecciones del tracto urinario acontecieron en un 9,4% con placebo, un 10,2% con empagliflozina 10 mg y un 8,3% con empagliflozina 25 mg. Las infecciones genitales se comunicaron en un 1,0% de los pacientes con placebo, un 4,6% con empagliflozina 10 mg y un 3,5% con empagliflozina 25 mg.
Conclusiones: Empagliflozina en combinación con otros tratamientos orales vs placebo disminuyó significativamente la HbA1c, el peso corporal y la presión arterial sistólica/diastólica, con un buen perfil de seguridad y tolerancia.

Introduction

Metformin is the first choice treatment to achieve adequate blood glucose control in patients with type 2 diabetes mellitus (T2DM), combined with nutritional therapy and physical activity.[1] However, this treatment becomes inadequate over time due to gradual impairment of insulin secretion by pancreatic β cells. The UKPDS study showed that therapeutic goals were not achieved in 40–50% of patients after two years of treatment with metformin,[2,3] and in 70% at three years.[4] Use of two or even three drugs when treatment goals are not achieved or maintained with metformin is currently recommended.[1] While pharmacological options of similar efficacy are available, these have some limitations, including risk of hypoglycemia, weight increase, gastrointestinal effects, etc., and/or specific contraindications.[5] Moreover, agents that stimulate insulin secretion lose efficacy when secretion is deficient due to loss of pancreatic β-cell function with disease progression.[6,7] There is therefore a need for developing agents that effectively decrease hyperglycemia through new mechanisms of action independent from insulin secretion and which are not associated per se to weight increase or risk of hypoglycemia. These are some of the factors that prevent achievement or maintenance of blood glucose control goals in a significant proportion of patients with T2DM.[8]

Sodium-glucose co-transporter type 2 (SGLT2) inhibitors are a new family of hypoglycemic agents for the treatment of T2DM. Their mechanism of action is inhibition of glucose reabsorption in the kidney, promoting urinary excretion of glucose, regardless of residual insulin secretion. These drugs have a low risk of hypoglycemia and are associated to decreases in body weight and blood pressure.[9]

Empagliflozin is a highly selective SGLT2 inhibitor[10] which has been shown to be effective for reducing HbA1c levels by decreasing fasting and postprandial plasma glucose, and to cause significant decreases in body weight and systolic (SBP) and diastolic (DBP) blood pressure. Empagliflozin is