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Original article

Effect of canagliflozin on liver function tests in patients with type 2 diabetes

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Abstract

Aims. – To report changes in liver function tests observed with canagliflozin, a sodium glucose co-transporter 2 inhibitor, across phase 3 studies in patients with type 2 diabetes, and to examine the relationship between changes in liver function tests and the weight loss and glycaemic improvements observed with canagliflozin.

Methods. – Data were pooled from four 26-week, placebo-controlled studies of canagliflozin 100 and 300 mg ($n = 2313$) and two 52-week, active-controlled studies of canagliflozin 300 mg versus sitagliptin 100 mg ($n = 1488$). Analysis of covariance was performed to determine the contribution of changes in body weight and HbA_{1c} to the changes in liver function tests.

Results. – Reductions in alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and gamma-glutamyl transferase, and increases in bilirubin were seen with canagliflozin 100 and 300 mg versus placebo (nominal $P < 0.001$ for alanine aminotransferase, aspartate aminotransferase and gamma-glutamyl transferase [both doses]; $P < 0.001$ for alkaline phosphatase and $P = 0.015$ for bilirubin [canagliflozin 300 mg only]) at week 26 and with canagliflozin 300 mg versus sitagliptin 100 mg (nominal $P < 0.001$ for alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase and bilirubin, and $P < 0.01$ for alkaline phosphatase) at week 52. Few patients met predefined limits of change criteria for liver function tests, and none met Hy's law criteria. In both populations, alanine aminotransferase, aspartate aminotransferase and gamma-glutamyl transferase reductions were fully explained by HbA_{1c} and body weight reductions.

Conclusions. – Canagliflozin provided improvements in liver function tests versus either placebo or sitagliptin treatments that were fully explained by the combined effects of HbA_{1c} and body weight reductions with canagliflozin.

Keywords: Body weight reduction; Canagliflozin; Glycaemic control; Liver function tests; Sodium glucose co-transporter 2 inhibitor; Type 2 diabetes mellitus

1. Introduction

Type 2 diabetes is a chronic and progressive metabolic disease that is associated with comorbidities, including obesity [1]. Accordingly, glucose-lowering strategies that improve hyperglycaemia and also have positive effects on body weight are considered particularly desirable for patients with type 2 diabetes. Canagliflozin is a sodium glucose co-transporter 2 (SGLT2) inhibitor developed for the treatment of adults with type 2 diabetes [2–15]. Canagliflozin promotes urinary glucose excretion, resulting in decreased plasma glucose, a mild osmotic diuresis and a net caloric loss [16–18]. Across placebo- and active-controlled, phase 3 studies, canagliflozin provided improvements in HbA_{1c}, body weight and systolic blood

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; ANCOVA, analysis of covariance; AP, alkaline phosphatase; AST, aspartate aminotransferase; BMI, body mass index; ΔBW, change in body weight; BW, body weight; CANA, canagliflozin; CI, confidence interval; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyl transferase; ΔHbA_{1c}, change in HbA_{1c}; LFT, liver function test; LOCF, last observation carried forward; LS, least squares; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NS, not significant; PBO, placebo; PDLC, predefined limits of change; SD, standard deviation; SE, standard error; SGLT2, sodium glucose co-transporter 2; SITA, sitagliptin; ULN, upper limit of normal.

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pressure, and was generally well tolerated [3–15]. Canagliflozin treatment has been associated with an increased incidence of adverse events (AEs) related to the mechanism of SGLT2 inhibition, including genital mycotic infections and osmotic diuresis–related AEs, and a low risk of hypoglycaemia [3–15]. Canagliflozin has also been associated with changes in liver function tests (LFTs) across studies, including reductions in alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT) and alkaline phosphatase (AP), and increases in bilirubin [3–13]. Improvements in glycaemic control and body weight reductions with canagliflozin likely contribute to the changes in measures of liver function that result from reduced glucotoxicity and lipotoxicity [19]; however, the extent to which these contribute to the changes in LFTs has not been previously assessed.

Here, we report changes in LFTs and examine the relationship between the changes in LFTs and the weight loss and glycaemic improvements that are observed with canagliflozin using pooled data from placebo- and active-controlled, phase 3 clinical trials.

2. Methods

2.1. Study design and patient populations

This analysis evaluated 2 separate, pooled datasets. The pooled, placebo-controlled population ($n = 2313$) included patients enrolled in four 26-week, placebo-controlled studies of canagliflozin (monotherapy [$n = 584$] [3], add-on to metformin [$n = 918$] [5], add-on to metformin plus sulphonylurea [$n = 469$] [6], add-on to metformin plus pioglitazone [$n = 342$] [7]); patients were randomised to receive canagliflozin 100 or 300 mg or placebo once daily in each study. The pooled, active-controlled population ($n = 1488$) included patients who received canagliflozin 300 mg or sitagliptin 100 mg in two 52-week studies (add-on to metformin [$n = 733$] [5] and add-on to metformin plus sulphonylurea [$n = 755$] [8]). Because there was no canagliflozin 100 mg arm in the add-on to metformin plus sulphonylurea study, the canagliflozin 100 mg arm of the add-on to metformin study was excluded from this analysis. Details of the study design, randomisation, treatments and eligibility criteria for these studies have been reported previously [3,5–8].

Institutional review boards and independent ethics committees for participating centres approved all studies in accordance with the ethical principles originating in the Declaration of Helsinki; all studies were consistent with Good Clinical Practices and applicable regulatory requirements. Patients provided informed written consent prior to participation.

2.2. Study endpoints and statistical analyses

Mean percent changes from baseline in ALT, AST, GGT, AP and bilirubin were assessed in each population. Missing data were imputed using the last observation carried forward (LOCF) approach. Between-group comparisons were made using analysis of covariance (ANCOVA), with baseline value as a covariate. Additionally, the proportion of patients meeting predefined limits of change (PDLC) criteria for increases in ALT, AST and bilirubin were calculated at the "any" and "last" post-baseline time points. The PDLC criteria used to assess changes in ALT and AST were defined as changes > 3, > 5 or > 8 times the upper limit of normal (ULN); PDLC criteria for changes in bilirubin included changes that were > ULN and > 25% increase from baseline. Mean changes from baseline HbA_{1c} and mean percent changes from baseline in body weight were assessed at week 26 or week 52 in the pooled, placebo-controlled population and in the pooled, active-controlled population, respectively. Due to the post hoc nature of this analysis, all P values reported are nominal P values.

To assess the contributions of weight loss and improvements in glycaemic control to the changes in LFTs, patients were divided into deciles based on change in body weight (ΔBW) or change in HbA_{1c} (ΔHbA_{1c}) within each treatment group in the pooled populations. Within each decile, the mean ΔBW or ΔHbA_{1c} and the mean change in LFTs (ΔLFT; i.e. ΔALT, ΔAST, ΔGGT) were calculated (the analyses were performed using ALT, AST and GGT as these measures showed more consistent changes with canagliflozin vs comparators than AP or bilirubin). ANCOVA was used with the resulting mean change data calculated for each decile, using ΔLFTs as response and ΔBW or ΔHbA_{1c} as a covariate. If both ΔBW and ΔHbA_{1c} were found to be significant contributors to ΔLFTs, a combined model including both ΔBW and ΔHbA_{1c} as covariates was used. Calculations were performed using MATLAB (version 8.4).

3. Results

3.1. Patients

Baseline demographic and disease characteristics for the pooled populations were similar across treatment groups and between both populations (Table 1).

3.2. Mean changes in LFTs

3.2.1. Placebo-controlled studies

At week 26, canagliflozin provided mean reductions from baseline in ALT, GGT, AST and AP, and increases in bilirubin, compared with placebo (Fig. 1A and Table 2). Canagliflozin 100 and 300 mg provided mean reductions in ALT of –6.9% and –9.9%, respectively, compared with an increase with placebo (4.4%); mean changes in GGT were –6.8%, –10.5% and 6.1% with canagliflozin 100 and 300 mg and placebo, respectively. Canagliflozin 100 and 300 mg also provided reductions compared with placebo in AST (–2.8%, –3.5% and 4.8%, respectively) and AP (–0.8%, –3.0% and 0.2%, respectively). The differences in ALT, GGT and AST with canagliflozin 100 and 300 mg versus placebo were statistically significant ($P < 0.001$ for all); the difference in AP with canagliflozin 300 mg versus placebo was also significant ($P < 0.001$). Mean increases in bilirubin were seen with canagliflozin 100 and 300 mg compared with placebo (7.9%, 9.3% and 2.9%, respectively); the difference was statistically significant only with canagliflozin 300 mg ($P = 0.015$).