1 ABSTRACT

Title

Comparison of Risk of Hospitalization with Acute Liver Failure Between Patients with Type 2 Diabetes Initiating Saxagliptin and Those Initiating Other Oral Anti-Diabetic Treatments.

Keywords

Saxagliptin, diabetes mellitus, pharmacoepidemiology, acute liver failure, acute liver injury.

Rationale and background

The risk of acute liver failure (ALF) associated with saxagliptin use among patients with type 2 diabetes mellitus (DM) in real-world settings is unknown.

Research question and objectives

Research question: What is the risk of hospitalization with ALF among patients with type 2 DM who are new initiators of saxagliptin compared to those who are new initiators of oral anti-diabetic drugs (OAD) in classes other than dipeptidyl peptidase IV (DPP-4) inhibitors?

Primary Objective: To compare the incidence of hospitalization with ALF between patients with type 2 DM who are new initiators of saxagliptin and those who are new initiators of OADs in classes other than DPP-4 inhibitors.

Secondary Objective 1: To compare baseline patient characteristics between type 2 DM patients who are new initiators of saxagliptin and those who are new initiators of OADs in classes other than DPP-4 inhibitors, and to identify important prognostic variables that should be balanced between the study groups and included in the propensity score used for the primary analysis evaluating ALF events.

Secondary Objective 2: To compare the incidence of hospitalization with acute liver injury (ALI) between patients with type 2 DM who are new initiators of saxagliptin and those who are new initiators of OADs in classes other than DPP-4 inhibitors.

Secondary Objective 3: To examine risk factors for ALF and ALI noted at higher risk among saxagliptin initiators, if any.

Study design

This was a prospectively-designed database cohort study of hospitalization with ALF among new initiators of saxagliptin compared to those who are new initiators of OADs in classes other than DPP-4 inhibitors.

Setting

This study used data from US Medicare, the HealthCore Integrated Research Database^{SM} (HIRD^{SM}), the Clinical Practice Research Datalink (CPRD, previously named the General Practice Research Database

[GPRD]), and The Health Improvement Network (THIN). This report represents the final analysis for the study and includes data from the respective data sources from between 2009 and 2014.

Subjects and study size, including dropouts Patients were eligible for inclusion if they were: 1) 18 years of age or older, 2) newly prescribed saxagliptin (with or without other OADs) or OAD in a class other than DPP-4 inhibitors (with or without other OADs), and 3) enrolled in the respective data source for at least 180 days prior to the (apparently) new prescription of saxagliptin or other OAD in a class other than DPP-4 inhibitors. Follow-up began on the date a patient was first prescribed or dispensed saxagliptin or an OAD in a different class, which represented the index date. Follow-up continued until the earliest of the following: study outcome, the end of study data, or discontinuation of saxagliptin or the index comparator OAD (i.e., no further prescription or drug claim within 30 days after the last prescription's days' supply).

Variables, data sources, and statistical analyses

The primary outcome was hospitalizations with ALF, determined based on diagnosis codes within each data source. Hospitalization with ALI was evaluated as a secondary endpoint. Based on an a priori decision, we requested hospital medical records from all patients who had a recorded diagnosis suggestive of these outcomes and confirmed them via adjudication by hepatologists. We sought to develop diagnosis coding algorithms that identified hospitalization for ALF and ALI with a positive predictive value (PPV) exceeding 80%. Within each data source (US Medicare, HealthCore Integrated Research Database^{SM}, Clinical Practice Research Datalink, The Health Improvement Network), descriptive statistics compared baseline characteristics between initiators of saxagliptin and comparator OADs in classes other than DPP-4 inhibitors. Propensity scores were developed within each data source using logistic regression, incorporating measured potential predictors of saxagliptin therapy as independent variables and comparison group status (saxagliptin group vs. comparator group) as the outcome. Incidence rates of ALF and ALI were determined within each cohort. Cox proportional hazards regression was used to determine adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) of ALF and ALI in saxagliptin initiators versus other OAD uses, adjusting for propensity score, prior OAD therapy, quarter of observation, and geographic region.

Results

Across all four data sources, we were unable to develop electronic diagnostic coding algorithms for the identification of hospitalizations with ALF or ALI with at least 80% PPV. Therefore, for these analyses, patients were classified as having had an ALF or ALI event if an electronically identified outcome was confirmed by medical record review. Additionally, we conservatively classified patients with electronically-identified outcomes, but who did not have medical records available for outcome confirmation, as having events. Patients who were adjudicated as not having had an event after medical record review were classified as such, and their follow-up time was censored at the ALF or ALI diagnosis date. There were no associations between saxagliptin initiation and hospitalization for ALF within US Medicare (fully adjusted HR, 0.72 [95% CI, 0.42-1.25]) or the HIRD^{SM} (PS-adjusted HR, 2.97 [95% CI, 0.49-18.11]). Additionally, there were no associations between saxagliptin initiation and hospitalization for

ALI within Medicare (fully adjusted HR, 0.81 [95% CI, 0.53-1.23]) and the HIRDSM (fully adjusted HR, 1.92 [95% CI, 0.63-5.87]). There were no electronically-identified ALF or ALI events within CPRD or THIN.