ABSTRACT

Title

Comparison of the Risk of Hospitalization for Infection between Patients with Type 2 Diabetes Mellitus Initiating Saxagliptin and Those Initiating Other Oral Anti-Diabetic Treatments.

Keywords

Saxagliptin, diabetes mellitus, pharmacoepidemiology, infection, T-lymphocyte dysfunction.

Rationale and background

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

Research question and objectives

Research Question 1: What is the risk of hospitalization for infection among patients with type 2 DM who are new initiators of saxagliptin compared to those who are new initiators of other oral anti-diabetic (OAD) treatments?

Research Question 2: What is the risk of hospitalization for an infection indicative of T-lymphocyte dysfunction (i.e., herpes zoster, tuberculosis, and non-tuberculous mycobacterial infection) among patients with type 2 DM who are new initiators of saxagliptin compared to those who are new initiators of other OAD treatments?

Primary Objective 1: To compare the incidence of hospitalization for infection between patients with type 2 DM who are new initiators of saxagliptin and those who are new initiators of OADs in classes other than dipeptidyl peptidase IV (DPP-4) inhibitors.

Primary Objective 2: To compare the incidence of hospitalization for an infection indicative of T-lymphocyte dysfunction (i.e., herpes zoster, tuberculosis, and non-tuberculous mycobacterial infection) 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 which should be included in the propensity score used for the primary analysis.

Secondary Objective 2: To compare the incidence of inpatient and outpatient diagnoses of herpes zoster, tuberculosis, and non-tuberculous mycobacterial infections (evaluated as a composite outcome) 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.

Secondary Objective 3: To examine risk factors for any infectious outcomes observed at higher risk among saxagliptin initiators, if any.

Study design

This was a database cohort study comparing hospitalization for infection and hospitalization with an infection indicative of T-lymphocyte dysfunction 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 DatabaseSM (HIRDSM), the Clinical Practice Research Datalink (CPRD, previously named the General Practice Research Database [GPRD]), and The Health Improvement Network (THIN). This report represents the results of 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 endpoint, 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

Two primary outcomes were evaluated for this study, determined based on diagnosis codes within each data source. The first primary endpoint was hospitalization for infection, as identified by an inpatient diagnostic code for an infection *plus* at least one of the following recorded within 7 days prior to the hospital admission: a) an outpatient prescription or pharmacy claim for an antimicrobial agent, b) an outpatient visit with a recorded diagnosis code for an infection, or c) an emergency department visit with a recorded diagnosis code for an infection.

The second primary endpoint was a composite outcome of hospitalization with herpes zoster, tuberculosis, or nontuberculous mycobacterial infection, as identified by inpatient diagnostic codes. Positive predictive values (PPVs) of diagnosis coding algorithms that identified hospitalizations of interest were determined.

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 outcomes were determined in each cohort. Cox proportional hazards regression was used to determine adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) of infectious outcomes in saxagliptin initiators versus other OAD uses, adjusting for propensity score, prior OAD therapy, quarter of observation, and geographic region.

Results

Within US Medicare, the HIRD[SM], and THIN, we developed an electronic diagnostic coding algorithm that identified a hospitalization for infection with a PPV greater than 80% compared to medical record-confirmed events. However, within CPRD, a diagnosis coding algorithm to identify hospitalizations for infection with a PPV of at least 80% was unable to be developed. In addition, across the four data sources, no coding algorithm could be developed that had at least 80% PPV for hospitalizations with infections indicative of T-lymphocyte dysfunction. Therefore, for analyses of these outcomes, electronically-identified diagnoses were classified as events if confirmed by medical record review, and we conservatively classified patients with electronically-identified diagnoses, but who did not have medical records available for outcome confirmation, as also having events. Patients who were adjudicated as not having had a diagnosis after medical record review were classified as not having had events, and their follow-up time was censored at the infection diagnosis date.

There were no associations between saxagliptin initiation and hospitalization for infection within US Medicare (fully adjusted HR, 0.97 [95% CI, 0.92-1.01]), the HIRD[SM] (fully adjusted HR, 1.07 [95% CI, 0.83-1.37]), CPRD (fully adjusted HR, 0.81 [95% CI, 0.63-1.06]), and THIN (fully adjusted HR, 0.64 [95% CI, 0.13-3.16]). Further, in a meta-analysis of the results, saxagliptin initiation was not associated with an increased risk of hospitalization with infection (fully adjusted HR, 0.97 [95% CI, 0.93-1.02]). Across the four data sources, there were no associations between saxagliptin initiation and hospitalizations with infections indicative of T-lymphocyte dysfunction (i.e., herpes zoster, tuberculosis, and non-tuberculous mycobacterial infections) in the primary analysis with the use of the best performing electronic algorithm.

We observed a decreased relative hazard of inpatient diagnoses of upper respiratory tract infections for saxagliptin initiators compared to other OAD initiators within US Medicare (fully adjusted HR, 0.92 [95% CI, 0.87-0.98]).

Saxagliptin initiation was also associated with outpatient diagnoses of non-serious infections within US Medicare (fully adjusted HR, 1.06 [95% CI, 1.04-1.08]) and with an increased risk of inpatient diagnoses of herpes zoster within CPRD (fully adjusted HR, 5.06 [95% CI, 1.35-18.98]). However, these associations were not consistent across the data sources, and a meta-analysis of outpatient diagnoses of non-serious infections across all four data sources demonstrated no association with saxagliptin initiation. Thus, these results should be interpreted with caution.