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1.0 ABSTRACT

Title

Association between therapy with dipeptidyl peptidase-4 (DPP-4) inhibitors and risk of ileus: A cohort study.

Keywords

Diabetes; alogliptin; ileus; cohort study;

Rationale and Background

There have been several different classes of medicines developed for the treatment of type 2 diabetes mellitus (T2DM) including DPP-4 inhibitors. Alogliptin is a selective and potent DPP-4 inhibitor that was approved by the Japanese Ministry of Health, Labour and Welfare in April, 2010, EMA in September of 2013, and FDA in January of 2013 for use in clinical practice for patients with T2DM. Recently, three cases of ileus, coincident with the use of DPP-4 inhibitors, in diabetic Japanese patients were published. Considering that there is relatively little available epidemiological data on ileus, and to bring new evidence to better understand the association if any between therapy with DPP-4 inhibitors including alogliptin, Glucagon-Like Peptide 1 (GLP-1) receptor agonists, voglibose and risk of ileus we conducted a pharmacoepidemiology cohort study of diabetic patients in Japan.

Study Objectives

The study objectives were to estimate and compare incidence rates of ileus among alogliptin users, other DPP-4 inhibitor users, users of GLP-1 receptor agonists, and voglibose using the Medical Data Vision (MDV) database in Japan.

Study Design

We used the MDV database in Japan to conduct this retrospective cohort study among T2DM patients who received a prescription for alogliptin, another DPP-4 inhibitor, a GLP-1 receptor agonist, or voglibose between April 1, 2010 and April 30, 2014 (study enrolment period).

Subjects and Study Size, Including Dropouts

Between April 1, 2010 and April 30, 2014 patients with T2DM who were new users of alogliptin, another DPP-4 inhibitor, a GLP-1 receptor agonist, or voglibose were selected.

New users were defined as adults 40 years of age or older at cohort entry date and having at least one year of enrollment in the MDV database without any previous prescriptions for alogliptin, other DPP-4 inhibitors, GLP-1 receptor agonists, or voglibose. Participants with a record of an ileus diagnosis in the year before or on the cohort entry date were excluded to avoid misclassification of prevalent ileus cases as incident cases.

Data Sources and Variables

We used administrative data from Medical Data Vision Co Ltd (MDV) in Tokyo, Japan in this retrospective cohort study. MDV is the commercial, electronic, record-based healthcare database that provides inpatient and outpatient anonymous information from 153 (mainly tertiary) hospitals on 8,140,000 patients and contains the detailed information on ambulatory services, hospitalizations, patients' demographic characteristics (e.g., age and gender), medical diagnoses [International Statistical Classification of Disease and Related Health Problems (ICD-10 codes)], as well as diagnosis on the prescription, information on medication use (i.e. dose, quantity and

number of days of supply), information on surgery, injections, tests, diagnosis procedure combination (DPC) claims and results of blood test and other laboratory tests. In addition, the MDV database has coverage of 5% of general hospital beds in Japan with overall data covering over 6.5% of the Japanese population. The MDV database is therefore generally representative of the overall Japanese population seeking secondary health care.

Drug Exposure:

Use of alogliptin, other DPP-4 inhibitors, GLP-1 receptor agonists, or voglibose was defined as receipt of at least one prescription for alogliptin, another DPP-4 inhibitor (sitagliptin, vilgdagliptin, saxagliptin, linagliptin, teneligliptin, or anagliptin), a GLP-1 receptor agonist (i.e. exenatide, lixisenatide, exenatide-LAR, and liraglutide), or voglibose during the study enrolment period (April 1, 2010 and April 30, 2014).

Outcome:

The primary outcome in our study was an incident diagnosis of ileus (identified by the ICD-10 codes of K56.7 for Ileus, unspecified and K56.0 for paralytic ileus) occurring after the cohort entry date (CED).

From the MDV database, we extracted data related to potential confounders. We included the following–comorbidities: chronic kidney disease, myocardial infarction, peripheral vascular disease, congestive heart failure, coronary artery disease, diabetic retinopathy, diabetic nephropathy, peripheral neuropathy, urinary infection and other potential confounders believed to affect the risk of ileus (abdominal surgery, intraabdominal infections/inflammation including

peritonitis, appendicitis, and diverticulitis; serious infection such as pneumonia; metabolic derangements including diabetic ketoacidosis or diabetic hyperosmolar coma; colorectal cancer, bowel disorders including irritable bowel syndrome (IBS), Crohn's disease and celiac disease; medications including calcium channel blockers, antihistamines, psychotropic including phenothiazines and tricyclic antidepressants, opiates).

Results

There were 82,386 patients with T2DM identified in the MDV database, of whom 9,663 (11.7%), 55,919 (67.9%), 1,904 (2.3%), and 14,900 (18.1%) were new users of: alogliptin, other DPP-4 inhibitors, GLP-1 receptor agonists, and voglibose, respectively. The overall (all risk windows) unadjusted incidence of ileus was 9.05 per 1000 person-years [(95% confidence interval (CI) 7.36-11.13)] for alogliptin, 10.26 per 1000 person-years (95% CI 9.50-11.08) for other DPP-4 inhibitors, 32.16 per 1000 person-years (95% CI 14.45-71.59) for GLP-1 receptor agonists, and 12.24 per 1000 person-years (95% CI 10.64-14.08) for voglibose.

In the adjusted model (model 1: alogliptin vs other DPP4 inhibitors – adjusted for age at cohort entry, abdominal surgery, metabolic derangement, congestive heart failure, insulin therapy; model 2: alogliptin vs GLP-1 receptor agonists- adjusted for age at cohort entry, insulin therapy, psychotropic medication; model 3: alogliptin vs Voglibose- adjusted for age at cohort entry, history of ileus, myocardial infarction, insulin therapy, psychotropic medication), there was no difference in risk of ileus among patients exposed to alogliptin compared with patients exposed to other DPP-4 inhibitors [Incidence rate ratio (IRR) 1.15, 95% CI: 0.75-1.75] or those exposed

to GLP-1 receptor agonists [IRR 0.42, 95% CI: 0.14-1.20]. The risk of ileus was lower among patients exposed to alogliptin compared with patients exposed to voglibose, (IRR 0.55, 95% CI: 0.35-0.88).

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