Assessing the association between dipeptidyl peptidase-4 inhibitors use and celiac disease through drug adverse event reporting

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Introduction

Dipeptidyl peptidase 4 (DPP4) enzyme is an endoprotease that removes N-terminal prolines from intestinal peptides.[1] These peptides include glucagon-like peptide-1 (GLP-1), which, as one of the main human incretin hormones produced by the gastrointestinal system, enhances insulin secretion in a glucose-dependent manner.[2] Inhibition of DPP4 thus raises GLP-1 levels and has a glucose-lowering effect.

DPP4 also cleaves other clinically relevant peptides. Celiac disease (CD) is a chronic digestive disorder characterized by an immune response to proteins from wheat and related grains.[3] Affected individuals display gluten-derived peptides to the immune system on human leukocyte antigen (HLA) haplotype DR3-DQ2 or DR4-DQ8, but only 2–3% of these haplotype carriers develop CD.[4] DPP4 cleaves peptides that are over-represented in the gluten epitopes that bind to HLA haplotype DR3-DQ2[1]; although a direct causal link has yet to be established, the activity of intestinal DPP4 is decreased in the acute and remission phases of CD,[5] suggesting a possible association between DPP4 level and CD.

DPP4 inhibitors (DPP4i), a common class of glucose-lowering drugs (GLDs), may increase the pool of gluten peptides with N-terminal prolines, potentially increasing the risk of CD. To investigate this potential association, we analyzed the United States Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database, which contains all adverse drug events (ADEs) spontaneously reported to FDA from the first quarter (Q1) of 2004 to Q4 of 2018.[6]

Methods

We compared DPP4i *versus* three groups: GLP-1 receptor agonists (GLP1RA); sodium-glucose cotransporter 2 inhibitors (SGLT2i); and all other non-DPP4i GLDs, excluding insulin. GLP1RA and SGLT2i were selected as comparators since they are new classes of GLDs that may have higher reporting frequency for ADEs similar to DPP4i. The group consisting of all other non-DPP4i GLDs, excluding insulin, was used to limit participants to type 2 diabetes of similar severity.

The proportional reporting ratio (PRR) with 95% confidence interval (CI) was calculated by dividing the reporting ratio of CD events reported for DPP4i by the reporting ratio of CD events reported for the comparator drug. A signal was defined as PRR $\geqslant$ 2 as previous studies.[7] In subgroup analyses, we calculated the PRRs of each individual DPP4i (sitagliptin, saxagliptin, linagliptin, alogliptin, and vildagliptin) *versus* GLP1RA to explore the difference between DPP4i agents. Data was pooled by a query within AERSMine (an open-access multi-cohort analyzing application designed to mine data effectively)[8] from Q1, 2004 to Q4, 2018. PRR was calculated using STATA 13.0.

Results

In total, 43 cases of CD were reported in association with DPP4i use. The disproportionality analysis demonstrated that the frequency of CD with DPP4i was significantly higher than that for GLP1RA (PRR 2.66, 95% CI 1.57–4.50), and all other non-DPP4i glucose lowering drugs, excluding insulin

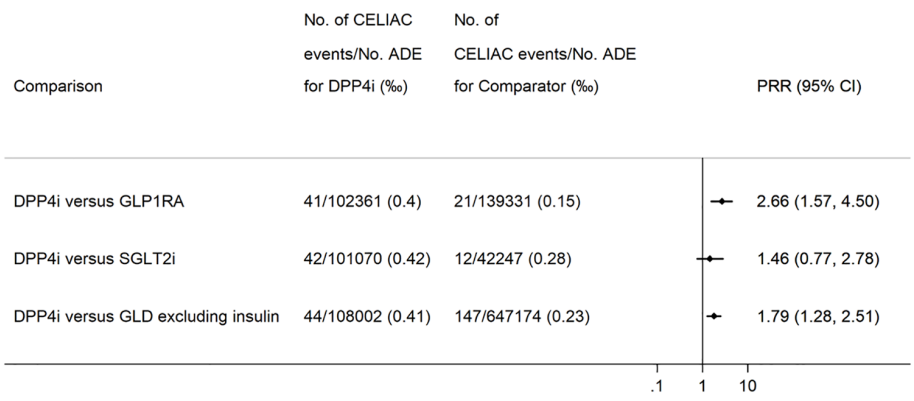

Figure 1. Number of celiac disease events and the proportional reporting ratio in different comparisons.
ADE, adverse drug events; GLD, glucose lowering drugs; GLP1RA, glucagon-like peptide-1 receptor agonists; PRR, proportional reporting ratio; SGLT2i, sodium-glucose cotransporter 2 inhibitors.

(PRR 1.79, 95% CI 1.28–2.51) (Figure 1). No signal of significant higher risk of DPP4i-related CD was found when compared with SGLT2i (PRR 1.46, 95% CI 0.77–2.78).

In the subgroup analysis, no cases of CD related to alogliptin and vidagliptin were found. Compared with GLP1RA, we detected a signal for sitagliptin (PRR 3.15, 95% CI 1.82–5.44), while signals for saxagliptin (PRR 2.57, 95% CI 0.88–7.48) and linagliptin (PRR 1.93, 95% CI 0.66–5.63) were weak due to a low number of events.

Discussion

In our study, the PRR of DPP4i *versus* GLP1RA was 2.66, suggesting that the inhibition of DPP4i may be associated with a possible higher CD risk.

This association between DPP4i use and diagnosis of celiac disease is biologically plausible. Gluten is a substrate for DPP-4, which removes N-terminal proline residues. HLA-DQ2 preferentially binds peptides with an N-terminal proline[1]; therefore, inhibition of DPP-4 may potentiate celiac disease by facilitating presentation of gluten peptides by HLA-DQ. Consistent with this, the activity of DPP-4 is depressed in patients with active CD and those in remission.[5]

Our disproportionality analysis has limitations. Although assessing disproportionality for safety signal is a useful approach to monitor rare adverse events, the FAERS database is prone to reporting bias, missing data, confounding, and cannot be used to calculate incidence; further population-based cohort studies are needed to investigate the possible risk of CD associated with DPP4i compared with therapeutic alternatives.

In conclusion, we detected a signal for higher risk of CD associated with DPP4i use compared with GLP1RA.

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Author contributions

TW and DL designed the study. DL performed statistical analysis. DL, JAS, JYY, YX, SZ, and TW were involved in data review and interpretation. DL wrote the first draft of the paper. JY, JAS, MJC, ASA, YX, and SZ, and TW contributed to critical revision of the manuscript for important intellectual content. All authors approved the final version of the manuscript.

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Conflict of interest statement

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Statement of Guarantors

DL is the guarantor of this work and had full access to all the data in the study and take responsibility of the integrity of the data and the accuracy of the data analysis.

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