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ORIGINAL REPORT

Glucagon-like peptide 1-based therapies and risk of pancreatitis: a self-controlled case series analysis

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ABSTRACT

Purpose Previous studies have suggested a link between glucagon-like peptide 1 (GLP-1)-based therapies and acute pancreatitis, while other studies have found no association. Because differences in diabetes severity may confound this relationship, a self-controlled case series (SCCS) analysis has been suggested as a means to control for individual-level confounding.
Methods We evaluated the relationship between GLP-1-based therapies and pancreatitis by SCCS method using a large observational database. We calculated the incidence density ratio of pancreatitis for exposure versus non-exposure to each drug. To examine the robustness of our findings, we performed sensitivity analyses by varying risk windows, using two pancreatitis definitions and including incident pancreatitis or all occurrences.
Results From dispensing data on 1.2 million patients, we found 7992 sitagliptin-exposed patients and 3552 exenatide-exposed patients between 2004 and 2009. Using an ICD9/CPT-based case definition of pancreatitis, we identified 207 sitagliptin and 82 exenatide cases. Augmenting this definition with laboratory criteria increased our cohort to 245 sitagliptin and 96 exenatide cases. For sitagliptin and exenatide cases, respectively, the mean duration of observation was 5.2 and 5.5 years, and the mean duration of drug exposure was 0.7 and 0.5 years. For all analyses (including different pancreatitis definitions, risk periods, and incident or recurrent events), the incidence density ratios for development of pancreatitis during exposure versus non-exposure ranged from 0.68 to 1.46, with all having 95% confidence intervals containing 1.
Conclusions We found no association between the use of GLP-1-based therapies and pancreatitis using SCCS analysis in a large observational database. Copyright © 2013 John Wiley & Sons, Ltd.

KEY WORDS—safety surveillance; electronic observational databases; self-controlled case series; GPL-1; pancreatitis; pharmacoepidemiology

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INTRODUCTION

Previous studies have suggested a link between glucagon-like peptide 1 (GLP-1)-based therapies and acute pancreatitis,[1,2] while other studies have found no association.[3,4] Because differences in diabetes severity may confound this relationship when using a matched case–control design, a self-controlled case series (SCCS) was suggested by Singh *et al*.[2] for controlling individual-level confounding in assessing the relationship between GLP-1-based therapy use and pancreatitis.

Self-controlled case series is appealing in database studies because of two major advantages[5]: (i) it elegantly controls for fixed (time-invariant) measured and *unmeasured* confounders by using each subject as his or her own control; and (ii) it may have higher efficiency than cohort methods when exposures are brief relative to observation periods.[6] Unmeasured confounders are a major source of bias in the analysis of observational data and can cause considerable problems in cohort methods and case–control methods. Case–control methods are known to be prone to selection bias, and both case–control and cohort methods cannot protect against bias when unmeasured confounders are present. Both types of methods need to adjust for a comprehensive and well thought-out list of covariates to adjust for confounding and to minimize bias. The sample size required increases as the number of covariates used in the analysis becomes large. SCCS automatically adjusts for time-invariant confounders, regardless whether measured or unmeasured, without explicitly putting them in the model; also, it uses cases only and therefore is economical in both time and

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cost. Given these advantages, we conducted a SCCS study looking at the relationship between GLP-1-based therapies and pancreatitis.

METHOD

Source population

The Indiana Network for Patient Care is a heath information exchange-based clinical repository containing medical records on over 11 million patients throughout the state of Indiana. The Regenstrief Common Data Model (CDM) database is a derivation of the Indiana Network for Patient Care containing coded medication, diagnosis, and observation data on 2.2 million patients between 1/1/2004 and 31/12/2009. These data were transformed specifically for research on adverse drug reactions through collaboration with the Observational Medical Outcomes Partnership (OMOP) using the OMOP CDM v2 specification.[7]

The total observation period for each patient was defined by the first and last dates of any activity (e.g., diagnosis, lab result, and prescription) recorded in the Regenstrief CDM database.

Exposure definition

In our study, an exposure was defined as a dispense event for either sitagliptin or exenatide at any point during the observation period. Note that exenatide was approved in 2005 and sitagliptin in 2006. Drug exposure start and stop dates were calculated using the dispense date and the number of days of supply information.

To define the period of drug exposure, multiple dispense events were combined into exposure intervals using a persistence window of 30 days. Thus, if the time interval between the stop date of one dispense event and the start date of the next dispense event was no more than 30 days, the two dispense events were combined to form one continuous exposure to the drug.[8]

Unexposed periods are time intervals during a patient's observation where there was no prescription coverage of the drug under investigation.

Pancreatitis definition

To define occurrence of pancreatitis within our population, we used the same definition as Singh *et al.* in their recent case–control study.[2] Specifically, we defined pancreatitis as the presence of (i) ICD9 diagnoses 577.0 or 577.8 or (ii) CPT procedures 48000, 48005, or 48105. Additionally, we conducted a separate analysis augmenting this original definition with laboratory data, adding to our cohort any patients with lipase values greater than 480 (three times the upper limit of normal).

In terms of pancreatitis events, because the same episode of care may include multiple ICD9 and CPT codes that meet our definition, we considered all pancreatitis codes occurring within a 30-day period to be part of a single clinical event of pancreatitis.[9] This "bridging" step attempts to avoid over-counting the number of events a patient experienced.

Study population and design

Using our database, we then identified patients with a dispense event for either sitagliptin or exenatide and an outcome of pancreatitis as defined previously. These patients are included in our analysis.

Data analysis

As noted, we used a SCCS approach. Unless otherwise stated, the SCCS analyses in this paper are bidirectional, that is, any other time periods in a patient's observation period but not in at-risk periods (defined in the succeeding text) serve as the reference period.

Self-controlled case series can be used to assess the association between an acute event and a transient exposure using cases only, without the need of a control group.[5,6] The method estimates the ratio of the risk rate of events (number of events per unit time) in the exposure periods of a drug and the risk rate of events in the non-exposure periods during the entire observation period. It assumes that events arise according to a non-homogeneous Poisson process with one rate as the effect during exposed eras and possibly a different rate as the effect outside of exposed eras. Specifically, for case i, let $exp(phi_i)$ denote the baseline (i.e., unexposed eras) event rate. Let $exp(beta)$ be the relative incidence associated with exposure. Additionally, it assumes that occurrence of one event does not alter the rate at which subsequent events might occur. Conditioning on the number of events n_i observed for case i during the observation period, the log-likelihood is multinomial, in which all the individual effects phi_i cancel out. If we use only the incident pancreatitis for each case, it amounts to a conditional logistic regression. If we use all recurrent pancreatitis events in the analysis, the analysis is conditional Poisson regression of which the conditional logistic regression is a special case.

We used OMOP's SAS macro "%sccs"[5] (SAS Institute Inc., 100 SAS Campus Drive Cary, NC 27513-2414, USA) to estimate the incidence density ratio (IDR) of pancreatitis for exposure versus non-exposure to each of the two drugs. To assess the robustness of our findings, we conducted sensitivity analyses by varying analytical choices in: (i) the start of the observation period and at-risk windows; (ii) the pancreatitis outcome definition; (iii) event type (incident or recurrent

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pancreatitis); (iv) consideration of each GPL-1 drug alone or GPL-1 drugs as a class. In the succeeding text, we further explain each of these analytical choices.

As noted, the observation period for each case is defined by the first and last dates of any activities a patient had in our system. Because a patient might have carryover medications from a previous health care system not captured in our database, the patient's exposure status is not possible to ascertain for the very beginning of the observation period. As a prescription is valid for a limited period, by setting the observation start date as the sooner of a certain number of days (delta) post a patient's entry date into our database and the date of his first ever recorded prescription, we can enhance the ascertainment of a patient's exposure status. We performed our analysis using 0, 30, 60, or 90 days for delta, with 0 implying that carryover prescriptions were not considered at all, and 30, 60, and 90 indicating that uncaptured prescriptions were assumed to exist in the 30, 60, or 90 days, respectively, before a patient came under observation in our database.

Adverse events may occur at various times during the use of a drug. In some cases, we may be interested in only those events that occur immediately upon starting a new medication. In other cases, we may be interested in events that occur both during the use of a drug as well as those during the period immediately following drug discontinuation. Thus, for our analysis, we created multiple definitions of "at-risk" periods for the patient: from the start date of exposure to 30 days later, or from the start date of the exposure to 0, 30, or 60 days post the end date of exposure. Different lengths of the at-risk period allow us to examine presentation of adverse events at different time intervals post exposure.

As noted previously, using all codes for pancreatitis may result in over-counting of a single pancreatitis event as multiple events. Therefore, we also performed analysis looking only at incident pancreatitis events, without consideration of repeat occurrences.

In total, we performed 64 bidirectional SCCS analyses, formed from the Cartesian product of four observation start dates, four at-risk windows, two pancreatitis definitions, and considering each drug as a separate exposure and both drugs combined.

In addition, we performed two additional sets of analyses to address issues unique to the potential relationship between GLP-1-based therapies and pancreatitis. First, some have raised the possibility that the risk for pancreatitis may persist indefinitely following any GLP-1 exposure. Thus, we conducted an analysis in which the at-risk period was defined as the entire time between the start date of the first drug exposure and the end of the observation period, regardless of whether the patient continued to take the drug.

Second, the majority of pancreatitis cases (~75%) have documented gallstone disease or alcohol use. Although drug exposure could, in theory, increase the risk of pancreatitis associated with even these conditions, the inclusion of such cases might confound our results. Thus, we conducted an additional analysis in which cases with evidence of gallstone disease (ICD9 577.8, 574.x, or 575.x) within 6 months before or after the pancreatitis occurrence or with documented alcohol abuse (303.x) occurring any time during the observation period were removed from the analysis set.

RESULTS

Drug dispensing data were available for 1.2 million patients, with 7192 patients having been exposed to sitagliptin and 3552 patients having been exposed to exenatide during the observation period. Using the ICD9/CPT-based definition of pancreatitis, we identified 207 cases among sitagliptin users and 82 cases among exenatide users. Augmenting the pancreatitis definition with laboratory values, we identified 245 sitagliptin cases and 96 exenatide cases. Table 1a and b summarize our cases' demographic information (sex, age and race), duration under observation, and duration under exposure for both case definitions. The mean observation duration for cases was 5.2 years for sitagliptin patients and 5.5 years for exenatide patients. The mean duration of drug exposure for cases was 0.7 years for sitagliptin and 0.5 years for exenatide. Table 2a and b contain results for both drugs for different at-risk windows (surveillance windows) and two event types, recurrent and incident events, for both case definitions. Using the ICD9/CPT-based pancreatitis definition, the IDR for development of pancreatitis at any time during exposure to sitagliptin was 0.99 (confidence interval [CI] 0.72–1.38) and the IDR for development within the first 30 days of use was 0.88 (CI 0.45–1.71) (Table 2a, recurrent event type). The IDR for pancreatitis occurrence during exposure and till 30 or 60 days following sitagliptin discontinuation was 0.97 (CI 0.72–1.31) and 1.09 (CI 0.82–1.44), respectively. The IDR for development pancreatitis at any time during exenatide exposure was 1.11 (CI 0.61–2.02) with an IDR of 0.73 (CI 0.23–2.31) for occurrence within the first 30 days of exposure. The IDR for pancreatitis occurrence during exposure and till 30 or 60 days following exenatide discontinuation was 1.27 (CI 0.77–2.10) and 1.32 (CI 0.83–2.10), respectively. IDRs and CIs for considering only incident pancreatitis

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Table 1. Summary of pancreatitis cases defined by (a) ICD9/CPT and (b) by ICD9/CPT and lab value of lipase > 480 for sitagliptin and exenatide

(a)

Variable	Sitagliptin, $N = 207$ n (%)	Exenatide, $N = 82$ n (%)
Gender		
Male	112 (54.1)	39 (47.6)
Female	95 (45.9)	43(52.4)
Age		
<25	0 (0)	0 (0)
25–34	4 (1.9)	2 (2.4)
35–44	18 (8.7)	11 (13.4)
45–54	44 (21.3)	27 (32.9)
55–64	70 (33.8)	30 (36.6)
65–74	39 (18.8)	8 (9.8)
>74	32 (15.5)	4 (4.9)
Race/ethnicity		
Asian	1 (0.5)	0 (0)
Black	20 (9.7)	1 (1.2)
White	40 (19.4)	21 (25.6)
Hispanic	1 (0.5)	0 (0)
Unknown	144 (69.9)	60 (73.2)
Mean observation duration in years (IQR)	5.2 (1.1)	5.5 (0.8)
Mean exposure duration in years (IQR)	0.7 (0.8)	0.5 (0.7)

(b)

Variable	Sitagliptin, $N = 245$ n (%)	Exenatide, $N = 96$ n (%)
Gender		
Male	134 (54.7)	44 (45.8)
Female	111 (45.3)	52(54.2)
Age		
<25	0 (0)	0 (0)
25–34	4 (1.6)	2 (2.1)
35–44	21 (8.6)	16 (16.7)
45–54	50 (20.4)	31 (32.3)
55–64	85 (34.7)	34 (35.4)
65–74	47 (19.2)	9 (9.4)
>74	38 (15.5)	4 (4.2)
Race/ethnicity		
Asian	2 (0.8)	0 (0)
Black	20 (8.2)	2 (2.1)
White	53 (21.6)	28 (29.2)
Hispanic	2 (0.8)	0 (0)
Unknown	168 (68.6)	66 (68.8)
Mean observation duration in years (IQR)	5.2 (1.1)	5.4 (0.8)
Mean exposure duration in years (IQR)	0.7 (0.8)	0.5 (0.7)

events in Table 2a are similar to the aforementioned results considering recurrent pancreatitis events.

For the analysis using the lab-augmented case definition (Table 2b), IDRs and 95% CIs are similar to those using the case definition of ICD9/CPT alone. Table 2a and b reflect the results of the analysis using the patients' entire observation period (i.e., delta being 0), but all sensitivity analyses (using delta 30, 60, and 90) showed consistent findings. We have included these additional tables in the Appendices 1–3.

For the analysis in which patients with gallstone disease or alcohol use were removed from the cohort, we had an expected decrease in cohort size (cohort $n = 64$ for sitagliptin and $n = 32$ for exenatide). Analysis of pancreatitis risk in this subset showed no significant association with IDRs ranging from 0.58 to 1.79 with all 95% CIs containing 1 (Table 2c). Additional tables are includes in Appendices 4–7.

For the analysis looking at persistent effects of GLP-1 inhibitors, in which all events following initial exposure were considered drug-induced even if the medication was no longer being taken, no significant association was seen. As shown in Table 2d (for delta = 0), IDRs ranged from 0.99 to 1.20 with all 95% CIs containing 1. Additional tables are includes in Appendices 8–11.

DISCUSSION

The potential risk of pancreatitis with use of GLP 1-based therapies has been studied extensively in recent years, generating conflicting evidence. One of the challenges in assessing this relationship is addressing the effect of diabetes severity on pancreatitis risk and the possibility that patients receiving GLP 1-based medications may have unmeasured confounders that distinguish them from control populations. To address this challenge, we have reported here the first self-controlled cases series analysis of this subject, asking the question of whether patients who took GLP-1 medications at some point and developed pancreatitis at some point were indeed more likely to have developed pancreatitis while on the drugs than while off. Our study revealed no such association, with these patients showing no heightened risk of pancreatitis during their drug exposure periods than during unexposed periods. Even when considering extended risk following exposure, the pancreatitis incidence per unit time was no higher before initial GLP-1 use than after.

Study strengths and weaknesses

By having patients serve as their own controls, we controlled for potential time-invariant unmeasured confounders. One important caveat, however, is that we do not account for changes in risk that may develop over the course of the observation period independent of drug exposure. Our SCCS model assumes that pancreatitis risk is stable for any given patient during the 5 years observation period.

Our study is strengthened by the use of multiple pancreatitis definitions and varying exposure windows to ensure that the results are robust to varying assumptions regarding both drug exposure and clinical outcome. We have also considered the most common

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Table 2. (a)–(d) Incidence density ratio of pancreatitis of exposure versus non-exposure to a drug and the 95% confidence limits for different choices of analytical parameters. Parameter "Surveillance window" defines the period of time that a patient is inferred to be "at-risk" based on drug prescription, dispensing, or administration. The four options are −30, 0, 30, and 60, corresponding to four risk intervals, from the index exposure date to 30 days post the start of exposure or to 0, 30, or 60 days post the end of exposure, respectively. Parameter "Event type" defines whether to consider in analysis all occurrences of pancreatitis (1 = Recurrent) or first occurrence (2 = Incident) for a patient

Exposure	No. cases	Event type	Surveillance window	IDR	95% CI lower limit	95% CI upper limit
(a)						
Sitagliptin	207	Recurrent	−30	0.88	0.45	1.71
			0	0.99	0.72	1.38
			30	0.97	0.72	1.31
			60	1.09	0.82	1.44
		Incident	−30	1.07	0.47	2.44
			0	0.81	0.52	1.26
			30	0.81	0.54	1.24
			60	0.94	0.64	1.38
Exenatide	82	Recurrent	−30	0.73	0.23	2.31
			0	1.11	0.61	2.02
			30	1.27	0.77	2.10
			60	1.32	0.83	2.10
		Incident	−30	0.79	0.19	3.27
			0	1.28	0.64	2.58
			30	1.46	0.79	2.67
			60	1.45	0.82	2.57
(b)						
Sitagliptin	245	Recurrent	−30	0.84	0.44	1.58
			0	0.97	0.72	1.31
			30	0.96	0.73	1.28
			60	1.05	0.81	1.37
		Incident	−30	1.05	0.49	2.23
			0	0.83	0.55	1.24
			30	0.85	0.58	1.24
			60	0.93	0.65	1.33
Exenatide	96	Recurrent	−30	0.66	0.21	2.07
			0	1.03	0.58	1.82
			30	1.15	0.71	1.87
			60	1.25	0.80	1.95
		incident	−30	0.69	0.17	2.83
			0	1.04	0.53	2.07
			30	1.18	0.65	2.14
			60	1.27	0.74	2.20
(c)						
Sitagliptin	64	Recurrent	−30	0.77	0.19	3.15
			0	1.04	0.54	2.01
			30	0.94	0.50	1.77
			60	1.01	0.55	1.83
		Incident	−30	0.58	0.08	4.19
			0	0.68	0.29	1.62
			30	0.57	0.24	1.36
			60	0.73	0.34	1.56
Exenatide	32	Recurrent	−30	0.66	0.09	4.83
			0	0.97	0.37	2.57
			30	1.79	0.85	3.73
			60	1.67	0.82	3.38
		Incident	−30	0.00	0.00	∞
			0	1.00	0.33	3.03
			30	1.61	0.66	3.91
			60	1.62	0.70	3.76
(d)						
Sitagliptin	207	Recurrent	−30	0.99	0.44	2.22
			0	1.06	0.82	1.38
		Incident	−30	1.09	0.40	2.93
			0	0.96	0.68	1.36
Exenatide	82	Recurrent	−30	0.00	0.00	∞
			0	1.20	0.82	1.75
		Incident	−30	0.00	0.00	∞
			0	1.08	0.65	1.79

Note: IDR 0 hereinafter is where Poisson algorithm did not converge.
IDR, incidence density ratio; CI, confidence interval.
(a) Results for pancreatitis defined by ICD9/CPT.
(b) Results for pancreatitis defined by ICD9/CPT and lipase value > 480.
(c) Results from modified analysis in which all patients with evidence of gallstones or alcohol use are removed from the cohort.
(d) Results from modified analysis in which at-risk period is any time following the first drug exposure.

pancreatitis risk factors, gallstone disease and alcohol use, and sought to minimize confounding by performing an analysis excluding these conditions. However, some cases of non-drug-induced pancreatitis may remain. Also, while we have used a large observational dataset derived from a broad statewide health information exchange, the possibility exists that a patient received care outside of our state or at a non-participating institution leading to missed capture of drug dispense events of pancreatitis outcomes. The timings of drug exposures can only be approximated by the timings of prescribing or dispensing. Also the capture of first (incident) pancreatitis event is limited by the time span (from 2004 to 2009) of the database. Furthermore, we did not adjust for time-varying confounders (new medications added, progression of diabetes severity etc. during the observation period). Lastly, we did not incorporate information sources such as provider notes that may provide additional indicators of a pancreatitis event.

CONCLUSIONS

In this SCCS analysis using a large observational database, we found no increased risk for pancreatitis associated with the use of GLP-1-based therapies. We varied analytic choices in sensitivity analysis, and all results were consistent with the null hypothesis (i.e., no association). Study limitations include the assumption that confounders do not change over the 5-year observation period as well as the inherent limitations of observational datasets regarding missing or inconsistent data. Further research is necessary to examine differences in recent study findings regarding GLP-1-based therapies and pancreatitis.

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CONFLICT OF INTEREST

This study received no external funding. The authors (X. L., Z. Z., and J. D.) have received funding from Merck for other research; however, there was no external involvement in any aspect of the conception, planning, data analysis, or drafting of this study.

This work was presented as a poster at NIDDK Pancreatitis Diabetes Pancreatic Cancer Workshop, 12–13 June 2013, Lister Hill Auditorium, NIH, Bethesda, MD, USA.

KEY POINTS

- SCCS study may provide effective confounding control by contrasting risk profiles within a patient.
- Our SCCS analysis shows no evidence of an association between the use of GPL-1-based therapies and pancreatitis in an electronic medical records database.
- Our results are robust in that risk estimates are consistent for variations in at-risk period definitions, pancreatitis definitions, incident or recurrent pancreatitis, exposure as defined individual drugs or combined as a GPL-1 drug class.

ETHICS STATEMENT

This study was approved by the Indiana University IRB (#1307011853). No informed consent is required as this is a retrospective analysis of existing de-identified data.

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