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ORIGINAL ARTICLE

A prospective, claims-based assessment of the risk of pancreatitis and pancreatic cancer with liraglutide compared to other antidiabetic drugs

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Aim: We evaluated the relationship between liraglutide and acute pancreatitis or pancreatic cancer in an ongoing post-marketing safety assessment programme.

Methods: Initiators of liraglutide, exenatide, metformin, pioglitazone or groups containing initiators of dipeptidyl peptidase-4 inhibitors or sulfonylureas were identified in a US commercial health insurance claims database (1 February 2010 to 31 March 2013) and followed for a median of 15 months. We estimated incidence rates (IR/100 000 person-years), rate ratio (RR) and 95% confidence intervals (CI) of new insurance claims with diagnoses of primary inpatient acute pancreatitis or pancreatic cancer from Poisson regression models.

Results: The IR for acute pancreatitis for liraglutide was 187.5 compared with 154.4 for all non-glucagon-like peptide-1 (GLP-1)-based therapies (adjusted RR 1.10; CI 0.81–1.49). The IR for pancreatic cancer was 19.9 for liraglutide compared with 33.0 for all non-GLP-1-based therapies (adjusted RR 0.65; 95% CI 0.26–1.60).

Conclusion: We did not observe excess risk of either outcome associated with liraglutide relative to individual or pooled comparator drugs.

Keywords: GLP-1, pharmaco-epidemiology, observational study

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Introduction

Liraglutide is a once-daily glucagon-like peptide-1 (GLP-1) analogue for the treatment of type 2 diabetes. Before FDA approval, we initiated a prospective surveillance programme to evaluate potential adverse effects of liraglutide in the USA. Thyroid cancer is the primary endpoint; however, acute pancreatitis and pancreatic cancer are evaluated in the programme. Recent publications have questioned the pancreatic safety of other GLP-1 receptor agonists (GLP-1RAs) [1–5], thus we performed this interim analysis on acute pancreatitis and pancreatic cancer with liraglutide.

Research Design and Methods

In the surveillance programme, we use a prospective cohort design within the Optum Research Database of national commercial health insurance claims. Accrual is ongoing through 2014. Here we report on all adult initiators (ages 18 and over) of liraglutide or a comparator from 1 February 2010 through 31 December 2012, excluding individuals without medical and pharmacy benefits or less than 6 months of continuous health plan enrollment preceding drug initiation.

Baseline covariates were derived from 6 months of data preceding the date of drug initiation. Follow-up began on the day following initiation and continued until the earliest of insurance disenrollment, claim for acute pancreatitis or pancreatic cancer (separately), or 31 March 2013.

Acute pancreatitis was defined as a hospitalization with an International Classification of Disease, 9th Edition (ICD-9) diagnosis code of 577.0x (positive predictive value 60%) in the primary (first) position on the claim [6]. Pancreatic cancer was defined by an inpatient claim with ICD-9 157.x in the primary position. Individuals with a baseline diagnosis of the outcomes of interest were excluded from the corresponding analysis reported in this article, but not the surveillance programme. Recognizing that early claims for malignancy may represent pre-existing disease, analyses were conducted using all observed pancreatic cancers after drug initiation and, separately, the subset occurring more than 90 days after initiation. We estimated incidence rates (IR/100 000 person-years), rate ratios (RR) and 95% confidence intervals (CI) for liraglutide versus

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individual and pooled comparators using Poisson regression models. The primary analysis was an 'intention to treat' design in which initiators of a study drug were assumed to be on that drug until they experienced a study outcome or were censored. In addition, we conducted an 'as treated' analysis in which exposed person-time was categorized based on observed pharmacy dispensings. In the pooled analysis using metformin, three sulfonylurea therapies, and pioglitazone as a combined comparison group, we excluded exenatide and three dipeptidyl peptidase 4 inhibitors (DPP-4Is), because DPP-4Is and GLP-1RAs have been associated with pancreatic outcomes in previous studies [7,8]. In multivariable Poisson analysis, we controlled for age, gender, healthcare utilization and the Diabetes Complications and Severity Index [9]. We measured healthcare utilization using an index of emergency room visits, diagnoses, inpatient stays, drugs dispensed and physician visits.

Results

Liraglutide initiators were more likely to be women than initiators of all combined comparators (54.2% vs. 49.5%); median age was 53.0 for both groups. Liraglutide initiators had more baseline claims for overweight/obesity (21.2% vs. 13.1%), more indicators of diabetes severity (diabetic neuropathy, nephropathy or retinopathy: 15.7% vs. 8.3%; baseline insulin use: 28.1% vs. 10.3%), and fewer baseline diagnoses of chronic pancreatitis (0.05% vs. 0.14%). Baseline healthcare utilization was generally higher for liraglutide initiators including total costs (median $3235 vs. $1661). The median length of follow-up was 15 months; 29% of the initiators had more than 2 years of follow-up.

The IR per 100 000 person-years of acute pancreatitis for liraglutide was 187.5 compared with 154.4 for pooled comparators (adjusted RR 1.10; 95% CI 0.81–1.49), with rates for individual comparators ranging from 142.4 for metformin to 199.6 for pioglitazone (Table 1). The IR per 100 000 person-years of pancreatic cancer for liraglutide initiators was 19.9 compared with 33.0 for pooled comparators (adjusted RR 0.65; 95% CI 0.26–1.60). Observed IRs for individual comparators ranged from 23.0 for exenatide to 52.9 for the sulfonylureas. The results for both outcomes across individual comparators were similar. Among currently exposed person-time in the 'as treated' analyses, the results were similar (pooled comparators: acute pancreatitis, adjusted RR 1.17, 95% CI 0.86–1.59; pancreatic cancer, adjusted RR 0.40, 95% CI 0.13–1.28).

The median time between drug initiation and initial diagnosis for pancreatic cancer was 270 days across all drugs; 22% of the diagnoses were within the first 90 days. Initiators of liraglutide or exenatide had no early diagnoses, while 7–28% of cancer diagnoses among comparators were within the first 90 days following initiation. Accordingly, in a separate analysis, we excluded diagnoses during the first 90 days of follow-up. The IR among liraglutide initiators remained the same (19.9/100 000 person-years) and for pooled comparators reduced to 25.2/100 000 person-years. The adjusted RR was 0.82 (95% CI 0.33–2.05), with adjusted RRs for individual comparators

Table 1. Association between liraglutide and treatment-emergent primary inpatient* acute pancreatitis and pancreatic cancer relative to other specific comparator drugs, and pooled comparator drugs†– intention to treat.

	No. of cases	Person-years‡	IR/100 000 person-years	Adjusted RR, liraglutide versus comparator§	95% CI
Acute pancreatitis					
Liraglutide	47	25 072	187.5		
Pooled comparator drugs, excluding exenatide and DPP-4 inhibitors	472	305 621	154.4	1.10	0.81–1.49
Exenatide (excluding extended release exenatide)	24	13 008	184.5	1.00	0.61–1.63
DPP-4 inhibitors (sitagliptin/saxagliptin/linagliptin)	69	40 364	170.9	1.06	0.73–1.56
Metformin	295	207 177	142.4	1.14	0.83–1.56
Sulfonylureas (glyburide/glipizide/glimiperide)	101	60 361	167.3	1.04	0.73–1.48
Pioglitazone	76	38 083	199.6	0.95	0.65–1.39
Pancreatic cancer					
Liraglutide	5	25 114	19.9		
Pooled comparator drugs, excluding exenatide and DPP-4 inhibitors	101	306,064	33.0	0.65	0.26–1.60
Exenatide (excluding extended release exenatide)	3	13 036	23.0	0.84	0.20–3.52
DPP-4 inhibitors (sitagliptin/saxagliptin/linagliptin)	15	40 424	37.1	0.71	0.25–2.00
Metformin	55	207,458	26.5	0.81	0.32–2.05
Sulfonylureas (glyburide/glipizide/glimiperide)	32	60 443	52.9	0.40	0.15–1.06
Pioglitazone	14	38 163	36.7	0.49	0.17–1.41

IR, incidence rate; CI, confidence interval; RR, relative risk.

*Both outcomes are identified by primary inpatient hospital claims only. Individuals with baseline claims for acute pancreatitis or pancreatic cancer were excluded from the analysis for that outcome.

†Follow-up time for all initiators of the six study drugs/drug combinations began on the day after they initiated the study drug(s) that defines their cohort. Follow-up ended on the earliest of the following: disenrollment from the health plan, primary inpatient claim for acute pancreatitis /pancreatic cancer or 31 March 2013.

‡Person-years vary slightly between the calculations for acute pancreatitis and pancreatic cancer because follow-up time is truncated at the occurrence of the event.

§Factors included in the Poisson regression equation include age, gender, healthcare utilization and Diabetes Complications and Severity Index.

ranging from 0.52 to 1.06, and none approaching statistical significance.

Conclusions

The IRs of health insurance claims representing acute pancreatitis or pancreatic cancer among recipients of liraglutide were similar to those among comparators. The findings for acute pancreatitis are similar to estimates from insurance claims analyses regarding exenatide [4,5,10].

The use of large insurance claims databases permits the rapid study of large numbers of patients under routine care. However, some limitations exist in our analysis regarding outcome ascertainment. The median follow-up time for the study subjects was 15 months. While the length of this period may be sufficient for acute pancreatitis, it may be inadequate for the long-latency outcome of pancreatic cancer. These interim results are based on un-adjudicated diagnoses and the IRs for both outcomes are likely overestimated. Up to 40% of individuals with a primary inpatient diagnostic code for acute pancreatitis will not have a confirmed diagnosis [6]. The accuracy of claims-based pancreatic cancer diagnoses is unclear. Limiting to primary inpatient claims is intended to reduce misclassification resulting from 'rule out' diagnosis or prior history of pancreatic cancer.

Patient attributes may impact the choice of specific therapy. For example, latent pancreatic cancer may affect glycemic control and result in the initiation of newer antidiabetic therapies, including liraglutide [11]. Alternatively, physicians may be less likely to prescribe liraglutide to patients with pancreatitis, a risk factor for pancreatic cancer, because concerns have been raised. Physicians may also monitor users of GLP-1RAs more closely for these outcomes [12], although we observed no claims for pancreatic cancer in the first 90 days of follow-up of liraglutide relative to comparators with up to 28%.

Other methodology issues need to be considered in interpreting these interim findings. There were differences between liraglutide initiators and comparators on several baseline variables. While attempts were made to statistically control for some of these differences, residual confounding may remain. We found similar results using the 'intention to treat' and the 'as treated' approaches, although the 'as treated' analysis may have greater residual confounding because, while exposure status was updated through follow-up, covariate status was not. Similarly, the 'as treated' analysis more strongly assumes that discontinuation of treatment is comparably prognostic for liraglutide and comparators, which is difficult to test.

In summary, we observed no increased risk for acute pancreatitis or pancreatic cancer in association with liraglutide treatment. Future analyses within this data resource will be based on larger cohorts, more follow-up time, and adjudicated outcomes of interest (through review of medical records). Analyses will consider actual treatment patterns in more detail and explore multiple drug combinations.

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Conflict of Interest

D. F. is an employee of Optum. K. A. C. was an employee of Optum at the time this work was done. H. G., A. M-P. and K. T. are employees of and hold minor portions of employee shares in Novo Nordisk A/S. D. F. participated in the design, conduct, analysis and writing. H. G., K. T. and A. M-P. participated in the writing, K. A. C. participated in the design, analysis and writing.

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