Incidence of health insurance claims for thyroid neoplasm and pancreatic malignancy in association with exenatide: signal refinement using active safety surveillance

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Abstract:

Objectives: As part of a regulatory postmarketing commitment, we assessed the risk of claims for thyroid and pancreatic cancer among users of exenatide using an active drug safety surveillance system.

Methods: This active surveillance assessment used cohort methodology and commercial health insurance claims data to identify initiators of exenatide and propensity score-matched initiators of metformin or glyburide between June 2005 and September 2009, with up to 1 year of follow up through December 2009. The primary analysis estimated absolute and relative risk (RR) of inpatient or outpatient claims with diagnosis codes for thyroid neoplasm (benign or malignant) or pancreatic malignancies after exclusion of patients with a history of the same diagnosis at baseline.

Results: Among the matched comparison cohorts ($N \approx 32{,}800$ each), there were 37 claims-suggested thyroid malignancies among exenatide initiators and 26 among metformin or glyburide initiators [RR 1.4; 95% confidence interval (CI) 0.8–2.4]. This association was attenuated when limited to inpatient thyroid cancer claims (RR 0.9; CI 0.3–2.6). Exenatide use was not associated with an increased risk of benign thyroid neoplasm (RR 0.7; CI 0.3–1.7), or pancreatic cancer (RR 0.8; CI 0.5–1.6).

Conclusions: Use of exenatide was associated with a modestly higher incidence of inpatient and outpatient claims, but not inpatient claims for thyroid malignancies. Exenatide was not associated with higher risk of benign thyroid neoplasm or pancreatic cancer. Misclassification of outcomes and exposure, and residual confounding remain limitations of this analysis to be considered when interpreting the results. We have initiated a formal epidemiologic investigation to explore these relationships.

Keywords: active safety surveillance, exenatide, pancreatic cancer, safety signal, thyroid cancer

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Introduction

Exenatide is an incretin mimetic that when taken twice daily enhances endogenous insulin production, suppresses postprandial glucagon, and reduces food intake [Byetta Prescribing Information, 2010]. Another incretin mimetic, liraglutide, was found to increase the risk of c-cell tumors in rodents exposed to clinically relevant doses, leading to concern about the occurrence of medullary thyroid cancer (MTC), a c-cell cancer, in humans [Victoza Prescribing Information, 2010]. In January 2010, the US Food and Drug Administration (FDA) approved liraglutide. The product's approval was contingent on the manufacturer conducting or sponsoring a number of post-marketing studies, including studies to assess the association between liraglutide and MTC, and thyroid cancer generally [Parks and Rosebraugh, 2010].

Following the rodent findings of c-cell cancers associated with liraglutide, concerns have been raised about thyroid cancer outcomes associated with all incretin mimetics. Concerns also exist about the risk of pancreatic cancer secondary to incretin mimetics [Elashoff *et al.* 2011]. In October 2009, the FDA approved a new indication for exenatide as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus, including monotherapy with exenatide. As part of the approval, the FDA requested that the manufacturer of exenatide conduct an assessment of the thyroid and pancreatic cancer signals using an active safety surveillance system. We report data from this active safety surveillance system (i3 Aperio, OptumInsight Epidemiology, Waltham, MA, USA) on the incidence of health insurance claims for thyroid neoplasm (benign or malignant separately and together) and pancreatic cancer in people who initiated exenatide relative to a propensity score-matched cohort that initiated metformin or glyburide, as a safety signal refinement exercise.

Patients and methods

Data source

The methods and data source of the safety surveillance system with respect to exenatide are published elsewhere [Dore *et al.* 2009]. The source population came from the Normative Health Information (NHI) database, a large, geographically diverse population of health insurance plan enrollees. The records in the NHI database include provider and facility claims, outpatient pharmacy dispensing records, and an enrollment file that contains demographic data and dates of insurance eligibility for people on the database.

Formation of comparison groups

The analysis included patients who initiated the twice-daily formulation of exenatide or metformin or glyburide and were listed on the NHI database between 1 June 2005 and 30 September 2009, with follow up through 31 December 2009. Initiation was defined as a dispensing of the study drug preceded by 6 months of continuous health plan enrollment without a dispensing of the same drug. Exposure status during follow up (exenatide or metformin/glyburide) was defined as the drug dispensed that qualified the patient for cohort entry. Patients in the exenatide cohort were matched to those in the metformin or glyburide cohort on the propensity score [Seeger *et al.* 2005]. The baseline covariates were ascertained from the 6 months of claims data preceding the date of study drug initiation.

The propensity score analysis involved two stages, the first being the development of the propensity score using baseline patient characteristics. These variables were determined from the NHI database from the time leading up to patients' entry into the cohorts. The second stage involved matching exenatide initiators to initiators of metformin or glyburide using a greedy matching algorithm that first identified patients with matching propensity scores to eight decimal digits of precision and was iteratively loosened by one decimal digit, stopping at the first decimal digit. Matching on propensity scores results in two study cohorts with similar prevalence of characteristics that are included in the model at the start of treatment [Rosenbaum and Rubin, 1983].

The final propensity score model included variables representing age, sex, geographic region, paid hospital costs, paid pharmacy costs, paid emergency room costs, total paid insurance costs, total paid patient costs, and the number of unique three-digit International Classification of Disease (ICD) diagnoses, drugs, physician visits, emergency room visits, hospital stay days, laboratory tests, procedures, days available for the baseline period, and total days of enrollment.

Outcomes and analysis

Follow up occurred from cohort entry until 1 year following initiation of the study drug or disenrollment from the health insurance plan, whichever was earliest. We tabulated the prevalence of baseline characteristics derived from insurance claims in the 6 months before cohort entry. The exposure classification was an analog of intention-to-treat analysis. Each day of follow up, the patient was considered to be exposed to the baseline exposure category (exenatide *versus* metformin or glyburide) and subsequent changes in the medication regimen were ignored. We estimated the cumulative incidence of thyroid neoplasm or pancreatic cancer, the relative risk (RR) across cohorts, and 95% confidence intervals (CIs). The outcomes were identified by the presence of one or more inpatient or outpatient claims during follow up associated with pancreatic cancer [ICD, 9th revision (ICD-9) 157.xx], benign thyroid neoplasm (ICD-9 226), or malignant

thyroid neoplasm (ICD-9 193). In the primary analysis, we limited estimation of the absolute and relative risk (using 2 × 2 tables) to patients who had no claim for the same diagnosis in the 6-month baseline period (treatment-emergent outcomes).

This assessment included three sensitivity analyses. The first analysis included a lag period between cohort entry and when follow-up person-time was considered at risk, an approach aimed at mitigating the potential attenuation of the RR that can result when patients are considered at risk for the outcomes immediately after the initiation of exposure, but when the outcomes are expected to occur after some induction or latency period. We excluded from the numerator of the risk calculations cases that occurred in the first 90 or 180 days, separately, using the primary (inpatient and outpatient) outcome definition. Second, we restricted identification of the outcomes to inpatient facility claims with the code of interest listed in the first position with the aim of understanding whether this approach might be less biased than the primary approach of also including outpatient physician claims for outcome identification. The third sensitivity analysis aimed to remove remaining imbalance in the utilization of healthcare services across the exposure cohorts through a stratified analysis. We estimated the RR of thyroid cancer based on the primary (inpatient and outpatient) outcome definition within strata defined by the number physician visits (1−3, 4−6, or ≥7) in the 6 months prior to cohort entry. The latter two sensitivity analyses were among all patients (before exclusion of prevalent cases) after the observation that exclusion according to cancer history did not appreciably alter the RR estimates.

Results

Table 1 lists select baseline characteristics of patients in the exenatide and metformin or glyburide cohorts. There were 32,894 patients in each matched cohort prior to exclusion for baseline history of the cancers of interest. A small number of patients were excluded from each cohort upon estimation of cancer incidence proportions (Table 2). The cohorts had similar age and sex distributions, with about two-thirds of the population aged between 40 and 59 years, and approximately 55% women. There were residual imbalances in a number of baseline patient characteristics, including a higher baseline prevalence of a recorded diabetes diagnosis, retinal disorders, use of lipotropics, and use of several antihyperglycemic drugs in the exenatide cohort.

The median days of drug supply received by the exenatide cohort was 140 days across a median of four dispensings (Table 2). The median time between first and last exenatide dispensing was 234 days and 33.9% of patients in the exenatide cohort received a dispensing of that drug within 30 days of the end of follow up, indicating ongoing or continued use.

The absolute risk of claims for all study outcomes was as high as 0.4% in the follow up of the overall cohorts (≤1 year), but was reduced to less than 0.2% after baseline exclusions for the same cancer (Table 3). After these exclusions, there were 46 patients with claims-suggested thyroid neoplasm among exenatide initiators and 40 among metformin or glyburide initiators (RR 1.2; 95% CI 0.7−1.8). The estimated risk of claims for benign thyroid neoplasms was similar across the two cohorts (RR 0.7; 95% CI 0.3−1.7), while we observed a somewhat higher risk of claims for thyroid malignancies (RR 1.4; 95% CI 0.8−2.4) in the exenatide cohort. The observed incidence of claims for pancreatic cancer was similar in the exenatide cohort relative to comparators (RR 0.8; 95% CI 0.5−1.6). The RR estimates from the cohorts before baseline exclusions were similar to the treatment-emergent values.

The results of the sensitivity analyses were generally consistent with the overall results. Restriction to outcomes identified from first-position diagnosis codes on inpatient claims resulted in a reduced RR for pancreatic and thyroid outcomes, but wider confidence intervals. For thyroid malignancy, the estimated RR was 0.9 (95% CI 0.3−2.6). The estimated RRs without cases from the first 90 or 180 days of follow up were similar to the main results. The RRs within the strata of one to three and four to six baseline physician visits were also similar to the overall results; however, the RR of thyroid cancer was attenuated among patients with at least seven baseline physician visits.

Discussion

We found that exenatide use was associated with a somewhat higher incidence of combined outpatient and inpatient health insurance claims, but no increased incidence of inpatient claims for

Table 1. Select baseline demographic and clinical characteristics of exenatide and metformin or glyburide initiators in the Normative Health Information database after propensity-score matching, 1 June 2005–30 September 2009.*

	Exenatide initiators (*N* = 32,894)		Metformin or glyburide initiators (*N* = 32,894)	
	N	%	*N*	%
Demographic characteristics				
Age				
≤ 19	93	0.3	100	0.3
20–39	3697	11.2	3528	10.7
40–49	8106	24.6	8100	24.6
50–59	13,043	39.7	13,156	40.0
≥ 60	7955	24.2	8010	24.4
Women	18,033	54.8	18,314	55.7
Race				
African American/non-Hispanic black	1603	4.9	1780	5.4
Asian	217	0.7	363	1.1
Hispanic	1669	5.1	1712	5.2
Non-Hispanic white	17,594	53.5	16,615	50.5
Other or unknown race	11,811	35.9	12,424	37.8
Baseline diagnoses				
Diabetes mellitus (ICD-9 250)	26,673	81.1	16,195	49.2
Disorders of lipid metabolism (ICD-9 272)	18,357	55.8	13,726	41.7
Essential hypertension (ICD-9 401)	18,185	55.3	15,659	47.6
Overweight, obesity, or other hyperalimentation (ICD-9 278)	4296	13.1	2355	7.2
Cardiac dysrhythmias (ICD-9 427)	1042	3.2	1190	3.6
Heart failure (ICD-9 428)	777	2.4	807	2.5
Acquired hypothyroidism (ICD-9 244)	3031	9.2	2640	8.0
Other retinal disorders (ICD-9 362)	1124	3.4	494	1.5
Chronic kidney disease (ICD-9 585)	682	2.1	294	0.9
Top 10 pharmacy dispensing				
Hypoglycemics, biguanide type (non-sulfonylureas)	16,383	49.8	3	0.0
Lipotropics	16,287	49.5	12,961	39.4
Hypoglycemics, insulin-release stimulant type	14,746	44.8	4902	14.9
Blood sugar diagnostics	13,522	41.1	7797	23.7
Hypoglycemics, insulin-response enhancer (non-sulfonylureas)	13,357	40.6	5434	16.5
Hypotensive, angiotensin-converting enzyme inhibitors	11,993	36.5	9125	27.7
Needles/needleless devices	10,196	31.0	1074	3.3
Analgesics, narcotics	8291	25.2	11,193	34.0
Hypotensive, angiotensin receptor antagonist	7686	23.4	5986	18.2
Insulins	7700	23.4	3373	10.3
Healthcare utilization				
Total costs, US$ (mean, median)	4799	2551	4967	2224
Number of physician visits (mean, median)	5.2	4.0	5.3	4.0
Number of drugs dispensed	11.0	10.0	11.1	10.0

*Data derived from claims for healthcare services in the 6 months prior to study drug initiation using the i3 Aperio (OptumInsight Epidemiology, Waltham, MA, USA) active drug safety surveillance system.
ICD-9, International Classification of Disease.

Table 2. Characteristics of utilization of exenatide and metformin/glyburide during follow up among exenatide and metformin or glyburide initiators, Normative Health Information database, 1 June 2005–31 December 2009.

	Exenatide initiators (*N* = 32,894)			Metformin or glyburide initiators (*N* = 32,894)		
	Mean	Median	IQR	Mean	Median	IQR
Exenatide use						
Number of people with at least one dispensing during follow up (*N*, %)	32,894	100.0		1,521	4.6	
Number of dispensings per person	4.8	4.0	5.0	3.7	3.0	4.0
Total days supplied per person	167.5	140.0	210.0	129.9	90.0	120.0
Drug strength (μg)	8.0	8.8	5.0	8.0	8.9	5.0
Time from first to last dispensing (days)	217.2	234.0	227.0	160.8	144.0	173.0
Medication possession ratio	0.8	0.8	0.4	0.9	0.8	0.4
Patients with dispensing within 30 days before end of follow up (*N*, %)	11,155	33.9		646	2.0	
Metformin or glyburide use						
Number of people with at least one dispensing during follow up (*N*, %)	20,101	61.1		32,894	100.0	
Number of dispensings per person	6.0	5.0	6.0	5.3	4.0	6.0
Total units dispensed per person (tablets)	627.3	540.0	570.0	382.3	300.0	450.0
Total days supplied per person	231.0	240.0	210.0	190.4	180.0	240.0
Quantity per day (tablets)	2.7	2.0	2.0	2.0	2.0	0.5
Time from first to last dispensing (days)	238.7	271.0	168.0	235.9	277.0	213.0
Medication possession ratio	0.9	0.9	0.3	0.8	0.9	0.4
Patients with dispensing within 30 days before end of follow up (*N*, %)	10,990	33.4		13,977	42.5	

IQR, interquartile range.

thyroid malignancy. Exenatide use was not associated with increased incidence of claims for benign thyroid neoplasm or pancreatic cancer compared with glyburide/metformin use. The surveillance system used for this evaluation is a signal generation and refinement tool that allowed for rapid (within 1 week of learning of the initial signal) assessment of a safety signal of these rare neoplasms in association with exenatide adding to information from clinical trials and spontaneous adverse drug reaction reports. The features of clinical trials that promote valid and efficient assessments of efficacy represent limitations in the context of safety surveillance. Their generally small size, homogeneous populations, and short-term follow up means that adverse outcomes occurring in less than 1 in 1000 patients tend not to be reliably identified and investigated [ICH, 1995], and this limitation cannot be addressed in the context of the premarket assessment without adding considerably to the time and expense of drug approval [Committee on the Assessment of the US Drug Safety System, 2007]. Active safety surveillance systems provide context to safety signals derived from spontaneous reports by allowing for a rapid assessment of signals in a population with a known denominator, allowing for estimation of incidence, and in the case of this analysis, control for some differences in baseline risk for the outcomes across the exposure cohorts through propensity-score matching.

However, the surveillance system and the source data have limitations that warrant discussion [Crystal *et al.* 2007; Walker, 2001]. Health insurance claims data are collected for the purpose of justifying and tracking reimbursement to providers and facilities for healthcare services rendered, and include certain descriptions of the patients and services performed for those

Table 3. Absolute and relative risk of treatment-emergent inpatient and outpatient claims associated with diagnoses of pancreatic and thyroid neoplasm among exenatide and metformin or glyburide initiators, Normative Health Information database, 1 June 2005–31 December 2009.

	Cases (*N*)	Patients (*N*)	Absolute risk (%)	Relative risk	95% CI
Cases identified from inpatient or outpatient claims					
All thyroid neoplasms					
Exenatide	46	32,807	0.1	1.2	0.7–1.8
Metformin/glyburide	40	32,828	0.1	1	reference
Benign thyroid neoplasms					
Exenatide	11	32,877	0	0.7	0.3–1.7
Metformin/glyburide	15	32,879	0	1	reference
Thyroid malignancies					
Exenatide	37	32,822	0.1	1.4	0.8–2.4
Metformin/glyburide	26	32,842	0.1	1	reference
Pancreatic malignancy					
Exenatide	21	32,889	0.1	0.8	0.5–1.6
Metformin/glyburide	25	32,878	0.1	1	reference
Cases identified from inpatient claims only					
All thyroid neoplasms					
Exenatide	7	32,894	0.0	0.7	0.2–2.0
Metformin/glyburide	10	32,894	0.0	1.0	reference
Benign thyroid neoplasms					
Exenatide	0	32,894	0.0	0.0	0.0–4.1
Metformin/glyburide	2	32,894	0.0	1.0	reference
Thyroid malignancies					
Exenatide	7	32,894	0.0	0.9	0.3–2.6
Metformin/glyburide	8	32,894	0.0	1.0	reference
Pancreatic malignancy					
Exenatide	12	32,894	0.0	0.5	0.2–1.1
Metformin/glyburide	23	32,894	0.1	1.0	reference

CI, confidence interval.

purposes. Because these descriptors are not collected for clinical care or research purposes, lack of correspondence between this information and true patient disposition can result in biased RRs [Lanes and de Luise, 2006]. Of particular relevance here is the correspondence between the diagnosis codes for the neoplasm outcomes and the patient's actual diagnosis (or lack thereof). Others have shown that assessments of cancer outcomes in health insurance claims data that define the cancer based on a single diagnosis code can be problematic because the outcome definition will have a low positive predictive value and misclassify some patients' cancer status [Setoguchi *et al.* 2007]. Indeed, the incidence estimates from our primary (inpatient and outpatient) data are substantially higher than the 5.2–15.2 cases per 100,000 person-years observed in population-based cancer surveillance, consistent with inclusion of false-positive cases from the health insurance claims; however, the diagnoses from first-position inpatient claims resulted in more plausible incidence estimates [Altekruse *et al.* 2010]. The analyses that did not exclude patients with claims for the cancer outcomes in the baseline period resulted in even higher incidence estimates relative to the treatment-emergent analysis, reflecting the identification of prevalent cases during follow up.

In studies based on health insurance claims data, this type of error resulting from the outcome definition will generally bias the RRs toward showing no effect – although this direction of bias need not be the case [Jurek *et al.* 2008]. A form of surveillance bias when thyroid cancer was more readily detected among exenatide users is one potential explanation for the finding of excess risk

of thyroid cancer claims in the exenatide cohort. This differential detection could plausibly occur if exenatide users sought more healthcare services during follow up, a difference that was evident in a previous study of exenatide [Dore *et al.* 2011]. We aimed to address this potential surveillance bias by stratifying the RR estimation by the number of physician visits observed in the baseline period among all patients (before exclusion) with the rationale being that within these strata, overall healthcare utilization might be similar during follow up.

Another consideration is that if the relationship between exenatide and these outcomes (should it exist) has a long induction or latency period, then any increase in the risk of the outcomes due to exenatide exposure would not be observed in this study, in which the average follow-up time was less than 1 year. In the absence of other biases, the estimated RR would be attenuated with insufficient follow up if there was a true effect of exenatide on thyroid cancer. With the outcome of thyroid malignancy in this study, in which the RR was 1.4, this type of bias did not appear to be sufficiently strong to obscure the signal altogether, but may still have biased the estimate toward showing no effect; or alternatively, any bias through this mechanism was negligible relative to other sources of bias (e.g. residual confounding).

Insufficient follow-up time might have resulted in a more severely biased RR estimate in a previous assessment of exenatide and thyroid cancer we conducted in the active safety surveillance system. In this previous assessment, cohort follow up was censored upon the apparent discontinuation of the study drug (exenatide or metformin/glyburide), reducing the average length of follow up. With this methodology, the analysis was consistent with no association between exenatide use and thyroid malignancy using the same outcome definitions and propensity score technique (data not shown).

It is also possible that the surveillance system's characterization of exposure to exenatide and metformin or glyburide affected the study results. First, this type of analysis assumes that pharmacy dispensings for the study drugs reflect patient consumption. While it is likely that some patients who received the study drugs did not take them as prescribed, these data are generally accepted as accurate [Crystal *et al.* 2007; McKenzie *et al.* 2000], and are at least as accurate as patient report [Leister *et al.* 1981; West *et al.* 1995]. Despite the probable accuracy of the pharmacy claims data, it remains possible that the average duration of exposure to exenatide in this assessment was insufficient to affect the incidence of thyroid malignancy and pancreatic cancer. To our knowledge, there are no data to inform whether the median apparent duration of exenatide exposure in this study (140 days) was sufficient to induce the malignancies of interest. Additionally, this analysis did not account for switching off study drugs; rather all patients were categorized as exposed from the time of cohort entry until the end of his or her follow up, although this exposure categorization may be appropriate for cancer outcomes.

The propensity-score matching applied by the active safety surveillance system removed many baseline differences in potential risk factors for the outcomes between the two exposure cohorts. Indeed, in the case of rare outcomes among large cohorts, propensity scores perform particularly well because they can account for many variables that might be associated with a higher risk of the outcomes among one of the exposure cohorts [Seeger *et al.* 2005]. However, residual differences in the baseline risk can remain if the propensity score does not include measures for all of the relevant predictors of the outcome, as might be the case with the parsimonious model the surveillance system employed for the present comparison [Rosenbaum and Rubin, 1983]. Depending on the association between these variables not included in the propensity score and the exposure and outcome, the observed RRs can be spuriously higher or lower as a result. This limitation of the present analysis is a reasonable alternative explanation for the observation of a higher risk of claims for thyroid malignancy in the exenatide cohort. We observed a higher prevalence of a number of indicators of diabetes severity in the exenatide cohort, and if diabetes severity or its treatment results in thyroid cancer, then residual confounding would potentially explain the observed results [e.g. Currie *et al.* 2009].

In summary, we observed a marginally higher incidence of combined outpatient and inpatient claims for thyroid malignancy, but no increased risk of inpatient claims only for thyroid malignancies. No increased risk of benign thyroid neoplasm or pancreatic cancer in association with exenatide use was observed in this rapid safety assessment program. These findings should be considered in

the context of the limitations outlined above, taken together, and greater clarity with respect to the long-term effect of exenatide will require further study so that appropriate benefit–risk evaluations can be made for the prescribing of exenatide. A formal epidemiologic study of exenatide use and thyroid cancer to address the limitations of this active safety assessment has been initiated.

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Conflict of interest statement

Drs Dore, Seeger, and Chan were employees of OptumInsight Epidemiology at the time this work was conducted. The research contract granted OptumInsight Epidemiology oversight of the study conduct, reporting, and interpretation, as well as final wording of any resulting manuscripts.

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