The Safety of Incretin-Based Therapies—Review of the Scientific Evidence

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Context: Antidiabetic therapies based on potentiation of incretin action are now widely used; however, understanding of their long-term safety remains incomplete.

Evidence Acquisition: We searched articles in PubMed for data assessing the safety of incretin-based therapies.

Evidence Synthesis: Three major areas of interest are reviewed: incretin action in the cardiovascular system, pancreatitis, and cancer. Incretin therapies reduce weight gain, minimize hypoglycemia, decrease inflammation, and are cardioprotective in preclinical studies. However, data permitting conclusions about whether incretin therapies modify the development of cardiovascular events in humans are not available. Case reports link incretin therapies to pancreatitis, but retrospective case control studies do not associate pancreatitis with glucagon-like peptide-1 receptor (GLP-1R) agonists or dipeptidyl peptidase-4 inhibitors. Preclinical studies of pancreatitis have yielded conflicting results, and mechanisms linking incretin receptor activation to pancreatic inflammation have not yet been forthcoming. GLP-1R activation promotes C-cell hyperplasia and medullary thyroid cancer in rodents; however, long-term clinical studies of sufficient size and duration to permit conclusions regarding cancer and incretin therapeutics have not yet been completed.

Conclusions: The available data on incretin action and incidence of cardiovascular events, pancreatitis, or cancer are not yet sufficient or robust enough to permit firm conclusions regarding associations with incretin-based therapies in humans with diabetes. The forthcoming results of long-term cardiovascular safety studies should provide more conclusive information about the safety of GLP-1R agonists and dipeptidyl peptidase-4 inhibitors in diabetic patients. (*J Clin Endocrinol Metab* 96: 2027–2031, 2011)

The efficacy and safety of therapies for type 2 diabetes mellitus (T2DM) remain a subject of intense interest, invigorated by recent discussions of the cardiovascular safety of thiazolidinediones and the ongoing debate about whether a putative link exists between insulin therapy and the incidence of cancer in patients with T2DM. Over 1 yr ago, we summarized available knowledge surrounding the risks and benefits of incretin-based therapies [dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists], with a focus on cardiovascular mechanisms of action and preclinical and epidemiological data on pancreatitis and medullary thyroid cancer (1). Because several new clinical and preclinical studies have recently been published that address the safety of incretin-based therapies (2–6), we now present a concise update incorporating recent information that further illuminates our understanding of the risks and benefits of these two new classes of antidiabetic agents.

Abbreviations: DPP-4, Dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; GLP-1R, GLP-1 receptor; T2DM, type 2 diabetes mellitus.

Cardiovascular Effects of Incretin Hormones

The cardiovascular actions of GLP-1 receptor (GLP-1R) agonists and DPP-4 inhibitors include cardioprotection in preclinical studies of normoglycemic and diabetic rodents and pigs and reductions in blood pressure, postprandial lipids, and markers of inflammation and oxidative stress in clinical studies (7, 8). Putative beneficial effects of GLP-1R agonists in human subjects with congestive heart failure have not yet been replicated (9). An increase in heart rate of several beats per minute may be seen in some patients treated with GLP-1R agonists, the clinical significance of which is uncertain. Available data from health care insurance claims database analyses reveal that patients treated with exenatide from 2005–2009 were significantly less likely to have a cardiovascular event or hospitalization relative to subjects treated with other glucose-lowering therapies (2). Nevertheless, the potential for incomplete capture of key variables in claims data, such as weight, smoking, alcohol consumption, lipids, blood pressure, and hemoglobin A1C, is a major limitation of such analyses. Multiple prospective adjudicated randomized long-term cardiovascular outcome studies are now under way with individual GLP-1R agonists and DPP-4 inhibitors that will provide important information about the cardiovascular safety of these agents (8).

Pancreatitis: Preclinical Studies

Preclinical studies of incretin-based therapies have yielded conflicting results and failed to reveal a mechanism linking GLP-1R activation or DPP-4 inhibition to the pathophysiology of acute pancreatitis. The observation that a single transgenic rat with marked overexpression of human amylin in pancreatic β-cells developed histological evidence for pancreatitis with sitagliptin (10) was followed by demonstration of acinar inflammation in 10 nondiabetic rats treated for 75 d with exenatide (11); however, the exenatide-treated rats lost 30% of their body weight, no weight-matched controls were included, and weight loss is a well-recognized risk factor for pancreatitis. In contrast, much larger studies of normal and diabetic mice and rats treated with exenatide, sitagliptin, or liraglutide before or after induction of experimental pancreatic injury did not find a relationship between incretin therapy and the development of pancreatitis (4, 6, 12). Remarkably, GLP-1R activation was associated, in two independent studies (6, 12), with attenuated expression of proinflammatory genes and proteins and reduction of histological injury in the exocrine pancreas. GLP-1R agonists may also modify cholangiocyte function; however, little data are available regarding the effects of GLP-1R agonists on bile composition or biliary tract motility in humans.

It seems likely that preclinical studies represent imperfect models for predicting the ability of incretin-based therapies to promote pancreatitis in human subjects. Animal studies generally employ healthy rodents exposed to drugs for brief periods, without concomitant pancreatic disease, obesity, dyslipidemia, or gallstones. In contrast, patients with T2DM may be frequently less healthy and exhibit multiple risk factors known to predispose them to pancreatitis. Hence, given these limitations, the lack of evidence or mechanism to date in studies probing a link between incretin pathways and the development of pancreatitis must be interpreted with caution.

Pancreatitis: Clinical Data

Because patients with T2DM exhibit significantly increased rates of acute pancreatitis (13, 14), large case control studies are required to ascertain whether a specific antidiabetic therapy independently modifies the risk of developing pancreatitis. Rates of hospitalization for acute pancreatitis were comparable in patients initiating exenatide, sitagliptin, metformin, or glyburide from June 2005 to June 2008 using the i3 Aperio administrative health care claims database (15). A related study using the Normative Health Information Database examined rates of acute pancreatitis (from emergency room or hospitalization records) in patients initiating antidiabetic therapy from June 2005 to December 2007. Exenatide therapy was not associated with an increased relative risk of developing pancreatitis compared with use of other antidiabetic agents (16). Similarly, pooled analysis of randomized controlled clinical trial data (10,246 patients) did not reveal an increased rate of pancreatitis in subjects treated with sitagliptin (4). Garg *et al.* (17) analyzed rates of acute pancreatitis in diabetic subjects treated with exenatide, sitagliptin, or other antidiabetic agents using data from the Medco National Integrated Database from January 2007 to June 2009. Although rates of pancreatitis were higher in diabetic *vs.* nondiabetic subjects, use of exenatide or sitagliptin was not associated with increased rates of pancreatitis (17). Rates of pancreatitis were slightly higher with liraglutide in the Liraglutide Effect and Action in Diabetes (LEAD) clinical trial program, but the small number of reported events and patients does not permit clear conclusions to be made (18). Hence, the available data from multiple independent sources does not currently support a mechanistic or epidemiological link between incretin therapies and the development of acute pancreatitis; however, longer studies with greater numbers of

patients are needed for more robust conclusions to be drawn. Moreover, the use of administrative claims databases for analysis of drug safety is imperfect because diagnoses may not always meet stringent clinical definitions, the prevalence of events may be underestimated due to underreporting, and individual cases are not always independently adjudicated and verified. However, these analyses provide defined numerators and denominators, information about medication use, baseline historical data, and the opportunity to interrogate large numbers of patient events over defined time periods.

Incretin Therapies and Cancer

Considerable epidemiological evidence supports a relationship between T2DM and an increased rate of certain cancers (19), and there is intense interest in understanding whether specific antidiabetic agents, notably metformin and insulin, modify the likelihood of developing cancer (20). The rodent calcitonin-producing thyroid C cell expresses functional GLP-1Rs, and sustained GLP-1R activation results in increased calcitonin secretion, C-cell hyperplasia, and medullary thyroid cancer, predominantly in rats (21). In contrast, C cells within the monkey and human thyroid gland exhibit lower levels of GLP-1R expression, and prolonged administration of liraglutide at very high doses does not produce C-cell proliferation in monkeys (21). Moreover, analysis of sequential changes in calcitonin levels in several thousand diabetic subjects did not reveal a relationship between liraglutide therapy and plasma calcitonin (5, 21). Hence, the considerable differences in the biology of the rodent *vs.* human thyroid GLP-1R system have led regulatory authorities to conclude that the risk for development of medullary thyroid cancer with GLP-1 therapy in humans is low and difficult to quantify (18).

Use of the AERS Database for Detection of Adverse Events

A recently published study using the AERS (Adverse Event Reporting System) database concluded that therapy with sitagliptin or exenatide was associated with a 6-fold increased risk of developing pancreatitis and increased reports of pancreatic cancer, and the first published proof reported more frequent reports of cancer in subjects treated with sitagliptin (3). Elashoff *et al.* (3) examined reports of adverse events associated with the use of sitagliptin or exenatide from 2004–2009 and compared the number of events (primary outcomes were pancreatitis and pancreatic and thyroid cancer) reported with these two incretin-based therapies with data reported for use of rosiglitazone, nateglinide, repaglinide, and glipizide (3). Additional reported events that were arbitrarily selected as controls for reporting were back pain, urinary tract infection, chest pain, cough, and syncope. Curiously, pioglitazone, initially selected as a control drug, was found to be associated with higher than expected reporting of control events, and hence it was arbitrarily excluded from the analysis. Elashoff *et al.* (3) concluded that the use of sitagliptin and exenatide was associated with significantly higher reported events for pancreatitis and pancreatic cancer; more thyroid cancer was reported with exenatide. In a revised proof made available several weeks after the first version published online, using the same data set, the authors subsequently found no link between other cancers and sitagliptin (3).

It may be useful to consider the different mechanisms of action of GLP-1R agonists *vs.* DPP-4 inhibitors in regard to contemplating potential mechanism-based toxicities. GLP-1R agonists such as exenatide and liraglutide exert their actions largely through activation of the GLP-1R. The levels of circulating GLP-1R agonist achieved after injection of these peptides are generally 3- to 5-fold higher than those achieved using DPP-4 inhibitors to stabilize postprandial levels of incretin hormones. Moreover, not only are levels of circulating incretin hormones much lower with DPP-4 inhibitors, these agents also lower glucose through both glucose-dependent insulinotropic peptide receptor- and GLP-1R-dependent mechanisms (22) and have the potential to modify levels of other bioactive DPP-4 substrates *in vivo* (23). Hence, it is not at all clear that one should predict an identical spectrum of adverse events that would be associated with the use of two substantially different mechanisms for potentiating incretin action.

How are we to reconcile the failure to find a link between pancreatitis and incretin therapies in the analysis of hundreds of thousands of patients using administrative heath care claims data and the 6-fold increased risk of pancreatitis reported by Elashoff *et al.* (3) using the AERS database? The AERS database can provide valuable information, particularly if a rare event is reported with unexpectedly high frequency, disproportionate to what might be expected based on available expectations and evidence. For example, much higher than expected rates of a very rare disease such as red cell aplasia in patients treated with specific forms of erythropoietin who developed antierythropoietin antibodies (24) may provide an early signal prompting more rigorous scientific evaluation of the incidence and putative association of rare adverse events with specific drugs. Nevertheless, the AERS database exhibits numerous and substantial limitations, including disproportionate reporting, failure to validate specific diagno-

ses, absence of information regarding comorbidities, confounding risk factors, and duration of drug exposure, and incomplete information about event ascertainment, drug compliance, and the complete range of medications a patient may have been exposed to before development of a specific adverse event (25). Moreover, population of the AERS database with case reports is clearly influenced by publicity linking specific drugs to reports of adverse events (26, 27). For these reasons, the Food and Drug Administration states that "AERS cannot be used to calculate the incidence of an adverse event in the U.S. population" (28). In general, well-done pharmacoepidemiological studies such as those that failed to demonstrate an excess of pancreatitis association of incretin-based therapies (10–12) are more widely regarded as scientifically valid compared with selective probing of the AERS system (17). Further pharmacoepidemiological studies of incretin-based therapies and adverse events and additional data from long-term prospective randomized trials, such as those under way for analysis of cardiovascular safety (8), will help establish whether or not there is a relationship between specific diabetes therapies, pancreatitis, and cancer.

Rapid advances in monitoring electronic health care information hold considerable promise for future improvements in our ability to detect and evaluate adverse events associated with the use of new medications (29). Nevertheless, current methods for evaluation of the safety of medications and technology remain imperfect, substantially limiting our ability to make firm conclusions about the safety of new drugs, in the absence of adequate data and appropriate analysis. The available evidence from both preclinical and clinical studies does not permit clear conclusions to be drawn about the risks of pancreatitis or cancer that might be associated with incretin-based therapies. Hence, the use of these agents must be based on consideration of demonstrated benefits (control of glycemia, prevention of weight gain, and reduced rates of hypoglycemia) *vs.* the side effect profile demonstrated in clinical trials, routine clinical use, and the theoretical risks gleaned from preclinical and clinical studies (1, 30).

All available methods for assessing the incidence and prevalence of adverse events have limitations. Retrospective database analyses may reflect underreporting of events, inadequate verification of events, assignment of different drugs to populations at different risk of events, and inability to adequately account for multiple confounding variables. Prospective trials carried out for assessment of drug efficacy may not always independently verify or carefully adjudicate adverse events and are often too short (6–12 months in duration) to provide meaningful data for events with long latency, such as cancer. The "gold standard," large randomized, controlled prospective trials of much longer duration should provide more accurate data for adverse effects of specific drugs; however, even these studies containing 5,000–15,000 subjects may not have sufficient power to provide accurate data for rare adverse events of interest, such as medullary thyroid cancer or pancreatic cancer. Given the potential for harm to patients arising from inaccurate reporting based on incomplete scientific information, clinicians, scientists, regulatory authorities, and the pharmaceutical industry must employ the highest scientific and ethical standards and a greater degree of transparency in ongoing efforts to understand the risks and benefits of new medications for the treatment of T2DM.

Acknowledgments

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