Incretin-Based Therapies for the Treatment of Type 2 Diabetes: Evaluation of the Risks and Benefits

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Type 2 diabetes is a complex metabolic disorder characterized by hyperglycemia arising from a combination of insufficient insulin secretion together with resistance to insulin action. The incidence and prevalence of type 2 diabetes are rising steadily, fuelled in part by a concomitant increase in the worldwide rates of obesity. As longitudinal studies of type 2 diabetes provide evidence linking improved glycemic control with a reduction in the rates of diabetes-associated complications, there is considerable interest in the therapy of type 2 diabetes (Fig. 1), with a focus on the development and use of new agents that exhibit improved efficacy and safety relative to current available medicines.

Although the number of patients with type 2 diabetes that successfully achieve target levels of A1C is steadily improving, a substantial number of subjects continue to fall short of acceptable treatment goals, leaving them at high risk for development of diabetes-associated complications (1). More importantly, a large number of subjects with type 2 diabetes fail to achieve target values for glucose, lipids, and blood pressure, with only 12.2% of patients meeting target values despite recent improvements in therapeutic agents targeting hyperglycemia, dyslipidemia, and hypertension (2). The development of multiple new agents for the treatment of type 2 diabetes has broadened the options for patient-specific therapy. However, no currently available agents exhibit the ideal profile of exceptional glucose-lowering efficacy to safely achieve target levels of glycemia in a broad range of patients. Hence, highly efficacious agents that exhibit unimpeachable safety, excellent tolerability, and ease of administration to ensure long-term adherence and that also clearly reduce common comorbidities and complications of diabetes are clearly needed (Fig. 1). Furthermore, most patients require combination therapy to achieve effective control of their disease (3). Recommended initial therapy generally includes comprehensive lifestyle management and patient education combined with metformin therapy. Although metformin is widely accepted as the preferred agent for the initial treatment of type 2 diabetes, there remains considerable uncertainty and lack of consensus in regard to choice of additional agents that need to be added to metformin to optimize glycemic control.

Recent recommendations have highlighted the use of insulin, sulfonylureas, and thiazolidinediones as second-line therapies because of their proven efficacy in long-term outcome studies. Nevertheless, more recent studies involving intensive use of these therapies in patients with clinical cardiovascular disease or multiple risk factors to achieve lower target glucose levels were associated with hypoglycemia, bone fractures, hospitalization for congestive heart failure, weight gain, and, in some analyses, increased mortality with modest benefit on rates of myocardial infarction. This has led to a re-examination of treatment recommendations to minimize the risk of cardiovascular morbidity and mortality (3,4) and specifically an interest in incretin-based therapies in this regard.

Incretin-based therapies: mechanisms of action and benefits

The two most recently approved classes of therapeutic agents for the treatment of type 2 diabetes, glucagon-like peptide-1 (GLP-1) receptor (GLP-1R) agonists and dipeptidyl peptidase-4 inhibitors (DPP-4i), exert their actions through potentiation of incretin receptor signaling. Incretins are gut-derived hormones, principally GLP-1 and glucose-dependent insulinotropic peptide (GIP), that are secreted at low basal levels in the fasting state. Circulating levels increase rapidly and transiently following food ingestion. As native GLP-1 displays a very short circulating half-life due to renal clearance and NH_2-terminal degradation by the enzyme DPP-4, degradation-resistant GLP-1R agonists have been developed. Exendin-4, a GLP-1R agonist structurally related to the native gut peptide, was approved for the treatment of type 2 diabetes in the U.S. in April 2005 and is currently administered as a subcutaneous injection (10 μg twice daily) for use as monotherapy in subjects not achieving adequate glycemic control on lifestyle modification alone or one or more oral agents. Liraglutide is an investigational human acylated GLP-1R agonist approved in Europe that binds noncovalently to albumin and exhibits a more prolonged duration of action suitable for once daily administration. A longer-acting microsphere preparation of exenatide suitable for once weekly administration, exenatide (once weekly), has also been studied in controlled clinical trials and appears to be somewhat more effective compared with exenatide twice daily (5).

Sitagliptin was the first DPP-4i approved in the U.S. in October 2006. It exerts its glucoregulatory actions through

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See accompanying editorial, p. 453.

Antihyperglycemic Agents in Type 2 Diabetes

Class	A1C Reduction	Hypo-Glycemia	Weight Change	CVD Risk Factors	Dosing (times/day)	Diabetes Comorbidity Contraindications
Metformin	1.5	No	Neutral	Minimal	2	Kidney, liver
Insulin, Long-acting	1.5 - 2.5	Yes	Gain	TG	1, Injected	None
Insulin, Rapid-acting	1.5 - 2.5	Yes	Gain	TG	1-4, Injected	None
Sulfonylureas	1.5	Yes	Gain	None	1	Essentially none
Thiazolidinediones	0.5 - 1.4	No	Gain	Variable	1	CHF, liver
Repaglinide	1 - 1.5	Yes	Gain	None	3	Essentially none
Nateglinide	0.5 - 0.8	Rare	Gain	None	3	Essentially none
Alpha-glucosidase Inhibitors	0.5 - 0.8	No	Neutral	Minimal	3	Essentially none
Amylin-mimetics	0.5 - 1.0	No	Loss	With weight loss	3, Injected	None
GLP-1R Agonist	0.5 - 1.0	No	Loss	With weight loss	2, Injected	Kidney
DPP-4 Inhibitor	0.6 - 0.8	No	Neutral	None	1	None
Bile acid sequestrant	0.5	No	Neutral	LDL	1-2	Severe TGs
Bromocriptine	0.7	No	Neutral	Minimal	1	Essentially none

Figure 1—*Relative comparison of properties exhibited by different classes of agents approved for the treatment of type 2 diabetes. CVD, cardiovascular disease; TG, triglycerides; CHF, congestive heart failure. A1C reduction depends on starting A1C.*

prevention of incretin degradation, leading to potentiation of GLP-1 and GIP action (6). Sitagliptin is administered as a single 100-mg daily tablet either as monotherapy or in combination therapy with oral antidiabetic agents. Sitagliptin is well tolerated and is not associated with nausea or vomiting as the levels of endogenous intact GLP-1 achieved following DPP-4 inhibition are at the upper limit of the normal physiological range; hence, it is not sufficient to induce an aversive response. Conversely, DPP-4i therapy is not associated with inhibition of gastric emptying or weight loss, and the available data suggest that long-acting GLP-1R agonists achieve more potent control of glycemia, relative to DPP-4i, due to more potent and sustained GLP-1R activation. Vildagliptin, a second DPP-4i, is approved in Europe and other countries, while saxagliptin has recently been approved in the U.S. and several other DPP-4i are under regulatory review.

GLP-1R agonists control blood glucose through regulation of islet function, principally with the stimulation of insulin and inhibition of glucagon secretion (7). Notably, these GLP-1R–dependent actions are glucose dependent, thereby minimizing the risk of hypoglycemia in the absence of concomitant sulfonylurea therapy. GLP-1R activation also inhibits gastric emptying and reduces food intake, leading to weight loss in the majority of treated subjects (8). The GLP-1R is expressed in cardiomyocytes and endothelial cells, and preclinical studies demonstrate that GLP-1R activation is associated with substantial cardioprotection and reduced infarct size in experimental models of coronary artery ischemia (9,10). Limited evidence suggests that GLP-1 may also preserve ventricular function and improve outcomes in human subjects with heart failure or myocardial infarction (11,12). Moreover, both exenatide and liraglutide reduce blood pressure, body weight, and plasma lipid profiles in subjects with type 2 diabetes (13), raising the hope that long-term treatment with these agents may reduce the incidence of cardiovascular events. Intriguingly, the GLP-1 metabolite, GLP-1 (9–36), also exerts cardioprotective actions in preclinical studies through mechanisms independent of the known GLP-1R (14); hence, ongoing research is directed at understanding the complexity of incretin biology in the cardiovascular system and the potential for incretin-based therapies to differentially modulate cardioprotective signals in the diabetic heart and blood vessel in vivo (15). The principal treatment-related adverse events associated with exenatide and liraglutide therapy are nausea and vomiting, which generally diminish over time (13). Analysis of the antidiabetic actions pursuant to GLP-1 administration has demonstrated that activation of the GLP-1R for 24 h provides more sustained and potent control of glycemia relative to shorter periods of GLP-1R agonism (16). In contrast, sustained GLP-1R activation may be associated with a modest reduction in control of postprandial glycemia (5,13), observations of interest to scientists studying the link between postprandial glucose and the development of cardiovascular morbidity and mortality. As exenatide requires twice daily administration and does not provide 24-h GLP-1R activation, there has been considerable interest in development of GLP-1R analogues with more prolonged durations of action (Fig. 2) suitable for once-daily or once-weekly administration (17). Consistent with the notion that continuous GLP-1R activation is required for optimal glucoregulation, liraglutide administered once daily and exenatide administered once weekly appear to be more potent glucose-lowering agents, relative to twice-daily exenatide (5,13). Furthermore, they seem to be associated with better tolerability and patient-reported outcomes as well as trends toward greater benefit on cardiovascular disease risk factors (Fig.

Exenatide and Long-Acting GLP-1 Agonists: *Similarities and Differences*

Properties/Effect	Exenatide[1]	Investigational >24 hr agonists[2,3]
Glucose-dependent insulin secretion and glucagon	Yes	Yes
Slows gastric emptying	Yes	Little or no
Effect on body weight	Weight loss	Weight loss
Effect on A1C	Reduction ~1%	Reduction ~1.5%
Effect on fasting glucose	Modest	Good
Effect on postprandial glucose	Good	Modest
Effect on CVD risk factors	Improve (with weight loss)	Improve
Common side effects	Nausea	Less nausea
Pancreatitis	Rare	Rare
Administration	Twice-daily	Daily or weekly
Rodent medullary thyroid cancer	Little to no signal	Signal

1. Amori RE, et al. *JAMA*. 2007; 298:194-206.
2. Exenatide LAR (once weekly): Drucker DJ, et al. *Lancet*. 2008; 372:1240-1250.
3. Liraglutide: Blonde L, et al. *Can J Diabetes*. 2008;32(suppl): A107.

Figure 2—*Comparison of features associated with exenatide twice daily versus the properties of the emerging class of long-acting GLP-1R agonists that achieve more prolonged and sustained GLP-1R activation. CVD, cardiovascular disease.*

2). There are now over a dozen long-acting investigational GLP-1R agonists being developed for the treatment of type 2 diabetes (8). Several recent reviews have emphasized the mechanisms of action and clinical results obtained in trials examining the efficacy of incretin-based therapies (8,17). Herein we examine adverse events and safety concerns associated with these agents.

Adverse events associated with GLP-1R agonists

Acute pancreatitis. Pancreatitis has been reported as a rare side effect of exenatide therapy principally through postmarketing surveillance. There are many risk factors and predisposing causes for acute pancreatitis, as well as over 200 drugs linked to the development of acute pancreatitis. The incidence of pancreatitis varies considerably among drugs, being relatively common for individuals taking 6-mercaptopurine and azathioprine (2–5%), but very uncommon for steroids and thiazide diuretics. The severity of the disease also varies; pancreatitis induced by 6-mercaptopurine is often quite severe, while that caused by cholinesterase inhibitors is usually mild. There are only two circumstances in which the mechanism of drug-induced disease is understood, drugs that cause hypertriglyceridemia (e.g., some HIV-protease inhibitors, estrogens, isotrentinoin) and drugs that are mitochondrial toxins. Drugs are not thought to cause chronic pancreatitis (with the exception of alcohol and smoking), although they have the theoretical potential to do so. Numerous animal models for pancreatitis have been developed; however, drugs that are associated with pancreatitis in humans rarely cause disease in rodents. Whether these species-specific observations reflect differences in drug metabolism, pancreatitis responses including inflammation, or the fact that some drugs may act as sensitizers and require other factors to cause disease, remains unclear.

Clinical data relating GLP-1R agonists and DPP-4i to pancreatitis come from a limited number of case reports, the U.S. Food and Drug Administration's (FDA) adverse event reporting system, and clinical trial records from pharmaceutical companies. A summary of initial 30 cases of individuals taking exenatide who developed acute pancreatitis was published in 2008 (18). The authors noted that in least 90% of these subjects, there were other factors that could predispose the individuals to pancreatitis. Rechallenge, a standard measure for assigning causality in drug-induced pancreatitis, was performed in only three patients but associated with recurrence of symptoms in each. However, the recurrence of symptoms with rechallenge was reported to occur only after weeks in some patients. In most patients with drug-induced pancreatitis, rechallenge usually causes disease within days. Subsequently, hemorrhagic pancreatitis and several deaths have been reported to the FDA in patients who previously used exenatide and similar cases but no deaths have been reported in patients treated with sitagliptin (19). A recent study used insurance records to determine that the risk of pancreatitis for subjects followed up to a year was 0.12% and 0.13% with sitagliptin and exenatide, respectively (20). These relative risks did not differ from a control cohort treated with metformin or glyburide. Data from the manufacturer of liraglutide reported a low incidence of acute pancreatitis (0.8 cases/1,000 patient-years). Notably, analysis of pancreatitis in subjects with type 2 diabetes suggests that their risk is increased threefold over nondiabetic subjects (21). Since only a fraction of this risk could be attributed to biliary pancreatitis, it seems likely that other factors such as obesity and hypertriglyceridemia might contribute to the increased risk in this population.

Several experimental studies have examined the effects of incretin-based agents on the pancreas in animal models. Koehler et al. (22) found no evidence of pancreatitis in mice treated with the GLP-1R agonist exendin-4 alone and no GLP-1R–dependent enhancement of pancreatitis responses in the caerulein-hyperstimulation model. In contrast, Nachnani et al. (23) detected histological evidence for acinar inflammation, cell drop-out and possible fibrosis and increased levels of serum lipase in Sprague-Dawley rats treated with exendin-4 for 75

days. A study by Matveyenko et al. (24) examined the effects of sitagliptin in human islet amyloid polypeptide (HIP) transgenic diabetic rats. The investigators reported that one of eight HIP rats receiving the drug developed acute pancreatitis and noted extensive pancreatic ductal proliferation and metaplasia and accompanying fibrosis in three HIP rats treated with sitagliptin. Some of the histological findings from the latter two studies were very similar, and reminiscence of changes was seen with chronic pancreatitis. The animal studies raise several confounding issues, namely might there be differences in pancreatitis responses between GLP-1R agonists and DPP-4i in humans versus rodents and in specific diabetic versus nondiabetic preclinical models? Though the relevance of the HIP transgenic rat model to human disease remains unclear, that study does suggest that DPP-4i might induce pancreatic metaplasia under specific experimental conditions. In summary, the clinical and experimental data linking GLP-1R agonists and DPP-4i to pancreatitis are still incomplete. More information is required to allow one to determine whether these agents substantially increase the risk of acute pancreatitis and whether such disease tends to be severe. However, patients receiving these medications will need to undergo continued surveillance for pancreatitis and clinicians should carefully exclude other causes of acute pancreatitis when it occurs in subjects receiving these drugs. Although the diagnosis of drug-induced pancreatitis would ideally be associated with confirmatory clinical data following drug rechallenge, physicians should exercise caution before considering a trial of drug rechallenge. As GLP-1R agonists may also affect smooth muscle responses and may regulate cholangiocyte function (25), their effects on the biliary tract and gallstone formation should also be examined.

Issues linking these agents with pancreatic metaplasia and chronic pancreatitis, as now suggested by two experimental studies, present a different challenge. Longer-term experimental studies using different GLP-1R agonists and DPP-4i in several species and experimental models of diabetes need to be undertaken to help clarify the importance of these findings. Hence, monitoring of pancreatic function and pancreatic disease in humans treated with GLP-1R agonists and DPP-4i in ongoing long-term prospective controlled clinical trials seems prudent.

Medullary thyroid cancer. Medullary thyroid carcinoma (MTC) is an uncommon neuroendocrine malignancy with an estimated U.S. annual incidence of fewer than 1,000 persons and a lifetime risk of development of 0.013% (26). When diagnosed early and still confined to the thyroid gland, the long-term survival of MTC is nearly 100% (27). About 25% of MTCs occur as part of an inherited autosomal dominant syndrome, either multiple endocrine neoplasia type II or familial MTC, and virtually all familial tumors are caused by inherited mutations in the *RET* proto-oncogene. Of sporadic MTCs, at least 40% are associated with somatic mutations and *RET*, and prognosis is worse in those mutated tumors.

The histological precursors to MTC in the inherited syndromes are well described, beginning with C-cell hyperplasia, leading to nodular C-cell hyperplasia, and then eventually to MTC. However, among the sporadically occurring MTCs, the role of this histological sequence is not defined, and the exact distinction between neoplastic and non-neoplastic C-cell hyperplasia is controversial (28,29). As a tumor derived from C-cells, MTCs generally secrete calcitonin, and high serum levels of calcitonin (>100 pg/ml) are nearly 100% specific for the presence of MTC (30,31). Nonetheless, the specificity of serum calcitonin concentrations between the upper end of the reference range and 100 pg/ml is considerably more limited. Other etiologies of mild degrees of hypercalcitoninemia include lymphocytic thyroiditis, chronic renal insufficiency, pancreatitis, hypercalcemia, hypergastrinemia (of any etiology), and even the postprandial state (31,32). Stimulation of calcitonin release with pentagastrin infusion has long been used to distinguish neoplastic from non-neoplastic causes of mild hypercalcitoninemia; however, pentagastrin is no longer available for human use in the U.S., and the diagnostic accuracy of testing with alternative stimulants such as calcium infusion remains to be established (31).

Animal models of MTC have limitations in regard to the biology and epidemiology of human MTC. Rats develop spontaneous age-related C-cell lesions at remarkably high frequency, especially nodular C-cell hyperplasia. Sporadic MTC occurs in 0.5–1% of most rat species evaluated, with increased frequency in males and with advancing age; spontaneous *RET* mutations have not been reported, and some typical histological features of human MTC are generally lacking. Mice develop spontaneous MTC less frequently, and most animal models in use are either transgenic or xenografts of the well-characterized TT cell line.

Food intake links incretin secretion with stimulation of calcitonin secretion in rodents, potentially via GLP-1 receptors expressed on rodent MTC cell lines, and GLP-1 stimulates calcitonin release in rodents in vivo (33–35). Analysis of data reported at the 2 April 2009 FDA Advisory Committee review of liraglutide revealed that preclinical toxicology studies with liraglutide reported C-cell hyperplasia and MTC with increasing exposure to liraglutide. At the highest drug exposures, MTC was reported in 14% of male and 6% of female Sprague-Dawley rats, which was above the rates observed in untreated rat controls. C-cell lesions were also reported to be more common with liraglutide in CD-1 mice, albeit at much lower frequencies; no C-cell lesions were described in the cynomologous monkey. In contrast, once-daily administration of exenatide in rodents is associated with a high frequency of nodular C-cell lesions but no carcinomas were reported (36). In safety monitoring of multiple liraglutide clinical trials, many patients with undetectable calcitonin levels before initiation of investigational (liraglutide, placebo, or active comparator) therapy were found to have levels that rose into the mid-reference normal range; rare patients developed mild hypercalcitoninemia during therapy. Across the trials, six patients were found to have C-cell findings at thyroidectomy following therapy (36). Of these patients, four were in liraglutide treatment arms, but three of these had elevated calcitonin levels before initiation of treatment. The remaining two patients were in the active comparator arms of trials, and one had an elevated calcitonin level before treatment. This single patient had MTC and was treated with an active non-GLP-1–based comparator; the patient had a markedly elevated calcitonin level before initiating non-GLP-1–based comparator therapy. All of the remaining patients who underwent thyroidectomy for hypercalcitoninemia were reported to have C-cell hyperplasia. According to the FDA briefing documents, no cases of C-cell lesions have been documented by histology in patients treated with exenatide. Several cases of papillary thyroid cancer have also been reported in the liraglutide clinical development program; however,

the small number of cases, the incidental histopathologic identification of the lesions, together with the lack of biological plausibility, suggest that this is an incidental finding not directly related to therapy with GLP-1R agonists.

In summary, rodents exposed to liraglutide and exenatide develop C-cell lesions at relatively high frequency, although the currently available data suggest that rodent MTC may be specific to long-acting GLP-1R agonists, likely due to sustained GLP-1R activation. Because of the historic difficulty of distinguishing neoplastic and non-neoplastic forms of C-cell hyperplasia in both rodents and humans, the diagnostic significance of C-cell hyperplasia is unclear. Minimal elevations of calcitonin levels are very nonspecific, and available methods of dynamic testing add little to clarify the etiologies. Given the extreme rarity of MTC in humans, the numbers of patients who would need to be treated for 10 years to yield one additional case of MTC may be extremely high (35–55,000 if risk is doubled; 10–15,000 if risk is quintupled). Moreover, the differences in rodent versus human C-cell biology with regard to responsivity to GLP-1R activation raise important questions about the suitability of mice and rats as models for understanding the effects of GLP-1R agonists on human C-cells.

Summary and conclusions

Incretin-based therapies provide new options for the treatment of type 2 diabetes and enable intensification of therapy while controlling body weight through mechanisms associated with a low rate of hypoglycemia. Investigational long-acting GLP-1R agonists require less frequent administration and appear to be more potent with respect to A1C reduction than twice-daily exenatide or once-daily sitagliptin with respect to A1C reduction. These long-acting GLP-1R agonists have considerable potential as antidiabetic therapies as they not only lower glucose as or more effectively than other noninsulin antihyperglycemic therapies, they do so in concert with weight loss, improvement in cardiovascular disease risk factors, and with very low risk of hypoglycemia. However, two safety issues have been raised—pancreatitis and medullary carcinoma of the thyroid.

The relationship between the use of incretin therapy and the development of pancreatitis remains unclear. These agents may not substantially increase the risk of acute pancreatitis in humans and might not affect the risk at all. The relevance to humans of the pancreatic metaplasia observed with these agents in two of the rodent studies is unknown. Continued clinical monitoring and more research are required to clarify the actions of GLP-1R agonists and DPP-4i on the normal and diabetic exocrine pancreas.

GLP-1R activation stimulates calcitonin secretion and promotes the development of C-cell hyperplasia and medullary thyroid cancer in rodents but not in monkeys, and the actions of GLP-1R agonists on human C-cells remain uncertain. Because of the rarity of medullary carcinoma of the thyroid and the lack of specificity of clinical markers, screening strategies, except in the setting of familial syndromes, almost certainly would be associated with an increase in morbidity and perhaps mortality as a result of false positives.

Taken together, the available evidence supports the use of incretin-based therapies for patients requiring effective control of glycemia and body weight while minimizing the risk of hypoglycemia. Ongoing scrutiny and further studies are required to clarify the potential significance of reports of pancreatic injury, including pancreatitis and metaplasia, and rodent medullary thyroid cancer for human subjects treated with GLP-1R agonists and DPP-4i.

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