Pancreatic Safety of Newer Incretin-Based Therapies: Are the “-tides” Finally Turning?

Incretin-based therapies have greatly improved therapy of diabetes due to not only their antidiabetic effects but also their beneficial effects on blood pressure, dyslipidemia, reduction in body weight, and potential cardioprotective and neuroprotective effects. The most common of these are glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which act via the G-protein–coupled receptors to stimulate insulin secretion from the pancreatic β-cells in a glucose-dependent manner; the latter eliminates the risk of hypoglycemia seen with other antidiabetes therapies (1). As these incretins can be inactivated in the native form in vivo by the enzyme (2) dipeptidyl peptidase-4 (DPP-4), incretin analogs have been developed that are resistant to DPP-4 cleavage or act via inhibiting DPP-4 enzyme. These can be classified as the GLP-1 receptor agonists (GLP-1RA), such as exenatide, liraglutide, and semaglutide, and the DPP-4 inhibitors, such as sitagliptin, vildagliptin, and saxagliptin. Several lines of evidence from clinical trial data have emerged pointing to their efficacy and multiple beneficial effects; however, recent studies have questioned their potential safety.

GLP-1RA, in addition to enhancing incretin signaling in pancreatic β-cells, also act on other pancreatic cells and tissues that express these receptors. Studies using rodent models have shown that these GLP-1RA enhance β-cell mass in vivo (3) and could stem the decline in β-cell mass and function observed with progressive diabetes. With regards to the mice studies, in diabetic mice, existing data suggest that the ability of GLP-1RA to enhance β-cell mass is possibly due to protection of pancreatic β-cells from apoptosis rather than actually regenerating new β-cells in the pancreas. However, as reviewed by Gale (4), these therapies are associated with an increased potential for pancreatitis, a known risk factor for subsequent pancreatic adenocarcinoma. In response to the increasing concern of this class of drugs on pancreatitis and pancreatic cancers, the U.S. Food and Drug Administration (FDA) has examined the adverse events database from studies involving these therapies (5,6). This report created even more confusion in the existing literature with regards to these classes of drugs. However, there were many problems associated with the FDA report. The controls chosen were four other antidiabetes drugs—rosiglitazone, nateglinide, repaglinide, and glipizide, which have been reported as either neutral or increasing the risk of pancreatic cancer. Metformin was excluded due to some epidemiologic studies stating that it can decrease pancreatic cancer risk. Also, the FDA Adverse Event Reporting System (FAERS) database depends on immediate reporting and thus may be affected by reporting bias. The FAERS database does not provide information regarding obesity, smoking habits, alcohol consumption, or chronic pancreatitis, which are well-established additional risk factors for pancreatic cancer. Therefore, reports that drugs such as exenatide and sitagliptin increase the risk of pancreatitis when administered as monotherapy and this risk is compounded with combination, should be treated with caution not only because of the possible biases mentioned but also because of the existence of other available contradictory data that should be taken into consideration.

As the adverse event data from long-term clinical trials assessing cardiovascular safety of these therapies are not yet available, the best data available so far are the examination of pancreatic histology in cadaveric samples of humans taking incretin-based therapies (7), which described various endocrine and exocrine pathologies in
subjects taking GLP-1RA and DPP-4 inhibitors, mainly exenatide and sitagliptin. However, the inherent disadvantages of the study design have been commented upon by numerous authors (8–11), including the obvious differences in age, diabetes duration, and other potential confounding factors of the control group. Also, it is important to note the structural differences that exist between exenatide and liraglutide, as the latter has more amino acid homology to human GLP-1 than the former (12).

Animal models (mice, rats, and monkeys) have been widely used in the recent literature to examine this question of adverse pancreatic findings. Data from 2-year toxicity studies with pharmacologic doses of liraglutide in Sprague-Dawley rats did not demonstrate any significant adverse pancreatic findings (13). Similarly, the previous studies in nonhuman primates treated with liraglutide did not reveal any pancreatic intraepithelial neoplasia lesions, even in a long-term treatment of 87 weeks (5 mg/kg per day) (13).

In this issue, Gotfredsen et al. (14) report on the extensive toxicologic studies conducted by Novo Nordisk on pancreas weight and toxicology in Cynomolgus monkeys treated with liraglutide for 87 weeks or semaglutide (a new GLP analog in phase 3 clinical development) for 52 weeks. With regards to pancreas weight, they did not observe any significant differences other than the increase in the female monkeys at the 52-week but not the 87-week duration. Quantitative histology of pancreas showed increase in exocrine cell mass at 52 weeks with liraglutide, but no significant increase in endocrine mass or exocrine or endocrine tissue proliferation rate. Specifically, no evidence for α-cell (glucagon-secreting) hyperplasia, acinar ductal metaplasia, or pancreatic intraepithelial lesions was observed in the treated animals. The distribution of endocrine cells (including single cells or clusters associated with ducts) was not significantly different from that in the control group and was comparable to the pattern described in the normal human pancreas. In this report of 138 nonhuman primates, there were no significant adverse effects on the pancreas with these two newer GLP-1 analogs.

While such data could alleviate concerns of potential pancreatic cancer with long-term use of this class of drugs, some of the weaknesses of this study include the use of historical controls for pancreas weights and the small numbers of animals in each of the groups. While this has been a common way to test for toxicologic data, the study would have been more meaningful if Gotfredsen et al. (14) had focused on the 87-week duration treatment and included more numbers of animals in control and experimental groups. This would have further complemented the comprehensive studies of Nyborg et al. (13).

In addition, the study would have been strengthened with approaches examining mechanistic pathways and if these treatment strategies affected known pathways known to be deregulated in pancreatic cancers, such as Ras signaling, and downstream effectors (including the MAP kinase or Akt signaling pathways) (15).

A recent perspective of the pancreatic safety of incretin-based drugs (16) clearly documents data from the FDA and European Medicines Agency (EMA), including liraglutide therapy, for a duration of 52 weeks or more and provides no compelling evidence for increased risk of pancreatitis or pancreatic cancers (9,17). The agencies also note the absence of incretin-based therapy–induced pancreatic tumors in rats and mice treated for their entire life span of 2 years with pharmacologic doses of drug, in both healthy and diabetic rodent models. These studies also included blinded histopathologic studies of endocrine and exocrine pancreas. To date, the body of literature that exists favors the continued use and development of these antidiabetes strategies, which have multigain benefits that far outweigh the purported risks. However, caution should be exercised in the use of such antidiabetes therapies in patients at risk for developing pancreatitis, and close monitoring is advocated. It is also comforting to note that the LEADER trial with liraglutide should be completed in 2015 and other larger trials are to be completed soon thereafter. These trials may be able to educate the community with regards to the actual risk of pancreatitis and pancreatic cancers.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

References

4. Gale EA. GLP-1 based agents and acute pancreatitis: drug safety falls victim to the three monkey paradigm. BMJ 2013;346:f1263


