COMMENTARY

Smoke or Fire? Acute Pancreatitis and the Liraglutide Trials

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Over the past few years, substantial clinical data have been presented showing that incretin-based therapies are effective glucose-lowering agents. Specifically, glucagon-like peptide 1 receptor agonists demonstrate an efficacy comparable to insulin treatment with minimal hypoglycemia and have favorable effects on body weight. Thus, many of the unmet clinical needs noted from prior therapies are addressed by these agents. However, even after many years of use, many continue to raise concerns about the long-term safety of these agents and, in particular, the concern with pancreatitis. This clearly remains a complicated topic. Thus, in this issue of *Diabetes Care*, we continue to update our readers on this very important issue by presenting two studies evaluating incretin-based medications and risk of pancreatitis. Both have undergone significant revisions based on peer review that provided significant clarification of the data. We applaud both author groups for being extremely responsive in providing the additional data and revisions requested by the editorial team. As such, because of the critical peer review, we feel both articles achieve the high level we require for *Diabetes Care* and are pleased to now present them to our readers. In keeping with our aim to comprehensively evaluate this topic, we asked for additional commentaries to be prepared. In the narrative outlined below, Prof. Edwin A.M. Gale provides a commentary on the report that focuses on clinical trials of liraglutide in the treatment of diabetes. In the narrative that follows Prof. Gale's contribution, Dr. Laurent Azoulay provides a commentary about the remaining uncertainty in this area and also discusses the results from a nationwide population-based case-control study. From the journal's perspective, both of the articles on pancreatitis and incretin-based therapies reported in this issue have been well vetted, and we feel both of the commentaries are insightful.

—William T. Cefalu
Editor in Chief, *Diabetes Care*

Are you "completely bored by this topic, or so ideologically polarized that little can be said to change [your] opinions"? If so, the comment that Leo Krall is said to have made 40 years ago about the University Group Diabetes Program (UGDP) study (1) applies to you. The safety of tolbutamide was never resolved to everyone's satisfaction following UGDP (2), and the same might be said about rosiglitazone and heart disease or pioglitazone and bladder cancer. We can at least hope to have answers on the cardiovascular safety of sulfonylureas with the CARdiovascular Outcome Study of LINAgliptin Versus Glimepiride in Patients With Type 2 Diabetes (CAROLINA) trial, which is comparing a sulfonylurea with a dipeptidyl peptidase-4 (DPP-4) inhibitor (2,3), but this has taken 50 years to accomplish. The diabetes community is evidently slow to resolve this type of dispute. Why should this be?

Uncertainty lies at the heart of safety disputes and for obvious reasons. Safety signals are not easy to identify, may point in different directions, and can be

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challenging to interpret—not least when there are enormous human, financial, and legal implications. Those who defend a drug face the difficult challenge of proving a negative; those who cast doubt have limited access to the data, face a sophisticated counterinformation campaign, and risk professional oblivion. Both sides lack confidence in the objectivity of their adversaries, and resolution is unlikely when those engaged in debate cast doubt on the motives or probity of those who oppose their views.

Acute pancreatitis is listed as an adverse event for all glucagon-like peptide 1 (GLP-1) agonists and DPP-4 inhibitors, and the incretins have, so far as I can ascertain, attracted more adverse event reports of this complication than any drug class in history (4). The regulators, meanwhile, have concluded that current data are inconsistent with a causal association but are unable to exclude it (5). Nine years into the debate, are we any nearer to closure?

The first thing to appreciate about the debate is that it is not really about acute pancreatitis. Although this is a highly unpleasant and occasionally fatal condition, the excess risk (if any) is, by common agreement, small—no more than one or two cases per thousand at the doses used for diabetes. Even a confirmed risk might be judged acceptable at this level. The debate, therefore, is not about pancreatitis but about what it might signify.

Sherlock Holmes cautioned that "it is a capital mistake to theorize before one has data. Insensibly one begins to twist facts to suit theories, instead of theories to suit facts" (6). The problem with drug disputes is that we have conflicting evidence and few, if any, confirmed facts. As the best available evidence comes from properly conducted clinical trials, Jensen et al. (7) are to be commended for publishing details of their experience with liraglutide in this issue of *Diabetes Care*.

The report focuses on clinical trials of liraglutide in the treatment of diabetes, updating a summary published in 2010 that reported seven cases of acute pancreatitis in 4,257 patients taking liraglutide versus one case in 2,381 treated with comparators (8). The current account, which runs to 19 April 2013, describes eight reports of acute pancreatitis in 6,345 patients exposed to liraglutide (5,021 patient-years), and one with an active comparator in 1,846 patients (1,354 patient-years). The reduced number of active comparators in the second analysis is due to exclusion of subgroups treated with sitagliptin or exenatide.

One report of acute pancreatitis on liraglutide did not meet the diagnostic criteria and was excluded. The reporting rates for acute pancreatitis were accordingly 1.6 cases per 1,000 patient-years of exposure for liraglutide versus 0.9 for the comparator group (excluding other incretins), or 0.7 if these are included. The relative risks with liraglutide, adjusted to the size of the comparator group, were 1.7 [95% CI 0.2–13.2] versus the active comparator group and 2.1 [0.3–16.0] versus total active comparators, with neither approaching statistical significance.

The adjudicated cases are then presented in more detail. Of the seven patients on liraglutide, one had pancreatitis immediately following endoscopic retrograde cholangiopancreatography, which is unlikely to be related to drug exposure. Two had gallstones, one had evidence of chronic pancreatitis, and one had a previous history of acute pancreatitis. The patient in the comparison group was on glimepiride and had gross hyperlipidemia. The authors conclude that five of the seven patients on liraglutide had other risk factors for pancreatitis and argue that this casts some doubt on the role of the drug. In response, it could be said that randomization is designed to balance baseline risk and that any resulting numerical imbalance is an outcome to be considered. Nor do preexisting risk factors for pancreatitis, frequently present in the population with diabetes, rule out a possible role for the drug in precipitating an acute episode: they might even increase the risk of this happening. Until the answer is known, it seems prudent to use the incretins with added caution in those at increased risk of pancreatitis.

Jensen et al. (7) also note the long latency between exposure to liraglutide (196–668 days) and an event of acute pancreatitis in six patients receiving the drug. Although this delay might be consistent with the hypothesis that pancreatitis is precipitated by exocrine expansion and duct compression, the authors point out that acute pancreatitis is typically associated with acute duct obstruction, as by a gallstone. While this is true, slow blockage of pancreatic ducts by tumor growth is an unusual but well-recognized cause of local (9) and generalized (10) pancreatic inflammation and is indeed a good model of the proposed mechanism.

Clinical trials in obese individuals without diabetes, not reported here, throw some light on the situation. They used a higher dose of liraglutide and are particularly informative because they exclude the possible confounders of diabetes or its medication. Acute pancreatitis was confirmed by adjudication in 9 (0.27%) of 3,291 patients on liraglutide, as against 1 (0.05%) of 1,843 placebo-treated patients. Three additional cases of acute pancreatitis occurred $<$14, 74, and 124 days after stopping the drug; in total, 1 person in 275 exposed to liraglutide experienced pancreatitis (11). Notably, those with preexisting risk factors for pancreatitis were excluded from this study.

In sum, two large series of well-performed and closely monitored clinical trials are consistent with an excess of acute pancreatitis, with a hint of more episodes at the higher dose. While this does not prove causal association, it seems reasonable to conclude that further investigation is warranted.

What are the potential implications? GLP-1 agonists and DPP-4 inhibitors are pharmacologically unrelated, indicating that any shared effect is likely to be mediated by GLP-1. GLP-1 has undoubted trophic effects on the exocrine pancreas in some experimental models (12), although not in others (13). Are there similar effects in humans? We do not know, but the only detailed investigation of human autopsy material indicated that this might be the case (14). The study by Butler et al. (14) has repeatedly been criticized or dismissed in high-profile reviews, but we have yet to see the demonstration that the human pancreas is unaffected by exposure to incretins. If increased cell proliferation or low-grade inflammation is indeed present, this would increase the rate of cell division and hence the risk of neoplastic changes (15). GLP-1 agonists have recently been shown to have trophic effects on mouse intestinal cells and to promote intestinal tumor formation by a mechanism analogous to that proposed for the exocrine pancreas (16,17).

When the flak starts to fly one is likely to be over the target, and the intensity of the incretin debate indicates that sensitive issues of fundamental importance are at stake. How then can we bring closure? It is frequently proposed that cardiovascular

safety studies of the incretins currently completed or under way will provide a definitive answer, but these studies were not designed to examine the issue of acute pancreatitis, and differences in data capture, classification, and adjudication could easily blur the results. Use of rigid diagnostic criteria for acute pancreatitis could result in low ascertainment and would exclude potential cases of "subclinical" or "mild" acute pancreatitis with mild pain or enzyme elevations that do not quite fit the strict clinical criteria. It will therefore be important for the raw data from these studies to be made fully available, rather than internally adjudicated conclusions.

In the last analysis, however, what matters is the human pancreas. The obvious course of action is to perform *1*) a much larger and fully independent review of postmortem pancreata in people exposed and not exposed to incretin therapy, *2*) prospective MRI studies of pancreatic size in people starting incretin therapy, and *3*) long-term intention-to-treat analyses of pancreatic cancer risk in people exposed to incretin therapy. As the UGDP investigators argued: "If, in major medical dilemmas the alternative is to pay the cost of perpetual uncertainty, have we really any choice?" (1).

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