DPP-4 Inhibitor–Related Pancreatitis: Rare but Real!

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Following the U.S. Food and Drug Administration (FDA) Guidance issued in 2008 to demonstrate cardiovascular safety for the purpose of regulatory approval of new glucose-lowering agents for type 2 diabetes management, the number of placebo-controlled randomized clinical trials has increased exponentially. As previously proposed by members of the *Diabetes Care* editorial committee (1), these regulatory-required large cardiovascular outcome trials (CVOTs) can provide unique opportunities to learn more about the overall safety and potential off-target effects of these new drugs beyond their cardiovascular safety. Carefully conducted pooled analyses of patient-level data emanating from these CVOTs can better estimate potential adverse events that may occur infrequently or perhaps may only be seen as tenuous inconclusive signals in smaller, shorter duration, randomized controlled phase 3 trials or may emerge once the new agents are widely prescribed in clinical practice.

Indeed, one such adverse event is acute pancreatitis related to incretin-based therapies consistently noted as numerical imbalances occurring in many randomized clinical trials (2). Acute pancreatitis has been a safety issue of major controversy with conflicting reports from observational retrospective studies often based on administrative insurance and prescription claim data and/or clinical practice registries. So far, reliable assessments of the relationship between pancreatitis and dipeptidyl peptidase 4 (DPP-4) inhibitors and glucagon-like peptide 1 receptor agonists based on these observational reports have been hampered by the inherent methodological shortcomings with limitations such as confounding by indication, missing data, lag-time biases, unknown residual confounding, etc. (3). Even rigorously conducted epidemiological analyses adjusting for multiple confounders cannot provide definitive answers (4). The FDA MedWatch reporting system is another unreliable source with incomplete clinical information often influenced by the media and difficult to interpret without data on the denominator.

Large-scale CVOTs have now been reported for three DPP-4 inhibitors: saxagliptin, alogliptin, and sitagliptin (5–7). There were clear numerical imbalances, with more cases of acute pancreatitis occurring with each of the three DPP-4 inhibitors than in the control groups, which failed to reach statistical significance in each of the individual trials; however, this lack of individual significance cannot provide reassurance, as the validity of statistics with such low numbers is questionable. Nevertheless, when it comes to safety signals, these numerical imbalances do need to be taken seriously and often pooled analyses are necessary to draw more convincing conclusions.

In this issue of *Diabetes Care*, one such meta-analysis on acute pancreatitis from these three CVOTs is reported (8). The strength of this meta-analysis was the substantial number of patients with relatively similar population characteristics and basically similar study designs testing the respective DPP-4 inhibitor versus placebo, allowing for a reliable estimate of the risk of acute pancreatitis. The estimated odds ratio for an increased risk of acute pancreatitis with DPP-4 inhibitors was 1.79 with an absolute increased risk of 0.13%, which translates to one to two additional cases of acute pancreatitis for every 1,000 patients treated for 2 years. The authors of a similar meta-analysis, published as a letter, give a more precise estimate of one additional case per 834 patients treated for 2.4 years (9). However, the calculation of number-needed-to-harm from a meta-analysis is not without statistical problems and criticisms (10). Translated to 1 million users in the U.S., a very conservative estimate, this would result in ~750 additional cases of acute pancreatitis per year.

A thorough analysis of adjudicated acute pancreatitis cases was previously reported for the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients

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with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) study that included cases of "possible" and "probable" acute pancreatitis that did not fully meet the strict Atlanta diagnosis criteria (11). This issue of *Diabetes Care* contains a dedicated analysis of the Trial Evaluating Cardiovascular Outcomes With Sitagliptin (TECOS) trial on adjudicated acute pancreatitis (12) that also revealed a numerical imbalance of more cases of acute pancreatitis with sitagliptin, coinciding with what was previously reported by the authors in the original core publication but including two fatal cases that interestingly were not previously reported in the initial core publication. Of further interest, and providing significant strength for this report, was the listing in the supplementary data of the clinical details for those 33 cases suspected by the investigators of having acute pancreatitis that were subsequently excluded by the adjudication committee (12). The authors are to be commended for the transparency of providing these interesting supplementary type of data that have not been so far reported by any of the other CVOT publications. This additional clinical information on those "excluded cases" may help corroborate the opinion of many in the field that the Atlanta criteria are too rigid to estimate the full spectrum of drug-induced acute pancreatitis. The issue is not with the performance of the adjudication committees, as they adhered to the charge of basing their decisions on the rigorous Atlanta criteria. The fundamental issue and main criticism of the adjudication process is indeed the use of such rigid Atlanta diagnosis criteria that makes the incidence of acute pancreatitis be substantially underestimated in these CVOTs. It is highly conceivable that the adjudication committees, by strictly using the Atlanta diagnostic criteria for acute pancreatitis, could have dismissed mild or subclinical drug-induced pancreatitis or even "probable" cases, as these supplementary data seem to suggest. According to the Atlanta criteria, patients with probable acute pancreatitis would be excluded if the adjudication committee felt that the abdominal pain was "not severe enough"; the elevated amylase or lipase was 2 or 2.5 but not >3 times elevated; or the abnormal imaging findings were "not convincing enough" or, as in many cases, never performed. In addition, those cases that met two out of the three criteria for the diagnosis of acute pancreatitis were probably not adjudicated as drug-related if there was evidence of gallstones; in these cases, the pancreatitis was probably attributed to gallbladder disease, dismissing the possibility that it may be precisely those patients at high risk for whom incretin-based therapies induce pancreatitis.

We were curious about how definitive the exclusion of acute pancreatitis was and decided to conduct our own blinded-testing exercise by removing information on the study drug and final outcomes from the list of those who were excluded by the TECOS adjudication committee as having acute pancreatitis. We asked two independent experienced gastroenterologists, one in Dallas and the other in Amsterdam, to assess in a masked fashion whether or not any of those subjects could have had acute pancreatitis. Interestingly, there was concordance with the assessment of both gastroenterologists, who estimated that acute pancreatitis was the most probable diagnosis in at least two-thirds of cases and still with a numerical imbalance of greater occurrence in those on sitagliptin. We invite the readers to do their own assessment exercise and judge for themselves!

The Atlanta diagnostic criteria are a well-established tool for the diagnoses of acute pancreatitis in clinical practice but one that may not be sensitive enough for randomized control trials to detect drug-induced pancreatitis, as it may miss subclinical, indolent, or mild pancreatitis and not be good enough for pharmacovigilance to ensure safety of drugs to be used long term. Clearly the use of the current adjudication criteria reduces the noise in the data, but it detects only very low incidences and thereby tends to inflate the number needed to harm, probably giving us false reassurances.

Pancreatitis is a multifactorial disease, with gallstones, alcohol, drugs, and diabetes itself playing a role, among others. It might be tempting to try to explain the cause of mild to severe and fatal cases reported in relation to DPP-4 inhibitors by pointing at such other factors to exonerate the potential drug effect. It is probably better to acknowledge that we cannot be sure about the relative contribution of different risk factors in an individual developing pancreatitis, and conceivably an incretin-based drug could be an important contributing factor affecting precisely those at risk for developing pancreatitis.

DPP-4 inhibitors are well-established agents, and their benefits clearly outweigh the risks. Acute pancreatitis is real, but its frequency is very low to impede the generalized use of DPP-4 inhibitors unless more efficacious agents are preferred. Can we identify people at increased risk for developing DPP-4 inhibitor–related pancreatitis? For those with a history of pancreatitis, avoiding these drugs is a sensible recommendation. However, avoiding its use in subjects with risk factors for pancreatitis may sound justified but solid data supporting such a strategy is lacking. Amylase and lipase levels can be mildly elevated with incretin-based therapies, but the levels fluctuate to a large extent and therefore the positive predictive value of an increased level seems so low that this cannot be used to identify people at risk (13). Thus, we can conclude that pancreatitis is an established but rare side effect of DPP-4 inhibitors that occurs at a very low frequency. We should inform patients on this potential side effect, and in people on DPP-4 inhibitors having even mild gastrointestinal symptoms suggestive of pancreatitis, it would be justified to measure pancreatic enzymes and appropriate to perform an abdominal ultrasound to exclude gallstones. On the basis of the evidence so far, perhaps in some patients when gallstones are present (even if asymptomatic) and/or when lipase levels are >3 times normal (even if fluctuating), there may be enough basis to consider replacing an incretin-based agent used and consider an alternative therapy.

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