LETTER

Pancreatitis During Treatment with Liraglutide

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Dear Sir:

A 67-year-old man presented with a 10-day history of nausea, vomiting, and constant pain in the epigastrium which radiated to the sides. Five months before admission, liraglutide (1.2 mg/day) had been started in addition to metformin and gliclazide for the treatment of type II diabetes and the dose had been stable. His previous history was otherwise unremarkable; he did not report any acute or chronic pancreatic disease and denied alcohol use, toxic habits or taking any other medications, including over-the-counter medications or herbal remedies, potentially associated with pancreatitis.

The patient was fully alert and oriented, apyrexial and had normal vital signs; physical examination yielded normal findings apart from a severely tender abdomen with no bowel sounds and no rebound tenderness. Laboratory data showed increased blood amylase (877 IU/L; reference range: 0-115 IU/L), lipase (653 IU/L; reference range: 0-190 IU/L), alanine aminotransferase (ALT) (275 IU/L; reference range 10-36 U/L), aspartate aminotransferase (AST) 326 IU/L (normal range 10-36 IU/L), and total bilirubin 2.6 mg/dL (normal range 0.2-1.0 mg/dL) with conjugated bilirubin 0.8 mg/dL; γ-glutamyltransferase, alkaline phosphatase, electrolytes, hematological variables, cholesterol, triglycerides, renal function tests, and blood gases were normal. The results of serologic tests for the *Mycoplasma* and *Chlamydia* species, viral hepatitis and a wide range of other viral infections, and an autoimmunity screening were also negative. Findings of magnetic resonance imaging showed a moderately enlarged and edematous pancreas and sludge in the gallbladder but no stones neither dilatation of intra- and extra-hepatic biliary ducts, nor common bile duct and Wirsung's duct.

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Liraglutide was discontinued and the patient was managed conservatively with bowel rest and intravenous fluids; five days after admission, enzymes returned to normal and he was free of symptoms. A re-challenge test was not performed for safety reasons.

We suspected, on clinical grounds, this patient had pancreatitis caused by exposure to liraglutide. This was lent support by scoring on the Naranjo probability scale that suggested a possible liraglutide-related event [1]. However, the finding of biliary sludge in the gallbladder is a confounding factor even though it was not associated with stones or sludge in, or dilatation of, the intra- and extra-hepatic biliary tract and Wirsung's duct on imaging studies. On a practical level, this substantially lessens the hypothesis of a biliary cause of pancreatitis in this patient. Furthermore, he had no prior history of acute or chronic pancreatic disorders and alternative causes of pancreatitis such as alcohol use, hypertriglyceridemia, hypercalcemia, autoimmunity, or an active viral infection were ruled out upon history, clinical presentation and laboratory studies.

Liraglutide is a glucagon-like-peptide-1 (GLP-1) receptor agonist, i.e. an incretin, that has been recently approved to improve glycemic control in adults with type 2 diabetes [2]. Even though diabetic patients have an increased base-line rate of pancreatitis as compared to the general population [3], safety concerns have been raised due to the possible increased risk of pancreatitis attributable to drugs that act through the GLP-1 pathway such as liraglutide, exenatide and sitagliptin [4]. Nine cases of acute or chronic pancreatitis have been reported among patients treated with liraglutide, which include seven cases recognized during clinical trials and two more patients in the post-marketing surveillance [4, 5, 6].

The mechanistic relationship, if at all, between the risk of pancreatic injury and exposure to liraglutide is unknown and predisposing factors remain uncertain. Activation of the GLP-1 pathway may lead to expression of several pancreatitis-associated genes but this did not translate into significant pancreatic inflammation, at least in a murine model of experimental pancreatitis [7]. Moreover, no evidence of pancreatic damage has been found by Nyborg *et al.*

among primates treated for up to two years with doses up to 60-times greater than maximal clinical doses of liraglutide [8], which suggests liraglutide has no direct toxic effect upon pancreas. A hypersensitivity or a metabolic idiosyncratic reaction triggered by liraglutide remains the most likely mechanism of pancreatic injury in the cases so far reported. This reaction probably involved also the liver in our patient, which may explain the elevated blood levels of aminotransferases and bilirubin that paralleled the course of pancreatitis in this case.

Our patient presented with acute pancreatitis after five months on liraglutide treatment; however, available reports did not provide any clear-cut relationship between the duration of liraglutide treatment and the risk of developing pancreatitis [4, 5, 6]. This indirectly reinforces the view hypersensitivity or idiosyncratic reactions are indeed the most common effectors of pancreatic injury among patients treated with liraglutide.

In the meanwhile the potential causal relationship between liraglutide and pancreatitis will be further investigated, we suggest great caution in using liraglutide in diabetic patients particularly among those with one or more additional risk factors for pancreatitis.

Conflict of interests None

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