CLINICAL VIGNETTE

Incretin Based Therapy – Another Risky Behavior?

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A 77-year-old woman was seen with poorly controlled diabetes. She has longstanding diabetes since 1975 as well as past history of breast cancer and obesity. Her diabetes is complicated by macrovascular disease (coronary artery disease, s/p stent but no MI or other manifestations) and microvascular disease with peripheral neuropathy manifesting as paresthesias of the feet, and nephropathy in the form of microalbuminuria, but without retinopathy. She had been on insulin and metformin, and in 2001 she was started on pioglitazone and maintained tight glucose control until at least 2007. In approximately 2006, she enrolled in the UCLA weight loss program and lost 90 pounds and was able to stop her insulin. Starting in 2009 she gradually gained back 30 pounds and she was seen in May, 2011 because of deterioration of her blood sugars with her fasting blood sugar going from consistently below 160 mg/dl to over 200 mg/dl. Her BMI at that time was 39, and her A1C was 8.8, and she was advised to re-start insulin. However, the patient did not want to be on an injectable medication and she was planning to re-enroll in the UCLA weight loss program in the near future. She was started on sitagliptin 100 mg, improved, and after September of 2011, did not follow up further with her endocrinologist.

In July of 2012, she presented to her primary care physician with light headedness, poor appetite, and over a 20 pound unintended weight loss. Labs revealed elevated liver enzymes with AST 274 IU/L (0-40), ALT 207 IU/L (0-40), and alkaline phosphatase 1000 IU/L (25-165). An abdominal CT scan revealed a mass at the head of the pancreas. She underwent surgery but the mass was found to be locally invasive and unresectable. She is planning to start chemotherapy.

This vignette raises the sometimes debated question of whether sitaglipton has a role in the development of pancreatic cancer.

Sitagliptin is one of a group of incretin based therapies. Incretins are gut derived hormones. The main incretins, glucagon-like peptide-1 (GLP-1) and glucose dependent insulinotropic peptide (GIP) act by increasing insulin in a glucose dependent matter, suppressing glucagon, slowing gastric emptying and suppressing appetite. Incretins are rapidly metabolized in the circulation by an enzyme, dipeptylpeptidase-4 (DPP-4). Sitagliptin inhibits this enzyme and thereby raises levels of the incretins.

In July 2009 Matveyenko[1] et al, while investigating islet cell dysfunction and beta cell loss in an animal model (HIP = human islet amyloid polypeptide transgenic Sprague-Dawley rats) of type 2 diabetes found hemorrhagic necrotizing pancreatitis in one of eight sitagliptin treated rats but in none of the 15 untreated animals. Further investigation found ductal metaplasia was also present in three of the eight sitagliptin treated rats but not in any of the non-sitagliptin treated rats. Quantification revealed that there was an increase in ductal proliferation in all eight sitagliptin treated rats but in only half as many untreated HIP rats. Interestingly, metformin seemed to markedly reduce the incidence of these cellular changes and prevented the sitagliptin associated increase in ductal proliferation.

These findings are potentially very worrisome since it is well accepted that ductal metaplasia and ductal proliferation are present in human pancreatitis, and that both of these as well as pancreatitis itself are risk factors for pancreatic cancer. In addition, there are GLP-1 receptors in pancreatic duct cells and it is therefore conceivable that the increment of GLP-1 caused by sitagliptin could be operating at these sites. The relevant issue for clinicians is whether and to what extent the above findings in a limited study of genetically altered inbred rats are applicable to human beings.

The answer to this issue is difficult to obtain for a variety of reasons one of which is the increased incidence of pancreatitis and pancreatic cancer in people for whom sitagliptin is ordinarily prescribed. Large studies including a prospective epidemiologic study in which 54,000 diabetics were observed for 12 years[2], and a prospective case-controlled, pooled

analysis of 12 studies covering 1,621 cases of pancreatic cancer and 1,719 match controls[3] found that diabetes is a significant risk factor for the development of pancreatic cancer. In addition, a retrospective study of human pancreases obtained from autopsies[4] found that both diabetes and obesity were risk factors for pancreatic ductal cell replication with diabetes increasing pancreatic duct replication fourfold and obesity causing a tenfold replication of pancreatic duct cells. The underlying increased incidence of pancreatic ductal proliferation, pancreatitis, and pancreatic cancer in patients with obesity or type 2 diabetes makes it more difficult to attribute any increase in those medical problems in patients on sitagliptin to the medication, rather than to the underlying diabetes or obesity for which it was prescribed.

Nonetheless, there is evidence that a variety of diabetic medicines have an impact on the incidence of pancreatic cancer. A hospital based case-control study conducted at M.D. Anderson from 2004-2008[5] looked at patients with pancreatic cancer with and without diabetes, controls with and without diabetes, other risk factors, and diabetic medications which had been used. Diabetes per se, consistent with the studies cited above, was associated with a more than doubling of the risk of pancreatic cancer. A weak but significant risk was also conferred by long term (>5 years) use of insulin. The correlation with use of thiazolidinediones (TZD's) did not reach statistical significance and the data on insulin secretagogues (sulfonylureas and meglitinides) was not consistent and was felt to warrant further study. Interestingly, a category of "other drugs" which included dipeptidyl dipeptidase-4 inhibitors such as sitagliptin as well as glucagon-like peptide analogues among others did not have any association with the incidence of pancreatic cancer. By contrast the use of metformin was clearly associated with a reduction in the incidence of pancreatic cancer.

A retrospective cohort study[6] which involved a group of 62,809 patients from a data base of 300 general practices from the UK covering 2.26 million living patients over a period of approximately 7 years, also noted the incidence of solid tumors increased in those using sulfonylureas or insulin but was less in those using metformin. Although there were no DPP-4 inhibitors monitored in this study, the use of metformin was associated with the elimination of the increased risk of cancer in those using sulfonylureas.

In yet another approach to sorting out whether sitagliptin might contribute to pancreatic cancer, Elashoff et al[7] examined the US Food and Drug Administration (FDA) adverse event reporting system (AERS) associated with sitagliptin and exenatide (a GLP-1 mimetic). The use of this data base for calculating the incidence of an adverse event in the population has been discouraged by the FDA on the grounds that it is likely to be inaccurate and has been criticized for multiple reasons[8]. Inaccuracies in this data base may occur from each of the following: reporting is not consistent and may be influenced by the news media, lack of information about comorbidities, lack of verification of events, unknown information regarding drug compliance and co-morbidities. Nonetheless, Elashoff et al went to great lengths to try to control potential sources of inaccuracy by including surveillance of both control drugs and control diagnoses. They concluded that there was a tenfold increase in the rate of pancreatitis and a 2.9 times increase in the rate of pancreatic cancer with the use of incretin based therapy (exenatide and sitagliptin considered together) over the use of other therapies. In contrast, Dore et al[9] used an insurance company data base covering 27,996 people who started exenatide and 16,276 who started sitagliptin and compared them to equal numbers of controls who had started metformin or glyburide. The authors argued that their use of an insurance data base was statistically sounder than the use of the AERS with its known problems. Using this methodology, they did not find an association between the incretin based therapies and the risk of developing pancreatitis.

Other information does support the idea that there is a link between incretin based therapies and pancreatitis and pancreatic cancer[10]. These include German data suggesting that the incidence of pancreatic cancer was very high in exenatide treated patients but not in DPP-4 treated patients. However, the data are subject to question since the duration of treatment (range 2-33 months) with exenatide is shorter than that usually considered necessary for induction of tumors and therefore exenatide might not be the causative factor. Likewise, there is contradictory information from laboratory studies where GLP1 receptors were not found in human pancreatic adenocarcinomas and in which exenatide did not affect the growth rate of pancreatic cell lines. Various animal studies in which mice and non-human primates have been subjected to incretin mimetics at extremely high doses have shown microscopic signs of pancreatitis but no pancreatic cancer or histological signs of proliferative or preneoplastic lesions.

In summary, there is sufficient information in the animal data and epidemiological studies to raise concerns that incretin based therapies are playing a role in the development of pancreatitis and possibly pancreatic cancer. This information, however, is far from consistent or definitive. Regardless, until more definitive information is known, it would seem prudent to use DPP-4 inhibitors and incretin mimetics judiciously, and preferably combined with metformin.

Returning to our patient, does it seem plausible that there was a connection between her sitagliptin use and her subsequent development of pancreatic cancer? This patient was at risk for pancreatic cancer because she was obese, had diabetes, and a previous history of breast cancer, another adenocarcinoma. She had taken the sitagliptin for less than 15 months, a time usually considered too short for a medicine to cause a malignancy. Finally, she had been on metformin, which if the animal data are correct, abolishes the effect of sitagliptin on ductal proliferation. In short, there is no reason to believe that there was any connection between this unfortunate patient's adenocarcinoma of the pancreas and her previous pharmacotherapy.

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