Diabetes therapy and cancer risk

(OCTOBER 2014)

TO THE EDITOR: I would like to add three points to the excellent review of diabetes therapy and cancer risk by Drs. Sun, Kashyap, and Nasr in the October 2014 issue of *Cleveland Clinic Journal of Medicine*.[1]

First, a recent 10-year prospective observational study of more than 190,000 patients showed no increase in bladder cancer with exposure to or long-term use of pioglitazone vs comparator when smoking status was controlled. Although publicly released, these 10-year data have not yet been published.

Second, a recent paper[2] from the US Food and Drug Administration and European Medicine Agency reviewed the pancreatic safety of incretin-based therapies. They concluded that there is no evidence that these agents increase the risk of pancreatitis or of pancreatic cancer. So I believe that the authors' comment that pancreatitis is a "potential side effect" of these agents is not quite accurate.

Lastly, the authors cite no substantial evidence that would support their statement to avoid using glucagon-like protein 1 (GLP-1) receptor agonists in those with a personal history of differentiated thyroid cancer. Indeed these patients, if adequately treated, should have no remnant thyroid tissue. The rodent data indicate an effect of GLP-1 agonists on rodent C cells, not thyroid follicular cells.[3] In addition, the prescribing information for these agents does not advise such a limitation on their use.

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IN REPLY: In regard to Dr. Weiss's first point, the Kaiser Permanente Northern California diabetes registry study aimed to assess the association between bladder cancer and pioglitazone in 193,099 patients. In their 2011 interim 5-year analysis, Lewis et al reported a modest but statistically significant increased risk of bladder cancer in patients with type 2 diabetes mellitus who used pioglitazone for 2 or more years.[1]

We appreciate Dr. Weiss's comment on the 10-year study conclusion data. As Dr. Weiss has indicated, the recent Takeda news release[2] showed that the primary analysis found no association between pioglitazone use and bladder cancer risk. Furthermore, no association was found between bladder cancer risk and duration of use, higher cumulative doses, or time since initiation of pioglitazone.[2]

Regarding Dr. Weiss's second point, we agree that at this time the cumulative data are not supportive of pancreatitis as per Egan et al.[3] Recent publication of the SAVOR-TIMI trial[4] of saxagliptin documented no increased risk of pancreatitis or pancreatic cancer over 2.1 years of follow-up in more than 16,000 patients over the age of 40 with type 2 diabetes. However, since amylase and lipase levels were not routinely checked in study participants, subclinical and asymptomatic cases may not have been recognized.[4] Therefore, we stand by our statement that pancreatitis is a potential side effect.

It is important to recognize that although the observational data reviewed by both agencies (the US Food and Drug Administration and European Medicine Agency) in the publication by Egan et al[3] are reassuring, we cannot yet say with absolute certainty that there is no associated risk. In fact, the concluding statements of the publication

are as follows: "Although the totality of the data that have been reviewed provides reassurance, pancreatitis will continue to be considered a risk associated with these drugs until more data are available; both agencies continue to investigate this safety signal."[3]

On September 18, 2014, the newest approved GLP-1 receptor agonist, dulaglutide, was approved with a boxed warning that it causes thyroid C-cell tumors in rats, that whether it causes thyroid C-cell tumors including medullary thyroid carcinoma (MTC) in humans is unknown, and that since relevance to humans could not be determined from clinical or nonclinical studies, dulaglutide is contraindicated in patients with a personal or family history of MTC, as well as in patients with multiple endocrine neoplasia syndrome type 2.[5]

It is important to recognize that despite these controversies, which have not been well-supported to date, incretin-based therapies have numerous metabolic benefits, including favorable glycemic and weight effects.

In regard to Dr. Weiss's last point, we would like to point out the study by Gier et al[6] in which GLP-1 receptor expression was found in 3 of 17 cases of human papillary thyroid cancer. The implication is that abnormal thyroid tissue does not behave the same way as normal tissue.

Furthermore, Dr. Weiss brings up the point that patients with thyroid cancer, if it is adequately treated, should have no remnant thyroid tissue. Certainly, adequate treatment would be an easy call to make if a stimulated thyroglobulin level is below the assay's detection limit and there is no imaging evidence of residual thyroid cancer. For example, in someone with a history of thyroid cancer diagnosed more than 10 years ago without biochemical or imaging evidence of disease, any potential concerns of GLP-1 receptor agonist use in regards to thyroid cancer would be nominal. But not everyone with thyroid cancer falls into this category.

We do not suggest that these potential risks preclude the use of these agents in all patients, but rather that a discussion should occur between physician and patient. Diabetes therapy, as in treatment of other medical conditions, should be tailored to the individual patient, and all potential risk and benefits should be disclosed and considered.

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