Diabetes, Cancer Link Is New Research Focus

BY MIRIAM E. TUCKER

VIENNA — Both diabetes itself and insulin therapy are associated with an increased risk for cancer, but the question of whether insulin glargine—or insulin analogues in general—is associated with a further increased risk remains open, five speakers said at a special symposium during the annual meeting of the European Association for the Study of Diabetes.

A series of studies in EASD's journal Diabetologia suggested that the insulin analogue glargine may be associated with an increased risk for cancer (www.diabetologia-journal.org/cancer.html) (INTERNAL MEDICINE NEWS, Sept. 1, 2009, p. 41).

"We're talking about what I think is one of the most interesting, challenging, and important issues to confront us since I came into the field of diabetes: the relationship between diabetes and cancer. Two areas of expertise have suddenly come together," said Dr. Edwin Gale of the University of Bristol (England) and Diabetologia editor-in-chief.

Dr. Jeffrey A. Johnson of the University of Alberta, Edmonton, said that strong associations have been found between diabetes and obesity and a variety of cancers (relative risk, 1.52 for all cancers in one large study), with a likely role for insulin resistance and hyperinsulinemia. Evidence also suggests that glucose-lowering medications that modulate these factors could have modifying effects with regard to cancer, he said.

Craig J. Currie, Ph.D., of Cardiff (Wales) University presented new data from an extension study of the one published online in July (Diabetologia 2009;52:1766-77). They examined 31,421 type 2 diabetes patients on metformin monotherapy, 5,035 on insulin plus metformin, and 4,829 on insulin only. There was a strong dose-response relationship between insulin exposure and first diagnosis of a solid cancer tumor. Compared with the crude rate of 10 cancers per 1,000 person-years for those taking metformin alone, the rates for those on insulin plus metformin increased from 9 for those using fewer than 7 insulin prescriptions per year to 11-12 for 8-14 prescriptions per year to 34 for more than 15 prescriptions per year, Dr. Currie reported.

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DR. SKYLER

Patients on insulin monotherapy showed an even greater dose response: Those using fewer than 7 prescriptions per year had a rate of 15 per 1,000 person-years, those with 7-15 prescriptions had 19, and those with more than 15 prescriptions had three times that rate, at 60 cancers per 1,000 person-years.

After adjustment for age, sex, and smoking status, hazard ratios in the insulin plus metformin groups were 0.87 per 1,000 person-years for metformin alone, 1.0 for 8-14 prescriptions a year, and 3.2 for those with more than 15 prescriptions a year. For those on insulin alone, hazard ratios were 1.05 for metformin alone, up to 5.73 for those with more than 15 prescriptions per year. The same pattern of association persisted after adjustment for other covariates such as weight, insulin exposure, and hemoglobin A_{1c}, he said. Some of the risk is attenuated in those using metformin with insulin, because metformin appears to have a protective effect, he noted.

Dr. Ulf Smith, president of the EASD, noted that insulin is not oncogenic, but may promote growth of cells that have already undergone oncogenic transformation. "I don't think anyone has suggested that insulin causes cancer, but it is a growth-promoting hormone." The mechanism is likely to relate to insulin's binding of insulinlike growth factor receptors on tumors, said Dr. Smith of the Sahlgrenska Center for Cardiovascular and Metabolic Research, Göteborg, Sweden.

Dr. Jay Skyler of the University of Miami spoke on behalf of glargine (Lantus) manufacturer Sanofi-Aventis. He noted that even in the original four Diabetologia studies, only one—the original German database analysis—showed any statistically significant increase in cancer risk with glargine, but that was only after adjustment for insulin dose, and that method has been called invalid by many experts.

The other three studies show no statistically significant overall increased risk for glargine, nor did a subsequent analysis conducted by Sanofi-Aventis of its data from 31 clinical trials involving a combined population of 10,880 people with 5,657 on glargine. For all cancers, the rates were no different from those in the general population. A further analysis from 26 uncontrolled trails also showed no indication of increased risk, Dr. Skyler said.

In the ongoing ORIGIN (Outcome Reduction With an Initial Glargine Intervention) study of more than 12,612 randomized subjects, no increased cancer risk has been found in more than 50,000 patient-years of exposure, he added. "The totality of the available evidence suggests that the headlines which suggested that 'Glargine Causes Cancer' are unsubstantiated, unwarranted, and unproven," Dr. Skyler commented.

Dr. David Russell-Jones gave an overview of a new meta-analysis of safety data conducted by Novo Nordisk for its long-acting insulin analogue, detemir. In studies lasting about 24 weeks, the risk for cancers of all types among 3,983 patients with either type 1 or type 2 diabetes on detemir was 0.36 per 1,000 person-years of exposure, compared with 0.92 for 2,661 similar patients using NPH insulin.

Those rates yielded an identical odds ratio of 2.53 when two different methods of statistical calculation were used, said Dr. Russell-Jones of the University of Surrey, Guildford, England.

Dr. Gale, in his closing remarks, referred to Diabetologia as the "epicenter of the storm." As a result, "many members of the medical community and the public have been confused, and in some cases angry. I think this has been one of the most difficult, confusing, emotive, and controversial issues I have ever had to deal with."

Acknowledging that he had received some criticism for publishing the articles in the first place, Dr. Gale said he has no regrets, noting, "The answer to the question may well be negative, but the question has to be asked."

Dr. Johnson declared he had participated as a speaker for Eli Lilly & Co. Dr. Gale, Dr. Smith, and Dr. Currie stated they had no conflicts of interest. Both Dr. Skyler and Dr. Russell-Jones declared financial relationships with other diabetes-related companies in addition to the ones they were representing at the symposium.

On Sept. 29, Sanofi-Aventis announced the launch of a research program to investigate whether there is a relationship between cancer and insulin use, including the analogues (http://en.sanofi-aventis.com/binaries/20090929_easd_lantus_en_tcm28-26400.pdf). ■

Metformin Investigated as Possible Anticancer Treatment

BY MIRIAM E. TUCKER

VIENNA — The glucose-lowering drug metformin is increasingly showing an anticancer effect.

The data come from studies conducted in both the diabetes and oncology research communities, according to experts at the annual meeting of the European Association for the Study of Diabetes.

The subject first caught the medical community's attention this summer, with the publication of a series of articles on the putative association between insulin glargine and cancer in EASD's journal Diabetologia (INTERNAL MEDICINE NEWS, Sept. 1, 2009, p. 41).

The question has been whether glargine or other insulin analogues could accelerate the growth of cancers in patients predisposed to the disease. At the meeting, representatives from Sanofi-Aventis, maker of insulin glargine (Lantus), and Novo Nordisk, maker of detemir (Levemir), presented data showing no statistically significant relationship between their products and cancer.

But evidence for a protective effect of metformin did appear in one of the Diabetologia studies that caused the furor. Craig J. Currie, Ph.D., of Cardiff (Wales) University and his associates found the lowest risk for cancer among users of metformin, compared with other diabetes treatments; adding metformin to insulin reduced the progression to cancer, compared with insulin treatment alone, with a hazard ratio of 0.54 in a retrospective cohort study of more than 62,809 diabetes patients.

The lowest cancer risk was in patients who used metformin, compared with other diabetes treatments.

DR. CURRIE

Several lines of investigation are now looking at metformin as a potential anticancer treatment outside of diabetes, said Dr. Edwin Gale, of the University of Bristol (England) and editor-in-chief of Diabetologia.

The Cardiff study showed that diabetes patients on insulin or insulin secretagogues were more likely to develop solid cancers than were those on metformin, while the combination with metformin abolished most of this excess risk. Metformin use was associated with lower risks of colon or pancreatic cancer, but did not affect the risk of breast or prostate cancer. Use of insulin analogues was not associated with increased cancer risk, compared with human insulin (Diabetologia 2009;52:1766-77).

Dr. Ulf Smith, president of the EASD, said that two just-published studies further support the notion that metformin may have a protective effect against cancer. One showed a better response rate to chemotherapy among diabetic patients with breast cancer who were taking metformin (J. Clin. Oncol. 2009;27:3297-302).

The other study, published online, supports the so-called "cancer stem cell" hypothesis, which suggests that, unlike most cancer cells within a tumor, cancer stem cells resist chemotherapeutic drugs and can regenerate the various cell types in the tumor, thereby causing relapse of the disease. Drugs that selectively target cancer stem cells offer promise for cancer treatment, particularly in combination with chemotherapy. In this study on mice, metformin inhibited cellular transformation and selectively killed cancer stem cells in four genetically different types of breast cancer, and the combination of metformin and doxorubicin killed both cancer stem cells and non-stem cancer cells in culture (Cancer Res. 2009 Sept. 14 [doi:10.1158/0008-5472.CAN-09-2994]).

"The story with metformin is extremely exciting," said Dr. Smith of the Sahlgrenska Center for Cardiovascular and Metabolic Research, Göteborg, Sweden. ■