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—are associated with a further increased risk remains open.

Those were among the conclusions from five speakers at a special symposium, "Diabetes Therapy and Cancer," held during the annual meeting of the European Association for the Study of Diabetes.

Although there has been a steady progression of research papers over the past decade on the relationship between diabetes and cancer, the topic was suddenly thrust into the spotlight in June with the release of a series of studies in EASD's journal Diabetologia, suggesting that the insulin analogue glargine may

'The answer to the question may well be negative, but the question has to be asked.'

DR. GALE

be associated with an increased risk for cancer (www.diabetologia-journal.org/cancer.html).

Since then, researchers have been refocusing efforts to shed further light on the complicated relationship between the two conditions. "What has emerged in the past few months is a whole new area of investigation," said Dr. Edwin A. M. Gale, Diabetologia editor-in-chief, who moderated the symposium that attracted a large proportion of the meeting's 18,000 attendees.

"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. Gale of the University of Bristol, England.

Dr. Jeffrey A. Johnson, who is professor at the School of Public Health, Health Policy and Management, University of Alberta in 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—including the thiazolidinediones and sulfonylureas as well as insulin—could therefore also have positive or negative modifying effects with regard to cancer, he said.

Craig J. Currie, Ph.D., of Cardiff (Wales) University, presented new data from a retrospective cohort study of a U.K. general practice population. In this 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 who were 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 those using 8-14 prescriptions per year to 34 for those using more than 15 prescriptions per year, Dr. Currie reported.

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 pre-

Continued on following page

Continued from previous page

scriptions 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, clarified a point that has caused confusion: Insulin is not oncogenic, but rather it may promote the 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. This has been known for some time."

The mechanism is likely to relate to insulin's binding of insulin-like growth factor receptors on tumors, noted Dr. Smith of the Salgrenska Center for Cardiovascular and Metabolic Research, Göteborg, Sweden.

The two final speakers presented information from the two relevant manufacturers: 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 that there was any statistically significant increase in cancer risk with glargine, and that was only after adjustment for insulin dose, a method that 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 than in the general population. A further analysis from 26 uncontrolled trials also showed no indication of increased risk, said Dr. Skyler.

And one more source of data, the ongoing ORIGIN (Outcome Reduction With an Initial Glargine Intervention) study of more than 12,612 randomized subjects has also found no increased cancer risk 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.

Some of the cancer risk was attenuated in those using metformin with insulin.

DR. CURRIE

Those rates yielded an identical odds ratio of 2.53 using two different methods of statistical calculation, said Dr. Russell-Jones of the University of Surrey, 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."

And while acknowledging that he had received some criticism for publishing the articles in the first place—given that they raised more questions about the glargine/cancer issue than they answered—Dr. Gale said he has no regrets or apologies, 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.

In September, Sanofi-Aventis announced the launch of a research program to investigate whether there is a relationship between cancer and insulin use, including the analogues. ■