Data Linking Glargine to Cancer 'Inconclusive'

BY MIRIAM E. TUCKER

ATLANTA — Reaction by medical societies and the Food and Drug Administration to articles suggesting a link between insulin glargine and cancer has been swift and unified: Patients with diabetes who are using glargine should not change their regimen because there is no clear evidence of such a relation.

The American Association of Clinical Endocrinologists, several other professional societies, and the FDA are cautioning patients and physicians not to overinterpret the inconclusive findings from four studies published online by the journal Diabetologia examining a possible association between glargine and cancer (www.diabetologiajournal.org/cancer.html).

In an editorial, Dr. Edwin A.M. Gale, editor of Diabetologia, and Dr. Ulf Smith, president of the European Association for the Study of Diabetes, state that "the studies reported are far from conclusive, but they do indicate the need for further investigation of the issue."

Because the cancer risk was seen within a short period of time from exposure to glargine, the data do not suggest that glargine (Lantus, Sanofi-Aventis) causes cancer, they said. Rather, glargine might accelerate the progress of preexisting malignancies.

But Dr. Paul Jellinger said the studies show no definitive evidence of such a mechanism. "The data are inconclusive, the studies contradict themselves, and it's premature to make any recommendations to change insulin regimens. Each patient's concerns should be addressed individually," said Dr. Jellinger, a clinical endocrinologist in Hollywood, Fla., and a past president of AACE. He participated in the writing of the AACE position statement, which was led by Dr. Yehuda Handelsman, a clinical endocrinologist in Tarzana, Calif. He added that "there's also a higher incidence of certain cancers in type 2 diabetes to begin with. The subject of diabetes and cancer merits further investigation."

Like the other groups, the American Diabetes Association advised patients not to stop taking their insulin without consulting their physicians until more information is available. The data comprise four studies published online simultaneously. (See box.)

The FDA noted that the duration of follow-up was shorter for all the studies than is generally considered necessary to evaluate cancer risk from a drug exposure. Further, "inconsistencies in findings within and across the individual studies raise concerns as to whether an association between the use of insulin glargine and cancer truly exists. Additionally, differences in patient characteristics across the treatment groups may have contributed to a finding of increased cancer risk."

The agency said it is reviewing several sources of safety data for glargine, including completed and ongoing controlled clinical trials, to better assess whether there is a risk of cancer associated with the insulin analogue. Discussions are taking place between the FDA and Sanofi-Aventis to determine if additional safety and efficacy studies will need to be performed. The FDA said it will communicate its findings to the public as soon as its review of insulin glargine is complete.

Sanofi-Aventis also issued a statement saying that the company "stands behind the safety of Lantus. … The results of these data clearly show that no definitive conclusions can be drawn regarding a possible causal relationship between Lantus use and the occurrence of malignancies."

Dr. Gale and Dr. Smith pointed to other noteworthy findings from the studies. For example, the results of the Welch study showed that hazard ratios for cancer increased for all insulin-based regimens is consistent with other data suggesting that insulin use overall increases the risk for malignancy.

The Welch study also demonstrated the protective effect of metformin, including the suggestion that adding metformin to monotherapy with sulfonylureas or insulin slowed the rate of cancer development.

"These observations suggest that metformin may come to play a major role in cancer prevention in diabetes. For present purposes, however, the points to note are that concomitant metformin use is potentially a major confounder when it comes to estimating the risks of insulin therapy. …Furthermore, the lack of effect of metformin on breast cancer, if confirmed, might help to explain why this particular cancer has tended to emerge from the analysis conducted in the previous two studies," they commented.

"We have no conclusive proof that Lantus is associated with a higher rate of cancer. The German study is suggestive, but relies on a statistical correction for insulin dose. The Swedish and Scottish studies are essentially negative in all respects except that of breast cancer. Individually, as we have emphasised, neither study is in any way conclusive. Taken together, however, they make it clear that there is indeed a case to answer," Dr. Smith said. He added that new data will be presented at the EASD meeting in Vienna in September.

Dr. Smith and Dr. Gale reporting having no conflict of interest. Dr. Jellinger is on the speakers' bureau for several pharmaceutical companies, including Novo Nordisk, Amylin Lilly, and Takeda. ■

Four Registry Studies on Insulin Glargine and Cancer Yield Different Results

The first of the four studies, reporting a dose-dependent increase in cancer risk with glargine compared with human insulin in a study of more than 100,000 patients, was submitted to Diabetologia last year, Dr. Gale and Dr. Smith explained in their editorial. Its findings suggested that, compared with people using similar doses of human insulin, out of every 100 people who used Lantus insulin over an average of about 1.5 years, 1 additional person was diagnosed with cancer (Diabetologia 2009 June 26; doi:10.1007/s00125-009-1441-5).

However, because of the study's limitations and its enormous implications, the European Association for the Study of Diabetes held the article and requested the three other analyses of data from national diabetes registries in Sweden, Scotland, and Wales to see if the findings could be replicated. All four studies were published simultaneously.

The German Study

The first study included 127,031 insulin-treated diabetic patients from a national health insurance database, all without known malignant disease at baseline and who had received first-time treatment exclusively with either human insulin (95,804), lispro (3,269), aspart (4,103), or glargine (23,855) exclusively (Diabetologia 2009 June 26; doi:10.1007/s00125-009-1418-4).

At a mean follow-up of 1.63 years, the unadjusted risk for developing a malignant neoplasm was actually lower in those using all three analogues. But because patients taking a combination of human and analogue insulins had been excluded from the study, the glargine patients were using much lower overall doses than were those on human insulin (median 22 vs. 37 IU/day). After adjustment for daily dose, the risk was significantly increased for those taking glargine, compared with those taking human insulin, with hazard ratios of 1.09 for 10 IU/day, 1.19 for 30 IU/day, and 1.31 for 50 IU/day. No such increases were seen with either of the short-acting analogues lispro or aspart.

The Swedish Study

The Swedish study followed 114,841 individuals aged 35-84 years who had a prescription dispensed for insulin during the latter 6 months of 2005 and linked them with cancer registry data during 2006-2007.

After adjustment for age and sex, the overall rate of malignancy was not elevated for glargine monotherapy, compared with other insulins, nor were the specific rates of prostate or gastrointestinal cancers. However, after adjustment for a variety of other factors, women who took glargine had a significantly higher rate of breast cancer than did women who took other types of insulins as monotherapy (relative risk 1.97).

The Scottish Study

The Scottish group examined a total of 36,254 people using insulin over a 4-month period from a database that includes almost every individual in the country with diabetes. In a 4-year follow-up, the overall group of 3,959 using glargine had the same incidence of all cancers as did those not using glargine (hazard ratio 1.02). However, the subset of 447 patients using glargine as their sole insulin had a significantly higher incidence of all cancers than did the 32,295 using other insulins only (HR 1.55), while those using glargine with other insulins had a slightly lower incidence (HR 0.81).

Overall, there was no increase in breast cancer rates associated with insulin glargine use (HR 1.49), and no differences in breast cancer or all cancers were seen among type 2 diabetic insulin users, they reported.

The authors noted important differences in baseline characteristics between the insulin treatment groups. For example, patients using glargine alone were older than were those on glargine plus other insulins (68 vs. 41 years) and users of other insulins (60 years). Those on glargine alone also were more overweight, more hypertensive, and more likely to be on oral glucose-lowering drugs.

The Welch Study

This study was a retrospective cohort study of 62,809 people treated in U.K. general practices that participate in a national health information network (Diabetologia 2009 June 26; doi:10.1007/s00125-009-1440-6).

These patients were all above age 40 at the time of diagnosis and were divided into four treatment groups: monotherapy with metformin or sulfonylurea, combination therapy with the two oral agents, or insulin. The insulin users were further subdivided into users of glargine, long-acting human insulin, biphasic analogue, or human biphasic insulin.

Metformin monotherapy carried the lowest risk of cancer, consistent with previous data suggesting that metformin may have a protective effect against malignancy. Compared with that group, the hazard ratio was 1.08 for those taking metformin plus sulfonylurea, 1.36 for sulfonylurea monotherapy, and 1.42 for insulin-based regimens. The latter finding is also consistent with other data suggesting that insulin use overall increases the risk for malignancy, Dr. Smith and Dr. Gale noted.

Adding metformin to insulin reduced the progression to cancer (HR 0.54). The hazard ratio for those on basal human insulin alone vs. glargine alone was 1.24, the authors noted.