Insulin Glargine and Incidence of Cancer—An Ongoing Debate

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Hemkens and colleagues[1] published a registry study that demonstrated a significantly increased risk of a cancer diagnosis associated with high dosages of insulin glargine [relative risk (RR), 1.18; 95% confidence interval (CI), 1.08–1.28, adjusted for various factors and insulin dosage]. However, the subsequent scientific discussion clearly revealed many methodological weaknesses of this study.[2,3] Nevertheless, this study raised concerns among health care professionals about exposing diabetes patients to an unnecessary cancer risk by use of insulin glargine. Therefore, follow-up on this matter, based on currently available data and a closer look at the original publication, may help to clarify further the putative cancer risk of insulin glargine.

The registry study[1] demonstrated a significantly higher incidence of cancer (5.26 versus 1.86 cases per 100 patient years) in patients who were receiving a rather high dosage of insulin glargine (>40 U daily) compared with low dosages (<20 U daily). But a dose-dependent increase in cancer incidence was also observed in patients who were receiving human insulin (3.1 versus 1.73 cases per 100 patient years). Interestingly, only 13.5% of patients on insulin glargine received a high dosage of >40 U daily, whereas 46% of patients on human insulin received this dosage.[1] In the previous discussion, this different *distribution* of the insulin dosages did not receive enough attention. Using the distribution data to standardize the cancer incidence, a standardized cancer incidence rate of 2.46 cases versus 2.68 cases per 100 patient years was the outcome among patients using insulin glargine versus human insulin (see **Table 1**). Thus it is unlikely that use of insulin glargine results in an increased cancer risk in the population.

All available data from randomized trials that used insulin glargine and a comparator insulin on the incidence of malignancies were combined in a recent meta-analytic study.[4] The RR of malignant cancer in the insulin glargine group was 10% lower than in the comparator groups (RR, 0.90; 95% CI, 0.36–1.36). Moreover, there were no significant differences between insulin glargine and the comparator groups with regard to the specific sites of cancer, such as skin, colon, rectum, breast, and gastrointestinal tract.

In the only long-term randomized study, patients received rather high insulin dosages (neutral protamine Hagedorn [NPH] insulin, 72.3 U daily, versus glargine, 61.8 U daily). At the 5-year follow-up, cancer incidence (RR, 0.90; 95% CI, 0.64–1.26) in the insulin glargine group was lower than in the NPH group.[5] Although this study was not powered to detect differences in cancer incidence rates, but rather to detect the progression of retinopathy, its findings are more robust than those of the registry study, because 2144 patient years were surveyed in subjects receiving a rather high dose of insulin glargine.[1] The registry study surveyed only 3226 patients who were receiving a high dosage of insulin glargine

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Abbreviations: (CI) confidence interval, (NPH) neutral protamine Hagedorn, (RR) relative risk

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(>40 U daily) for a total observation time of 1959 patient years (mean observation time 7.3 months per patient). Given the biological implausibility of promoting cancer in such a short time, it seems very likely that these results are due to chance, causing unnecessary concerns among patients and health care professionals. Thus, these findings clearly corroborate the conclusion of Garg and associates[6] that the association of insulin glargine and cancer is unsubstantiated.

Table 1.
Standardized Cancer Incidence According to Reported Insulin Dosage[1]

Insulin dosage (units per day)	Percentage treated (%)	Observed cancer incidence per 100 patient years	Standardized cancer incidence per 100 patient years
Insulin glargine			
<20	45.4	1.86	0.92
20–40	41.1	2.03	0.83
>40	13.5	5.26	0.71
			total: 2.46
NPH insulin			
<20	23.4	1.73	0.55
20–40	30.6	2.36	0.72
>40	46.0	3.10	1.41
			total: 2.68

Disclosures:

Norbert Hermanns received honoraria for lectures or workshops from Eli Lilly Company, Berlin Chemie, Novo Nordisk, and Sanofi Aventis. Norbert Hermanns is member of a global education advisory board of Eli Lilly Company and a member of the German DAWN advisory board of Novo Nordisk. Bernd Kulzer received honoraria for lectures or workshops from Eli Lilly Company, Berlin Chemie, Novo Nordisk, and sanofi-aventis. Bernd Kulzer is member of an advisory board of Roche Diagnostics and a member of the German DAWN advisory board of Novo Nordisk.

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