THE ENDOCRINE SOCIETY

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STATEMENT FOR PROVIDERS
POTENTIAL ASSOCIATION OF INSULIN GLARGINE WITH MALIGNANCY
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Recently, you and your patients may have become aware of press reports about a potential relationship between malignancy and the use of insulin glargine. These reports are based on a series of five retrospective observational studies (4 papers and one letter) published on-line in Diabetologia, accompanied by a lengthy editorial. The studies differ considerably in patient populations, confounding variables, and analytic methods, as well as in conclusions, so that drawing a consensus recommendation as to how to advise your patients about the safety of insulin glargine becomes problematic.

Certain factors should be kept in mind as one considers this new information. Obesity, diabetes (particularly Type 2), and insulin resistance all appear to be associated with occurrence of malignancy (especially breast, colon, and pancreas). Insulin is a dose-dependent mitogen under various experimental paradigms, and there appears to be a positive correlation between insulin dosage and occurrence of malignancy in diabetic patients. Genetic modification of the insulin amino-acid sequence can alter hormonal conformation and interaction with receptors, potentially leading to changes in insulin's hypoglycemic and/or mitogenic activity, or the ratio between these two.

The index paper from Germany by Hemkens et al examined records of 127,000 individuals who began monotherapy with a single type of insulin (native, lispro, aspart, or glargine) and were followed retrospectively over an average time of 1.6 years for the development of malignancy. The key finding, determined with a Cox multiple regression model, was that use of insulin glargine monotherapy was associated with a statistically higher chance of malignancy, for any given dose of insulin, than use of native insulin monotherapy; the adjusted hazard ratio increased from 1.09 for daily insulin doses of 10 units up to 1.31 for daily insulin doses of 50 units.

In considering these results, there are several aspects of this study that should be kept in mind: 1) The follow-up period was very short in terms of development of malignancy, so that the investigators were probably examining growth of pre-existing cancers rather than initiation of de-novo malignancy; 2). The results were not adjusted for differences in weight or BMI, factors known to be associated with malignancy; and 3) There was no breakdown of the malignancy occurrence by site of cancer.

Furthermore, it should be emphasized that this paper's conclusion of an association between insulin glargine and malignancy was the result of a complicated statistical analysis in which insulin dosage played a key role. Analysis of the raw data, reflecting the real-life situation rather than the prediction of a statistical model, showed that absolute cancer incidence was actually 15% *lower* with insulin glargine monotherapy. Furthermore, the gross all-cause mortality was considerably *lower* with insulin glargine (hazard ratio 0.68; CI 0.65-0.72). Consequently, it is

difficult to assess, from this study alone, whether insulin glargine is helpful or harmful, compared to native insulin, in a clinical practice environment.

The other papers reported in Diabetologia, considered as a whole, did not support a clear-cut answer to the question of potential harm from insulin glargine, and these studies also came to a series of perplexing conclusions. For example, a Swedish study reported an increased risk of breast cancer with insulin glargine (relative risk 1.99), but also showed that women using insulin glargine had lower all-cause mortality (relative risk 0.83). A Scottish study suggested that insulin glargine monotherapy was associated with cancer occurrence, but that insulin glargine combined with other insulins seemed to be beneficial as far as cancer incidence. One surprising finding was that metformin use seemed to be strongly protective against cancer, another plus in favor of this popular medication.

A particular concern in all of these studies is the possibility of "allocation bias": differences in underlying cancer-predisposing factors (especially weight and age) between the insulin glargine group and the comparator group that may not have been corrected for by the statistical methods used and which might account for some or all of the differences noted in purported cancer incidence.

Taken together, these studies do not clearly indicate that inclusion of insulin glargine in a treatment regimen for diabetes leads to worse overall health or, for that matter, better overall health. Nevertheless, the possibility of increased cancer occurrence with insulin glargine use under some circumstances does raise concern. In evaluating all of this information, the editorial concluded "The evidence presented in this set of papers is sufficient to establish that there is a case to answer, but is entirely insufficient to bring in a verdict. Certain reassurances do, however, seem justified. There is no evidence that insulin, however formulated, causes cancer. There is no evidence of an overall increase in the rate of cancer development in patients on insulin glargine, and some suggestion that the risk may actually be reduced. There is no evidence of harm in type I diabetes or in premenopausal breast cancer."

In terms of clinical practice, there does not appear to be sufficient evidence to recommend against use of insulin glargine. Practitioners who treat diabetes have a variety of potential treatment regimens in their armamentarium, and they should continue to individualize their recommended therapy based on each patient's situation. Diabetic patients, like other individuals, should be strongly encouraged to follow current recommendations regarding screening tests for cancer (mammogram, colonoscopy) and avoid dangerous habits (smoking) regardless of the specific treatment program followed.

As experts continue to pore over this mass of new data, The Endocrine Society looks forward to development of additional analyses that may help practitioners find their way through this confusing and unsettled area.