Insulin analogues and cancer: a possible link that needs further investigation

Diabetologia, the journal of the European Association for the Study of Diabetes (EASD), has just published a series of research papers that have examined a possible link between one of the insulin analogues and the risk of being diagnosed with cancer. This report provides a summary of the information available.

There are more than 200 million people with diabetes worldwide. About 10% of these people develop diabetes early in life, and most of them have what is known as type 1 diabetes. People with type 1 diabetes have an absolute reliance upon insulin treatment for their continued health and well-being. Type 2 diabetes, which affects the remaining 90%, typically develops later in life and may be associated with excess weight. People with type 2 diabetes are able to make some of their own insulin, which means that they can usually be treated with diet and tablets in the early stages. At a later stage, however, many patients with type 2 diabetes lose the ability to produce their own insulin, and will then need insulin injections to maintain their health.

Human insulin has been very widely used for decades and its safety is established beyond doubt. More recently, insulin manufacturers have developed modified insulins, known as insulin analogues, which are intended to provide smoother or more precise control of blood glucose levels. Some of these have been modified to give a very rapid onset of action, and others have been designed to give a slow sustained release. The new information relates to a long-acting analogue known as insulin glargine, or Lantus insulin. This is a popular insulin that has been in widespread use since its introduction in 2000.

A study from Germany has raised some questions about Lantus—in particular whether it might in some circumstances accelerate the development of cancer. In the light of these preliminary findings, the EASD requested other diabetes research groups in Sweden, Scotland and England to see if these findings could be reproduced in other independent studies. All four papers are published online today and will subsequently appear in the print issue of *Diabetologia*.

What is the problem, and what is known about it so far?

Insulin glargine, also known as Lantus insulin, is a member of the new class of insulin analogues used in the treatment of diabetes. It has a very similar structure to human insulin, and lowers blood glucose in exactly the same way. Lantus passed the standard safety checks required for all insulins before they go into clinical use, but was noted to promote the growth of some cell types in the laboratory. This raised the theoretical possibility that it might have the same effect on cancer cells growing in the body. It has not previously proved possible to examine this possibility in large patient populations.

What did the researchers do in these particular studies?

The risk of all cancers, and of specific cancers commonly seen in type 2 diabetes, was examined in the course of four separate studies based on large patient databases in Germany, Sweden, Scotland and England. The rate of tumour diagnosis was compared in patients with mainly type 2 diabetes taking Lantus as against other types of insulin. Between them, these studies included details of about 300,000 patients, more than 10% of who were on Lantus insulin. One of the studies also looked at cancer risk in tablet-treated patients.

Who was studied?

The study groups included 127,031 insulin-treated patients from a German insurance database, 114,841 insulin-treated patients from Swedish Diabetes and Cancer registers, 49,197 patients from Scottish National Diabetes and Cancer registers, and 10,067 patients from a UK GP database. This made a total of 301,136 insulin-treated patients, 34,392 of who were on Lantus insulin alone.

How were the studies done?

The German study compared the rate of all solid tumours in patients on Lantus alone versus other insulins. Diagnosis of cancer was ascertained from the same database, as was the dose of insulin prescribed for each patient. Individual cancer types were not examined.

The Swedish study focused on the rate of cancer development in patients treated with Lantus insulin alone, as against any insulin other than Lantus, or Lantus taken in combination with another insulin. Overall cancer risk was examined, and also the risk for cancer of the breast, prostate or gastrointestinal tract.

The Scottish study was designed in the same way as the Swedish study. Patients were divided into the same three categories of insulin treatment, i.e. Lantus insulin alone, as against any insulin other than Lantus, or Lantus taken in combination with another insulin. Overall cancer risk was examined, and also the risk for cancer of the breast, colon or pancreas.

The UK study, based on a general practitioners' (GP) registry, used a pre-existing dataset that had examined cardiovascular risk in patients who were taking different forms of treatment for their diabetes. This study included patients on tablets as well as insulin. Patients on Lantus insulin alone were compared with patients on human NPH insulin alone, and with patients treated with premixed human or analogue insulin preparations. The study compared the rate of cancer for all cancers, and for cancers of the breast, colon, pancreas and prostate.

Standard statistical adjustments were made in all the studies reported here for other factors that might influence cancer risk, such as age and sex.

What did the researchers find?

The German study found no overall difference in cancer risk between patients treated with Lantus and those treated with human insulin. Following statistical adjustment for insulin dose, however, the analysis showed that a patient on Lantus was rather more likely to be diagnosed with cancer than a patient on the same dose of human insulin. This difference was roughly equivalent to one extra cancer diagnosed for every 100 people taking Lantus insulin for 1 year.

The Swedish study found no increase in cancer risk, compared with human insulin, in patients who took Lantus insulin together with other types of rapid-acting insulin. Those on Lantus alone were, however, almost twice as likely to be diagnosed with breast cancer.

There were no other differences in cancer risk between the groups. This difference would be equivalent to about one new case of breast cancer for every 1000 women treated for 1 year.

The Scottish study found a slightly reduced cancer risk, compared with human insulin, in those who took Lantus insulin with other insulins. As a group, however, these people were younger and more likely to have type 1 than type 2 diabetes. In contrast, the group on Lantus insulin alone, who were rather older than those in the two other groups, were more likely than those on other insulins to have any form of cancer, breast cancer included, although the difference for breast cancer did not reach statistical significance.

The UK study found no difference in risk of any cancer, including breast cancer, between the four insulin regimens studied. Patients on metformin tablets were less likely to be diagnosed with cancer than those people on other forms of treatment, and this was also seen when metformin was taken in combination with other tablets, or with insulin.

What did the researchers conclude?

The researchers involved in these four studies all agree that these findings are not conclusive. The need for caution arises mainly from the fact that these are observational studies, and not clinical trials. A clinical trial ensures that patients on different treatments are exactly alike in every respect apart from the treatment. An observational study examines groups of people who may differ in many ways, such as age or type of diabetes, and then makes statistical adjustments to allow for these differences. Even carefully performed analyses, such as those reported here, cannot exclude the possibility that differences in cancer risk may be due to differences between the groups of people included in the analysis, rather than to differences between the treatments they are on. This means that further studies are needed before we can reach a final conclusion. The EASD has already started discussions with sanofi-aventis, the makers of insulin glargine, as to how these studies might be conducted.

Insulin itself is a very safe form of treatment, and the researchers would emphasise that there is no evidence whatsoever to suggest that treatment with this insulin analogue actually causes cancer: at worst, it might promote growth of cancers that are already present but have yet to be diagnosed.

What are the implications of these results for patients currently using insulin analogues?

Lantus is a popular and widely used insulin. Many physicians and patients have found it helpful on an individual basis, but systematic evidence from clinical trials has not shown it to provide better overall glucose control than human insulin. There is little or no systematic benefit in type 2 diabetes, although some patients with troublesome hypoglycaemia may find it useful.

The EASD does not recommend that you stop taking insulin glargine (Lantus) on the basis of the evidence presented here, particularly if you have found it helpful in the management of your own diabetes. People with diabetes do, however, have the option of using long-acting human insulin or a mixture of long- and short-acting human insulin twice a day instead of the once-daily analogue. You may wish to consider this option if you already have a cancer, or, for women, if there is a family history of breast cancer.

You should not make any change in your insulin treatment without consulting your own doctor, and you should on no account stop taking your insulin.

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