EASD European Association for the Study of Diabetes

**Smith**

My name is Ulf Smith, and I am the President of the European Association for the Study of Diabetes, an academic association of physicians and scientists and I am here together with Edwin Gale, Editor-in-Chief of Diabetologia as today we have some information for you regarding a possible safety concern relating to one of the newer insulins, known as the insulin analogues.

Worldwide, there are over 200 million people with diabetes. About 10% of these develop diabetes in early 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 still able to make their own insulin, which means that they can usually be treated with diet and tablets in its early stages. At a later stage, however, many patients gradually lose the ability to produce their own insulin, and will also come to need insulin injections to maintain their health.

Insulin is essential for the health and well-being of millions of people. The discovery of insulin was one of the great medical breakthroughs of the 20th century. Insulin has been used by millions of people for nearly 90 years, and it has an excellent safety record if used correctly. The insulin manufacturers have worked hard over many years to produce insulins which can give better and more predictable control, and a number of valuable improvements have been made. More recently, the manufacturers modified the human insulin molecule itself to produce the latest types of insulin, which are known as the insulin analogues. Some of these have been modified to give a very rapid onset of action, and others have been designed to give slow sustained release. The new information we will be talking about today relates to a long-acting analogue known as insulin glargine, or Lantus insulin.

**Gale**

My name is Edwin Gale, and I am the Editor-in-Chief of Diabetologia, the journal of the European Association for the Study of Diabetes and the reports we will tell you about have all just been published in this journal. Lantus insulin was introduced within the past 10 years, and has proved very popular with many doctors and patients. It is most widely valued in type 1 diabetes, but there is some debate as to its benefits in type 2 diabetes. Initial safety concerns were expressed some years ago because it has been shown to cause some types of cells, including cancer cells, to grow and divide more rapidly in cell culture conditions in the laboratory. Other studies proved negative, however, so the significance of these laboratory observations has remained in doubt.

Last year, however, a research paper was submitted to our journal, describing the analysis of more than 100,000 insulin treated patients in Germany; twenty thousand of these were treated with Lantus insulin only, and almost all of them had type 2 diabetes. The investigators initially found no overall increase in the number of cancers in patients taking glargine, but the picture changed when they adjusted the analysis to allow for the amount of insulin taken. It then emerged that, on a dose for dose basis, people on glargine were more likely to be diagnosed with cancer in a given year. To give some idea of scale, we are talking of a difference that might affect one person in a hundred in a given year.

It is important to emphasise that this is a very simple summary of a very complex analysis which relies on statistical modelling techniques. It is notorious that these can sometimes provide misleading results. This paper was in fact sent to 6 leading experts for comment, and three of these recommended rejection. Many of their concerns were ironed out in the course of revision, but not all their objections could be answered. To take one example, it was not possible to break the analysis down according to type of cancer. We therefore concluded that it could be misleading to publish these results in isolation, and the authors of the German paper were therefore invited to wait while other European groups attempted to confirm their findings in other countries. The authors agreed to these conditions.

**Smith**

In the event, three further studies have now been performed by diabetes and cancer specialists in other countries with access to large patient databases. All four papers have now been published online. The first of these papers came from Sweden, and was produced by matching national databases for cancer and diabetes. This analysis included more than 100,000 insulin-treated patients, 6,000 of who were on Lantus insulin only. Briefly, this study found no increase in cancer risk in patients who took Lantus insulin together with other types of quick acting insulin: as a group these patients were younger and were more likely to have type 1 diabetes. Analysis of those on Lantus insulin alone, however, most of who had type 2 diabetes, showed a two-fold increase in breast cancer, but no difference in any other type of cancer. This finding was considered robust, in that it was unaffected by any one of a number of statistical corrections.

Although the Swedish experience took the story a bit further forward, the investigators have been very careful to point out that their findings are far from conclusive. In particular, there is the concern that patients treated with Lantus alone are different in a number of other respects from patients treated with other insulin regimens. As a group they are, for example, typically older than patients on other types of insulin treatment. Statistical analysis always works best when like is compared with like. When two very different groups are compared, there is always the risk that any differences between two groups have arisen because they are different types of people, rather than because they are on different types of treatment.

**Gale**

And here the story is taken up by investigators in Scotland. As in Sweden, these were able to match findings from a national diabetes database with the national cancer registry. Briefly again, their findings were largely consistent with the Swedish findings. In this case, however, it was even more evident that Lantus users fell into two fairly distinct groups – those who took Lantus with other insulins, most of whom were relatively young and had type 1 diabetes, and those who were on Lantus alone, who were older and had type 2 diabetes. The first group had a lower than average cancer risk, as compared with human insulin, and the group on Lantus alone had a slightly higher risk. Many of these differences disappeared when appropriate statistical corrections were made. The finding of particular note, however, was that there was once again an excess of breast cancers in the women

treated with Lantus alone, of about the same magnitude as that seen in the Swedish study.

It is obviously a matter of considerable concern that the same finding emerged from two separate studies with respect to breast cancer, but it is important to emphasise that the investigators concerned consider the results to be far from conclusive. This was for two main reasons. The first was that the number of breast cancers was very small, meaning that these findings could have occurred by chance, and the second, as with the Swedish study, was that the patient groups were very different – which means that the differences in cancer risk might not be related to the type of insulin they were using. In other words, it is possible to say that more women treated with Lantus alone developed breast cancer in Sweden and Scotland, but it is not possible to say that their breast cancer was in any way related to the type of insulin they were using.

Finally, a fourth study, commissioned by the EASD examined cancer risk in relation to a range of different therapies for diabetes, and we will come back to these findings in a moment. For present purposes, however, we can note that this study found no increase in the risk of any type of cancer, breast cancer included, in patients treated with Lantus. The sample size was however smaller than in the other studies, and once again allows no definite conclusions to be drawn.

**Smith**

We believe that people are entitled to know that use of Lantus insulin might be associated with greater risk, but this must be also be balanced against the possibility that we might be causing unnecessary alarm by raising these concerns. Consideration of the facts will not be helped if alarmist headlines appear in the newspapers. Before we try to reach a conclusion, therefore, a number of important points need to be made. The first is that there is no question whatsoever that Lantus or any other insulins included, actually *causes* cancer. Cancers typically take many years to develop, and the reports we have been discussing all relate to a very short period of treatment. The question, therefore, is not whether this type of insulin *causes* cancer, but whether it causes existing cancer cells to grow and divide more rapidly – which might explain why more cancers come to be diagnosed over such a short period of observation.

The next point to make is that large observational studies such as these are notoriously hard to interpret. We can detect differences between groups, but we cannot be certain as to the *reasons* for these differences. There are also a number of unexplained puzzles arising from the studies we have discussed – for example why patients on Lantus alone should apparently behave differently from patients on Lantus plus a quick-acting insulin.

So what conclusions can we draw? It is important to emphasise that 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.

How can this be done? Well, EASD has already communicated these findings to EMEA, the European regulatory authorities, and we are now in contact with sanofi-aventis, the manufacturers of Lantus. A large combined analysis of the best available databases world-wide is however the best way forward, and EASD and sanofi-aventis are pledged to carry this investigation forward until we have either confirmed these preliminary observations or, more hopefully, finally put them to rest.

**Gale**

In the meanwhile, what do these findings mean for patients on insulin? The most important thing to emphasise is that the safety of insulin therapy is established beyond doubt, and has not been affected in any way by this very searching analysis. The concerns that have been raised only affect one particular type of insulin and then, only when used on its own. There is no need for concern if you are taking human insulins, or rapid acting analogues such as Novorapid, Humalog or Apidra. There is another long-acting analogue called insulin detemir, otherwise known as Levemir, which is modified in a different way from Lantus. Levemir was introduced more recently, and we have yet to examine it in the same way as Lantus.

The concerns raised by these studies therefore relate only to Lantus when used alone. There is currently no evidence whatsoever of increased risk in children or other people on multiple injection therapy with Lantus. Furthermore, three of the studies found no overall increase in cancer risk in patients taking Lantus on its own, or with other therapies, as compared with human insulin, although two of these did observe an increase in breast cancers in women taking Lantus alone. To put this risk in perspective, the added risk of breast cancer, if confirmed, would be of the order of one or two extra cases diagnosed each year for every 1000 users. The German study did however suggest a small all-round increase in the likelihood that any cancer might be diagnosed in someone with diabetes of either sex, and further breakdown of this information should become available later this year.

Finally, we have some good news to announce, arising from one of the four studies which examined all forms of diabetes treatment, tablets included, in relation to the risk of cancer. It has already been shown that people with diabetes are less likely to develop cancer, as compared with other therapies for diabetes, if they take a tablet called metformin, which has been available for many years, and which is readily available, safe and effective. Our fourth study provides further evidence that metformin use is associated with a lower risk of cancer, whether taken on its own, in combination with other tablet treatments for diabetes, or in combination with insulin.

If you are concerned about these findings, you should discuss them with your doctor or your diabetes specialist. You should on no account stop taking your insulin, uncontrolled diabetes is indeed very dangerous to your health. If you are a woman with type 2 diabetes, you do have the option of changing to the human insulin equivalent of Lantus, which has been shown to be equally effective in controlling blood glucose levels. This may be of particular concern if someone in your family has previously developed cancer of the breast. Finally, we would emphasise that Lantus is a very popular and effective form of insulin which has helped many people to achieve better control of their diabetes, and our advice for the great majority of patients is to keep on going as you are with this insulin until further information becomes available, which should not take more than a few months.

**Smith**

In conclusion, there are important questions which currently need to be answered with respect to the safety of Lantus when used alone, but there is no clear evidence pointing to an increase in cancer risk. If you, or someone close to you, is taking this insulin, there is no immediate need for action, and

you should certainly not stop taking Lantus until you have had the opportunity to discuss these issues with your own doctor. The European Association for the Study of Diabetes is working hard to clarify these issues, and will inform its members and the public of any new developments. New data will be presented at a special symposium on the occasion of the EASD meeting in Vienna in September of this year.