DIABETES CLOSE UP

Dr. Tina Vilsboll has been working on GLP-1 since 1998 and defended her doctoral thesis on the effect of GLP-1 and GIP in the pathophysiology of diabetes. She is a full-time clinician at the Steno Diabetes Center in Denmark and has been working on liraglutide studies since 2003. Approximately half her patients are type 1 and half are type 2. She has used liraglutide in experimental short-term trials with a focus on evaluating the beta cell function.

On her patients' experience with liraglutide:

Although the study is blinded and she doesn't know which patients receive liraglutide, one patient lost 10 cm in his waist. All of her patients "*feel so well*." Liraglutide lowers body weight in subjects with type 2 diabetes and the underlying mechanism is most likely a combination of effects on the gastrointestinal tract and the central nervous system. Some patients have experienced some diarrhea in the beginning, for one to two weeks. Although nausea is not as much of a problem as with exenatide, side effects are primarily GI and include some nausea, diarrhea, sometimes constipation; these are transient and are not correlated with weight loss, according to Dr. Vilsboll.

On the details of the liraglutide study:

Entry criteria were that patients had to have a starting A1c of between 7.5% and 10% for diet-treated patients, or between 7.0% and 9.5% for patients initially on monotherapy. Dr. Vilsboll said that about 20% of the enrollees were on diet and exercise, with the rest on monotherapy (either metformin or sulfonylurea). Those on an oral agent had a four-week wash-out period. The pre-wash-out A1c was between 7.8% and 8.1%. Following the wash-out, prior to randomization, the A1c's were between 8.1% and 8.5%, so there was an increase of 0.2-0.4%. Dr. Vilsboll believes that the optimal situation would be to do a 12-week wash-out, because then you would begin with an A1c representing the last three months, but this was not possible because it would have been unethical. (There were type 2 patients on monotherapy who had a risk of going on placebo, so a three-month wash-out period would not have been viable.) The rationale for the wash-out was that the study was of liraglutide in monotherapy, so investigators wanted to be sure that other anti-diabetic drugs were cleared. At the point of randomization, subjects who had a fasting BG of over 15 mmol/L (~250 mg/dL) were withdrawn, as they were too poorly regulated. Drop-outs occurred in the patients who were assigned to placebo. There was no drop-out due to adverse events.

On the administration of liraglutide:

In the study, patients took liraglutide with the same flex pen that Novo Nordisk uses for detemir, and Dr. Vilsboll said that it was a "*very thin needle*."

On the results:

There was an improvement in fasting plasma glucose of more than 3 mmol/L (~50 mg/dL). Dr. Vilsboll said that there was a decrease in absolute postprandial glucose values to levels, that in average, were not much higher than the recommended 10 mmol/l (~170 mg/dL).

On the timing of liraglutide's release:

Dr. Vilsboll would only say that " *the sooner the better,*" noting that phase 3 started here in February, though she could not give any specific dates. We would look for a 2008 FDA submission and a 2009 acceptance.

On whether GLP-1 analogs are delaying the move to insulin:

Dr. Vilsboll said she hoped this was the case, but it is too early to tell. She hopes that GLP-1 analogs will preserve beta cell function and postpone the onset of insulin. It may eventually be used with early phase diabetes, impaired glucose tolerance (IGT), or in first-degree relatives of those with diabetes.

On differentiating between GLP-1 agonists:

We caution against comparing Byetta and liraglutide since they were not evaluated directly in the same study. Until a head-to-head study of the two drugs is done, we won't know how the drugs compare, as different baseline A1Cs, patient populations, length of study, and study design invalidate explicit comparisons between separate studies.

In the studies presented at ADA, investigators saw a 1.7% drop in A1c over 14 weeks for liraglutide when compared to placebo. The change in the placebo group was 0.3%. In the recent study with liraglutide, the main adverse events were from the gastrointestinal (GI) system; diarrhea was the most frequent, with an incidence of 19.5% and 12.5% in the high-dose liraglutide group and in the placebo group, respectively. In the high-dose group 10% of the subjects experienced nausea. The frequency of GI events decreased over time, Dr. Vilsboll said. Dr. Vilsboll attributed the lower number of side-effect when compared to previous GLP-1 analogue studies to the profile to the peptide action; she likened liraglutide's profile to that of a basal insulin (no peak).

Dr. Vilsboll emphaisized that liraglutide has a significant effect on fasting level. In her studies, there was a fasting effect of more than 3 mmol/L (54 mg/dL). Asked whether the greater effect on fasting glucose indicated a lesser effect on postprandial values, Dr. Vilsboll said only that the postprandial values are significantly lower with liraglutide than they are with placebo.

Dr. Vilsboll said that the effect of the GLP-1 is a class effect. Which GLP-1 to use, she said, she would leave up to phase 3 studies on liraglutide.

On whether Novo is working on something LAR-like and her thoughts on Byetta LAR:

Dr. Vilsboll said that she had no information on that but said the problem with a longer-acting analog is that it takes more time to reach steady state. It is harder to change the dose of the medication. She characterized the Byetta LAR results presented at ADA as very interesting, and stressed that it should be considered a pilot study because of the small size. She noted that with the middle dose of LAR, there was no reduction in weight, and a good deal of hypoglycemia was seen with the low dose; but with the high dose there is no hypoglycemia, which was surprising.

On choosing between DPP-4 inhibitors and Byetta:

Dr. Vilsboll said she that it was positive that they both have come so far but that we need to see the phase 3 results of the DPP-4 inhibitors in order to see the true effect. Dr. Vilsboll said that if DPP-4 inhibitors can preserve the beta cell, she could imagine giving a pill to a newly diagnosed patient, and this would be more feasible than injections – although she laughed about the perceived resistance (apparently breaking down!) to injections in the US. She noted that of course, the major difference between GLP-1 and DPP-4 is the weight loss. She emphasized that we need to look at DPP-4's effects on beta cells, and that it would be better to give the analog sooner *if* it does help preserve the beta cell – still a big if. She could foresee a combination therapy with metformin in the early stages.

On the anti-diabetic effects of the byproduct of DPP-4 degradation of GLP-1:

There is some, but the effect is very little. This was discussed in several sessions in the meeting. The compound that is released after DPP-4 degrades GLP-1 does not have a very pronounced effect on glucose regulation compared to the primary GLP-1 compound.

On DPP-4 inhibitors:

Dr. Vilsboll said that she is not worried about their safety and that DPP-4 inhibitors have fewer side effects than metformin. She said there is room for both DPP-4 inhibitors and GLP-1 analogs. The evidence on the beta cell function is not as strong so far and DPP-4 inhibitors do not show a weight decrease, although they are oral. Ultimately, Dr. Vilsboll said the choice between DPP-4 inhibitors and GLP-1 depends on the patient and on the effect on beta cell function.

On the population that will be appropriate for liraglutide:

Dr. Vilsboll said that depends on the results of the phase 3 study. She said that liraglutide has a beautiful effect on glycemic control and weight loss, and it may be used for type 2s very early after diagnosis. Part of the phase 3 research is to determine whether it should be given after diet, after monotherapy, or later in the course of disease. A larger indication might result if there are positive effects on the beta cell. Dr. Vilsboll said that if it has a beneficial effect on the beta cell, it might be used to treat patients even before they have diabetes.

On the feasibility of doing a study in an IGT population:

Dr. Vilsboll said that it is definitely a good idea to do such a study, but it will require considerable effort even to identify appropriate subjects. Only 10% of subjects with IGT progress to diabetes each year, so it would have to be a large, long-term study.

On the evidence for beta cell preservation or regeneration:

The data are very strong in rodents for both liraglutide and exenatide. Dr. Vilsboll said that increased proliferation and decreased apoptosis have both been seen, but it's still an open question with respect to human beta cells. We do not know how long the human beta cell needs to be exposed in order to proliferate. Dr. Vilsboll estimated one year would be needed to assess the influence of a drug on beta cell function. She said that you need to evaluate differences in beta cell function a number of months after the medication has been stopped. A sustained A1c drop cannot necessarily be attributed to an increase in beta cell mass.

On how to study beta cell preservation:

Dr. Vilsboll could not comment on whether Novo has a trial planned to study the effect of liraglutide on beta cell preservation, but she suggested a few ways this could be studied. Those with IGT could be treated with liraglutide to compare how many become diabetic compared to those in the control group. Investigators could evaluate beta cell function progress or time to diagnosis. The HOMA test, she said, sometimes called a "poor man's test," is not good enough for a prospective study. A FSIGT or a clamp study is the gold standard, but they are complicated to set up and require experienced investigators.