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POSTER perspectives

Insulin and Injectable Therapy Posters and Abstracts From San Diego

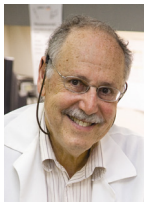
Overview

Mayer Davidson, MD, and **Vivian Fonseca, MD,** provide their perspectives on the clinical importance of 10 posters presented at the 77th Scientific Sessions of the American Diabetes Association from June 9–13, 2017.

Content Areas:

- Basal insulins- degludec and glargine U-300
- Prandial insulins- faster aspart, ultra-rapid lispro, follow-on lispro
- Glucagon-like peptide-1 receptor agonists- dulaglutide, exenatide, lixisenatide, semaglutide
- Glucagon-like peptide-1 receptor agonist via implantable mini-pump
- Fixed-ratio basal insulin/glucagon-like peptide-1 receptor agonist

Faculty



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CE/CME Information

Target Audience
This activity was developed for endocrinologists, primary care physicians, physician assistants, nurse practitioners, nurses and other health care professionals who have an interest in type 1 and 2 diabetes.

Learning Objectives
At the conclusion of this activity, participants should be better able to:

- Summarize the latest research developments in the treatment of type 1 and type 2 diabetes with insulin and other injectable therapies
- Incorporate evidence-based research into clinical practice

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Introduction

Vivian Fonseca, MD

The treatment of patients with type 2 diabetes has evolved significantly over the past decade or so due, in part, to the introduction of several new classes of medications and improvements in others. Injectable medications, that is basal and prandial insulins and glucagon-like peptide-1 receptor agonists, are partly responsible for reshaping our treatment approach. These are exciting times to be sure.

This is Dr. Vivian Fonseca, professor of medicine and pharmacology at Tulane University in New Orleans, Louisiana. In this poster perspective, Research Developments with Insulin Injectable Therapies, Dr. Mayer Davidson from UCLA and I, comment on translational research presented at the 77th Scientific Sessions of the American Diabetes Association from June 9–13, 2017.

We selected 10 posters that we think will be of interest to endocrinologists, primary care physicians, physician assistants, nurse practitioners, nurses, and other health care providers, who wish to improve the care they provide for persons with type 1 or type 2 diabetes.

We summarize the latest research developments on key mechanisms in the pathogenesis of type 2 diabetes mellitus and how they are modified by basal and prandial insulins and glucagon-like peptide receptor agonists.

In addition, Dr. Davidson and I provide our thoughts into the clinical implications of clinical trial results regarding the efficacy, safety, and tolerability of the basal insulin analogs degludec and glargine U-300 and the investigational prandial insulins faster aspart, ultra-rapid lispro and follow-on lispro. We include discussion of several GLP-1 receptor agonists, including one that is administered by an implantable osmotic mini pump as well as fixed-ratio combinations of basal insulin and GLP-1 receptor agonists.

On behalf of Dr. Davidson, I invite you to join us as we highlight these important research findings.

Dulaglutide vs. Glargine, Both Combined with Lispro, Mitigated eGFR Decline in People with Type 2 Diabetes and Moderate-to-Severe Chronic Kidney Disease (AWARD-7)

Vivian Fonseca, MD

Hello this is Dr. Vivian Fonseca, professor of medicine and pharmacology and chair of the Section of Endocrinology at Tulane University School of Medicine. I will be discussing Dulaglutide vs. Glargine, Both Combined with Lispro, Mitigated eGFR Decline in People with Type 2 Diabetes and Moderate-to-Severe Chronic Kidney Disease- The AWARD-7 Study. This poster was presented by Dr. Katherine Tuttle and colleagues at the 77th Scientific Session of the American Diabetes Association from June 9–13, 2017.

In summary, this study in patients with type 2 diabetes and moderate-to-severe kidney disease showed that the glucagon-like peptide receptor agonist dulaglutide mitigated a decline in the estimated GFR over 26 weeks. In addition, dulaglutide reduced albuminuria. The benefits of lessening loss of kidney function and reducing albuminuria were most evident in patients with urine albumin-to-creatinine ratio greater than 300 mg/g at baseline.

This study's important because chronic kidney disease is a common complication of type 2 diabetes mellitus, and is an important target for prevention of treatment. Dulaglutide may be a good treatment option for these patients.

And now here are the comments from Dr. Tuttle, the principal investigator of this study.

Principal Investigator Commentary

- Study involved patients with T2DM and CKD stages 3-4 with
  - mean HbA1c 8.6%
  - mean eGFR 38 mL/min/1.73 m^2
  - median urine albumin-to-creatinine ratio 200 mg/g
- At the end of the study at 26 weeks, the 2 dose levels of dulaglutide (0.75 mg and 1.5 mg weekly) produced
  - equivalent lowering of HbA1c compared to insulin glargine
  - significantly fewer episodes of hypoglycemia

- *The study involved patients with type 2 diabetes and chronic kidney disease stages 3-4 with mean HbA1c 8.6% and estimated glomerular filtration rate 38 mL/min/1.73 m^2 and median urine albumin-to-creatinine ratio 200 mg/g at baseline. At the end of the study at 26 weeks, the 2 dose levels of dulaglutide (0.75 mg and 1.5 mg weekly) produced equivalent lowering of HbA1c compared to insulin glargine and significantly fewer episodes of hypoglycemia.*
- *In the 45% of patients with macroalbuminuria, the urine albumin-to-creatinine ratio was significantly lowered by 25% in the dulaglutide 0.75 mg weekly group and approximately 40% in the dulaglutide 1.5 mg weekly group. The 10% reduction in the insulin glargine group was not significantly reduced from baseline. No significant reductions in the urine albumin-to-creatinine ratio were observed in participants without macroalbuminuria.*

- *In the 45% of patients with macroalbuminuria, the 4% and 11% declines in the estimated glomerular filtration rate with dulaglutide 0.75 mg and 1.5 mg, respectively, were significantly less than the 17% decline with insulin glargine. No significant reduction in the estimated glomerular filtration rate was observed in patients without macroalbuminuria.*

Principal Investigator Commentary
(cont)

The study will impact the management of patients with type 2 diabetes mellitus:

- Dulaglutide can be given safely to patients with T2DM and CKD stages 3-4
- Glycemic control is comparable to insulin glargine as basal therapy with fewer episodes of hypoglycemia
- Benefits of greater albuminuria reduction and lesser decline in the estimated glomerular filtration rate after just 26 weeks of treatment with dulaglutide
- Longer-term data will determine if these benefits translate to reductions in clinical endpoints, such as rates of eGFR decline ≥40% or kidney failure and end-stage renal disease

- *Dulaglutide can be given safely to patients with type 2 diabetes and chronic kidney disease stages 3-4. Glycemic control is comparable to insulin glargine as basal therapy with fewer episodes of hypoglycemia. This study also demonstrated benefits of greater albuminuria reduction and lesser decline in the estimated glomerular filtration rate after just 26 weeks of treatment with dulaglutide. Longer-term data will determine if these benefits translate to reductions in clinical endpoints, such as rates of eGFR decline ≥40% or kidney failure and end-stage renal disease.*

Study Design and Methods

- Prespecified secondary analysis of a phase 3 study
- The phase 3 study
  - compared dulaglutide 0.75 mg or 1.5 mg once weekly to daily titrated insulin glargine, both combined with insulin lispro
  - involved patients with T2DM and stages 3 or 4 CKD
  - demonstrated dulaglutide to be non-inferior to insulin glargine in reducing HbA1c over 26 weeks
- This secondary analysis reports on the effects of dulaglutide on estimated glomerular filtration rate and albuminuria

Here is the summary of the study. This study was pre-specified secondary analysis of a phase 3 study. The phase 3 study compared dulaglutide 0.75 mg or 1.5 mg once weekly to daily titrated insulin glargine, both combined with insulin lispro in patients with type 2 diabetes mellitus, and stages 3 or 4 chronic kidney disease. The phase 3 study demonstrated dulaglutide to be non inferior to insulin glargine in reducing HbA1c over 26 weeks. This secondary analysis reports on the effects of dulaglutide on estimated GFR and albuminuria.

Results Summary

- At baseline, patients had a mean
  - eGFR 38 mL/min/1.73 m^2
  - HbA1c 8.6%
  - age 64.6 years
  - duration of T2DM 18 years
- At baseline
  - 30% had an eGFR <30 mL/min/1.73 m^2
  - 45% had a urine albumin-to-creatinine ratio >300 mg/g

The key findings of the study are that at baseline, patients had a mean eGFR of 38 mL/min/1.73 m^2, HbA1c 8.6%, their age was 64.6 years, and they had a duration of diabetes of 18 years. Thirty percent of patients had an eGFR less than 30 mL/min/1.73 m^2, and 45% had a urine albumin-to-creatinine ratio greater than 300 mg/g.

Results Summary (cont)

- At week 26, eGFR
  - remained stable with dulaglutide
  - declined 1.9 mL/min/1.73 m^2 with glargine
- The urine albumin-to-creatinine ratio declined in the 3 treatment groups over the 26 weeks
  - -26.7% for dulaglutide 0.75 mg
  - -27.7% for dulaglutide 1.5 mg
  - -16.4% for glargine
- Patients with urine albumin-to-creatinine ratio >300 mg/g had
  - less decline in eGFR with both doses of dulaglutide
  - greater reduction in the urine albumin-to-creatinine ratio with dulaglutide 1.5 mg

At week 26, the eGFR remained stable with dulaglutide, but declined 1.9 mL/min/1.73 m^2 with glargine. The urine albumin-to-creatinine ratio declined in the 3 treatment groups over the 26 weeks. The decline was -26.7% for dulaglutide 0.75 mg, -27.7% for dulaglutide 1.5 mg, and -16.4% for glargine. Patients with urine albumin-to-creatinine ratio greater than 300 mg/g had less decline in eGFR with both doses of dulaglutide, and a greater reduction in the urine albumin-to-creatinine ratio with dulaglutide 1.5 mg.

Here are my thoughts and analysis of this study.

Faculty Commentary

The highlight of the study is that

- A reduction in progression of eGFR decline and albuminuria are both novel findings in relation to a drug (dulaglutide) designed to reduce blood glucose as very few diabetes drugs are known to have such benefits

The main point from my perspective is that a reduction of progression of eGFR decline and albuminuria are both novel findings in relation to a drug designed to reduce blood glucose, as very few diabetes drugs are known to have such benefits.

Implications for Practice

- The mitigation of a decline in eGFR is very important clinically as it would delay the development of the need for dialysis or transplantation
  - This needs to be confirmed over the long-term
- A reduction in albuminuria indicates a beneficial effect on the integrity of the endothelium and may have implications for cardiovascular disease as well
- Some of this benefit may relate to the known reduction in blood pressure with GLP-1 RAs
  - It is possible that there is a more direct effect on kidney function

How will these results impact the current state of patient management? Firstly, mitigation of a decline in eGFR is very important clinically as it could delay the development of the need for dialysis and transplantation. However, this needs to be confirmed over the long term. Second, a reduction in albuminuria indicates the beneficial effect on the integrity of the endothelium, and may have implications of cardiovascular disease as well.

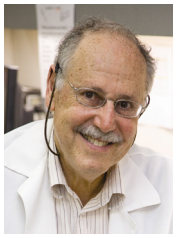
Some of these benefits may relate to the known reduction in blood pressure with GLP-1 receptor agonists, but it is possible that there is a more direct effect on kidney function.

Implications for Practice (cont)

- Further research is needed to determine the impact on clinical management because decline in kidney function occurs over a very long time and is multifactorial
- Nonetheless, these results are very promising and are likely to stimulate further research in this area

How will these results impact the future state of patient management? And what questions remain unanswered? Well, further research is needed to determine the impact on clinical management because decline in kidney function occurs over a very long time and is multifactorial. However, these results are very promising, and are likely to stimulate further research in this area to help us understand what will happen over the long term.

Switching to Insulin Degludec Improves Glycemic Control in Patients with T2DM in a Real-World Setting



Mayer Davidson, MD

Hello, this is Dr. Mayer Davidson, professor of medicine at Charles R. Drew University and the David Geffen School of Medicine at UCLA. I will be discussing Switching to Insulin Degludec Improves Glycemic Control in Patients with T2DM in a Real-World Setting. This poster was presented by Dr. Schultes and colleagues at the 77th Scientific Sessions of the American Diabetes Association from June 9–13, 2017.

In summary, this real-world, non-interventional study showed that switching to insulin degludec from other basal insulins substantially improved glycemic control with a weight-neutral effect and reduced risk of hypoglycemia in patients with type 2 diabetes mellitus under conditions of routine care. Degludec is a basal insulin with a long duration of action and low day-to-day variability in glucose lowering effect. And the importance may be that not all patients treated with a basal insulin achieve glycemic control, often due to frequent episodes of hypoglycemia. Switching to another basal insulin, in this case, insulin degludec, may prove to be beneficial.

Principal Investigator Commentary

- Switching to insulin degludec form other basal insulins for a period of 1 year in a broad population of insulin-treated adult patients with type 2 diabetes was associated with:
  - Improvement in diabetes control (mean reduction in HbA1c of -0.5%)
  - Reduction in the rates of hypoglycemic episodes by more than 60%
  - Reduction in daily insulin dose by approximately 4% with no change in body weight

Principal Investigator Commentary
(cont)

- The clinical implications are that switching patients with T2DM from basal insulin to insulin degludec slightly improves glycemic control and significantly reduces the risk of hypoglycemia in routine clinical practice

And now here are the comments from the principal investigator of this study.

Switching to insulin degludec from other basal insulins for a period of 1 year in a broad population of insulin-treated adult patients with type 2 diabetes was associated with: 1) improvement in diabetes control (mean reduction in HbA1c of -0.5%); 2) reduction in the rates of hypoglycemic episodes by more than 60%; and 3) reduction in daily insulin dose by approximately 4% with no change in body weight. The clinical implications of

Study Design and Methods

- Multicenter, retrospective, chart review of patients with type 2 diabetes mellitus in Europe
- All patients had their basal insulin switched to degludec at least 6 months prior to the start of data collection
- Baseline was defined as the most recent recording during the 3-month period prior to the first prescription for degludec
- Outcome data were collected at 6 and 12 months in the time periods before and after switching to degludec

this study are that switching insulin-treated patients with type 2 diabetes to insulin degludec from other basal insulins improves glycemic control and significantly reduces the risk of hypoglycemia in routine clinical practice.

The methods were as follows: It was a multi-centered, retrospective, chart review of patients with type 2 diabetes mellitus in Europe. All patients had their basal insulin switched to degludec at least 6 months prior to the start of data collection. Baseline was defined as the most recent recording during the 3-month period prior to the first prescription for degludec. Outcome data were collected at 6 and 12 months in the time periods before and after switching to degludec.

Results Summary

- 833 adults with mean
  - age 64.6 years
  - duration of diabetes 17.5 years
  - body weight 97.2 kg
  - HbA1c 8.4%
  - dose of insulin glargine 71.3 units

The key findings were as follows: There were 833 adults with a mean age of 64.6 years, duration of diabetes of 17.5 years, body weight 97.2 kg, and a hemoglobin A1c level of 8.4% at baseline. Their mean dose of insulin glargine at baseline was 71.3 units.

Results Summary (cont)

- After switching to degludec
  - HbA1c decreased -0.5% from baseline to 6 months
  - Maintained at 12 months
    - Decreases were highly statistically significant at both time periods
  - Total daily insulin dose decreased by 2.5 units
  - Body weight remained stable
- This demonstrates the effectiveness of insulin degludec in further reducing HbA1c in patients with inadequate glycemic control with basal insulin therapy in this real-world setting

After switching to degludec, hemoglobin A1c decreased -0.5% from baseline to 6 months. And this was maintained at 12 months. And these decreases were highly statistically significant at both time periods demonstrating the effectiveness of insulin degludec in further reducing hemoglobin A1c in patients with inadequate glycemic control with basal insulin therapy in this real-world setting. And the total insulin dose decreased by 2.5 units from the baseline of 71.3 units. The body weight remained stable over 12 months.

Results Summary (cont)

- Comparing the rates of hypoglycemia for the 6 months prior to switching vs the 6 months after switching to degludec showed:

Hypoglycemia (events/patient-year)	6 mos before switch	6 mos after switch
Overall	3.08	1.21
Non-severe nocturnal	1.05	0.1
Severe	0.08	0.006

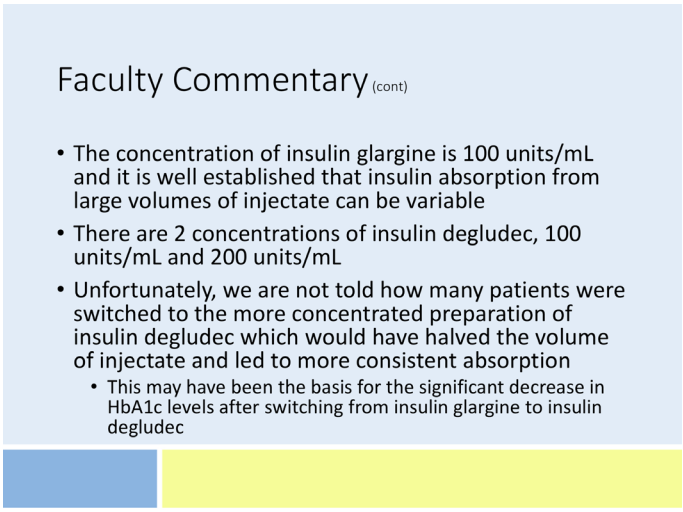
- These data show much less hypoglycemia with degludec than with other basal insulins

Now, comparing the rates of hypoglycemia for the 6 months prior to switching vs the 6 months after switching to degludec showed the following: Overall hypoglycemia, 3.08 events-per-patient-year for the 6 months before switching and 1.21 events-per-patient-year for the 6 months after switching. Non-severe, nocturnal, hypoglycemia 1.05 vs 0.1 episodes-per-patient-year. Severe hypoglycemia 0.08 vs 0.006 episodes-per-patient-year. And, not surprisingly, all of these differences in hypoglycemia were statistically

Principal Investigator Commentary (cont)

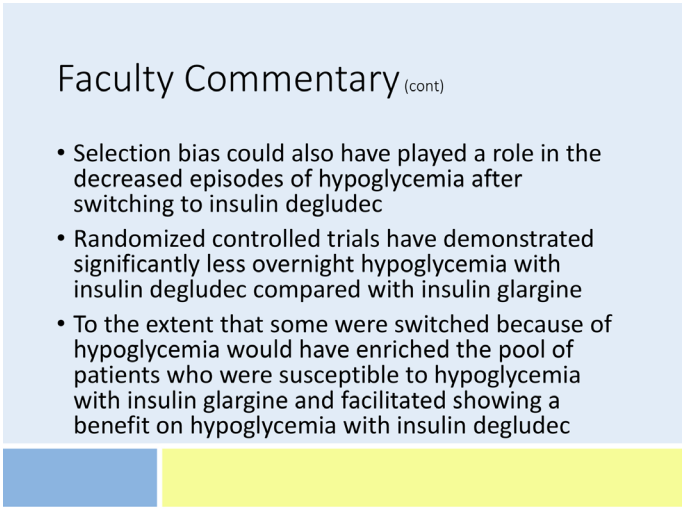
- The clinical implications are that switching patients with T2DM from basal insulin to insulin degludec slightly improves glycemic control and significantly reduces the risk of hypoglycemia in routine clinical practice

significant. So these data show much less hypoglycemia with degludec than with other basal insulins.



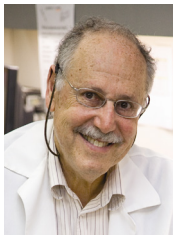
Here are my thoughts on this real-world study. This real-world observational study showed that switching from insulin glargine to insulin degludec in patients with a mean hemoglobin A1c level of 8.4% resulted in a significant decrease of 0.5%. This is in contrast to several randomized control trials in which the hemoglobin A1c levels was the same in response to the 2 insulins. How to explain these discordant results? Well, there may be a selection issue here. The patients were probably changed to insulin degludec because their control was unsatisfactory on insulin glargine. Now, the mean dose of insulin glargine was 71.3 units at baseline in these obese, older patients indicating that many of them were taking upwards of 100 units.

The concentration of insulin glargine is U-100 or 100 units/mL and it is well established that insulin absorption from large volumes of injectate can be variable. There are 2 concentrations of insulin degludec, 100 and 200 units/mL. Unfortunately, we are not told how many patients were switched to the more concentrated preparation of insulin degludec, which would have halved the volume of injectate and led to more consistent absorption. And this may have been the basis for the significant decrease in hemoglobin A1c levels after switching from insulin glargine to insulin degludec.



Now, selection bias could also have played a role in the decreased episodes of hypoglycemia after switching to insulin degludec. The randomized control trials demonstrated significantly less overnight hypoglycemia with insulin degludec compared with insulin glargine. To the extent that some of these patients were switched because of hypoglycemia, that would have enriched the pool of patients who were susceptible to hypoglycemia with insulin glargine and facilitated showing a benefit on hypoglycemia for insulin degludec.

Ultra-rapid BioChaperone Lispro (BCLIS) Improves Postprandial Blood Glucose (PPG) Excursions vs. Insulin Lispro (LIS) in a 14-Day Treatment Study in Subjects with Type 1 Diabetes (T1DM)



Mayer Davidson, MD

Hello, this is Dr. Mayer Davidson, professor of medicine at Charles R. Drew University and the David Geffen School of Medicine at UCLA.

I will be discussing Ultra-rapid BioChaperone Lispro Improves Postprandial Blood Glucose Excursions vs. Insulin Lispro in a 14-day Treatment Study in Subjects with Type 1 Diabetes. This poster was presented by Dr. Hardy and colleagues at the 77th Scientific Sessions of the American Diabetes Association from June 9–13, 2017.

In summary, BioChaperone Lispro is an ultra-rapid formulation of insulin lispro and it was shown to be safe, well tolerated, and effective, over 14 days, in patients with type 1 diabetes mellitus. In addition, BioChaperone Lispro significantly reduced postprandial glucose compared with insulin Lispro. There was no difference in the response to BioChaperone insulin injected before or 15 minutes after starting the meal.

The importance of this is that a common barrier to the use of prandial insulin is the need to coordinate dosing and food consumption. This can be a particular problem in patients who may not finish a meal but have already taken their usual preprandial dose. This study showed that, if taken after a meal, the insulin dose can be adjusted downward relative to the amount of food that was actually eaten.

The method was as follows. It was a double-blind, randomized, crossover study involving 36 subjects with type 1 diabetes mellitus treated with multiple daily insulin injections. Postprandial glucose was assessed with individualized, solid mixed meal tests with both insulins administered at the start of, and BioChaperone given 15 minutes after the meal started, on several study days.

Study Design and Methods

- Double-blind, randomized, crossover study
  - 36 subjects with type 1 diabetes mellitus treated with multiple daily insulin injections
- Comparison of insulin lispro with BioChaperone lispro
- Postprandial glucose was assessed with individualized solid mixed meal tests with both insulins administered at the start of and BioChaperone lispro given 15 minutes after meal start on several study days

Study Design and Methods (cont)

- Subjects used individualized BioChaperone or insulin lispro doses at the start of the meal during two 14-day outpatient periods with unchanged basal insulin
- Pharmacokinetics was assessed for doses administered at the start of the meal

Subjects used individualized BioChaperone or insulin lispro doses at the start of the meal during 2 14-day outpatient periods with unchanged basal insulin. Pharmacokinetics was assessed for doses administered only at the start of the meal.

Results Summary

- 36 subjects with mean
  - age 45 years
  - body mass index 24.3 kg/m^2
  - HbA1c 7.2%
- Safety and tolerability were similar with BioChaperone lispro compared with insulin lispro
- There were 12% less hypoglycemic episodes with BioChaperone lispro during outpatient treatment.
- There were no injection site reactions

The key findings were as follows: 36 subjects had a mean age of 45 years, the body mass index of 24.3 kg/m^2, and hemoglobin A1c levels of 7.2% at baseline. Safety and tolerability were similar with BioChaperone Lispro compared with the insulin lispro. There were 12% less hypoglycemic episodes with BioChaperone Lispro during outpatient treatment and there were no injection site reactions.

Results Summary (cont)

- When administered at the start of the meal, the absorption of BioChaperone lispro was significantly faster than with insulin lispro
- The higher, early postprandial exposure of BioChaperone lispro resulted in a 30%-50% reduction in the 1-2 h postprandial glucose excursion compared with insulin lispro
  - The difference persisted over the 14 days of the study
- In contrast, there was no difference in postprandial blood glucose control between BioChaperone lispro injected 15 minutes after the start of the meal and insulin lispro injected at the start of the meal

When administered at the start of the meal, the absorption of BioChaperone Lispro was significantly faster than with inulin Lispro. The higher, early postprandial exposure of BioChaperone Lispro resulted in a 30% to 50% reduction in the one- to two-hour postprandial glucose excursion compared with insulin Lispro. This difference persisted over the 14 days of the study. In contrast, there was no difference in postprandial blood glucose control between BioChaperone Lispro injected 15 minutes after the start of the meal and insulin Lispro injected at the start of the meal.

Faculty Commentary

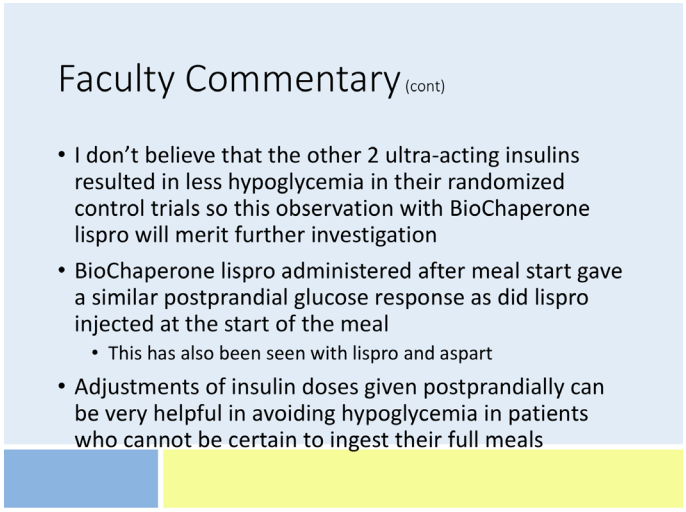
- The main finding is that BioChaperone lispro given pre-prandially appears in the circulation faster than lispro insulin
  - Blunts the postprandial rise of glucose compared to the rapid-acting insulin lispro
- Let's call BioChaperone lispro "ultra-rapid' and it joins faster aspart and inhaled insulin, 2 other "ultra-rapid-acting" insulins
  - All 3 appear in the circulation faster than the "rapid-acting" insulins, lispro, aspart and glulisine, and decrease early postprandial excursions of glucose

From my perspective, the main findings of this study were that BioChaperone insulin given postprandially appears in the circulation faster than Lispro insulin and blunts the postprandial rise of glucose compared to the rapid-acting insulin Lispro. Let's call BioChaperone insulin "ultra-rapid" and it joins faster aspart and the inhaled insulin Afrezza to other rapid-acting insulins. All 3 appear in the circulation faster than the rapid-acting insulins Lispro, aspart, and glulisine and decrease early postprandial excursions of glucose.

Faculty Commentary (cont)

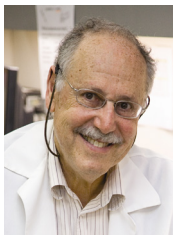
- However, neither faster aspart nor inhaled insulin has led to greater reductions in HbA1c levels in randomized control trials, probably because of the large 20%-30% variability in the day-to-day response to insulin in the same individual
  - It is likely that the same outcome will be seen with BioChaperone lispro as well

However, neither faster aspart nor Afrezza has led to greater reductions in hemoglobin A1c levels in randomized control trials—probably because of the large 20% to 30% variability in the day-to-day response to insulin in the same individual. It is likely that the same outcome will be seen with BioChaperone insulin as well.



I don't believe that the other 2 ultra-acting insulins resulted in less hypoglycemia in their randomized control trials so this observation with BioChaperone will merit further investigation. BioChaperone insulin administered after a meal start gave a similar postprandial glucose response as did Lispro injected at the start of the meal. This has also been seen with Lispro and aspart. And as suggested previously in those papers, adjustments of insulin doses given postprandially can be very helpful in avoiding hypoglycemia in patients who cannot be certain to ingest their full meals.

Evaluation of Early Postprandial Suppression of Endogenous Glucose Production with Faster Aspart vs. Insulin Aspart



Mayer Davidson, MD

Hello, this is Dr. Mayer Davidson, professor of medicine at Charles R. Drew University and the David Geffen School of Medicine at UCLA.

I will be discussing the Evaluation of Early Postprandial Suppression of Endogenous Glucose Production with Faster Aspart vs. Insulin Aspart. Now this poster was presented by Dr. Basu and colleagues at the 77th Scientific Sessions of the American Diabetes Association, from June 9–13, 2017.

The summary of fast-acting aspart is a new formulation of insulin aspart, with added excipients to provide faster, early absorption and improved postprandial glucose control. This study investigated the mechanisms behind the lower postprandial glucose with fast-acting aspart, in subjects with type 1 diabetes mellitus. Results show that the improved control of postprandial glucose was partly due to earlier and greater suppression of endogenous glucose production. The importance is that endogenous glucose production is elevated in persons with poorly controlled type 1 diabetes. Treatments that target this abnormality should be helpful in improving glycemic control in this patient population.

Principal Investigator Commentary

- The highlights of the study are to:
  - understand the physiological mechanism by why which faster aspart lowers postprandial glucose concentrations
  - understand the gold standard non-invasive method to estimate glucose fluxes
  - realize the significance of mechanistic integrative physiology studies on how such medications work
- The impact of the study on patient care is likely to be:
  - providers will be able to better understand how the insulin works and will be able to advise better on food habits

And now here are the comments from the principal investigator of this study.

> *The 3 important highlights or summary points of the study are an understanding of: 1) the physiological mechanism by which the faster aspart lowers post-prandial glucose concentrations; 2) the gold standard noninvasive method to estimate glucose fluxes; and 3) the significance of mechanistic integrative physiology studies on how such medications work. In terms of impact on the care of patients, providers will be able to better understand how prandial insulin works and will be able to better advise on food habits.*

Study Design and Methods

- Randomized, double-blind, crossover study
  - 40 patients with type 1 diabetes mellitus received identical doses of fast-acting aspart and insulin aspart
- Dose ranged from 0.06 to 0.28 units/kg given subcutaneously at the start of a standardized meal
- Postprandial glucose turnover was assessed by the triple-tracer method

This was a randomized, double-blind, crossover study in which 40 patients with type 1 diabetes mellitus received identical doses of fast-acting aspart and insulin aspart. The doses ranged from 0.06 to 0.28 units/kg, given subcutaneously at the start of a standardized meal. Postprandial glucose turnover was assessed by the triple-tracer method.

Results Summary

- At baseline
  - Mean age 42 years
  - Mean body mass index 24 kg/m^2
  - Mean HbA1c 7.3%

The key findings are that the patients have a mean age of 42 years, with a body mass index of 24 kg/m^2, and hemoglobin A1c level of 7.3%.

Results Summary (cont)

- Early insulin exposure was greater for faster aspart
  - Led to a smaller postprandial glucose increment at 1 hour than with insulin aspart
- The primary mechanism behind smaller postprandial glucose increment was significantly greater suppression of endogenous glucose production at 30 and 60 minutes with faster aspart
  - Accounted for an estimated 78% of the smaller postprandial glucose increment with faster aspart

Early insulin exposure was greater for faster aspart, leading to a smaller postprandial glucose increment at 1 hour, than with insulin aspart. The primary mechanism behind this was significantly greater suppression of endogenous glucose production at 30 and 60 minutes with faster aspart, accounting for an estimated 78% of the smaller, postprandial glucose increment.

Results Summary (cont)

- Also contributing was significantly higher glucose disappearance with faster aspart than insulin aspart
- Contributing to both of these was a 36% greater suppression of free fatty acids for faster aspart vs insulin aspart

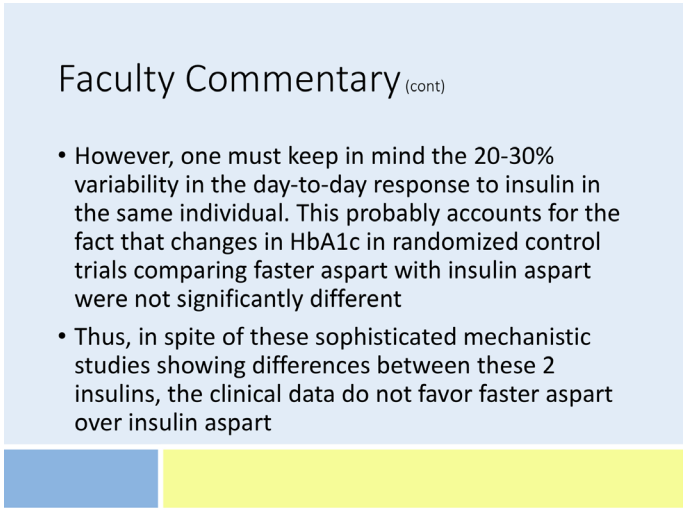
Also contributing was significantly higher glucose disappearance with faster aspart than with insulin aspart. Contributing to both of these was a 36% greater suppression of free fatty acids for faster aspart vs insulin aspart.

Faculty Commentary

- Study shows statistically significant differences between faster aspart compared with insulin aspart in
  - Suppression of endogenous glucose production by the liver
  - Free fatty acid release by adipose tissue
  - Increase in glucose disposal during the first hour following a meal
- Changes were probably due to the more rapid appearance of insulin in the circulation
- Mechanistically, the changes in glucose metabolism could be due in large part to the greater suppression of free fatty acids since increased free fatty acids are related to increased hepatic gluconeogenesis and decreased peripheral disposal of glucose

From my perspective, this study shows statistically significant differences between faster aspart compared with insulin aspart, in suppression of endogenous glucose production by the liver and free fatty acid release by adipose tissue, and an increase in glucose disposal during the first hour following a meal. These changes were probably due to the more rapid appearance of insulin in the circulation.

Mechanistically, the changes in glucose metabolism could be due in large part to the greater suppression of free fatty acids since increased free fatty acids are related to increased hepatic gluconeogenesis and decreased peripheral disposal of glucose.



However, from a clinical perspective, one must keep in mind the large 20% to 30% variability in the day-to-day response to insulin in the same individual. This probably accounts for the fact that changes in hemoglobin A1c levels in randomized control trials comparing faster aspart with insulin aspart were not significantly different. Thus, in spite of these sophisticated mechanistic studies showing differences between these 2 insulins, the clinical data do not favor faster aspart over insulin aspart.

Semaglutide Provides Superior Glycemic Control across SUSTAIN 1-5 Clinical Trials

Vivian Fonseca, MD

Hello, this is Dr. Vivian Fonseca, professor of medicine and pharmacology and chair of the Section of Endocrinology at Tulane University School of Medicine. I will be discussing Semaglutide Provides Superior Glycemic Control Across SUSTAIN 1 through 5 Clinical Trials. This poster was presented by Dr. Andrew Ahmann and colleagues at the 77th Scientific Session of the American Diabetes Association on June 9–13, 2017.

In summary, a pooled analysis of the SUSTAIN 1 through 5 trials showed that semaglutide provided superior and clinically meaningful improvements in glycemic control vs comparators in patients with type 2 diabetes. There were no new safety issues.

The importance of this finding is that semaglutide is an investigation GLP-1 receptor agonist. If approved, it is expected that it will be available for subcutaneous and oral administration.

Study Design and Methods

- The SUSTAIN 1-5 trials evaluated semaglutide administered subcutaneously in patients with T2DM
- Semaglutide was compared with
  - Placebo
  - Sitagliptin
  - Exenatide for once-weekly administration
  - Insulin glargine
  - As add-on to insulin
- The trials were either 30 weeks or 56 weeks in duration

Let me summarize this study. The SUSTAIN 1 through 5 trials evaluated semaglutide administered subcutaneously in patients with type 2 diabetes. In SUSTAIN trials, semaglutide was compared with placebo, sitagliptin, exenatide for once-weekly administration, insulin glargine, and as an add-on to insulin. The trials were either 30 weeks or 56 weeks in duration.

Results Summary

- In the SUSTAIN trials, baseline HbA1c ranged from 8.1% to 8.4%
- HbA1c reduction from baseline was significantly greater with semaglutide
  - Semaglutide (-1.2% to -1.8%)
  - Comparators (-0.02% to -0.9%)
- Significantly more patients achieved HbA1c <7.0% with semaglutide
  - Semaglutide 0.5 mg (57% to 74%)
  - Semaglutide 1 mg (67% to 79%)
  - Comparators (11% to 40%)

Here are the key findings of this analysis. In the SUSTAIN trials, the baseline A1c ranged from 8.1% to 8.4%. The A1c reduction from baseline was significantly greater with semaglutide ranging from -1.2 to -1.8% vs comparators which ranged from -0.02 to -0.9%.

Significantly more patients achieved a HbA1c less than 7% with semaglutide than comparators. Semaglutide 0.5 mg this ranged from 57% to 74%.

Results Summary (cont)

- Mean reductions of the fasting plasma glucose were significantly greater with semaglutide
  - Except between semaglutide 0.5 mg and insulin glargine
  - Semaglutide (-29 to -51 mg/dL)
  - Comparators (-9 to -38 mg/dL)

With semaglutide 1 mg it ranged from 67% to 79%. And with the comparators, it ranged from 11% to 40%.

The mean reduction of the fasting glucose was significantly greater with semaglutide vs comparators, except with semaglutide 0.5 mg and insulin glargine. Reductions ranged from -29 to -51 mg/dL for semaglutide and -9 to -38 mg/dL for comparators.

Faculty Commentary

- The analysis demonstrates a powerful glucose lowering effect of semaglutide in a wide range of patients in a variety of combinations and against a range of comparative treatments

Here are my thoughts and analysis of this study. The main highlight of this study is that the analysis demonstrates a powerful glucose lowering effect of semaglutide in a wide range of patients, in a variety of combinations, and against a range of comparative treatments.

Implications for Practice

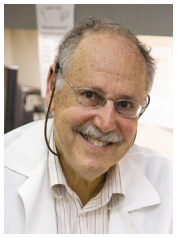
- Semaglutide is not yet available, but when available, may be preferred as a treatment for patients who need a large amount of glucose lowering
- Semaglutide provides another option for a glucagon-like peptide-1 receptor agonist for once-weekly administration
- The long-term safety of semaglutide is unknown

How do these results impact the current state of patient management? While semaglutide is not yet available, but when available, may be preferred as a treatment for patients who need a large amount of glucose lowering.

So what are the implications on future patient management? Well, it provides another option for GLP-1 receptor agonist when used weekly, and provides a level of glucose lowering that appears to be better than a range of comparators.

Are there unanswered questions? Yes, the long-term safety of semaglutide is currently unknown.

More Physiological Circulating Insulin and Modulation of Hepatic Glucose Production with Insulin Glargine U300 vs. U100 in Type 1 Diabetes



Mayer Davidson, MD

Hello, this is Dr. Mayer Davidson, professor of medicine at Charles R. Drew University and the David Geffen School of Medicine at UCLA.

I will be discussing More Physiological Circulating Insulin and Modulation of Hepatic Glucose Production with Insulin Glargine U300 vs. U100 in Type 1 Diabetes. And this poster was presented by Dr. Porcellati and colleagues at the 77th Scientific Sessions of the American Diabetes Association from June 9–13, 2017.

In summary, this pharmacokinetic and pharmacodynamic comparison of insulin glargine U-300 vs U-100 in patients with type 1 diabetes mellitus, glargine U-300 resulted in similar physiological insulin levels in the first 12 hours after injection but higher levels during the final 12 hours compared to glargine U-100. Hepatic glucose production observed with glargine U-300 was significantly higher at night but significantly lower in the afternoon compared with glargine U-100. The insulin dose was 23% higher in the glargine U-300 group compared with the U-100 group.

The importance of this is as follows: Compared with glargine U-100, the slightly higher nocturnal hepatic glucose production observed with glargine U-300 may reduce the risk for nocturnal or morning hypoglycemia, while the significantly lower afternoon hepatic glucose production may favor better pre-dinner glucose control with U-300.

Study Design and Methods

- Patients were treated with glargine U-100 or U-300 for 3 months after which they were crossed over to the other treatment
- Fasting plasma glucose was titrated to 100 mg/dL
- At 3 months, patients underwent a euglycemic clamp study with their dose of insulin glargine administered at 8 PM
- The clamp was carried out for 24 hours during which time the patients were fasted
- Glucose concentrations were maintained at 100 mg/dL during the clamp

The methods were as follows: Patients were treated with glargine U-100 or U-300 for 3 months after which they were crossed over to the other treatment. Fasting plasma glucose was titrated to 100 mg/dL. In 3 months, patients underwent a euglycemic clamp study with their dose of insulin glargine administered at 8 PM. The clamp was carried out for 24 hours during which time the patients were fasted. Glucose concentrations were maintained at 100 mg/dL during the clamp.

Results Summary

- 10 patients with type 1 diabetes mellitus with mean
  - age 40 years
  - duration of diabetes 27 years
  - body mass index 23.3 kg/m^2
  - HbA1c 7.1%
- Compared with glargine U-100, the plasma physiological plasma insulin level for U-300 was
  - non-significantly lower from 8 PM to 8 AM
  - significantly higher from 8 AM to 8 PM
- This resulted in a significantly lower glucose infusion rate during the overnight 12-hour period after the U-300 injection compared with the U-100 injection

The key findings in this study were as follows: The study involved 10 patients with type-1 diabetes mellitus. Compared with glargine U-100, the plasma physiological plasma insulin level for U-300 was non-significantly lower from 8 PM to 8 AM. In contrast, it was significantly higher from 8 AM to 8 PM for U-300 vs U-100. This resulted in a significantly lower glucose infusion rate during the overnight 12-hour period after the U-300 injection compared with the U-100 injection.

Results Summary (cont)

- Conversely, the glucose infusion rate was significantly higher during the second 12-hour period after the U-300 injection compared with the U-100 injection
- There was no difference in glucose infusion rates over the entire 24-hour period between the 2 insulin preparations
- As might be expected, hepatic glucose production was
  - significantly less suppressed with U-300 from 8 PM to 8 AM
  - significantly more suppressed during the final 6 hours of the 24-hour period

Conversely, the glucose infusion rate was significantly higher during the second 12-hour period after the U-300 injection compared with the U-100 injection. There was no difference in glucose infusion rates over the entire 24-hour period between 2 insulin preparations. As might be expected, hepatic glucose production was significantly less suppressed with the U-300 from 8 PM to 8 AM and significantly more suppressed during the final 6 hours of the 24-hour period.

Faculty Commentary

- Randomized control trials comparing glargine U-300 with glargine U-100 revealed significantly less nocturnal hypoglycemia but no difference in HbA1c levels
- The weaker effect on suppressing hepatic glucose production overnight with glargine U-300 could well explain this difference in hypoglycemia as the authors have suggested
- They have also suggested that the greater suppression of hepatic glucose production between 18 and 24 hours after injecting glargine U-300 compared with glargine U-100 would favor better control during the afternoon as reflected in lower pre-dinner glucose

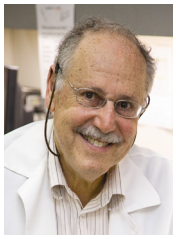
My thoughts on this study are as follows: Randomized control trials comparing U-300 insulin glargine, now called Toujeo, with U-100 insulin glargine, called Lantus, revealed significantly less nocturnal hypoglycemia but no difference in hemoglobin A1c levels. The weaker effect on suppressing hepatic glucose production overnight with Toujeo could well explain this difference in hypoglycemia as the authors have suggested. They have also suggested that the greater suppression of hepatic glucose production between 18 and 24 hours after injecting Toujeo, compared with Lantus, would favor better control during the afternoon as reflected in the lower pre-dinner glucoses.

Faculty Commentary (cont)

- These subjects were fasted for 24 hours after the 8 PM injections.
- The insulin levels achieved during this fasting period were less than 10 microunits per milliliter.
- The effect of these low levels of insulin due to the basal insulin injection would be much less important compared with the effect of the much higher levels of insulin following a pre-lunch injection of a rapid- or short-acting insulin.
  - The latter would overwhelm any effect of a basal insulin during this afternoon period.

Now, these subjects were fasted for 24 hours after the 8 PM injections. The insulin levels achieved during this fasting period were less than 10 microunits per milliliter. The effect of these low levels of insulin due to the basal insulin injection would be much, much less important compared with the effect of the much higher levels of insulin following a pre-lunch injection of a rapid- or short-acting insulin. The latter would overwhelm any effect of a basal insulin during this afternoon period.

Similar Glucose Control, Postprandial Glucose Excursions, and Safety in People with T2DM Using SAR342434 or Insulin Lispro in Combination with Insulin Glargine (Gla-100): SORELLA 2 Study



Mayer Davidson, MD

Hello, this is Dr. Mayer Davidson, professor of medicine at Charles R. Drew University and the David Geffen School of Medicine at UCLA.

I will be discussing Similar Glucose Control, Postprandial Glucose Excursions, and Safety in People with T2DM Using SAR342434 or Insulin Lispro in Combination with Insulin Glargine: SORELLA 2 Study. That's the name of the study, and this poster was presented by Dr. Derwahl and colleagues at the 77th Scientific Session of the American Diabetes Association from June 9–13, 2017.

In summary, SAR342434 is a rapid-acting follow-on insulin lispro with a similar pharmacokinetic and pharmacodynamic profile with reference to insulin lispro, also called Humalog U-100. In this study, 26 weeks of treatment, in combination with once-daily glargine, showed SAR342434 to be noninferior to insulin lispro with regard to reduction of hemoglobin A1c. The safety and tolerability were also similar, and by way of explanation, follow-on, in this case, means that another pharmaceutical company has developed and tested insulin lispro. The importance of this is that follow-on insulins offer the possibility of lower acquisition cost relative to the insulin products being marketed by another company. And this study provides reassurance that the follow-on insulin lispro SAR342434 is highly similar to the referenced insulin lispro regarding key aspects of efficacy, safety, and tolerability.

Study Design and Methods

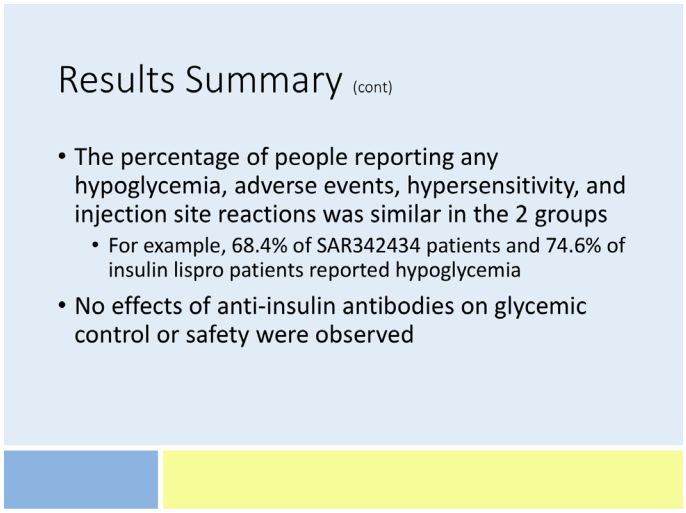
- 6-month, randomized, controlled, open-label, phase 3 study
- Objective
  - Compare the efficacy and safety of the follow-on insulin lispro SAR342434 with insulin lispro, both in combination with once-daily insulin glargine
- 505 patients with type 2 diabetes mellitus were randomized 1:1 to multiple daily injections of
  - Follow-on insulin lispro SAR342434
  - Insulin lispro
- Insulin doses were adjusted to achieve fasting and 2-h postprandial glucose targets recommended by the American Diabetes Association

This 6-month, randomized, control, open-label phase 3 study compared the efficacy and safety of the follow-on insulin lispro SAR342434 with insulin lispro, both in combination with once-daily insulin glargine. Five hundred five patients with type 2 diabetes were randomized 1:1 to multiple daily injections of either prandial insulin. And the insulin doses were adjusted to achieve fasting and 2-hour postprandial glucose targets as recommended by the American Diabetes Association.

Results Summary

- From a baseline of 8.0%, reduction of the HbA1c at 6 months was
  - -0.92% in the SAR342434 group
  - -0.85% in the insulin lispro group
  - The difference was not statistically significant demonstrating non-inferiority of SAR342434 to insulin lispro
- The change in 7-point self-monitored plasma glucose profiles were similar at 6 months
- The basal and prandial insulin doses also were similar in the 2 groups

The key findings were that from a baseline of 8.0%, reduction of the hemoglobin A1c was -0.92% in the SAR342434 group and -0.85% in the insulin lispro group at the end of 6 months of treatment. The difference between the 2 treatments was not statistically significant, demonstrating non inferiority of SAR342434 to insulin lispro. The change in 7-point self-monitored plasma glucose profiles were similar at 6 months. The basal and prandial insulin doses also were similar in the 2 groups.



The percentage of people reporting any hypoglycemia, adverse advents, hypersensitivity, and injection site reactions were similar in the 2 groups.

For example, 68.4% of SAR342434 patients and 74.6% of insulin lispro patients reported hypoglycemia. No effects of anti-insulin antibodies on glycemic control or safety were observed.

ITCA 650 Improves Glycemic Control and Reduces the Need to Advance Antidiabetes Therapy

Vivian Fonseca, MD

This is Dr. Vivian Fonseca, professor of medicine and pharmacology and chair of the Section of Endocrinology at Tulane University School of Medicine. I will be discussing ITCA 650 Improved Glycemic Control and Reduces the Need to Advance Antidiabetes Therapy. This poster was presented by Dr. Robert Henry and colleagues at the 77th Scientific Sessions of the American Diabetes Association on June 9–13, 2017.

In patients with type 2 diabetes inadequately controlled with one or more oral agents, the administration of exenatide by ITCA 650 results in significantly improved and stable glycemic control without advancement of antidiabetes therapy in the majority of patients. ITCA 650 is an osmotic mini-pump in development that delivers exenatide subcutaneously for up to 6 months after subdermal placement. Patient adherence with twice-daily or once-weekly exenatide is suboptimal, often resulting in inadequate glycemic control. Administration of the glucagon-like peptide-1 receptor agonist exenatide by mini-pump improves glycemic control, perhaps by insuring patient adherence to therapy.

Implications for Practice

- Improving glycemic control long-term will result in less need for additional medication, making it easier to manage the disease long-term
- With such an approach, we are more likely to see well-controlled patients long-term
- It is not known whether such an approach will decrease long-term complications– both microvascular and macrovascular
- The long-term safety of continuous stimulation of the GLP-1 receptor needs to be established

So here's a summary of the study. This study was a pooled analysis of patients with type 2 diabetes. In the 39-week FREEDOM-1 and the 52-week FREEDOM-2 studies. FREEDOM-1 compared ITCA 650 with placebo in patients on one or more oral agents. FREEDOM-2 compared ITCA 650 with sitagliptin 100 mg in patients uncontrolled on metformin. The ITCA 650 group was treated with exenatide 20 micrograms per day for 13 weeks, and then 60 µg per day thereafter.

Study Design and Methods (cont)

- Objective
  - Measure the need for advancement of antidiabetes therapy for glycemic control as a surrogate measure of the effectiveness and sustainability of exenatide therapy delivered using the mini-pump (ITCA 650)
- The addition of or increase of therapy from baseline was protocol mandated based on predefined criteria and was required after week 26 for HbA1c >8%

The objective of this pooled analysis was to measure the need for advancement of antidiabetes therapy for glycemic control as a surrogate measure of the effectiveness and sustainability of exenatide therapy delivered using the mini-pump. The addition of or increase of therapy from baseline was protocol mandated based upon predefined criteria and was required after week 26 for HbA1c >8%.

Results Summary

- 814 patients
  - 414 randomized to ITCA 650
  - 257 randomized to sitagliptin
  - 143 randomized to placebo
- Mean baseline HbA1c 8.6%

Here are the key findings of the study. The study included 814 patients. Four hundred forty treated with ITCA 650, 257 with sitagliptin, and 143 with placebo. The mean baseline A1c was 8.6%.

Results Summary (cont)

- Antidiabetes treatment was advanced in fewer patients treated with ITCA 650
  - Over the first 26 weeks, treatment was advanced in
    - 4.6% of ITCA 650 patients
    - 7.4% of sitagliptin patients
    - 23.1% of placebo patients
  - Over the 52 weeks, treatment was advanced in
    - 13.5% of ITCA 650 patients
    - 35.4% of sitagliptin patients
    - 39.2% of placebo patients

Antidiabetes therapy was advanced in fewer patients treated with ITCA 650. Over the first 26 weeks, treatment had been advanced in 4.6% of ITCA 650 patients, 7.4% of sitagliptin patients, and 23.1% of placebo patients.

Over the 52 weeks, treatment had been advanced in 13.5% of ITCA 650 patients, 35.4% of sitagliptin patients, and 39.2% of placebo patients.

Here are my thoughts and analysis of this study.

Faculty Commentary

- ITCA 650 provides good glycemic control not only by providing a drug, exenatide, but also ensuring almost universal compliance with the medication since it is implanted
- Further, GLP-1 and its analogs are known to improve beta-cell function and slow the progression of diabetes, at least while the patient is taking the medication. Since the latter is assured by using ITCA 650, the need to add medication is decreased

The main points of the study from my perspective, are that ITCA 650 provides good glycemic control, not only by providing a drug exenatide, but also insuring almost universal compliance with the medication since it is implanted. Further, GLP-1 and its analogs are known to improve beta-cell function and slow the progression of diabetes, at least while the patient is taking the medication. Since the latter is assured by the mode of administration, the need to add medication is decreased.

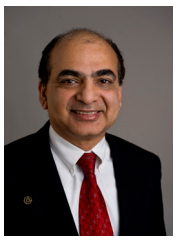
Implications for Practice

- Improving glycemic control long-term will result in less need for additional medication, making it easier to manage the disease long-term
- With such an approach, we are more likely to see well-controlled patients long-term
- It is not known whether such an approach will decrease long-term complications– both microvascular and macrovascular
- The long-term safety of continuous stimulation of the GLP-1 receptor needs to be established

I think improvement in glycemic control, long-term, will result in less need for additional medication, making it easier to manage the disease long-term. With such an approach, we are more likely to see more controlled patients long-term.

There are, of course, unanswered questions. It's not known whether such an approach will decrease long-term complications, both microvascular and macrovascular. And the long-term safety of continuous stimulation of the GLP-1 receptor needs to be established.

iGlarLixi Reduces A1C to a Greater Extent than Basal Insulin Therapy Regardless of A1C Levels at Screening



Vivian Fonseca, MD

Hello this is Dr. Vivian Fonseca, professor of medicine and pharmacology and chair of the Section of Endocrinology at Tulane University School of Medicine. I will be discussing iGlarLixi Reduces A1C to a Greater Extent than Basal Insulin Therapy, Regardless of the A1C levels at Screening. This poster was presented by Dr. Elisabeth Niemoeller and colleagues at the 77th Scientific Sessions of the American Diabetes Association, from June 9–13, 2017.

In summary, the study showed that the fixed-ratio combination of insulin glargine and lixisenatide was more effective than insulin glargine alone in controlling HbA1c, regardless of initial A1c level. The greatest reduction of HbA1c with both treatments, was observed in patients with a higher initial HbA1c level.

The importance of this study is that the combination of basal insulin and glucagon-like peptide receptor agonist is recommend as a treatment option for patients with inadequate control with basal insulin, with or without oral agents.

Study Design and Methods

- LixiLan-L was a 30-week study in patients with T2DM and HbA1c 7.5% to 10% despite basal insulin with or without oral agents
- 6-week run-in with insulin glargine followed by randomization to
  - Fixed-ratio combination of insulin glargine and lixisenatide
  - Insulin glargine
- Patients on metformin at baseline continued metformin

Let me summarize this study. The study is also called LixiLan-L, which was a 30-week study in patients with type 2 diabetes mellitus, HbA1c of 7.5% to 10%, despite taking basal insulin with or without oral agents.

Patients underwent a 6-week run-in with insulin glargine, after which they were randomized to the fixed-ratio combination of insulin glargine and lixisenatide, or insulin glargine. Patients on metformin at baseline continued metformin.

Results Summary

- 656 patients completed the study
- Mean HbA1c 8.5% at baseline
- Mean HbA1c reduction was significantly greater with iGlarLixi
  - IGlarLixi (-1.7%)
  - Glargine (-1.1%)

Here are the key findings. 656 patients completed this study. The mean HbA1c was 8.5% at baseline. Mean HbA1c reduction was significantly greater with iGlarLixi than glargine with -1.7% reduction vs -1.1% reduction.

Results Summary (cont)

- Patients were grouped by screening HbA1c level:
  - ≤8%
  - 8% to 9%
  - >9%
- For each HbA1c category, HbA1c at study end was
  - ≤7% for iGlarLixi
  - >7% for glargine
- HbA1c reductions were significantly greater for iGlarLixi vs glargine in all 3 categories
  - For example, for baseline HbA1c ≤8%, the HbA1c reduction was
    - -1.1% for iGlarLixi
    - -0.5% for glargine

Patients were grouped by screening A1c levels. In less than 8%, 8% to 9%, and greater than 9%. The respective mean observed A1c levels at the study end were all less than 7% with iGlarLixi, but were greater than 7% for glargine. Reductions of HbA1c were significantly greater for iGlarLixi vs glargine in all 3 categories. For example, in patients with a baseline HbA1c less than 8%, the A1c reduction was -1.1% for iGlarLixi, and -.5% for glargine.

Faculty Commentary

- This is a large study in patients not controlled on basal insulin
- The fixed-ratio combination iGlarLixi provided superior glycemic control compared with optimizing the basal insulin

Here are my thoughts in analysis of this study. This is a large study in patients not controlled on basal insulin. The fixed-ratio combination provided superior glycemic control compared with optimizing the basal insulin.

Implications for Practice

- The study provides additional evidence that the combination of insulin with GLP-1 receptor agonist is beneficial for glucose lowering
  - iGlarLixi now available as a fixed-ratio combination with a single injection
- There are many patients who do not achieve glycemic goals with basal insulin added on to oral agents. Using a combination fixed-ratio of insulin and GLP-1 receptor agonist is more likely to achieve goals
  - May become the injectable of choice in many patients
- Further studies are needed to obtain FDA approval for use in patients with inadequate glycemic control with oral agents

How will the results of this study impact the current state of patient management? The study provides additional evidence that the combination of insulin with the GLP-1 receptor agonist is beneficial for glucose lowering, and now does so in a fixed-ratio combination therapy with a single injection.

What's the impact of this study on future patient management? There are many patients who do not achieve glycemic control with basal insulin added onto oral agents. Using a combination of the fixed-ratio of insulin and GLP-1, such as iGlarLixi, is more likely to achieve goals and may become the injectable of choice for many patients.

Are there unanswered questions? Further studies are needed to obtain FDA approval for the use of this combination as the first injectable to be used in patients with inadequate glycemic control with oral agents.

Mechanisms of Prandial Glucose Regulation with Lixisenatide (Lyxumia)

Vivian Fonseca, MD

Hello, this is Dr. Vivian Fonseca, professor of medicine and pharmacology and chair of the Section of Endocrinology at Tulane University School of Medicine. I will be discussing Mechanisms of Prandial Glucose Regulation with Lixisenatide (Lyxumia). This poster was presented by Dr. Martin Whyte and colleagues at the 77th Scientific Sessions of the American Diabetes Association from June 9–13, 2017.

In summary, this study showed that in patients with type 2 diabetes mellitus, the glucagon-like receptor agonist lixisenatide slowed glucose appearance at the blood following a meal, compared with placebo. This resulted in a smaller increase in the postprandial glucose level compared with placebo. Lixisenatide also slowed gastric emptying, suggesting that slowed gastric emptying is the mechanism responsible for the slow appearance of glucose following a meal, and a smaller increase in postprandial glucose observed with lixisenatide. This finding is important because an increase in gastric emptying contributes to postprandial hyperglycemia in patients with type 2 diabetes. The ability of lixisenatide to reduce postprandial glucose by slowing the gastric emptying rate is consistent with the other short acting glucagon-like receptor agonist, exenatide for twice daily administration.

Principal Investigator Commentary

- Lixisenatide, a short-acting glucagon-like peptide-1 analog, completely suppressed the postprandial glucose rise after a mixed meal
- Lixisenatide led to a small rise in insulin release, but most of the effect on postprandial glucose control was achieved through suppression of gastric emptying
- There was no incremental suppression of endogenous glucose production compared with placebo

And now, here are the comments from Dr. Whyte, the principal investigator of this study.

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- *Lixisenatide led to a small rise in insulin release, but most of the effect on postprandial glucose control was achieved through suppression of gastric emptying*
- *There was no incremental suppression of endogenous glucose production compared with placebo.*

Principal Investigator Commentary (cont)

- Significant prandial glucose control that is relatively insulin independent might explain some of the efficacy of the glucagon-like peptide-1 analogs in insulin-deficient states
- Whether similar efficacy may be seen in patients who have intrinsic slow gastric emptying remains to be determined

- *Significant prandial glucose control that is relatively insulin-independent might explain some of the efficacy of the glucagon-like peptide-1 analogs in insulin-deficient states. Whether similar efficacy may be seen in patients who have intrinsic slow gastric emptying remains to be determined.*

Study Design and Methods

- Double-blind crossover trial with a 4-week washout
- 8 men with T2DM were administered lixisenatide or placebo 30 minutes prior to a standard meal
  - Acetaminophen was also consumed to measure the gastric emptying rate
- Endpoints measured after each arm
  - Glucose appearance in blood
  - Endogenous glucose production
  - Glucose disappearance from blood

Let me summarize this study. Eight men with type 2 diabetes, were administered lixisenatide or placebo in a double-blind crossover trial with a 4-week washout. After each arm, glucose appearance in blood, endogenous glucose production, and glucose disappearance from blood were studied following a standard meeting. Study drug or placebo was administered 30 minutes prior to the meal. Acetaminophen was also consumed to measure the gastric emptying rate.

Results Summary

- Endpoints significantly lower with lixisenatide than placebo
  - Plasma glucose $AUC_{0\text{-}360}$
  - Insulin $AUC_{0\text{-}360}$
  - Total glucose appearance
  - Glucose appearance in blood following a meal
  - Acetaminophen $AUC_{0\text{-}360} \rightarrow$ slowed gastric emptying
- Endpoints similar with lixisenatide and placebo
  - Endogenous glucose production
  - Glucose disappearance from blood

The key findings of the study are that plasma glucose area under the curve over 360 minutes ($AUC_{0\text{-}360}$), and the insulin area under the curve ($AUC_{0\text{-}360}$) were significantly lower with lixisenatide than placebo.

Total glucose appearance and glucose appearance in blood following a meal was significantly lower with lixisenatide. Acetaminophen area under the curve over 360 minutes was also significantly lower with lixisenatide indicating slowed gastric emptying. Endogenous glucose production was similar with lixisenatide and placebo. There was no difference between lixisenatide and placebo in glucose disappearance from blood.

Here are my thoughts and analysis of this study.

Faculty Commentary

The highlights of the study are that

- Lixisenatide has a profound effect on postprandial glucose excursion demonstrating that most of this effect is secondary to its slowing of gastric emptying
  - Confirms the importance of the speed of gastric emptying on nutrient delivery and subsequent absorption
- The lack of effect on endogenous glucose production is surprising since this is a known effect of GLP-1
  - May result from the small number of patients and a relatively short duration study

The highlights from my perspective are that, first, lixisenatide has a profound effect on postprandial glucose excursion and this demonstrates that most of this effect is secondary to slowing of gastric emptying. It also confirms the importance of the speed of gastric emptying on nutrient delivery and subsequent absorption. Second, the lack of effect on endogenous glucose production is surprising since this is a known effect of GLP-1. It is possible that this lack of effect relates to the small number of patients and a relatively short duration of this study.

Implications for Practice

- The study highlights the importance of lixisenatide when postprandial hyperglycemia is being targeted
  - Particularly in combination with drugs that lower only fasting glucose such as metformin and basal insulin
- The long-term safety of lixisenatide and the impact on complications of such significant postprandial glucose lowering remain unanswered

How will the results of this study impact the current state of patient management? It highlights the importance of lixisenatide as a drug to use when postprandial hyperglycemia is being targeted.

Will it have an effect on future patient management? Well, lixisenatide will be used to regulate postprandial hyperglycemia, particularly in combination with drugs that lower only fasting glucose such as metformin or basal insulin.

What questions remain unanswered? The long-term safety of lixisenatide and impact on complications of significant postprandial glucose lowering are unknown and need to be studied further.

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