β-Cell Function and Glycemic Control Following 1-Year Exenatide Therapy, and After 12-Week Washout, in Patients With Type 2 Diabetes
Presented by Michaela Diamant, on behalf of Mathijis Bunck

β-Cell function continues to decline in patients with type 2 diabetes mellitus (T2DM), and current therapies have little effect altering this process. Exenatide (EXEN) has demonstrated clinical effects such as improving glycemic control and promoting weight reduction; however, the ability of EXEN to modulate β-cell function has not been extensively studied. This randomized trial evaluated the β-cell C-peptide secretion following 1 year of EXEN treatment (n = 36) compared to 1 year of insulin glargine (GLAR) (n = 33) in patients with T2DM taking metformin (baseline age = 58 years, BMI = 30 kg/m², A1C = 7.5%, and disease duration = 5 years). During a hyperglycemic clamp (15 mm), the arginine-stimulated C-peptide secretion was 146% greater with EXEN compared with that of GLAR, P < .0001. Despite improved β-cell secretion during treatment, response was not maintained after EXEN discontinuation; after a 4-week washout, all functional parameters returned to pretreatment values. Consistent with previous findings, EXEN reduced A1C similar to GLAR, ~ 0.8% and ~ 0.7%, respectively. EXEN reduced body weight to a greater extent at 52 weeks: – 3.6 kg and + 1 kg, P < .0001. Again, positive benefits of EXEN or glargine on glycemic control and EXEN on weight reduction were lost with treatment discontinuation. The study investigators conclude that EXEN improves β-cell secretory function; however, ongoing treatment may be necessary.

Efficacy of Exenatide Therapy Over 2 Years in a “Real World” Setting
Presented by Jennifer Loh

In this oral presentation, a retrospective review of patient charts was undertaken to determine the 2-year clinical practice experience in patients using exenatide (EXEN) therapy (105-OR). EXEN was initiated in 30 patients (age = 58 years, BMI = 103 kg, BMI = 35 kg/m², A1C = 7.6%) who were already receiving oral medication, basal insulin, or a combination of both as part of their regular diabetes care. At the end of Year 1, 15 patients remained on EXEN, and at Year 2, 12 patients remained on EXEN. At 6-months, patients lost an average of 3.5 kg. At 1 year, weight loss was 2.05 kg, and at 2 years, weight loss was 1.53 kg, not statistically significant from baseline (P = .786), and there was no change in A1C from baseline to 2 years. Sixty-three percent of patients discontinued EXEN after 2 years. In the subgroup of patients receiving EXEN (n = 12), A1C and body weight (BW) decreased significantly (P < .05). A trend toward greater reductions in A1C and BW were found for those patients receiving oral medications plus EXEN (– 1.0% and – 4.9 kg) compared with those receiving basal insulin plus EXEN (0.22% and 0.36 kg). Investigators conclude that EXEN efficacy may only extend to a subgroup of patients in the “real world” and that future studies are needed to identify factors that predict favorable clinical response.

Liraglutide, a Once-Daily Human GLP-1 Analog, Reduces Fat Percentage, Viseral and Subcutaneous Adipose Tissue, and Hepatic Steatosis Compared With Glimepiride When Added to Metformin in Subjects With Type 2 Diabetes
Presented by Johan Jendle

This LED 2 study is a placebo-controlled, double-blind, randomized 26-week study of the efficacy of the human GLP-1 analog liraglutide when added to metformin (MET) (106-OR). This subanalysis (N = 160) of the LED 2 study was designed to evaluate the effect of body composition in patients with type 2 diabetes mellitus (T2DM). Patients taking MET (1 g twice a day) were randomized into one of the following groups: liraglutide (LIRA; 0.6, 1.2, or 1.8 mg sc daily), glimepiride (GLIM, 4 mg daily), or placebo (PBO). Body composition was studied using dual energy x-ray absorptiometry (DEXA) and CT. Results are presented in Table 1. Body weight reduction that occurred with LIRA was dose dependent and was distributed between fat and lean tissue in a ratio of approximately 2:1, as compared with an approximate 1:1 ratio in the weight loss seen with PBO and the weight gain seen with GLIM. There was a significant reduction in the percentage of fat in the 1.2- and 1.8-mg LIRA groups compared with GLIM (P < .05). A significant change in liver/epididymal fat ratio was seen for the highest dose of LIRA demonstrating a reduction in hepatic steatosis (P < .05).

Table 1. Effect of liraglutide on body composition and hepatic steatosis

<table>
<thead>
<tr>
<th>Parameter, unit</th>
<th>LIRA 0.6 + MET</th>
<th>LIRA 1.2 + MET</th>
<th>LIRA 1.8 + MET</th>
<th>PBO + MET</th>
<th>GLIM + MET</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔFat mass, kg</td>
<td>-0.74*</td>
<td>-1.64*</td>
<td>-2.40*</td>
<td>-1.13</td>
<td>+1.13</td>
</tr>
<tr>
<td>ΔLean body mass, kg</td>
<td>-0.26*</td>
<td>-0.84*</td>
<td>-1.54*</td>
<td>-1.33</td>
<td>+1.28</td>
</tr>
<tr>
<td>ΔVisceral fat, %</td>
<td>0.5</td>
<td>-1.1*</td>
<td>-1.2*</td>
<td>-0.2</td>
<td>+0.4</td>
</tr>
<tr>
<td>ΔSubcutaneous fat, %</td>
<td>5.2</td>
<td>-7.8*</td>
<td>-8.5*</td>
<td>-4.2</td>
<td>+3.4</td>
</tr>
<tr>
<td>ΔLiver/epididymal fat ratio</td>
<td>0.02</td>
<td>+0.02</td>
<td>+0.10*</td>
<td>-0.00</td>
<td>-0.00</td>
</tr>
<tr>
<td>Mean least-squares changes from baseline</td>
<td>P &lt; .05 vs GLIM + MET.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Eight Weeks of Treatment With the Long-Acting Human GLP-1 Analog Taspoglutide (R1583) Improves Glycemic Control and Lowers Body Weight in Subjects With Type 2 Diabetes Treated With Metformin: A Double-Blind, Placebo-Controlled Phase 2 Study
Presented by Michael Nauck

The results of a randomized, placebo-controlled, 8-week trial to study the efficacy of taspoglutide (R1583), a long-acting human GLP-1 analog given either once weekly (QW) or every 2 weeks (Q2W) in patients with T2DM (age 55 years; BMI = 32.7 kg/m²; A1C = 7.9%; duration of type 2 diabetes = 5 years) were presented (108-OR). A1C was significantly decreased relative to placebo at all doses tested (P < .0001), and was most markedly decreased relative to baseline in taspoglutide QW at a dose of 10 or 20 mg (~ 1.2%), with smaller decreases seen in the 5-mg QW and 10-mg and 20-mg Q2W groups (~ 1%). Significant weight loss from baseline (P < .05) was seen in the 10-mg QW group (2 kg), 20-mg QW group (2.8 kg), and in the 20-mg Q2W group (1.9 kg).
A large retrospective trial (N = 1784) found 6-month exenatide (EXEN) efficacy in clinical practice to be similar to controlled trials, and 12-week treatment with metformin (MET), and combination therapy with MET and sulfonylurea (SAXA) resulted in greater reductions in total weight compared with placebo (PBO) and GLIM. In addition, a greater reduction in total weight was seen with 12-week treatment with saxagliptin (SITA) compared with placebos in all treatment arms. A1C reductions in both EXEN and SITA were associated with weight loss and a reduction in hypoglycemic events related to GLIM (Table 1).

**Table 1. Efficacy and safety of LIRA monotherapy compared with glimepiride**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>ΔA1C (P)</th>
<th>ΔFPG, mg/dL</th>
<th>Δ2-hour-PPG, mg/dL</th>
<th>% reporting nausea</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIRA 1.2 mg</td>
<td>-1.4*</td>
<td>-0.7</td>
<td>-3.2</td>
<td>4</td>
</tr>
<tr>
<td>LIRA 1.8 mg</td>
<td>-2.0*</td>
<td>-0.3</td>
<td>-6.1</td>
<td>7</td>
</tr>
<tr>
<td>GLIM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. Efficacy and safety of LIRA as add-on therapy to metformin**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>ΔA1C (%)</th>
<th>ΔFPG, mg/dL</th>
<th>Δ2-hour-PPG, mg/dL</th>
<th>% reporting nausea</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO + MET</td>
<td>-0.7</td>
<td>-0.2</td>
<td>-0.7</td>
<td>27</td>
</tr>
<tr>
<td>PBO + MET + LIRA</td>
<td>-1.7*</td>
<td>-0.3</td>
<td>-1.4</td>
<td>32</td>
</tr>
<tr>
<td>GLIM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 3. Efficacy and safety of LIRA as add-on therapy to metformin**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>ΔA1C (%)</th>
<th>ΔFPG, mg/dL</th>
<th>Δ2-hour-PPG, mg/dL</th>
<th>% reporting nausea</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO + MET</td>
<td>-0.9</td>
<td>-0.3</td>
<td>-1.0</td>
<td>33</td>
</tr>
<tr>
<td>PBO + MET + LIRA</td>
<td>-2.0*</td>
<td>-0.4</td>
<td>-1.7</td>
<td>26</td>
</tr>
<tr>
<td>GLIM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 4. Efficacy and safety of LIRA as add-on therapy to sitagliptin**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>ΔA1C (%)</th>
<th>ΔFPG, mg/dL</th>
<th>Δ2-hour-PPG, mg/dL</th>
<th>% reporting nausea</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO + SITA</td>
<td>-0.7</td>
<td>-0.3</td>
<td>-1.0</td>
<td>39</td>
</tr>
<tr>
<td>PBO + SITA + LIRA</td>
<td>-1.5*</td>
<td>-0.4</td>
<td>-1.5</td>
<td>34</td>
</tr>
<tr>
<td>GLIM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 5. Efficacy and safety of LIRA as add-on therapy to saxagliptin**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>ΔA1C (%)</th>
<th>ΔFPG, mg/dL</th>
<th>Δ2-hour-PPG, mg/dL</th>
<th>% reporting nausea</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO + SAXA</td>
<td>-0.9</td>
<td>-0.3</td>
<td>-1.0</td>
<td>33</td>
</tr>
<tr>
<td>PBO + SAXA + LIRA</td>
<td>-1.7*</td>
<td>-0.4</td>
<td>-1.7</td>
<td>26</td>
</tr>
<tr>
<td>GLIM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 6. Efficacy and safety of LIRA as add-on therapy to exenatide**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>ΔA1C (%)</th>
<th>ΔFPG, mg/dL</th>
<th>Δ2-hour-PPG, mg/dL</th>
<th>% reporting nausea</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO + EXEN</td>
<td>-0.7</td>
<td>-0.3</td>
<td>-1.0</td>
<td>39</td>
</tr>
<tr>
<td>PBO + EXEN + LIRA</td>
<td>-1.4*</td>
<td>-0.5</td>
<td>-1.6</td>
<td>35</td>
</tr>
<tr>
<td>GLIM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 7. Efficacy and safety of LIRA as add-on therapy to sitagliptin**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>ΔA1C (%)</th>
<th>ΔFPG, mg/dL</th>
<th>Δ2-hour-PPG, mg/dL</th>
<th>% reporting nausea</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO + SITA</td>
<td>-0.7</td>
<td>-0.3</td>
<td>-1.0</td>
<td>39</td>
</tr>
<tr>
<td>PBO + SITA + LIRA</td>
<td>-1.7*</td>
<td>-0.4</td>
<td>-1.7</td>
<td>35</td>
</tr>
<tr>
<td>GLIM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 8. Efficacy and safety of LIRA as add-on therapy to saxagliptin**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>ΔA1C (%)</th>
<th>ΔFPG, mg/dL</th>
<th>Δ2-hour-PPG, mg/dL</th>
<th>% reporting nausea</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO + SAXA</td>
<td>-0.9</td>
<td>-0.3</td>
<td>-1.0</td>
<td>33</td>
</tr>
<tr>
<td>PBO + SAXA + LIRA</td>
<td>-1.7*</td>
<td>-0.4</td>
<td>-1.7</td>
<td>26</td>
</tr>
<tr>
<td>GLIM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 9. Efficacy and safety of LIRA as add-on therapy to exenatide**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>ΔA1C (%)</th>
<th>ΔFPG, mg/dL</th>
<th>Δ2-hour-PPG, mg/dL</th>
<th>% reporting nausea</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO + EXEN</td>
<td>-0.7</td>
<td>-0.3</td>
<td>-1.0</td>
<td>39</td>
</tr>
<tr>
<td>PBO + EXEN + LIRA</td>
<td>-1.4*</td>
<td>-0.5</td>
<td>-1.6</td>
<td>35</td>
</tr>
<tr>
<td>GLIM</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
BREAKING NEWS on INCRETIN-BASED THERAPIES Summary Conference Report
In conjunction with the 2008 American Diabetes Association’s 68th Annual Scientific Sessions · June 6-10, 2008 · San Francisco, CA

Program Overview
Type 2 diabetes (T2D) is a complex and heterogeneous disorder associated with numerous pathophysiologic defects. Many conventional therapies address only a single defect, not the constellation of pathophysiologic challenges associated with T2D. Further, most conventional therapies do not offer the potential to correct underlying pathophysiologic defects and, as such, tend to lose efficacy as the disease progresses. Conventional therapies are associated with a number of perceived clinical challenges, including weight gain and hypoglycemia. Incretin-based therapies, however, address numerous pathophysiologic defects in T2D with limited side effects. They offer the potential to alter the course of the disease.

Breaks News on Incretin-Based Therapies: Summary Conference Report in Conjunction With the 2008 American Diabetes Association’s 68th Annual Scientific Sessions is an educational activity designed to increase awareness and understanding of the role of incretin-based therapies in the treatment of patients with T2D. The report provides a practical overview of the most clinically relevant data on incretin-based therapies presented through posters and oral presentations at the 68th Scientific Sessions of the American Diabetes Association in San Francisco, June 6-10, 2008.

Intended Audience
This activity is intended for endocrinologists, diabetologists, diabetes educators, nurses, and other healthcare professionals (HCPs) who treat patients with T2D.

Learning Objectives
After participating in this activity, participants should be able to:
• Summarize current data that describe the clinical efficacy and safety of DPP-4 inhibitors for the treatment of T2D
• Discuss current data that describe the clinical efficacy and safety of incretin mimetics for the treatment of T2D
• Discuss the appropriate clinical application of incretin-based therapies, including proper patient selection based on clinical need and current glycemic control

Please evaluate how well the following learning objectives were met:


LEARNING OBJECTIVES

CONTINUING EDUCATION CREDIT ATTESTATION

I certify that I completed this educational activity. The actual amount of time I spent in this activity was:

Date: ____________________________

IMNE designates this educational activity for a maximum of 0.75 contact hours (0.075 CEUs). Accreditation by the ANCC’s Committee on Accreditation refers to recognition of educational activities and does not imply approval or endorsement of any product.

ANCC-accredited providers have been approved by the National Certification Board for Diabetes Educators (NCBDE) as providers of continuing education (CE). Individuals seeking recertification from the NCBDE can use the CE contact hours received through participation in this activity.

See reverse side for Disclosures

Acknowledgment of Commercial Support
This activity was supported by an educational grant from Novo Nordisk Inc.

CME/CNE INFORMATION

Release Date: June 26, 2008

Expiration Date: June 26, 2009

CME/CNE Accreditation Statements

For Physicians
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Baylor College of Medicine at UCLA

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Disclosure information for additional contributing authors of 69th Scientific Sessions presentations are published in American Diabetes Association, Abstracts—Disclosure information, Diabetes. 2009;58(suppl 1): A65–A94.

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5. Speaker’s Bureau
6. Spouse Employee
7. Spouse/Stock/Shareholder
8. Stock/Shareholder
9. Other Relationship

Thank you for participating in this educational activity.

Please fold and cut here

OUTCOME ASSESSMENT

To assess impact on clinical behavior, outcomes surveys are conducted to gauge the extent to which the educational activity influenced your practice. These surveys are sent through the mail or electronically. Your feedback is valued highly and is appreciated. Please participate in the evaluation process by completing the survey and return it to the following address:

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POSTER/WEB-WEBSITES

For each of the following questions, circle the answer that best describes your experience:

6. Which of the following agents was shown to reduce hepatic steatosis?

a. Alogliptin
b. Liraglutide

c. Sitagliptin
d. Sitagliptin mimetics

7. In phase 3 studies, alogliptin lowered A1C by approximately ___.

a. 0.5–0.8%
b. 0.8–1.0%
c. 1.0–1.5%
d. 1.5–2.0%

8. Which of the following antidiabetic agents was...

a. Used as a comparator in the...
Liraglutide and Others

Speaker: David D’Alessio

Glucagon-like peptide-1 (GLP-1) is an incretin hormone that has been shown to have a wide range of actions that promote glucose homeostasis. However, endogenous GLP-1 in the human body is rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4). This presents a challenge for incretin-based therapeutics, as it leaves incretin mimetic compounds that are resistant to this degradation (exenatide (EXEN) or liraglutide (LIR)) or to extend the half-life of endogenous GLP-1 by inhibiting the enzymatic breakdown of endogenous GLP-1 by DPP-4 (incretin enhancers, such as sitagliptin, saxagliptin, vilaglaptin, albiglutide).

LIRA is a human GLP-1 analog with modifications designed to extend its half-life, including an amino acid substitution and an attachment of a C16 octyl chain. These modifications promote albumin binding and result in a plasma half-life that makes it suitable for once-daily dosing. Research has demonstrated that once-daily LIRA injection has a half-life of approximately 24 hours, making it a selective secretagogue and reduces meal-related increases in plasma insulin secretion. In a 14-week study of LIRA monotherapy, patients treated with LIRA had a more normal insulin secretory response, a lower A1C and FPG, with a dose-dependent weight loss. At the higher tested doses of LIRA, the A1C change was approximately −1.5%.

EXEN long-acting release (LAR), another incretin mimetic in development, has been shown to have a plasma half-life of 2 weeks. LAR has been injected weekly in clinical trials in patients with type 2 diabetes and has been shown to produce a reduction in A1C by −1.7%. EXEN and LIRA have been compared with other antidiabetic treatments in a number of clinical trials.

Other incretin mimetics in development include R1983 (taspoglutide), AVE-0100, CJ11334-PIC, and albiglutide. The profile of action for incretin mimetics currently available and in clinical studies suggests that incretin mimetics represent a promising class of compounds to treat type 2 diabetes. These agents use a variety of pharmacologic strategies to improve glucose homeostasis and decrease appetite and promote weight reduction.

Dipeptidyl Peptidases – Physiological Functions and Overlapping Activities

Presented byCarolyn F. Deacon

In this oral presentation, the role of inhibiting the ubiquitous enzyme dipeptidyl peptidase 4 (DPP-4) to sustain endogenous glucagon-like peptide 1 (GLP-1) activity was discussed. Circulating GLP-1 has a half-life of less than 1 minute due to rapid degradation by DPP-4, and selective inhibition of this enzyme by DPP-4 inhibitors prolongs the half-life of active GLP-1. It is well known that GLP-1 is secreted by the intestinal L cells in response to food intake, which in turn improves insulin secretion and inhibits glucagon release to lower blood glucose concentrations.

For patients with type 2 diabetes, it has been shown that blood concentrations of GLP-1 are considerably lower compared with normal controls. Thus, increasing circulating GLP-1 levels in patients with type 2 diabetes has become an important therapeutic goal. Two classes of drugs address this need: (1) GLP-1 analogs (incretin mimetics) that are resistant to DPP-4 degradation and have long circulating half-lives, and, as discussed in this presentation, (2) DPP-4 inhibitors (incretin enhancers), which sustain circulating levels of endogenous GLP-1.

Table 1: DPP-4 inhibitors

<table>
<thead>
<tr>
<th>DPP-4 inhibitor</th>
<th>Half-life (hours)</th>
<th>% Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin</td>
<td>8-24</td>
<td>80</td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>15-45</td>
<td>&gt;60</td>
</tr>
<tr>
<td>Albiglutide</td>
<td>12-21</td>
<td>80</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>2-4</td>
<td>80</td>
</tr>
<tr>
<td>BI 1356</td>
<td>10-40</td>
<td>80</td>
</tr>
</tbody>
</table>

DPP-4 is an ubiquitously expressed serine dipeptidase membrane protein that is also soluble in circulation. DPP-4 not only has a major role in glucose metabolism but also immune regulation, as it is part of the T-cell surface antigen (CD26). Because of DPP-4’s many roles, selectivity for the glucose modulating pathway is an important concern. The catalytic site of DPP-4 is located in the center of the molecule, such that small molecule inhibitors of DPP-4 do not disrupt the external structure of the enzyme. However, DPP-4 has many substrates and is part of larger families of enzymes. The clinical effects on this vast number of substrates that DPP-4 inhibitors have the potential to affect are still unknown. In vitro studies demonstrate that all of the small molecule DPP-4 inhibitors listed in Table 1 have high selectivity for DPP-4. Compared with other inhibitors, vildagliptin has the greatest selectivity and least activity in DPP-4, yet at doses that inhibit DPP-8 and DPP-9, vildagliptin was found. So far clinical studies show good safety profiles with the DPP-4 inhibitors sitagliptin and vildagliptin. Urinary tract infections and headaches were noted as the most common adverse events; however, more long-term studies are needed.

Like GLP-1 analogs, DPP-4 inhibitors reduce fasting and postprandial plasma glucose control to hyperglycemia. However, unlike GLP-1 analogs, DPP-4 inhibitors are weight neutral, do not slow gastric emptying, and have minimal gastrointestinal side effects. The modest enhancement of circulating levels of endogenous GLP-1 with DPP-4 inhibitors is more physiologic, compared to a pharmacologic increase in GLP-1 with the injection of an incretin mimetic. The modest enhancement of circulating levels of endogenous GLP-1 by DPP-4 is one of the reasons why DPP-4 inhibitors are suitable as initial pharmacotherapy for patients with type 2 diabetes, with a more gradual effect on glycemia, compared with other antidiabetic agents. Research has shown that once-daily LIRA has a plasma half-life that makes it suitable for once-daily dosing.

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The Clinical Experience With Incretin-Based Therapies

Presented by Carol Wysham

Dr Wysham described the results of a retrospective chart review of the clinical experience with DPP-4 inhibitors and GLP-1 analogs in a multidisciplinary clinic by analyzing data from patients who had been on exenatide (EXEN) or liraglutide (LIR). The results are presented in Table 1.

Table 1: Selected results of a retrospective chart review of clinical experience with incretin-based therapies

<table>
<thead>
<tr>
<th>Results</th>
<th>DPP-4 inhibitors</th>
<th>GLP-1 analogs</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C (%)</td>
<td>−0.1</td>
<td>−0.2</td>
</tr>
<tr>
<td>% of patients with final A1C &lt; 7%</td>
<td>0.4</td>
<td>0.6</td>
</tr>
<tr>
<td>If baseline A1C &lt; 9%</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>If baseline A1C &gt; 9%</td>
<td>0.4</td>
<td>0.6</td>
</tr>
<tr>
<td>Duration &gt; 10 y</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>ΔA1C (%), ΔFPG (%)</td>
<td>−0.1</td>
<td>−0.2</td>
</tr>
</tbody>
</table>

Dr DeFronzo acknowledged that we have known the pathophysiologic roles of the Triumvirate of type 2 diabetes—the liver, pancreas, and muscle—for a long time. He described the well-known course of β-cell decline in type 2 diabetes. Dr. DeFronzo reviewed data that demonstrate that β-cell failure occurs earlier and is more severe than previously thought. These data show that β-cell function will be lost in 90% of patients with IGT (impaired glucose tolerance) by the age of 60 years and 50% of patients with IGT have retinopathy. In patients with IGT, increased A1C levels are associated with increased incidence of retinopathy.

He went on to describe how, along with the Triumvirate, 5 additional factors—adipose tissue, incretin hormones, alpha cells, kidneys, and the brain—make up the Ominous Octet of type 2 diabetes. Elevated lipolysis from the adipose tissue increases insulin resistance. Increased release of glucagon from the α cells and increased renal tubular reabsorption of glucagon lead to elevated serum glucagon levels. Diminished glucagon sensitivity in the hypothalamus reduces appetite suppression. In addition, the incretin hormones, glucagon-like peptide 1 (GLP-1) and glucagon-dependent insulinotropic peptide (GIP) are important regulators of satiety, peripheral glucagon, postprandial insulin, and gastric acid empyting. Dr. DeFronzo, specifically, referred to incretin hormones as the fifth member of the Quintessential Quintet. He described altered secretion of incretin hormones as a key part of glucose regulation and appetite control.

Dr DeFronzo emphasized that effective management of type 2 diabetes requires early treatment with multiple agents targeting the pathophysiologic abnormalities simultaneously. MONARCH+ (liraglutide) and others are the most commonly prescribed antidiabetic agents (ie, metformin and sulfonylurea) do not preserve β-cell function. In Dr DeFronzo’s opinion, drug classes that have strong evidence of β-cell preservation are the thiazolidinediones (TZDs) and DPP-4 inhibitors. In the late 1980s and early 1990s, the introduction of the first incretin mimetics (Amylin/M_hour) was hailed as a major new approach for treating patients with type 2 diabetes, while acknowledging that his recommendation is a major paradigm shift from current clinical practice. Dr DeFronzo closed his speech with the following quotation: “When it’s new, of course it isn’t so. And when it’s proven, it isn’t any longer new.”

He described that, for clinical practice, the initial ideal therapy for managing patients with type 2 diabetes should be a combination of lifestyle management with pharmacologic agents metformin, TZD, and GLP-1 analog used as well to address early on the pathophysiology anomalies that promote β-cell decline and function. He suggested that further clinical studies be developed that measure the effects of this type of initial approach for treating patients with type 2 diabetes, while acknowledging that his recommendation is a major paradigm shift from current clinical practice. Dr DeFronzo closed his speech with the following quotation: “When it’s new, of course it isn’t so. And when it’s proven, it isn’t any longer new.”

Join a growing community of healthcare professionals dedicated to high-quality care for patients with diabetes. Membership is free. Benefits include online access to premium scientific content, notification of CME/CE activities and e-mail updates on CDEF news.
Selected Oral presentations from Sunday, June 8, 2008

Liraglutide, a Once-daily Human GLP-1 Analog, Added to a Sulfonylurea (SU) Offers Significantly Better Glycemic Control and Favorable Weight Change Compared With Rosiglitazone and SU Combination Therapy in Subjects With Type 2 Diabetes Presented by Michel Marre

The LEAD 1 clinical trial (13-OR) was a 26-week, prospective, randomized, placebo (PBO)-controlled, double-dummy study that compared the effects of 3 different doses of liraglutide (LIRA) (0.6, 1.2, and 1.8 mg/d) added to SU with SU monotherapy, as well as with the active comparator rosiglitazone (ROSI) (4.0 mg/d), also added to SU. ROSI 4.0 mg was selected because that dose is approved for use in all the countries where LEAD 1 was conducted. A total of 1041 patients with type 2 diabetes from 21 countries at 116 sites were enrolled in LEAD 1. The LEAD 1 patients were aged 18-80 years (mean 56 years), with BMI = 30 kg/m², and mean A1C = 8.4%. Patients were stratified by the number of oral antidiabetic drugs (OADs) they were taking at baseline. A1C and FPG were reduced in all LIRA treatment arms relative to the PBO arm, and higher doses of LIRA also yielded significant improvements in glycemic control relative to ROSI (Table 1). Patients previously treated with 1 OAD had consistently greater changes in A1C from baseline (AAIC) than patients previously treated with 2 OADs. A reduction in body weight relative to ROSI was observed in all doses of LIRA. Notably, patients previously treated with metformin who were switched to GLIM for LEAD 1 typically gained weight. Minor hypoglycemic events occurred about 3 times more often at the 2 highest LIRA doses than in the PBO group, and nausea was reported in 5.1%-10.5% in the LIRA treatment arms. Dose-dependent increases in the presence of antibodies were also noted in the LIRA arms, although the rate was relatively low.

Table 1. Selected study outcomes for LIRA + GLIM combination therapy relative to baseline in the LEAD 1 trial

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LIRA 0.6 + GLIM</th>
<th>LIRA 1.2 + GLIM</th>
<th>LIRA 1.8 + GLIM</th>
<th>ROSI 4.0 + GLIM</th>
<th>PBO + GLIM</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C, %</td>
<td>7.9</td>
<td>7.5</td>
<td>7.5</td>
<td>8.0</td>
<td>8.7</td>
</tr>
<tr>
<td>A1C, %</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>1 OAD subgroup</td>
<td>-0.8</td>
<td>-1.08**</td>
<td>-1.13**</td>
<td>-0.44</td>
<td>+2.33</td>
</tr>
<tr>
<td>2 OAD subgroup</td>
<td>-0.4</td>
<td>-0.7</td>
<td>-0.7</td>
<td>-0.1</td>
<td>+0.7</td>
</tr>
<tr>
<td>FPG, mg/d</td>
<td>+2.9**</td>
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</tr>
<tr>
<td>BMI, kg</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>C-peptide</td>
<td>0.17</td>
<td>0.51</td>
<td>0.47</td>
<td>0.12</td>
<td>0.17</td>
</tr>
<tr>
<td>% reporting nausea</td>
<td>5.1</td>
<td>10.5</td>
<td>8.8</td>
<td>2.5</td>
<td>1.7</td>
</tr>
<tr>
<td>% with LIRA antibodies</td>
<td>10.9</td>
<td>12.7</td>
<td>9.3</td>
<td>NR</td>
<td>NR</td>
</tr>
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∆A1C, %< .0001 vs PBO + GLIM; *P < .0001 vs ROSI + GLIM; hypo, hypoglycemic; NR, not reported.

Safety and Tolerability of High Doses of the Long-Acting Human GLP-1 Analog Taspoglutide (R1583) in Diabetic Subjects Treated With Metformin: a Double-Blind, Placebo-Controlled Phase 2 Study Presented by Robert Ratner

Taspoglutide (TASPO), a long-acting human GLP-1 analog, was tested in subjects with type 2 diabetes (N = 133, aged 57 years, BMI = 32.4 kg/m², A1C = 7.9%, duration of diabetes = 7 years, 18-OR). Patients treated with metformin were randomized to also receive placebo (PBO) or TASPO 20 mg weekly for 4 weeks, followed by either a 4-week continuation of 20 mg (2020) or a dose escalation to either 30 (2030) or 40 mg (2040) of once-weekly TASPO. All 3 TASPO groups had meaningful improvements in both A1C and fasting plasma glucose. Higher TASPO doses were associated with higher rates of withdrawal from the trial: PBO (3%; 1 subject), 2020 mg (18%; 3 subjects), 2030 mg (18%; 6 subjects), and 2040 mg (18%; 6 subjects). Any nausea that occurred was usually decreased with continued therapy. Seven withdrawals were due to GI AEs; 3 TASPO-treated patients discontinued the trial because of GI AEs. Therefore, the authors concluded that the maximum effective and safest dose of TASPO was 20 mg.

Effect of Exenatide With or Without Daclizumab on Endogenous Insulin Secretion in Long-Standing Type 1 Diabetes Mellitus Presented by Kristina I. Rother

Dr Rother presented the results of a small study (N = 20) to determine the efficacy of exenatide (EXEN) on β-cell function in patients with type 1 diabetes mellitus (T1DM). In 2000, a prior study of patients with T1DM found that, contrary to expectation, approximately 38% of screened patients had measurable C-peptide levels (> 0.5 ng/mL), despite more than 20 years of T1DM. Patients rejected from the previous study were then invited back to determine if residual β-cell function could be improved with EXEN therapy.

To overcome the concern that EXEN might stimulate the original autoimmune response in these patients, daclizumab (an IL-2 receptor CD25 antagonist) was added to the treatment regimen. During a 2- to 4-month run-in period, 20 patients (age = 40.6 years, age at onset = 18.1 years, duration of T1DM = 21.5 years, weight = 78.7 kg, BMI = 25.9 kg/m², A1C = 7.3%) were managed to achieve stable blood glucose levels. Patients were then randomized to 1 of 4 treatment arms: 1) insulin plus EXEN (2.5 mg titrated to 10 mcg 4 × daily) plus daclizumab (2 mg/kg IV each month); 2) insulin plus EXEN; 3) insulin plus daclizumab; 4) insulin only. After 6 months of therapy, patients receiving EXEN discontinued therapy, and patients not receiving EXEN in the first 6 months started EXEN therapy for an additional 6 months: all other patients not receiving EXEN in the first 6 months switched to GLIM for LEAD 1 typically gained weight. Minor hypoglycemic events occurred about 3 times more often at the 2 highest LIRA doses than in the PBO group, and nausea was reported in 5.1%-10.5% in the LIRA treatment arms. Dose-dependent increases in the presence of antibodies were also noted in the LIRA arms, although the rate was relatively low.

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