Tesaglitazar Helps Insulin-Resistant Nondiabetic Patients

Speaker: Bjorn Fagerberg, MD, PhD, Professor of Medicine, Department of Medicine, Sahlgrenska University Hospital and Göteborg University, Göteborg, Sweden.

Tesaglitazar (Galida™, AstraZeneca), a dual peroxisome proliferator–activated receptor (PPAR) alpha/gamma agonist being developed to treat the insulin resistance–related glucose and lipid abnormalities associated with type-2 (non–insulin-dependent) diabetes and the metabolic syndrome, significantly improved lipid and glucose control after meals in nondiabetic patients with insulin resistance, potentially reducing their cardiovascular risk. (The metabolic syndrome, characterized by overweight or obesity, physical inactivity, and genetic factors, tends to elevate the risk of coronary disease and diabetes.)

Because abnormalities in postprandial lipid handling and glucose tolerance are common in insulin-resistant patients and are strongly related to vascular morbidity and mortality, a study was designed to examine the effect of tesaglitazar on postprandial metabolism in insulin-resistant, nondiabetic patients.

In this 12-week, randomized, double-blind, placebo-controlled phase 2 study, part of the Study in Insulin Resistance (SIR) trial, 390 patients were assigned to receive either tesaglitazar 0.1 mg, 0.25 mg, 0.5 mg, or 1 mg or placebo for 12 weeks to assess the drug’s effects on the lipid and glucose abnormalities associated with insulin resistance.

The initial results demonstrated that tesaglitazar, in a dose-dependent fashion, reduced fasting triglyceride levels by 37% at the 1-mg dose, the primary efficacy measure of the study. There was also a significant increase of up to 16% in high-density lipoprotein-cholesterol (HDL-C), a reduction of fasting plasma glucose of up to 8.5 mg/dl, and an improvement in fasting insulin, at 1 mg, as measured by the Homeostasis Model Assessment.

Of the 222 patients whose lipid and glucose levels were assessed after meals, 195 patients were considered evaluable in this intent-to-treat analysis. Placebo-corrected changes in the area-under-the-concentration (AUC) time curve were determined for several variables, including serum triglycerides and glycerol; plasma free fatty acids (FFAs); insulin after a lipid-rich meal; and plasma glucose after an oral glucose tolerance test.

Tesaglitazar markedly reduced the postprandial AUC concentration for triglycerides in a dose-dependent manner. Mean placebo-corrected reductions from baseline were 20% with 0.25 mg, 30% with 0.50 mg, and 41% with 1 mg. Tesaglitazar 1 mg produced major changes in all variables examined, with reductions of 29% in FFAs, 34% in postprandial glycerol, and 31% in postprandial insulin. This dose also significantly improved glucose tolerance by 27% two hours after a glucose tolerance test.

All patients receiving tesaglitazar 1 mg had normal glucose tolerance after 12 weeks of treatment, compared to 85% of these patients at the baseline evaluation.

Vildagliptin Improves Insulin Sensitivity in Type-2 Diabetes

Speaker: Bo Ahrën, MD, Professor of Medicine, Lund University, Lund, Sweden.

When added to metformin (Fortamet®, Andrex Labs), vildagliptin (Novartis)—an investigational dipeptidyl peptidase IV (DPP-IV) inhibitor that extends the action of insulin while suppressing the release of glycogen—results in greater...
pancreatic beta-cell function and improved insulin sensitivity in patients with type-2 diabetes.

A 52-week, phase 2 double-blind study was designed to examine whether DPP-IV inhibition affected meal-related beta-cell function and insulin sensitivity. In a 12-week core study, 107 patients with poorly controlled type-2 diabetes were randomly assigned to take oral vildagliptin 50 mg once daily or placebo, added to an ongoing oral metformin treatment of 1.5 to 3 mg once daily. This plan was followed by a 40-week extension study of 71 patients. Standardized meal tests were performed at the baseline, at 12 weeks, at 24 weeks, and at 52 weeks for evaluating insulin secretion, dynamic insulin sensitivity, and the fasting proinsulin–insulin ratio.

Fasting glucose values were reduced with vildagliptin/metformin therapy but were elevated with the placebo/metformin combination. A significant difference of 1.2 ± 0.3 mmol favored vildagliptin. Insulin secretion was enhanced in the vildagliptin-based therapy but was reduced with placebo/metformin.

The measure of dynamic insulin sensitivity during meal ingestion was increased for vildagliptin/metformin but remained unchanged for placebo/metformin.

Patients’ scores, as measured by an adaptation index that multiplied insulin secretion by dynamic insulin sensitivity, were enhanced by the addition of vildagliptin to metformin and remained unchanged with placebo/metformin.

**Exenatide Injection Offers Sustained Improvements in Type-2 Diabetes**

**Speaker:** David M. Kendall, MD, Chief of Clinical Services and Medical Director, International Diabetes Center, Minneapolis, Minnesota.

Exenatide (Byetta™, Amylin/Eli Lilly), an agent that mimics the antidiabetic actions of naturally occurring human hormones called incretins, improved blood glucose control and progressive weight reduction over 1.5 years of therapy in type-2 diabetes that had been uncontrolled with metformin and/or a sulfonylurea.

Close to 90% of patients completing 30 weeks of therapy in the exenatide pivotal phase 3 studies chose to continue in an open-label extension. All patients received exenatide 10 mcg twice daily along with their usual previous dose of metformin or a sulfonylurea or both. Over 82 weeks, exenatide, in combination with metformin and/or a sulfonylurea, resulted in sustained blood glucose reductions and in progressive weight reductions. Glycosylated hemoglobin (HbA1c), the measure of fasting blood glucose, fell by 1.2 ± 0.1%, and weight was reduced by 4.6 ± 3.0 kg. This latter benefit was especially significant because many therapies for type-2 diabetes cause weight gain.

Administration of exenatide for 82 weeks also produced clinically meaningful improvements in cardiovascular risk factors, including positive changes associated with an increase in HDL-C, reduced levels of triglycerides, and decreased systolic and diastolic blood pressures. In general, these improvements were greatest in patients who lost the most weight.

**Pioglitazone/Statin Combination in Type-2 Diabetes**

**Speaker:** Mehmoood Khan, MD, Senior Vice President of Medical and Scientific Affairs, Takeda Pharmaceuticals North America, Inc., Lincolnshire, Illinois.

According to results from a recent study, switching type-2 diabetic patients from the thiazolidinedione (TZD) rosiglitazone (Avandia®, GlaxoSmithKline) to the TZD pioglitazone (Actos®, Takeda), while maintaining concomitant statin therapy for diabetic dyslipidemia, resulted in significant improvements in key lipid parameters (low-density lipoprotein-cholesterol (LDL-C), triglycerides, and total cholesterol) beyond those resulting from traditional cholesterol-lowering agents.

This multicenter, single-arm, 17-week, open-label study enrolled 305 patients with type-2 diabetes. The patients were taking statins along with rosiglitazone therapy, alone or in combination with another oral antidiabetic agent, for more than 90 days.

At the baseline, the patients ended rosiglitazone therapy and were switched to pioglitazone 30 mg once daily while continuing previous statin therapy and other lipid-lowering agents at unchanged doses throughout the study. Pioglitazone could be titrated to 45 mg at the discretion of the investigators. Blood glucose and lipid levels, including fasting triglycerides, total cholesterol, LDL-C, and HDL-C, were measured at the start of the study (when the patients were receiving rosiglitazone) and throughout the study (when they received pioglitazone).

At week 17, conversion from rosiglitazone to pioglitazone resulted in constant glycemic control and no changes in free fatty acids, C-reactive protein, or blood pressure. There was a significant mean percentage reduction in lipid levels. Triglycerides were reduced by 20.8%, total cholesterol declined by 10.5%, and mean levels of apoprotein A1 increased by 9.7 mg/dl. Apo-A1 is a lipid component necessary for HDL-C metabolism and biosynthesis. Mean levels of apoprotein B, a component of atherogenic lipoproteins, decreased by 2.6 mg/dl.

**Metaglidasen for Patients with Type-2 Diabetes**

**Speaker:** Julio Rosenstock, MD, Clinical Professor of Medicine at the University of Texas–Southwestern Medical Center, and Endocrinologist, Dallas Diabetes and Endocrine Center, Medical City, Dallas, Texas.

In a multicenter clinical trial, metaglidasen (Metabolix, Inc.) improved blood glucose control with efficacy comparable to that reported with currently marketed thiazolidinediones. Metaglidasen is a novel oral insulin sensitizer that modulates the genes needed for insulin sensitization but not those genes responsible for edema and weight gain. This effect was observed without the dose-limiting effects of edema or weight gain often experienced by patients taking those drugs.

This randomized, double-blind, placebo-controlled, phase 2 trial involved 217 patients with type-2 diabetes who were taking concomitant insulin therapy and who had inadequate control of blood glucose. The patients received metaglidasen, 200 or 400 mg, or placebo once daily, while maintaining their insulin dose, for 12 weeks. Glycemic control, lipids, and adverse-effect profiles were assessed.

Metaglidasen 200 mg lowered HbA1c levels by 0.9%; the 400-mg dose lowered these values by 1%. The rate with placebo was 0.3%, for a difference of 0.7% favoring metaglidasen 400 mg.

Triglyceride levels declined by 21% with the 400-mg dose of...
metaglidasen, compared with placebo. The remainder of the lipid components remained unchanged. The drug was well tolerated. Weight gain was lower than with insulin alone: +0.3 kg with 200 mg, +0.7 kg with 400 mg, and +0.8 kg with insulin alone. There was no increase in the incidence of edema with metaglidasen therapy (11% with 200 mg, 7.2% with 400 mg). The incidence of edema was 20% for those taking insulin plus placebo.

**Add-on Insulin Glargine in Uncontrolled Type-2 Diabetes after Oral Monotherapy**

**Speaker:** Luigi F. Meneghini, MD, Associate Professor of Clinical Medicine, Miller School of Medicine, and Director, Koskow Diabetes Treatment Center, Miami, Florida.

Insulin glargine (Lantus®, Sanofi-Aventis), a basal, long-acting, synthetic insulin of recombinant DNA (rDNA) origin, administered as adjunctive therapy in patients with type-2 diabetes that had not been controlled with an oral sulfonylurea (glipizide [Glucotrol XL®, Pfizer] or glyburide [DiaBeta®, Sanofi-Aventis]), or metformin monotherapy provided superior glycemic control over the oral TZD pioglitazone (Actos®), even though adding pioglitazone substantially reduced HbA1c levels.

A 48-week, parallel group, two-arm, open-label study was performed to compare glycemic control. The patients continued their pre-study doses of a sulfonylurea or metformin and randomly received either insulin glargine given subcutaneously (SQ) once daily at bedtime starting at 15 mg once daily. The drugs were then titrated to a target fasting plasma glucose value of greater than 72 mg/dl and less than 100 mg/dl, according to a specified algorithm, for the first 24 weeks of the study.

Starting at week 26 and throughout the remainder of the study, insulin glargine was administered to maintain glycemic control (range, from below 95 mg/dl to above 70 mg/dl). A total of 259 patients were randomly selected, 191 patients completed the study, and 247 patients made up the modified intent-to-treat population.

After 48 weeks, the addition of insulin glargine resulted in a significantly greater reduction in HbA1c (-2.7%), compared to the addition of pioglitazone (-2.3%). The mean HbA1c was 6.7% with insulin glargine and 7% with pioglitazone, demonstrating the value of insulin glargine as an earlier add-on therapy for patients who were not achieving the HbA1c goal of below 7% with sulfonylurea or metformin monotherapy.

There was no difference in the efficacy or safety between metformin and the sulfonylurea. Overall, insulin glargine had a better safety profile than pioglitazone, causing less edema, headache, and weight gain. However, four patients in the insulin glargine group experienced hypoglycemia, compared with one patient in the pioglitazone group.

**Inhaled Insulin Powder Holds Promise for Type-1 Diabetes**

**Speaker:** Satish Garg, MD, Professor of Pediatrics and Medicine, University of Colorado School of Medicine Health Sciences Center, and Chief, Young Adult Clinics at the Barbara Davis Center for Childhood Diabetes, Denver, Colorado.

A phase 2 clinical study suggests that human insulin inhalation powder (HIIP), taken before meals (via the Lily/Alkermes Inhaled Insulin Delivery System), achieved blood sugar levels similar to those reached with injected insulin.

A randomized, open-label, non-inferiority crossover study was conducted to compare the safety and efficacy of the powder and SQ injected insulin. A total of 259 patients with type-1 diabetes and normal lung function were assigned to take the pre-meal powder (n = 133) or SQ insulin injections (n = 126) plus insulin glargine (Lantus®, Sanofi-Aventis) once a day for 12 weeks.

The primary endpoint was based on the non-inferiority of HbA1c values between inhaled insulin and injected insulin. Safety measures assessed included hypoglycemia rates, fasting blood glucose, and carbon monoxide lung-diffusing capacity (DLCO), a measure of gas exchange capacity of the lung.

On the basis of the HbA1c levels, the powder and the injected insulin treatments were equivalent in controlling blood glucose. HbA1c levels averaged 7.9% with the powder and 8% with SQ insulin.

With regard to safety, rates for any hypoglycemia were comparable: 8.8% for the powder and 8.1% for SQ insulin. Rates for severe hypoglycemia were 0.17% with HIIP and 0.13% for SQ insulin. No clinically meaningful differences between the two modalities were observed with respect to fasting blood glucose or DLCO.

**Rimonabant for the Treatment of Multiple Problems in Type-2 Diabetes**

**Speaker:** Andre Scheen, MD, PhD, Professor of Medicine and Clinical Pharmacology, and Head, Division of Diabetes, Nutrition, and Metabolic Disorders, University of Liege, Belgium.

Rimonabant (Acomplia®, Sanofi-Aventis), a selective cannabinoid type-1 (CB1) receptor blocker, offered a broad range of improvements in cardiometabolic factors for the comprehensive management of patients with type-2 diabetes who were taking oral medications and who required further glucose control.

The Rimonabant in Obesity–Diabetes (RIO) study was a multicenter, randomized, double-blind, placebo-controlled, phase 3 clinical trial that enrolled 1,047 patients with type-2 diabetes. All of these patients had been treated with metformin (two thirds of patients) or one of several sulfonylureas for six or more months at the time of entry into the trial. The patients were assigned to receive rimonabant 5 mg or 20 mg, or placebo once daily for one year. The study was designed to compare the effects of rimonabant and placebo on HbA1c, values, waist circumference, body weight, the metabolic syndrome, and other cardiovascular risk factors (e.g., dyslipidemia, blood pressure).

The results reported here include 336 patients who received rimonabant 20 mg and 345 patients who received placebo. The differences between placebo and rimonabant 5 mg were too minor to be of value.

The percentage of patients reaching the American Diabetes Association’s recommended treatment target of less than 7% HbA1c was 67.9% for those taking rimonabant 20 mg and 47.6%
for those taking placebo. No differences were observed whether patients were taking metformin or a sulfonylurea.

Patients lost 11.7 pounds with rimonabant and 3.11 pounds with placebo, a mean difference of 8.6 pounds. The proportion of patients with at least a 5% body weight loss at one year was 49.4% with rimonabant 20 mg and 14.5% with placebo. Changes in waist circumference paralleled weight loss; there was an average difference of 1.3 inches in loss between those taking rimonabant 20 mg and those taking placebo.

Changes in the lipid profile included an 8.4% difference in increased HDL-C and a 16.4% difference in reduction of triglycerides, both favoring rimonabant 20 mg. The total cholesterol/HDL-C ratio was significantly decreased by rimonabant.

Significantly fewer rimonabant patients met the criteria for the metabolic syndrome. Of the 79% of patients who had metabolic syndrome at study entry, 64% of those receiving rimonabant 20 mg and 73% of those taking placebo still had the syndrome at the end of one year.

**Pregabalin and Reduction of Pain in Diabetic Peripheral Neuropathy**

**Speaker:** Brett Stacey, MD, Associate Professor of Anesthesiology and Perioperative Medicine, Oregon Health & Science University, Portland, Oregon.

Pregabalin (Lyrica™, Pfizer) provided significant improvement over placebo in pain associated with diabetic peripheral neuropathy, even by the end of the first day of treatment.

Using data from six randomized, double-blind, placebo-controlled trials encompassing 1,346 patients with painful diabetic peripheral neuropathy, researchers compared 437 patients receiving placebo and 873 patients receiving pregabalin to determine the time it took for pain to diminish after the initiation of pregabalin treatment. Because the magnitude of pregabalin’s analgesic effect has been correlated with the daily dose, the investigators studied the time to significant effect in patients grouped according to their target dose of pregabalin and to the speed of titration. Three treatments were evaluated:

- **Low:** patients received the minimum therapeutic dose of 150 mg/day.
- **Slow:** 300 and 600 mg/day were titrated slowly, so that less than half of the target dose was reached after the fourth day of treatment.
- **Fast:** 300 and 600 mg/day were titrated rapidly, so that half or more of the target dose was reached on or before the fourth day of treatment.

Patients recorded their pain scores daily on a scale of zero to 10 points, from no pain to the worst possible pain.

An analysis of the data demonstrated that pregabalin had a rapid onset of action, as recorded in the patients’ daily pain diaries on an 11-point scale. Observed reductions in pain scores ranged from as high as 2.6 points in the “Fast” treatment group to 2.56 points in the “Slow” group to 2.04 points in the “Low” group, compared with 1.49 points in the placebo group. These significant pain score reductions were observed as early as day one for all three pregabalin groups.