# Rosiglitazone: At 10 Years, No Liver Toxicity Seen

## *Experience in more than 7,000 patients shows the agent to be free of troglitazone's side effect.*

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SAN DIEGO — Rosiglitazone has shown no hint of excess liver toxicity in 10 years of safety monitoring by GlaxoSmithKline, Alexander R. Cobitz, M.D., Ph.D., reported at the annual scientific sessions of the American Diabetes Association.

The withdrawal of the first thiazolidinedione, troglitazone, from the market in 2000 because of liver toxicity prompted concern about the entire thiazolidinedione class of glucose-lowering agents, and resulted in strict label requirements for frequent liver monitoring in patients using the second-generation agents rosiglitazone and pioglitazone. These requirements have since been relaxed to simply measuring liver function at the time of initiation of therapy and as clinically indicated.

Now, after 10 years of safety monitoring in more than 7,000 patients, no cumulative evidence of hepatotoxicity has been seen in nearly 9,000 patient-years of exposure. "In the shadow of troglitazone, there were requirements put on the other two. … However, each of these molecules is markedly different," said Dr. Cobitz, director of metabolism, clinical development, and medical affairs at GlaxoSmithKline, King of Prussia, Pa.

Included in his analysis were the phase III data on 4,327 patients with 2,493 patient-years of exposure that were submitted to the U.S. Food and Drug Administration for the new drug application for rosiglitazone (Avandia) in 1998, along with subsequent postmarketing surveillance data comprising an additional 256% in drug exposure since it entered the U.S. market. In all, the data include 38 double-blind and open-label clinical studies of rosiglitazone treatment in North America and Europe.

Patients in all the trials had baseline liver function test results at or below 2.5 times the upper limit of normal. Liver function was assessed at screening, at baseline, every 4 weeks for the first 3 months, and at 6- to 12-week intervals thereafter.

Among 7,429 patients enrolled in the trials—including 3,194 on rosiglitazone monotherapy and the rest on rosiglitazone in combination with metformin, sulfonylurea, or insulin—a total of 0.3% experienced a serum alanine aminotransferase (ALT) level more than 3 times the upper limit of normal. That same proportion was also seen among the 2,792 patients who received comparators without rosiglitazone in the trials—placebo, metformin, sulfonylurea, or insulin.

The number of person-years of exposure among the rosiglitazone subjects ranged from 892 with rosiglitazone plus insulin to 8,851 with monotherapy. Among the comparator groups, the range was from 186 person-years of exposure to placebo up to 1,186 person-years of exposure to sulfonylurea.

"The rate of hepatic events per patient-year is similar, if not better, than for the comparators," Dr. Cobitz pointed out.

There were no differences between rosiglitazone and the comparators in threefold elevations of aspartate aminotransferase or alkaline phosphatase levels, or for elevations of 1.5 times the upper limit of normal in total bilirubin levels.

In all groups, those proportions ranged from 0% to 0.8%, with 0.8% being the percentage of 1.5-fold total elevations in bilirubin levels in the placebo group. Among the rosiglitazone recipients, 0.5% had that amount of elevation in bilirubin levels.

Further analysis showed no differences in ALT levels between three and five times the upper limit of normal (0%-0.3% for all rosiglitazone and comparator groups) or in ALT between five and eight times the upper limit of normal (0%-0.2%).

These data support the idea that although the chemical structures of all thiazolidinediones are identical on the right-hand side, their different left-hand structures result in very different biochemical and metabolic features, Dr. Cobitz said. ■

# Novel Agent Lowers Glucose Without Edema, Weight Gain

SAN DIEGO — Metaglidasen is a novel insulin sensitizer that appears to lower blood glucose as effectively as the thiazolidinediones without causing weight gain or edema, Julio Rosenstock, M.D., reported at the annual scientific sessions of the American Diabetes Association.

The investigational agent, manufactured by Metabolex Inc., is a partial agonist/antagonist of the peroxisome proliferator-activated receptor (PPAR)–gamma. In contrast, the TZDs rosiglitazone and pioglitazone are full PPAR-gamma agonists.

While the TZDs are associated with significant reductions in hemoglobin $A_{1c}$ levels, their use is limited by high rates of weight gain and fluid retention, said Dr. Rosenstock, a practicing endocrinologist in Dallas and clinical professor of medicine at the University of Texas Southwestern Medical Center, Dallas.

He presented the results of a phase II multicenter trial conducted in 217 patients with type 2 diabetes who were inadequately controlled on insulin, with a mean baseline hemoglobin $A_{1c}$ of 9.1%. This group was chosen to study first because the risk for fluid retention with TZDs is greatest among patients who use them in combination with insulin, he explained.

After being taken off all oral medications but remaining on the same dose of insulin, the patients were randomized to receive 200 mg or 400 mg of metaglidasen or placebo once daily for 12 weeks. A total of 208 patients completed at least 67 days, the duration deemed necessary to establish drug effect. The numbers who discontinued due to adverse events did not differ between the two metaglidasen groups and placebo.

At 12 weeks, reductions in hemoglobin $A_{1c}$ were statistically significant for both doses of metaglidasen combined with insulin (0.9 percentage point reduction with 200 mg and 1.0 with 400 mg), compared with just 0.3 with placebo plus insulin.

This effect on $A_{1c}$ is comparable to the drop of 0.8-1.2 percentage points typically seen when TZDs are added to insulin therapy, Dr. Rosenstock noted.

Other statistically significant changes included a 41-mg/dL drop in fasting plasma glucose with the 400-mg dose of metaglidasen, compared with placebo; reductions in uric acid of 7.5% with the 200-mg and 20% with the 400-mg doses; and dose-dependent increases in adiponectin levels, also significant for both the 200-mg and 400-mg doses. There was also a 21% reduction over placebo in triglycerides with the 400-mg dose of metaglidasen, which did not reach statistical significance due to variability but was still noteworthy, he said.

Both doses of metaglidasen were well tolerated and had no significant effect on liver or muscle enzymes, kidney function, or hematopoietic parameters.

The incidence of edema was 11% for the 200-mg dose of metaglidasen and 5.8% for the 400-mg dose, compared with 17.3% with the placebo group. Weight gains of 0.6 kg occurred in each of the two metaglidasen dose groups, compared with a 1.3-kg increase with placebo.

As expected with an insulin sensitizer, hypoglycemia was slightly higher, with episodes occurring in 37% of the 200-mg group and 36% with 400 mg, compared with 29% in the placebo group.

Metabolex is now moving forward with a second phase II study using a higher dose of metaglidasen and is actively preparing for phase III, according to a company statement. ■

# *Spironolactone Effectively Counteracts Rosiglitazone-Associated Edema*

SAN DIEGO — Spironolactone appears to be the most effective antidiuretic for the management of rosiglitazone-associated fluid retention, Janaka Karalliedde, M.D., reported at the annual scientific sessions of the American Diabetes Association.

Edema is a common side effect of the insulin sensitizer rosiglitazone, occurring in approximately 5% of patients with type 2 diabetes when used as monotherapy or in combination with other glucose-lowering agents, and in about 15% of patients who use it in combination with insulin.

The precise mechanism is unclear, although the phenomenon is reflected in a reduction in both hematocrit and hemoglobin, which is indicative of plasma volume expansion, said Dr. Karalliedde of the department of endocrinology and internal medicine, Kings College and Guys Hospital, London.

In a study sponsored by GlaxoSmithKline, 4 mg of rosiglitazone was given twice daily for 12 weeks to 381 patients with type 2 diabetes (67% male, mean age 60 years). One-fourth of the patients were already being treated with sulfonylurea alone, and the rest with sulfonylurea plus metformin. Their mean baseline hemoglobin $A_{1c}$ was 7.5%, and mean body mass index was 30 kg/m².

A total of 68% showed evidence of volume expansion, defined as a reduction in hematocrit of at least 0.5%. Those 260 patients were then randomized to one of five 1-week treatment arms: continuation of rosiglitazone, continuation of rosiglitazone with the addition of either 40 mg/day of furosemide, 25 mg/day of hydrochlorothiazide, 50 mg/day of spironolactone, or discontinuation of rosiglitazone (with placebo).

Among the three diuretic groups, the dose of diuretic was doubled to 100 mg/day in the 33% whose urine output did not increase by at least 30% in the first 24 hours.

After the initial 12 weeks on rosiglitazone, those who were subsequently randomized had a mean reduction in hematocrit level of 2.9%, with a mean weight gain of 1.8 kg.

Plasma sodium levels rose significantly, while plasma aldosterone fell significantly. Both systolic and diastolic blood pressures dropped slightly, Dr. Karalliedde reported.

After randomization, hematocrit continued to fall in the group that continued taking rosiglitazone without a diuretic, with a total drop of 0.89% by day 7.

This reduction was attenuated to 0.7% in the furosemide group, to 0.12% in those who were withdrawn from rosiglitazone, and 0.02% with hydrochlorothiazide.

With spironolactone, however, hematocrit actually increased by 0.24% despite continuation of rosiglitazone. These results were statistically significant for both spironolactone and hydrochlorothiazide, he noted.

Total body weight fell in all diuretic groups, but the 1.2-kg loss with spironolactone was the greatest.

Only that and the 1-kg loss with hydrochlorothiazide reached statistical significance, compared with the group that continued taking rosiglitazone without a diuretic, Dr. Karalliedde said. ■