New Japanese Drug Pemafibrate Improves Lipid Profiles in Diabetes

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Pemafibrate (Kowa Company), a novel selective peroxisome proliferator-activated receptor alpha (PPARα) modulator (or fibrate), may significantly improve lipid profiles and insulin resistance in patients with type 2 diabetes and hypertriglyceridemia, the results of a Japanese phase 3 trial indicate.

The findings, published online January 3 in *Diabetes Care*, follow those of several large-scale clinical trials which show that treatment with fibrates decreases triglyceride levels and increases high-density lipoprotein (HDL) cholesterol levels, and subsequently reduces atherosclerotic cardiovascular disease risk in patients with type 2 diabetes.

For example, in extended follow-up of the ACCORD study, fenofibrate added to statins was associated with a significant reduction in the composite endpoint of fatal and nonfatal myocardial infarction and stroke among the subgroup of type 2 diabetes patients with hypertriglyceridemia and low HDL, at a hazard ratio of 0.73 vs placebo.

The current study, which involved over 160 patients, indicates that pemafibrate also significantly reduces triglyceride and non-HDL levels, and increases HDL levels, compared with placebo.

And pemafibrate was associated with significant decreases in insulin resistance, although glycemic control and low-density lipoprotein (LDL) cholesterol levels were unaffected.

The agent "demonstrated excellent efficacy in the amelioration of lipid abnormalities and was well tolerated in patients with type 2 diabetes," write the researchers, led by Eiichi Araki, MD, PhD, Department of Metabolic Medicine, Faculty of Life Sciences, Kumamoto University, Japan.

They add, "These findings provide significant information on the management of lipid abnormalities in patients with type 2 diabetes comorbid with hypertriglyceridemia."

Dr Araki told *Medscape Medical News* that pemafibrate was approved for the treatment of hyperlipidemia in Japan in 2017.

Kowa Company is now conducting the global PROMINENT trial, which will assess the impact of pemafibrate on cardiovascular outcomes in patients with type 2 diabetes and atherogenic dyslipidemia. Dr Araki said that, if positive, the results will be used as the basis for approval applications for the drug around the world.

24-Week Data in Patients With Type 2 Diabetes on Oral Agents

The current placebo-controlled, randomized, double-blind, parallel-group phase 3 study was conducted at 34 centers in Japan in patients with type 2 diabetes and comorbid hypertriglyceridemia. Participants were required to be aged ≥ 20 years and, for women, postmenopausal, with HbA_{1c} ≥ 6.2% and fasting serum triglyceride levels ≥ 150 mg/dL on two consecutive visits. In addition, patients had to have completed ≥ 12 weeks of dietary or exercise guidance.

Individuals with serum triglyceride levels > 1000 mg/dL and those with poorly controlled diabetes, thyroid disorders, or hypertension, or who required treatment with insulin, amongst several other criteria, were excluded.

In total, 167 patients were randomized to placebo (n = 57), pemafibrate 0.2 mg/day (n = 54), or pemafibrate 0.4 mg/day for 24 weeks. Participants continued with treatment for another 28 weeks (during which the placebo group was switched to a 0.2-mg dose of pemafibrate), however, the current analysis focuses on the initial 24-week period.

The mean age of patients was 60.5 years, 72.9% were men, and mean body mass index was 25.9 kg/m^2.

The mean duration of diabetes was 5.7 years, and 44.6% of patients were receiving one or two antidiabetic agents. Statins were also prescribed in 39.2% of patients. There were no noteworthy differences between treatment groups.

Baseline fasting mean serum triglycerides were 284.3 mg/dL in the placebo group, 240.3 mg/dL in the 0.2-mg/day pemafibrate group, and 260.4 mg/dL in the 0.4-mg/day pemafibrate group.

At 24 weeks, the percentage change in fasting serum triglyceride levels was -10.8% for placebo ($P < .01$ vs baseline), -44.3% for the 0.2-mg dose ($P < .001$), and 45.1% for the 0.4-mg dose ($P < .001$), respectively, and both pemafibrate groups had significant reductions vs placebo ($p<0.001$).

Furthermore, the pemafibrate groups showed significant reductions in non-HDL cholesterol, remnant lipoprotein cholesterol, and some apolipoprotein measures, as well as significant increases in HDL cholesterol.

However, LDL cholesterol levels did not significantly change in patients receiving pemafibrate.

Patients treated with pemafibrate 0.2 mg/day experienced significant reductions in HOMA insulin resistance scores vs placebo. The drug was also associated with significant increases in levels of fibroblast growth factor 21.

There were, however, no significant changes in fasting plasma glucose, fasting insulin, glycoalbumin, or HbA_{1c} associated with pemafibrate.

In terms of safety, there were no significant differences in the rate of any adverse events between the placebo and pemafibrate groups.

"Pemafibrate significantly ameliorated lipid abnormalities and was well tolerated in patients with type 2 diabetes comorbid with hypertriglyceridemia," the researchers conclude.

Pemafibrate Promising for High Triglycerides, Low HDL

Discussing the findings, Dr Araki said that, although pemafibrate did not improve LDL cholesterol levels, this "can be basically managed with statins and, hence, pemafibrate would be a promising treatment option to manage elevated triglyceride and reduced HDL cholesterol, which are highlighted as residual lipid risks beyond LDL cholesterol."

He added that it "is not clear at this point" why insulin resistance was significantly improved with the drug but that there was no corresponding improvement in glycemic control, as assessed by HbA_{1c} levels.

"Because pemafibrate is not an antidiabetic agent, marked improvement of glycemic control may not be expected, but at least pemafibrate did not show adverse effects on glycemic control."

He added that "accumulation of real-world data" and results in non-Japanese patients are needed "to confirm the efficacy and safety of pemafibrate in patients with type 2 diabetes."

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