Saroglitazar Improves Liver Health in Those With Fatty Liver and NASH

The treatment improved ALT liver enzymes, fat accumulation in the liver, insulin resistance and blood lipid levels.

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Saroglitazar magnesium improved various measures of liver health in a recent study of individuals with non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH).

Samer Gawrieh, MD, of Indiana University, presented findings from the prospective, multicenter, double-blind, Phase II randomized EVIDENCES IV trial of saroglitazar at The Liver Meeting, the Annual Meeting of the American Association for the Study of Liver Diseases, in Boston this month.

Saroglitazar is a novel non-thiazolidinedione, non-fibric acid dual PPAR alpha-gamma agonist that plays a role in the oxidation of free fatty acids and reduces the production of triglycerides in the liver, thereby improving insulin sensitivity and glucose metabolism.

The study could include adults (ages 18 to 75) with a body mass index (BMI) of at least 25 (meaning they were at least overweight, if not obese), a documented diagnosis of NAFLD within 24 months of the study's screening period and a liver biopsy showing NASH or simple steatosis (accumulation of fat in the liver).

The study excluded men who had more than three drinks daily and women who had more than two drinks daily. It also excluded those who had had more than a 5% change in weight within the previous three months, had started vitamin E at a dose greater than 100 international units per day during the previous three months, were taking thiazolidinedione medications, changed doses of statins or fibrates within the previous three months, had cirrhosis or had a history of other chronic liver diseases.

The study screened partcipants for NAFLD and NASH during a four-week period during which they had two visits. Those included in the study needed to have an ALT liver enzyme level of at least 50 units per liter at both visits with no more than a 30% variation between these two levels.

At the end of the screening period, 106 people were randomized into four groups to receive 1 milligram (26 people), 2 mg (26 people) or 4 mg (27 people) of saroglitazar or a placebo (28 people) for 16 weeks.

All those in the 1 mg and 4 mg treatment groups completed the study and were included in the final analysis. In the 2 mg treatment group, five people did not complete the study, including one who did not adhere to the regimen, one who withdrew from the study and three who stopped treatment because of adverse health events. This meant that there were 25 people from this group in the study's safety analysis and 23 people in the overall analysis. In the placebo group, three people did not complete the study, including one who was lost to follow-up and two who withdrew from the trial. Everyone from this group was still included in the overall analysis.

In the placebo, 1 mg, 2 mg and 4 mg groups, the changes in ALT liver enzymes during the study were an increase of 4.2% and decreases of 27.3%, 33.2% and 44.4%, respectively. The difference in these shifts between the placebo group and the saroglitazar treatment groups was statistically significant, meaning it was unlikely to be the result of chance.

Hereafter, the difference in the figures cited for the placebo group compared with those cited for the saroglitazar treatment groups is statistically significant unless otherwise noted. If any of the treatment groups are not mentioned, it means that there was no significant difference in these groups with respect to the outcome in question.

The proportion of participants in the placebo, 1 mg, 2 mg and 4 mg groups who had at least a 25% reduction in their ALT levels was 17.9%, 73.1%, 73.9% and 70.4%, respectively. The proportion that had at least a 50% reduction in ALT was 3.57% in the placebo group and 51.9% in the 4 mg group.

The placebo group experienced a 0.3% decline in liver fat content while the 4 mg group experienced a 4.2% decline. The proportion of these two groups who experienced more than a 20% reduction in liver fat content was 16.0% and 48.2%, respectively. The proportion who experienced more than a 30% decline was 8.0% and 40.7%.

Fasting insulin declined by an average of 6.1 and 13.8 microunits per milliliter in the placebo and 4 mg groups, respectively. The treatment had no significant association with changes in fasting glucose or HbAlc levels.

Triglycerides increased by 1.9 mg per deciliter in the placebo group and declined by 29.6 mg per dl in the 4 mg group. HDL cholesterol declined by 0.3% in the placebo group and increased by 10.9% in the 4 mg group. The treatment had no significant impact on total cholesterol or LDL cholesterol.

Those in the placebo group experienced a 22.0% increase in their APRI score (an indicator of the likelihood of advanced fibrosis or cirrhosis), while the 1 mg, 2 mg and 4 mg groups experienced a 19.4%, 23.2% and 27.6% decline in their scores, respectively. Enhanced liver fibrosis test scores rose by 3.9% in the placebo group and declined by 2.5% in the 4 mg group. The treatment had no significant impact on CK-18 (a NASH biomarker) or liver stiffness.

Treatment with saroglitazar had no significant effect on creatinine levels or BMI.

Saroglitazar was generally well tolerated. Two people experienced serious adverse health events, both of which were considered unrelated to treatment. One person who discontinued treatment did so for a reason deemed probably related to treatment: a mild rash on the abdomen and neck.

There were no deaths or cardiovascular health events in the study.

“Saroglitazar magnesium 4 mg significantly improved serum ALT, hepatic steatosis, insulin resistance and [irregular blood lipids] in patients with NAFLD/NASH and elevated baseline ALT,” the study authors concluded.

To read the conference abstract, click here.
