MSDC-0602K Shows Promise for People With NASH

Well-tolerated insulin sensitizer may play a role in the treatment of fatty liver disease.

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MSDC-0602K, an experimental insulin sensitizer, led to improved glucose metabolism and lower liver enzyme levels in people with non-alcoholic steatohepatitis (NASH), though it did not significantly improve liver biopsy findings, according to a report presented at The Liver Meeting, the annual meeting of the American Association for the Study of Liver Diseases, this month in Boston.

NASH and its less severe form, non-alcoholic fatty liver disease (NAFLD), are responsible for a growing proportion of advanced liver disease. The buildup of fat in the liver triggers inflammation, which over time can lead to fibrosis (buildup of scar tissue), cirrhosis (severe scarring) and liver cancer.

There are currently no effective approved medical therapies for NASH, and management relies on lifestyle changes, such as weight loss. The past few years have witnessed the failure of several experimental NAFLD/NASH therapies in clinical trials after they appeared promising based on biomarkers in earlier studies.

Fatty liver disease is increasingly recognized as a manifestation of metabolic syndrome, a cluster of conditions that include elevated blood glucose, abnormal blood fat levels, excessive abdominal fat and high blood pressure. Researchers have therefore attempted to treat NAFLD/NASH by addressing related manifestations such as insulin resistance.

Stephen Harrison, MD, of Pinnacle Clinical Research in San Antonio, presented results from a study of MSDC-0602K, a novel insulin-sensitizing drug, in people with NASH. The findings were also published in the Journal of Hepatology.

A drug of this type currently approved for type 2 diabetes, pioglitazone (available as the brand-name drug Actos as well as generics), can have a beneficial effect on fatty liver disease, but side effects such as swelling and bone loss limit its use. These harmful effects are thought to occur because the drug activates a receptor known as PPAR-gamma that regulates glucose metabolism. MSDC-0602K, from Cirius Therapeutics, is a second-generation insulin sensitizer with minimal PPAR-gamma binding.

The Phase IIb EMMINENCE trial included 392 people with biopsy-confirmed NASH and mild to advanced fibrosis. They had NAFLD activity scores of 4 or higher, with a score of at least 1 for each component of the composite score, including steatosis (fat accumulation), liver cell ballooning and inflammation.

Nearly 60% were women, and the median age was 56. About 40% had mild fibrosis (stage F1), nearly 60% had moderate or severe fibrosis (F2 or F3) and just over half had type 2 diabetes.

Study participants were randomly assigned to receive one of three oral doses of MSDC-0602K (62.5, 125 or 250 milligrams) or a placebo. After 12 weeks, they underwent another liver biopsy.

As expected given its mechanism of action, glucose metabolism and insulin resistance improved significantly in those treated with the two higher doses of MSDC-0602K.

People who received the higher doses also showed improvement in levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP), enzymes that can signal liver damage and inflammation. A third of those taking the highest dose of MSDC-0602K saw their ALT level fall into the normal range, compared with just 6.8% of those taking the placebo.

However, the study did not meet its primary aim of showing that MSDC-0602K improved liver health as shown on the second biopsy, defined as at least a 2-point decrease in the NAFLD activity score with no worsening of fibrosis. This occurred in 29.7%, 29.8%, 32.9% and 39.5% of participants in the placebo, 62.5 mg, 125 mg, and 250 mg dose groups, respectively. This difference did not quite reach the threshold for statistical significance, meaning it could have been driven by chance. Harrison noted that for unknown reasons, the response rate in the placebo group was higher than that typically seen in other NASH studies.

A post hoc, or unplanned, analysis using a method Harrison said was closer to the industry standard did show that the 250 mg dose of MSDC-0602K was significantly more likely than the placebo to lead to NASH resolution, with at least a 2-point score improvement and no worsening of fibrosis (26.7% versus 13.8%, respectively).

MSDC-0602K was generally safe and well tolerated. Overall adverse events and serious adverse events—including side effects such as swelling and bone fractures that are a concern with this drug class—occurred with similar frequency across all groups. More people actually stopped treatment because of adverse events in the placebo group. However, weight gain was greater among those taking the study drug (median +2.28 kilogram in the 250 mg group versus -0.54 kg in the placebo group).

“Insulin resistance is a cause of both diabetes and NAFLD, which lead to increased cardiovascular risk; therefore, a safe compound that increases a body’s sensitivity to insulin has the potential to address the underlying pathophysiology of both diseases,” Cirius chief medical officer Howard Dittrich, MD, said in a company press release. “These results indicate that MSDC-0602K can be dosed to full insulin-sensitizing pharmacology without dose-limiting side effects, with the greatest

effects in patients with more severe liver injury and poorer glycemic control, a group who have an elevated risk for adverse cardiovascular outcomes.”

Click here to read the study abstract.
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