Anti-inflammatory Drug May Improve Fibrosis

Cenicriviroc, a drug that blocks receptors on immune cells, reduced fibrosis in people with fatty liver disease.

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Cenicriviroc, a drug that blocks both CCR5 and CCR2 receptors on immune cells, may be a potential treatment for liver fibrosis in people with severe fatty liver disease, according to the results of a Phase II study.

Published in the August 17 online edition of Hepatology, the study showed that while cenicriviroc did not decrease liver steatosis (fat accumulation) or liver inflammation in patients with non-alcoholic steatohepatitis (NASH), it did reduce liver fibrosis significantly more than a placebo did.

Fatty liver disease, often associated with obesity and metabolic syndrome, is a leading cause of liver problems in the United States. Non-alcoholic fatty liver disease (NAFLD) and its more severe form, NASH, refer to the buildup of fat in the liver in people who do not drink heavily. Over time, fat accumulation and the accompanying inflammation and buildup of scar tissue (fibrosis and cirrhosis) can interfere with normal liver function and lead to liver cancer. To date there are no good treatments for NAFLD, but several are under study.

Cenicriviroc, developed by Tobira Therapeutics (now owned by Allergan), blocks CCR5, one of the two co-receptors HIV uses to enter T cells. It was previously studied as an HIV treatment, with moderately promising results. It also blocks CCR2, which mobilizes monocytes and other cells during an immune response and therefore has anti-inflammatory properties.

Scott Friedman of the Icahn School of Medicine at Mount Sinai in New York and colleagues conducted a study to evaluate cenicriviroc for the treatment of people with NASH accompanied by liver fibrosis.

The Phase IIb CENTAUR study included 289 people with NASH and mild to severe liver fibrosis in the United States, Europe, Australia and Hong Kong. Just over half were men, the average age was 54, nearly 90 percent were white and 16 percent were Latino (a group that appears more likely to develop fatty liver disease).

NASH was defined as having a NAFLD activity score of 4 or higher. This score takes into account the presence of large fat droplets in liver cells, inflammation of structures in the liver called lobules and “ballooning” of liver cells. Almost all participants were overweight with signs of metabolic syndrome, half had type 2 diabetes and 38 percent had advanced liver fibrosis at the start of the study.

Study participants were randomly assigned to take 150 milligrams of cenicriviroc or a placebo once daily for a year. The main study endpoint was the proportion of people who had at least a two-point improvement in NAFLD activity scores with no worsening of fibrosis. Other outcomes included improvement in steatohepatitis (fat accumulation with inflammation) and fibrosis, as well as changes in liver biopsies, liver “stiffness” as assessed by FibroScan imaging and biomarkers of systemic (whole body) inflammation.

After one year, 16 percent of people in the cenicriviroc group and 19 percent of those in the placebo group had at least a two-point NAFLD score improvement without worsening fibrosis. These proportions were statistically similar, so the study did not meet its primary endpoint. Complete resolution of steatohepatitis was also about equally likely in the two groups, 8 percent and 6 percent, respectively.

However, more people in the cenicriviroc group than in the placebo group had at least a one-point improvement in fibrosis with no worsening of steatohepatitis: 20 percent versus 10 percent, respectively. This difference was statistically significant, meaning it probably was not due to chance. The researchers saw the greatest improvement in people who started out with the worst liver inflammation and fibrosis at baseline.

People taking cenicriviroc showed greater decreases in systemic inflammation biomarkers such as high-sensitivity C-reactive protein and interleukin-6, though there was no significant change in lobule inflammation. Biopsies showed a reduction in collagen, a protein that makes up fibrosis scar tissue.

Cenicriviroc was generally safe and well tolerated, with similar adverse events in both groups, and serious laboratory abnormalities were uncommon.

"After one year of cenicriviroc treatment, twice as many subjects achieved improvement in fibrosis and no worsening of steatohepatitis compared with placebo," the study authors concluded.

The researchers noted that worse liver fibrosis is the strongest risk factor for liver-related and overall mortality among people with NAFLD and NASH, so reducing fibrosis “is expected to improve the long-term clinical outcomes” for these patients.

The results of CENTAUR are “potentially paradigm-shifting,” the authors suggested, because they challenge the common assumption that therapies for NASH can work only by improving underlying metabolic disease, instead showing the beneficial effects of directly targeting inflammation and fibrosis.

The Phase III AURORA study of cenicriviroc to treat liver fibrosis in people with NASH is currently enrolling.

Click here to read the study abstract.

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