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NAFLD

# Obeticholic acid for the treatment of fatty liver disease—NASH no more?

The quest for effective agents to treat NASH has moved a step forward with the demonstration that treatment with obeticholic acid can improve the histological features of the disease, with reported antifibrotic activity.

NAFLD, which encompasses a spectrum of disease from simple steatosis to NASH, fibrosis and cirrhosis, is becoming increasingly common worldwide. With no approved agents for NAFLD or NASH currently available, NAFLD is predicted to become the primary cause of end-stage liver disease and need for liver transplantation ahead of viral hepatitis. NASH in particular is a more progressive form of NAFLD, and NASH progresses to cirrhosis in around one-fifth of patients.

Obeticholic acid is a synthetic analogue of the natural bile acid chenodeoxycholic acid and is a potent activator of the farnesoid X receptor (FXR, also known as bile acid receptor). Existing evidence has shown that bile acids (particularly when bound to FXR) are modulators of metabolism and insulin sensitivity. "Animal data showed a beneficial effect of FXR ligands for treating or preventing fatty liver disease, but the human data was very limited," explains first author Brent Neuschwander-Tetri.

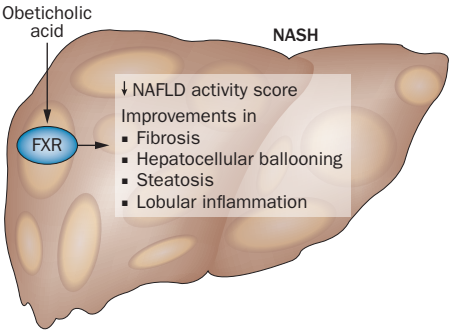
In a new study published in *The Lancet*, Neuschwander-Tetri and colleagues report the results from a multicentre, double-blind, placebo-controlled, parallel group, randomized controlled trial to assess the efficacy of obeticholic acid for the treatment of NASH. Conducted across several medical centres in the USA, patients with biopsy-proven NASH but without cirrhosis were enrolled to the trial and randomly allocated to receive either 25 mg obeticholic acid daily ($n = 141$) or placebo ($n = 142$) for 72 weeks. Crucially, more than 50% of each study group were patients with concomitant diabetes, which is known to increase the risk of progression of liver disease.

In the primary intention-to-treat analysis, 50 of 110 (45%) patients in the obeticholic acid group had improved liver histology compared with only 23 of 109 (21%) in the placebo group (relative risk 1.9, 95% CI 1.3–2.8, $P = 0.002$); a 2-point or more improvement in the NAFLD activity score was recorded without worsening of fibrosis. Compared with controls, more patients receiving obeticholic acid had improvements in steatosis, hepatocellular ballooning, lobular inflammation and fibrosis. However, despite these improvements the proportion of patients with complete resolution of NASH did not differ between those receiving placebo and those receiving obeticholic acid.

In terms of nonhistological secondary outcomes, substantial reductions in serum levels of liver enzymes (alanine aminotransferase and aspartate aminotransferase) were observed over the first 36 weeks and were sustained for the duration of treatment. Once obeticholic acid treatment was stopped, there was no longer any difference in liver enzyme levels between the study groups.

Importantly, treatment with obeticholic acid was associated with increased concentrations of total serum cholesterol and LDL cholesterol, and decreased concentrations of HDL cholesterol; these changes developed within 12 weeks of the start of treatment, decreased in magnitude during treatment and were not sustained upon treatment discontinuation. Clinical adverse effects were reported, with 23% of the obeticholic acid group developing pruritis compared with only 9% of the placebo group. Moreover, pruritus was more severe in the obeticholic acid group, with some participants requiring antiprurtitic medications or withholding of treatment, and one patient discontinued treatment altogether.

"This is the largest and most comprehensive trial to date for the treatment of NASH, and the results are very encouraging, adding to the mounting evidence that this disease might be treatable with medications," notes Scott Friedman who was not involved in the study, but has acted as a consultant for Intercept Pharmaceuticals (who developed the drug). "Larger, longer phase III trials will be essential to determine the long-term safety and efficacy of this agent," he cautions, although he is hopeful that new effective therapeutic agents for NASH will ultimately slow disease progression.




Treatment with obeticholic acid improves NASH.

Neuschwander-Tetri echoes these thoughts. "What is needed now is a phase III trial that includes a larger number of patients and more attention focused on emergent changes in serum lipids and how these changes can be managed; improvement in liver fibrosis was also seen ... and future trials would ideally be longer in duration to determine how significant these changes are." He adds that reversal of fibrosis would be welcome given that progressive fibrosis can ultimately lead to cirrhosis and death from liver failure or liver cancer in patients with NASH.

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**Original article** Neuschwander-Tetri, B. A. *et al.* Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. *Lancet* doi:10.1016/S0140-6737(14)61933-4