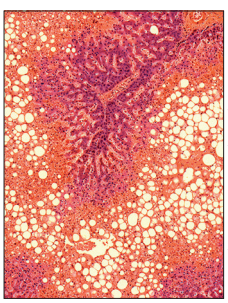
Obeticholic acid: towards first approval for NASH



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Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease, affecting about a quarter of the global population.[1] Non-alcoholic steatohepatitis (NASH), the progressive form of NAFLD, is characterised by hepatic inflammation with balloon degeneration, and portends progression to fibrosis and cirrhosis. Some people with NASH can develop hepatocellular carcinoma, even those who do not have cirrhosis. NASH is a multisystem disease; although it is on course to become the main indication for liver transplantation,[2] it also increases the risk of type 2 diabetes and cardiovascular disease.[3,4]

The current standard of care for fatty liver disease includes lifestyle modification that focuses on weight loss and exercise.[5] Although about 8–10% reduction in bodyweight reverses not only steatosis but also fibrosis, most patients fail to achieve and, more importantly, maintain this degree of weight loss. No pharmacological treatment has been licensed for the treatment of NASH, and thus it is not surprising that the drug development pipeline exploded with more than 300 agents in clinical trials in 2018.[6] The market for approved drugs for NASH is estimated to be worth US$20–35 billion per year by 2025.

Accumulating evidence from multiple longitudinal studies suggests that patients with intermediate and advanced fibrosis, but not other histological features of NASH, are at greatest risk of overall and disease-specific mortality.[7] Hence, this subgroup has been identified as the principal target population for investigational drugs in current phase 3 trials. For all current trials, histological features as surrogates of liver-related outcomes have been accepted by the regulatory authorities for accelerated or conditional approval.[8]

In *The Lancet*, Zobair Younossi and colleagues[9] report findings of the 18-month interim analysis of a phase 3 study that evaluated the safety and efficacy of two doses of obeticholic acid, 10 mg or 25 mg daily, relative to placebo in 931 patients (539 [58%] females) with biopsy-proven stage F2–F3 fibrosis. Obeticholic acid is a synthetically modified analogue of chenodeoxycholic acid and acts as a potent agonist of farnesoid X receptor, which is a bile-acid binding transcription factor with a master regulatory role in glucose and lipid metabolism, and inflammation.[10]

The primary outcome of the study was defined as NASH resolution with no worsening of fibrosis or fibrosis improvement by at least one stage without worsening of NASH. One of these outcomes (improvement of fibrosis) was achieved in 71 (23%) of 308 patients in the obeticholic acid 25 mg group compared with 37 (12%) of 311 patients in the placebo group (p=0·0002). The study is ongoing with patients expected to have follow-up for at least 4 years to evaluate the long-term clinical benefits of treatment.

This study is a pivotal step for the development of drugs to treat NASH and is likely to be the first to receive regulatory approval. The strengths include the stringent protocol adherence and the central assessment of all biopsies by two designated pathologists.

Although the study has yielded encouraging results and is the first phase 3 trial in NASH to show a beneficial treatment effect, some questions remain. The effect of obeticholic acid on the co-primary endpoint of NASH resolution was not achieved. Furthermore, patients receiving obeticholic acid were more likely to use a statin during the study than those receiving placebo, raising the question as to whether the observed reduction in fibrosis stage with obeticholic acid might at least partly be attributed to a statin effect. However, the authors note that no clear pattern of fibrosis response by statin use was observed.

The safety and metabolic consequences of obeticholic acid also remain a concern. Obeticholic acid has several side-effects, including pruritus and elevated LDL cholesterol levels. The deaths of 19 patients treated with obeticholic acid for primary biliary cholangitis, its current approved indication, have also raised concerns about safety post marketing, but it should be noted that the deaths are likely to be attributable to inappropriate dosing.[11] In particular, the effect of obeticholic acid on the lipid profile is of particular relevance because patients with NAFLD exhibit a substantial increase in the risk of cardiovascular disease, the main cause of death in this population.[3] A recent modelling study suggests that moderate increases in LDL cholesterol in patients with biopsy-proven NAFLD would result in worsening of cardiovascular disease risk in about 7·8% of all patients without a history of cardiovascular disease, which might blunt the beneficial effects from improved liver fibrosis.[12]

In this study,[9] LDL cholesterol increased by approximately 20% from baseline levels, which is similar to other reports.[13,14] However, the increase in LDL cholesterol was suggested to be transient and controlled with statins, as it returned to baseline levels at month 6 and baseline levels were sustained through month 18. Therefore, LDL cholesterol would need to be monitored and managed as required. Notably, studies of the combination of obeticholic acid with lipid-lowering agents are ongoing.

In summary, the study by Younossi and colleagues[9] has introduced obeticholic acid as a treatment option for patients with NASH. Final results will hopefully clarify effects of obeticholic acid on liver and cardiovascular clinical outcomes. If approved, in the long term, safety and efficacy must be assessed in real-world populations, especially with regard to tolerability and cardiovascular risk.

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We declare no competing interests.

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