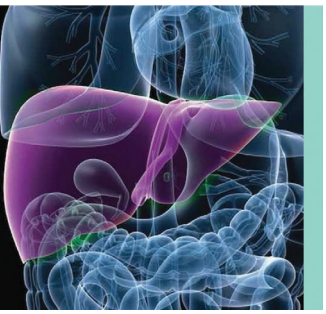

Obeticholic Acid for the Treatment of Nonalcoholic Steatohepatitis

Vlad Ratziu, M.D., Ph.D.

Obeticholic acid (OCA) is a synthetic analogue of chenodeoxycholic acid designed to have a much stronger, nanomolar potency as a farnesoid X receptor agonist than the native bile acid.[1] Because of its biliary structure, OCA is conjugated in the intestine and thus undergoes an enterohepatic cycle. Farnesoid X receptor (FXR) agonism by OCA takes place both in the ileal epithelial cell (where it induces secretion of fibroblast growth factor 19 (FGF19) in the circulation) and in the hepatocyte. The concerted action of FGF19 acting in the hepatocyte through its cognate receptor and of direct hepatocyte agonism of FXR results in a tight control and downregulation of bile acid synthesis from cholesterol.[2,3] However, FXR agonism in the hepatocytes also has other effects: mostly an inhibition of lipogenesis, inhibition of neoglycogenesis, as well as anti-inflammatory actions.[3] The antifibrotic actions of FXR agonism do not seem to be exerted directly on stellate cells but are rather indirect, by reducing inflammatory mediators in macrophages and sinusoidal endothelial cells.[4] OCA, which is approved for patients with primary biliary cholangitis refractory or intolerant to ursodeoxycholic acid, has also been tested successfully in nonalcoholic steatohepatitis (NASH). Remarkably, it is so far the only drug for which a large phase 3 trial, the REGENERATE trial, has confirmed, at an interim analysis,[5] the results of a phase 2b smaller trial with histological endpoints.[6]

REGENERATE is a large international trial that randomized close to 2500 patients to receive 25 mg OCA daily, 10 mg OCA daily, or placebo. All patients had to have active NASH (measured by NAS, a histological composite score of steatosis, inflammation, and hepatocyte ballooning, of 4 or more) with moderate/advanced fibrosis (stage 2 or 3 fibrosis) on a recent biopsy, read centrally. The interim analysis, designed to study efficacy on surrogate histological endpoints, was performed after 18 months of therapy. The study is ongoing for several more years (up to 5 years) to evaluate whether the differences observed in histological surrogates translate into differences in clinical outcomes between active arm(s) and the placebo arm. The clinical outcomes are defined as a standard composite of survival, liver-related mortality, and complications of cirrhosis (i.e., decompensation events), including hepatocellular carcinoma with the important addition of progression to cirrhosis. Particularly important is that progression to cirrhosis, even if documented by histology only, is considered a clinical outcome; given the slow course

Abbreviations: ALT, alanine aminotransferase; FXR, farnesoid X receptor; NASH, nonalcoholic steatohepatitis; OCA, obeticholic acid.

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of the disease, most of the expected events will thus be progression to cirrhosis rather than death or purely clinical complications. Clinical outcomes are adjudicated by an independent outcome committee.

The interim analysis was performed on the first 931 patients and has shown that more patients treated with 25 mg OCA achieved a one-stage reversal of fibrosis without worsening of NASH than those treated with the lower dose of 10 mg or with placebo: 23% versus 18% versus 12% ($P = 0.0002$ and $P = 0.045$, respectively, versus placebo, intention-to-treat analysis). When considering fibrosis alone, 2.9 times as many patients treated with OCA 25 mg improved versus worsened, while this ratio was close to 1 in patients receiving placebo (Fig. 1). Interestingly, the antifibrotic effect was significant both in patients with stage 2 and in those with stage 3 fibrosis; it was also significant regardless of the diabetes status. A two-stage improvement in fibrosis was seen in 10% of the OCA 25 mg arm participants versus only 5% of those in the placebo arm (intention-to-treat analysis). Particularly relevant is the difference in the rate of progression to cirrhosis: 6.6% in OCA 25 mg versus 10% in placebo. This difference is expected to get bigger with prolonged duration of therapy and increased sample size. This result is highly relevant because progression to cirrhosis is expected to be the major contributor to clinical outcomes.

Unfortunately, the study was not formally positive for the second primary outcome, which was resolution of NASH without worsening of fibrosis: 8%, 11%, and 12% in the placebo, 10 mg, and 25 mg arms, respectively. There is reason to believe, however, that OCA does contribute to the resolution of NASH. First, when looking at individual lesions that define steatohepatitis, such as lobular inflammation and hepatocyte ballooning, which were secondary endpoints, OCA was statistically superior to placebo. Second, when defining resolution of NASH not based on a score but an overall pathologist assessment, the difference was again significant. Third, when expanding the population to an additional 287 stage 1 patients (included for safety and tolerability assessments), the same significant result was achieved. It is unclear why differences in definitions of NASH resolution have such an impact on between-group differences, other than to say that the score-based definition is more stringent than the pathologist overall assessment reading.

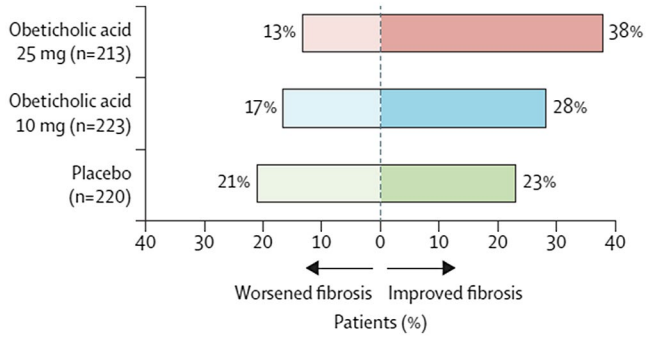

FIG 1 The proportion of patients with improved or worsened fibrosis by at least one stage in 656 patients of the per-protocol population with available fibrosis stage data at month 18 or the end of treatment. Reproduced with permission from *Lancet*.[5] Copyright 2019, Elsevier Limited.

The phase global 3 REGENERATE trial has thus confirmed histological improvement in patients with active and fibrotic NASH, which was first documented in the much smaller phase 2b FLINT trial performed in eight centers only.[6] This histological efficacy was strongly corroborated by biochemical improvement: 66% of OCA-treated patients with elevated alanine aminotransferase (ALT) at baseline normalized their ALT levels compared with 36% of placebo-treated patients. Importantly, the reduction in ALT was more marked in histological responders than in nonresponders.

The adverse events and tolerability issues with OCA are now well characterized and deserve specific guidance for management. Both REGENERATE and the earlier FLINT trials have confirmed an increase in low-density lipoprotein (2.8 mg/dL for 25 mg OCA in REGENERATE versus –3 mg/dL in the placebo arm), which occurs early, in the first month of therapy, and in virtually every treated patient. This increase can be reversed to baseline levels by introducing or reinforcing statins. It is unclear whether the increase concerns the most atherogenic low-density lipoprotein subparticles[7,8] and whether this depends on duration of exposure. Other, milder changes are a decrease in high-density lipoprotein and in serum triglycerides. It remains to be determined whether these lipid changes result in a longer-term shift in risk category for cardiovascular events. Short-term exposure to OCA in morbidly obese patients results in an increase in bile lithogenicity,[9] and the REGENERATE trial reported an increase in gallstones in the 25 mg arm (19 patients) versus placebo (2 patients). Although it is unknown how many of these gallstones were present at baseline, the trial did not document an increase in biliary pancreatitis. Finally, there have been reports of hepatic decompensation induced by OCA in patients with primary biliary cholangitis and primary sclerosing cholangitis.[10] There is little evidence,

if any, of hepatic toxicity in patients with NASH, including those with compensated cirrhosis.

The most concerning and immediate tolerability issue with OCA is pruritus. Pruritus is dose dependent and can occur or persist throughout the whole period of therapy, as shown in the REGENERATE trial. Fifty-one percent of patients in the 25 mg arm and 28% of those in the 10 mg arm experienced pruritus versus an unexpectedly high proportion of 19% in the placebo arm, probably because of the particular focus devoted to this side effect when interrogating trial participants. Severe pruritus was rare but occasionally led to trial discontinuation. Based on earlier, 6-week clamp studies in patients with diabetes that documented a dose-related increase in insulin sensitivity,[11] treatment with OCA was expected to improve glycemic parameters. Unfortunately, the REGENERATE trials did not show such benefit but rather a minimal increase in hemoglobin A1c in participants with diabetes.

Taken together, the FLINT and REGENERATE trials are a unique example of a pharmacological agent with confirmed histological antifibrotic benefit in patients with NASH. Other phase 3 trials are underway in an attempt to confirm histological benefit proven or suggested in phase 2 trials.[12-15] The challenge for all these phase 3 trials will be to demonstrate that the histological improvement at the interim analysis will translate into longer-term clinical improvement.

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