Hyperlipidemia with obeticholic acid in the treatment of nonalcoholic steatohepatitis

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Nonalcoholic fatty liver disease (NAFLD) is characterized by the presence of hepatic steatosis in the absence of a secondary etiology for fat accumulation (1). Over the last three decades, the prevalence of NAFLD has increased in the United States, with the most recent estimate to be at 31% of the US population (2). This rise coincides with the increased prevalence of obesity and diabetes mellitus, both independent risk factors for NAFLD (2). The presence of NAFLD is worldwide, with the global prevalence estimated at 25% (3). Nonalcoholic steatohepatitis (NASH) is a severe form of NAFLD characterized by hepatocyte injury, inflammation, and fibrosis (1). Progressive disease can eventually lead to cirrhosis and hepatocellular carcinoma. As such, NASH remains as the second leading indication for liver transplantation in males in the United States (4,5), and the first leading indication in females (5).

The mainstay of treatment for NASH currently includes aggressive lifestyle interventions such weight loss, diet, and physical activity (1,6,7). A prospective study of 293 patients with biopsy- proven NASH noted that 5% body weight loss was associated with steatosis improvement, while 7% weight body weight loss showed improvement in NAFLD Activity Score (NAS) (6). However, the maximum benefit of steatohepatitis resolution was seen in patients who had at least 10% body weight loss. In terms of dietary management, a 30% decrease in calorie consumption has been shown to decrease intrahepatic lipid levels in overweight and obese patients (8). Improvement in liver fat and insulin resistance have been seen in NAFLD patients with type 2 diabetes placed on a high protein diet alone (9).

Patients on either an ad libitum low fat or a Mediterranean diet have also been observed to have improvement in hepatic triglyceride content, despite only a mild weight loss (2.1–2.3%) from their baseline (10).

There are limited pharmacological options currently recommended for NAFLD. The most recent American Association for the Study of Liver Disease (AASLD) and European treatment guidelines suggest that vitamin E in non-diabetic patients and Pioglitazone may be considered (1,11). Vitamin E has been observed to have beneficial effects on hepatic steatosis in several studies (12-14); however, these studies were generally small and sometimes used vitamin E in combination with other therapies. Pioglitazone is a thiazolidinedione, which is an agonist for peroxisome proliferator activated receptor. Pioglitazone is used in diabetic patients and alters insulin sensitivity and lipid metabolism. Treatment with pioglitazone in NASH patients with and without diabetes has shown improvement in both histology and metabolic parameters (13,15,16), although increased weight gain has been an unwanted side effect in most patients (16). Given these limited options, future pharmacological therapies are being explored.

Obeticholic acid (OCA) is a selective farnesoid X receptor (FXR) agonist that was shown to improve histological features in patients with NASH in the multicenter, randomized, placebo-controlled FLINT trial (17). However, during the study, the OCA-treated group was found to have a significant elevation in lipid levels and treatment was discontinued in some affected patients. In a recent issue of *Journal of Hepatology*, Siddiqui *et al.* investigated the

role that OCA had on atherogenic lipoproteins (18). The study looked at the data of 196 patients (99 OCA and 97 placebo) from the FLINT trial who had baseline and end-of-treatment (EOT) liver biopsies and obtained comprehensive lipoprotein profiles from these patients' stored serum. Patients in the OCA-treated group had significant elevations in total cholesterol and low-density lipoprotein (LDL) with a corresponding decrease in high-density lipoprotein (HDL) compared to placebo. Specifically, there was a change of +23%, +8%, and –7% of LDL, cholesterol, and HDL, respectively, at week 12 of therapy. Though total very LDL (VLDL) levels were unchanged, there was an overall decrease in large particle VLDL particles (>60 nm) and increase in small particles VLDL (29–42 nm). Interestingly, increases in LDL were driven primarily by large LDL particles (20.5–23 nm), which are thought to be less atherogenic (19). These increases from baseline were no longer present after treatment was stopped and data were collected at week 96. The findings suggest that OCA has a direct impact on circulating LDL, HDL, and cholesterol levels.

The effect of this finding on cardiovascular disease risk has not been determined. Though the authors did show similar patient baseline statin use in both arms, dosing and type of statin was not recorded. For this reason, a second trial was performed using a combination of OCA and statin therapy to prevent the elevation of lipids. The study, called Combination OCA aNd sTatins for the monitoring Of Lipids (CONTROL), was a randomized, double blind, placebo-controlled, phase 2 trial investigating the effects of 10 or 20 mg of atorvastatin therapy on patients treated with OCA (20). In this study, 84 biopsy confirmed NASH patients were randomized to either placebo, 5, 10, or 25 mg OCA therapy. Patients who were previously on statin therapy had their statins held for a 5-week washout period before the study began. Patients were then initiated on a standardized atorvastatin 10 mg dose at week 4 of the study and 20 mg dose at week 12. At week 4, an increase in LDL cholesterol (LDLc) and mean LDL particle concentration (LDLpc) was seen in the OCA group. Furthermore, the increase in LDLpc again appeared to be driven primarily by large LDL particles, which are less atherogenic (19). Similar increases were seen in total cholesterol, though no statistical difference was seen in triglycerides and VLDL at week 4.

After initiation of atorvastatin 10 mg, the concentrations of LDL, VLDL, cholesterol, and triglycerides were all below baseline levels after 4 weeks of statin treatment. This reduction was sustained to week 16 after increasing the atorvastatin dose to 20 mg per study protocol. HDL values decreased from baseline in the OCA-treated groups, however the mean value was greater than 40 mg/dL throughout the study. At the end of the study, 77 patients (92%) of the patients enrolled into a long-term safety extension phase of the study.

Siddiqui *et al.* provided a careful and needed analysis of OCA-associated dyslipidemia that was noted during the initial FLINT trial (18). Although the effect of this dyslipidemia on cardiovascular risk in these patients is unclear at this time, it is obviously of concern in a population where co-morbidities for heart disease already exist. The CONTROL trial has shown that atorvastatin therapy given at doses as low as 10 mg daily can effectively reverse the elevations in LDL and cholesterol that were caused by OCA. The use of statins as an adjunct to treat therapy-induced dyslipidemia may be standard in future studies. Indeed, statin therapy has improved the lipid changes associated with the FGF19 analogue, NGM282, in a recent study of NASH patients (21). Furthermore, because metabolic syndrome and hyperlipidemia are commonly found comorbidities in patients with NAFLD/NASH (2), many patients would already qualify for statin therapy based on the recent cardiovascular disease society guidelines (22).

Once approved by regulatory agencies for use in NASH patients in the US and European Union, OCA will require regular monitoring of lipid profiles and treatment with statin therapy as indicated. The recent phase 3 trial for OCA in patients with F1-F3 fibrosis stage NASH supports this strategy (23). 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 patients taking OCA 25 mg compared with 37 (12%) of 311 patients in the placebo group (P=0.0002). OCA was associated with a 4.0 mg/dL increase in LDL cholesterol from baseline and, not surprisingly, patients receiving OCA were more likely to use a statin during the study than those receiving placebo (23). It is unclear at this time what recommendations regulatory agencies will place on the label for the 25 mg dosage formulation of OCA regarding preemptive use of statins *vs.* careful monitoring and initiation of statins based on current guidelines.

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Footnote

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