

Treatment of Nonalcoholic Steatohepatitis by Obeticholic Acid: Current Status

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ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) is one of the major and prevalent liver diseases from the national and global perspectives. It appears that considerable numbers of the general population have been suffering from NAFLD. When a patient with NAFLD also exhibits inflammation of the liver, the condition is regarded as nonalcoholic steatohepatitis (NASH). Nonalcoholic steatohepatitis is a pathological entity that may progress to cirrhosis of the liver (LC) and hepatocellular carcinoma (HCC). It is acceptable by all that the health burden of NAFLD and NASH is tremendous. Due to the increased prevalence of these pathologies, extensive research has been conducted regarding pathogenesis, diagnostic tools, and staging of the diseases. However, adequate and approved pharmacotherapy for these pathologies is lacking.

The farnesoid receptor (FXR) is a bile acid-activated receptor. It regulates lipid, glucose, bile acid metabolism. Farnesoid receptor is also endowed with anti-inflammatory and anti-fibrotic properties on the liver. Obeticholic acid (OCA), a potent and selective FXR ligand, may become a promising molecule to combat NASH and advanced fibrosis.

The present review briefly discusses the current recommendation of NASH management with available pharmacological treatments. The scope of OCA with a focus on recent data of major randomized controlled trials (RCTs) is discussed. On the basis of current data and recent interim analysis, OCA seems to improve insulin resistance, steatohepatitis, levels of alanine transaminase (ALT) and fibrosis in NASH. Dose-related adverse effects like pruritus and dyslipidemia may limit its usage. Also, its usage may be restricted in patients with NASH cirrhosis. More adequately powered RCTs that would contain NASH patients with different and heterogeneous properties would be required to develop consensus about these issues. The safety profile of different doses of OCA needs to be established in these patients as well as there remain considerable queries about these.

Keywords: Farnesoid-X-receptor, Nonalcoholic fatty liver disease, Nonalcoholic steatohepatitis, Novel drug, Obeticholic acid.

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INTRODUCTION

Nonalcoholic fatty liver disease is a spectrum of liver disease involving 25% of the world population.¹ Most professional liver organizations have defined NAFLD as a pathological entity characterized by hepatic steatosis (HS), either by imaging or histology, and lack of secondary causes of hepatic fat accumulation.² Histological insights indicate two entities of NAFLD; nonalcoholic fatty liver (NAFL) and NASH. Nonalcoholic fatty liver is characterized by steatosis of $\geq 5\%$ of hepatocytes without evidence of hepatocellular injury comprised. On the contrary, NASH may be considered as steatosis $\geq 5\%$ of hepatocytes and hepatic inflammation with or without notable fibrosis. In parallel to the ongoing worldwide obesity pandemic and the rapid surge of other metabolic diseases like diabetes. Approximately a quarter of NAFLD patients are suffering from NASH and this can progress to liver cirrhosis at a rate of 25% in 7–8 years. This scenario can ultimately lead to decompensation at a rate of 25% in 10 years and HCC at the rate of approximately 1% per year.³

The prevalence of NAFLD in Bangladesh is around 33.86%, higher than the prevalence of NAFLD in Asia (27.4%).⁴ As of today, the main and reliable approach to the diagnosis of NAFLD is liver biopsy. Due to invasiveness, adverse effect profile, and lack of expert centers, alternative non-invasive quantification of HS, steatohepatitis prediction, and advanced fibrosis assessment are emerging worldwide. A few have been evaluated in day-to-day clinical practice despite extensive research, e.g., APRI, FIB-4, NAFLD fibrosis score.

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The NAFLD activity score (NAS), developed and proposed by the NASH Clinical Research Network (NASH-CRN), represents a viable histologic scoring system of NAFLD. A NAS score ≥ 4 is indicative of the diagnosis of NASH.⁵ In addition, the progression of hepatic fibrosis is usually related to the diagnosis of NASH. An increase in NAS score delineates more progressive liver fibrosis. So the reduction of the NAS score remains an effective endpoint in various researches of drug development.

Current pharmacological management for NASH has many limitations. Newer drug discovery and development targeting different molecular pathways and receptors are ongoing. FXN, a bile acid (BA) nuclear receptor, represents a target for innovation in the development of new and novel drugs for NASH.

CURRENT STATUS OF NASH MANAGEMENT

Lifestyle modification comprising diet, exercise, and weight loss are fundamental pillars of NASH management. A hypocaloric diet (500–1000 kcal energy defect), independent of nutrient composition in the diet is recommended. Moderate-intensity aerobic physical activities in the form of brisk walking are helpful. Also, cycling at the frequency of 150–200 minute/week in 3–5 sessions is usually preferred as physical activity that is recommended by European Association for the Study of the Liver (EASL).⁶

A factor like weight loss is the ultimate goal of a dietary restriction. Studies have shown that weight loss $\geq 7\%$ can result in NASH resolution, and weight loss $\geq 10\%$ can lead to fibrosis resolution.⁷

However, this is not an easy dome to achieve. Even if this can be achieved, sustaining of loss of weight becomes another challenge. Thus, the rebound of weight after loss of weight is a natural phenomenon in many cases. Various modes of bariatric surgery are effective for the management of obese NASH patients. But its scope is limited in real-life situations. The constraints are high cost, reduced access, increased morbidity, and mortality. Endoscopic Bariatric and Metabolic Therapy (EBMT) has created much interest within therapeutic endoscopists as a less invasive intervention to reduce obesity. But this has not been recommended as a regular event in most cases.

Pioglitazone and Vitamin E are considered standard pharmacotherapy by leading liver organizations and authorities. Some pilot studies, RCTs, and meta-analysis have shown their efficacy in improving steatosis, inflammation, ballooning, and reducing NASs.^{8–11} Despite these promising results, they could not stand the test of time. The longest duration of their use in NASH reported by different studies is 18 and 24 months for Pioglitazone and Vitamin E, respectively. Pioglitazone can be used in diabetic NASH patients, but vitamin E has been studied in only non-diabetic NASH patients. Neither of them has been approved for NASH cirrhosis. Pioglitazone is also endowed with some significant adverse effects, e.g., pedal edema ($\leq 27\%$), weight gain (3.0 kg over 36 months), cardiac failure ($\leq 8\%$), bone loss in females. In searching for new drugs for NASH, scientists move their interest and efforts to various molecules, pathways, and receptors. With a search for an ideal pharmacotherapy for NASH, scientists have started exploring molecular receptors and pathways. More than 900 studies have registered in "Clinical trials.gov" to discover new molecules targeting various receptors involving intrahepatic and extrahepatic metabolic, fibrogenesis, and inflammatory pathways.¹² Farnesoid X receptor represents one such target of interest. One of the synthetic ligands of FXR, obeticholic acid, has come out as an emerging molecule for NASH treatment.

Table 1: Regulatory role of FXR ligands in NASH

<i>Metabolism</i>	<i>Inflammation</i>	<i>Liver fibrosis</i>
Decrease lipogenesis	Reduce inflammation	Inhibit hepatic stellate cell activation
Decrease gluconeogenesis	Decrease NF- κ B	Reduce collagen deposition
Increase glucose oxidation	Decrease hepatocyte apoptosis	
Increase glycogen synthesis		
Increase β oxidation of fatty acids		
Increase triglyceride clearance		

FARNESOID X RECEPTORS (FXR) AND ITS ROLE IN NASH

Bile Acid-activated Receptor Superfamily (BAR)

BAR represents a family of cell surfaces and receptors that includes FXR and the G Protein Bile Acid Receptor (GPBAR)-1. Chenodeoxycholic acid is the most potent natural agonist for FXR in humans, followed by cholic acid and deoxycholic acid.¹³ The expression of FXR has been detected in hepatocytes and stellate cells of the liver. It is also expressed on enterocytes of the small intestine and kidney, ovary, and adrenal gland. Farnesoid X receptor is capable of regulating several metabolic, inflammatory, and fibrotic pathways in the liver. This has been shown in Table 1.

Role of FXR in Bile Acid Metabolism

One of the main properties of FXR-induced inhibition of bile acid synthesis by regulating Small Heterodimer Partner (SHP). This includes inhibition of the transcriptional activity of liver-related homolog-1 (LRH-1). This also represses Cyp7a1, a crucial enzyme in bile acid synthesis. Farnesoid X receptor also regulates bile acid concentrations in hepatocytes. The underlying mechanism is related to downregulating of sodium taurocholate cotransporting polypeptide (NTCP) and organic-anion-transporting polypeptide (OATP) and upregulating bile salt export pump (BSEP) multidrug resistance-associated protein 2 (MRP2). The final result is the efflux and secretion of bile acids into the gallbladder and circulation. In this way, FXR the toxic effects of bile acids are prevented.

Excessive accumulation of bile acids is also harmful to the intestines. Farnesoid X receptor inhibits expression of apical sodium-dependent bile salt transporter (ASBT) and upregulates ileal bile acid-binding protein (IBABP), induces expression of basolateral organic solute transporter alpha (OST α) and organic solute transporter beta (OST β). This coordinated regulation reduces the absorption of bile acids to enterocytes. As a totality, the intracellular movement of BA from the apical to the basolateral membrane causing releases of BA to the portal venous system is regulated. Thus, a reduction in the concentration of BA in the intestines is observed.¹³

FXR in Lipid Metabolism

Fatty acid oxidation is regulated via the expression of peroxisome proliferator-activated receptor (PPAR α) and secretion of hepatic fibroblast growth factor 21 (FGF21). Farnesoid X receptor is capable of suppressing the synthesis of triglycerides and fatty acid (FA) as a result of SHP-dependent inhibition of SREBP-1c. This is a positive regulator of genes involved in lipogenesis; acetyl-CoA carboxylase

(ACC), fatty acid synthase (FAS), and stearoyl CoA desaturase (SCD). Lipoprotein metabolism is also controlled by FXR due to upregulating ApoE and phospholipid transfer protein (PLTP). Also, a very low-density lipoprotein receptor (VLDLR) influences the process.

FXR in Carbohydrate Metabolism

The expression of phosphoenolpyruvate carboxykinase (PEPCK) and glucose 6-phosphatase (G6Pase) is inhibited by FXR and increases the phosphorylation of glycogen synthase kinase 3 beta (GSK3 β) in the liver, which increases the activity of glycogen synthase. Along with overexpression of Ark1b7, these molecular pathways ultimately lead to decreased hepatic gluconeogenesis, increased hepatic glycogen synthesis, and decreased plasmatic glucose levels. Farnesoid X receptor inhibits hepatic gluconeogenesis by inducing intestinal fibroblast growth factor 15 (FGF15) in the experimental mice model.¹⁴

Anti-inflammatory Effects of FXR

Monocyte chemoattractant protein-1 (MCP-1) is decreased by FXR ligands. This inhibits the expression of inflammatory mediators activated by nuclear factor- κ B (NF- κ B). Also, reduction of C-reactive protein (CRP) production by interleukin-6 (IL-6) is achieved by this process. Taken together, these events lead to a reduction of hepatic inflammation in NASH.

OBETICHOLIC ACID (OCA)

Obeticholic Acid or 6 α -ethyl-chenodeoxycholic acid represents a semisynthetic entity of the primary human BA chenodeoxycholic acid (CDCA). Both OCA and CDCA are agonists of the FXR. Obeticholic Acid is about 100 times the more potent agonist of FXR.¹⁵

The volume of distribution of OCA is 618 L, with almost all of the compound (>99%) is bound to protein. Obeticholic Acid is conjugated in the liver to glyco- and tauro-obeticholic acid. These metabolites undergo enterohepatic recirculation and are converted to OCA again by intestinal microbiota. This OCA is either reabsorbed or excreted mainly by feces (~87%) and partly by urine (~3%). The peak plasma concentration of OCA is usually reached within ~1.5 hours, although glyco- and tauro-obeticholic acid may take 10 hours to do so.¹⁶

OCA IN PRIMARY BILIARY CHOLANGITIS (PBC)

Obeticholic Acid can directly regulate genes involved in different BA activities. This may be regulated by FXR signalling. As a result, various international guidelines suggested a combination usage of this with ursodeoxycholic acid (UDCA) or as monotherapy in patients with PBC who show inadequate response to UDCA or intolerance to UDCA, respectively.¹⁷ The food and drug administration (FDA) approved OCA for PBC, which is marketed under the trade name "Ocaliva". The detailed discussion of OCA use, indications in PBC are beyond the scope of this review.

MAJOR TRIALS OF OCA IN NASH

OCA turns out to be an appealing pharmacotherapy for clinical trials considering these insulin-sensitizing, anti-steatotic, anti-inflammatory, and anti-fibrotic effects in animal models.

FLINT STUDY

"The Farnesoid X Receptor Ligand Obeticholic Acid in NASH Treatment" (FLINT) study is a 72-week, phase 2b RCT. It enrolled 283 patients with NASH (determined by NAS score ≥ 4 on index biopsy). The fundamental purpose of the study is to compare the effect of OCA 25 mg ($n = 141$) vs placebo ($n = 142$) on hepatic histology in NASH patients without cirrhosis. A minimum 2-point decrease in NAS score and non-deterioration of fibrosis was the primary endpoint of the study. This endpoint was met in more patients on OCA (45%) than placebo (21%) ($p < 0.001$). Also, OCA group (vs placebo) revealed improvements in most of the secondary endpoints, such as HS (61 vs 38%, respectively, $p = 0.001$), lobular inflammation (53 vs 35%, respectively, $p = 0.006$), hepatocellular ballooning (46 vs 31%, respectively, $p = 0.03$) and fibrosis (35 vs 19%, respectively, $p = 0.01$). Furthermore, the OCA group compared to placebo had shown significant improvements in serum ALT, aspartate aminotransferase (AST), and γ -glutamyl transpeptidase (GGT) concentrations ($p < 0.001$ for all). Weight loss was another significant finding in the OCA group (-2.3 kg vs 0.0 in placebo, $p = 0.008$).¹⁸

REGENERATE TRIAL

The REGENERATE trial is an ongoing phase 3 study that included 2,480 subjects NASH (NAS of at least 4) and F2/F3 or F1 fibrosis stage without cirrhosis (F4) with at least one comorbidity. This may be type 2 diabetes mellitus (T2DM), increased body mass index of (BMI) ≥ 30 kg/m², or ALT $> 1.5 \times$ upper limit of normal (ULN). The patients were randomly assigned to a placebo, and two OCA groups (10 and 25 mg). The 18-month interim analysis comprised data on 931 patients who had undergone a repeat liver biopsy. The primary endpoints were set after 18 months. These included improvement of fibrosis by ≥ 1 stage without worsening of NASH or NASH resolution without worsening of fibrosis after 18 months of treatment. After 7 years, the trial will assess the effect of OCA compared to placebo on all-cause mortality and liver-related clinical outcomes.

The fibrosis improvement endpoint was attained at higher rates in patients on OCA 25 mg (23%) or OCA 10 mg (18%) than placebo (12%) ($p = 0.0002$). The NASH resolution endpoint was not met in OCA than the placebo group [12, 11, and 8, respectively, ($p = 0.13$)]. Although the results on clinical outcomes are pending, this interim analysis delineated that OCA 25 mg significantly improved fibrosis and key components of NASH disease activity among patients with NASH.¹⁹

Another phase 3, double-blind, randomized, placebo-controlled, multicenter study named "Study Evaluating the Efficacy and Safety of OCA in Subjects with Compensated Cirrhosis due to NASH" (REVERSE) is ongoing in patients with NASH-related compensated cirrhosis.²⁰

Potential effects of pioglitazone, vitamin E and OCA on different parameters in patients with NASH and comparison of their adverse effects are summarized in Table 2.^{21,22}

ADVERSE EFFECTS OF OCA

The significant adverse effect of OCA is pruritus, which was reported in 23% ($n = 33$) of patients in the FLINT trial compared to 6% ($n = 47$) in placebo. Pruritus is dose-dependent, which was evident from the safety data of the REGENERATE study. In

Table 2: Potential effects of pioglitazone, vitamin E and OCA on different parameters in patients with NASH and comparison of their adverse effects

Clinical, biochemical and histological parameters	Pioglitazone	Vitamin E	OCA
Insulin resistance	Decrease	Unknown	Decrease
ALT	Decrease	Decrease	Decrease
Nonalcoholic fatty liver disease activity (NAS) score	Decrease	Decrease	Decrease
Hepatic steatosis	Decrease	Decrease	Decrease
Hepatic inflammation	Decrease	Decrease	Decrease
Hepatic fibrosis	No decrease in PIVENS trial, but found to have decrease in meta-analysis	No decrease in PIVENS trial, but found to have decrease in meta-analysis	Decrease
Effect on weight	Weight gain	Unknown	Decrease
Use in cirrhosis	Caution	Not recommended	Caution in compensated cirrhosis, Not recommended in advanced cirrhosis
Major adverse effects	Edema, weight gain	Increase all-cause mortality	Pruritus

this study, 28% of patients who received OCA 10 mg developed pruritus; whether in the group of patients receiving 25 mg OCA, more than half (51%) developed pruritus, of whom 9% of patients discontinued the drug.

A significant increase in low density lipoprotein-cholesterol (LDL-C) was reported in both trials. In the REGENERATE trial, 17% (109 in 10 mg group, 115 in 25 mg group) of the OCA treatment groups had increases in LDL that required treatment compared to 7% ($n = 47$) in placebo. Cholelithiasis or cholecystitis were reported in 3% ($n = 19$) of OCA 25 mg group, 1% ($n = 7$) of OCA 10 mg, and <1% ($n = 2$) of placebo over the 18-month duration.²² Moderate and serious adverse events occurred in 49–51% and 11–14% of patients, respectively, higher than placebo.

CAUTION OF OCA USE IN DECOMPENSATED AND ADVANCED CIRRHOSIS

As the post-marketing safety data of OCA use in PBC emerged, FDA issued a black-box warning regarding the risk of hepatic decompensation and failure in patients with PBC with decompensated cirrhosis (Child pugh B and C). FDA restricted the initial, titrated, and maximum dose of OCA to 5 mg once weekly,

5 mg twice weekly, and 10 mg twice weekly respectively in patients with decompensated cirrhosis.

In a recent clinical observation, the authors found 25 cases of severe liver injury leading to liver decompensation or liver failure associated with the use of OCA. Eighteen and seven cases of liver injury occurred in patients with compensated and decompensated cirrhosis, respectively. Two patients from decompensated group died.²³ So, FDA restricted the use of OCA in patients with PBC with advanced liver disease in a drug safety bulletin published on May 26, 2021.²⁴

CONCLUSION

Improvement in NAS and fibrosis have been evolved as primary endpoints in clinical trials in NASH patients. Reduction of hepatic fibrosis in NASH can halt the progression to advanced disease. Fibrosis improvement remains the primary target for drug development in NASH, as evident from few RCTs. OCA is such a promising drug that can reduce and improve various histological, metabolic and biochemical abnormalities in patients with NASH. Although the final analysis report of the REGENERATE trial is still pending, the NASH resolution endpoint was not met despite improvement in fibrosis in higher dosage (25 vs 10 mg daily).

Pruritus and increase in LDL have emerged as two important adverse events in the RCTs. Although these are dose-dependent, we need more prospective studies with different dosage regimens and prolonged follow-up periods to observe the frequency of these adverse effects and the number of drop-outs. More alarming is the risk of developing decompensation, liver failure, and death in patients with advanced liver disease, which lead to dose reduction. Whether improvement in liver fibrosis remains significant using the reduced dosage in patients with advanced liver diseases, needs to be validated in more prospective RCTs. If sustained beneficial effects remain evident in future studies with reasonable adverse effects profiles, OCA may be a future hope for NASH management.

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