First-Stage Biliary Cholangitis with Obeticholic Acid

Elena Brown *

Editorial Office, Journal of Health and Medical Research, Belgium

*Corresponding Author**
Elena Brown
Editorial Office, Journal of Health and Medical Research, Belgium E-mail: medicalres@peerjournal.org

Received: 03-Aug-2022, Manuscript No. JHMR-22-76454; **Editor assigned:** 04-Aug-2022, Pre QC No. JHMR-22-76454 (PQ); **Reviewed:** 17-Aug-2022, QC No. JHMR-22-76454 (Q); **Revised:** 19-Aug-2022, Manuscript No. JHMR-22-76454 (R); **Published:** 27-Aug-2022,doi: 10.37532.jhmr.2022.4(5).125

Abstract

A rare autoimmune cholestatic liver illness called Primary Biliary Cholangitis (PBC) can proceed to fibrosis and/or cirrhosis. There are currently few choices for treatment. Ursodeoxycholic Acid (UDCA), a medication that has been shown to normalize serum markers of liver malfunction, stop the histologic disease from progressing, and extend the time without a transplant, is the first-line treatment for this illness. Unfortunately, 30%-40% of patients do not benefit from this first-line treatment. The sole drug approved for second-line treatment of UDCA nonresponders is Obeticholic Acid (OCA). We describe the mechanism of action, tolerance, and effectiveness of OCA in PBC patients in this review with a focus on its pharmacological characteristics. We also discuss current theories regarding potential treatments for this illness in the future.

Keywords: Primary biliary cholangitis • Obeticholic acid • Ursodeoxycholic acid • Farnesoid X receptor

Introduction

Primary Biliary Cholangitis (PBC) is a chronic condition that can lead to cirrhosis, end-stage liver disease, hepatocellular carcinoma, and even death. It is characterized by the buildup of bile acids in the liver. It has been commonly reported that gender inequalities exist in PBC development. Indeed, girls are more likely than males to develop PBC. With a female: male ratio of 9:1 and 1.76 new cases diagnosed per 100,000 individuals per year, the prevalence in the global population has been observed to be 14.6 instances per 100,000 people. Over the past 30 years, the definition and prognosis of PBC have been reexamined, changing from a severe symptomatic disease characterized by symptoms of portal hypertension to a milder disease with a long natural history due to more meticulous routine testing and/or incompletely understood changes in environmental factors. Many patients are therefore asymptomatic, and the majority of new diagnoses (up to 60%) are made following the identification of elevated serum biochemical indicators of liver function during examinations carried out for unrelated reasons. Over 90% of patients with this autoimmune cholestatic disease had high titers of Antimitochondrial Antibodies (AMAs), a PBC-specific anti-nuclear antibody, and elevated plasma levels of Alkaline Phosphatase (ALP). According to the most recent EASL recommendations, PBC can be diagnosed in adult patients who have cholestasis but no other systemic disorders, have a raised ALP value and have AMAs with a titer >1:40. The gold standard for PBC therapy is Ursodeoxycholic Acid (UDCA), which is typically given orally once a day. In PBC patients, including those with early-stage and advanced disease, as well as in patients who did not satisfy the recognized criteria for UDCA response, UDCA therapy increases Liver Transplantation (LT)-free survival. Patients gain long-term from UDCA treatment in terms of enhanced survival, despite the limited improvement in biochemical indicators.

Nevertheless, non-responders make up about 30%-40% of all UDCA-treated patients and, internationally, are more likely to experience PBC progression, require a transplant, and die earlier than responder patients. An increased risk of biochemical response to UDCA therapy has been linked to the young age at diagnosis and male sex in a large cohort analysis from the UK-PBC study group. As a result, a different sizable, multicenter long-term follow-up research (n=4355) discovered that young PBC patients (aged 45) had considerably lower UDCA response rates than their older counterparts (aged>65). The molecular reasons underlying this clinical finding in UDCA non-responders, however, are still not fully understood.

Therefore, the suggestion of a second-line therapy targeted to UDCA non-responders offers the justification to get over the reported pharmacological efficacy constraints. Obeticholic Acid (OCA) is the only second-line therapy that is now advised for nonresponder PBC patients who are UDCA intolerant or who have not responded to a 12-month course of treatment. Clinical trials have shown that OCA is successful in improving the serum and histology endpoints of PBC patients receiving monotherapy, including the phase III POISE study that is covered in detail below.

Pharmacological actions of OCA

The Farnesoid X Receptor (FXR), a crucial nuclear receptor mostly expressed in the liver and gut, is agonized by OCA, a synthetic derivative of the Bile Acid (BA) chenodeoxycholic acid. The FXR orchestrates complicated signaling pathways related to the homeostasis of Bile Acids (BAs). OCA is an FXR agonist with potency 100 times greater than endogenous BAs, according to in *vitro* pharmacological investigations. Hepatic cholesterol serves as the beginning point for BA production in the liver. Due to their emulsifying properties, BAs are secreted into the gut after being created to aid in digestion and, as a result, the absorption of nutrients, particularly lipids and liposoluble vitamins. About 95% of BAs that are secreted are then reabsorbed from the terminal ileum and enter the enterohepatic circulation. By modulating FXR activation, BAs themselves take part in the carefully calibrated regulation of their synthesis and secretion. The enterohepatic circulation of BAs is compromised in PBC-related cholestasis, resulting in hepatic inflammation and injury.

When activated, the FXR interacts with the retinoid X receptor in a manner akin to that of other nuclear receptors. The Small Heterodimer Partner (SHP) gene is induced by the FXR-RXR heterodimer's binding to DNA-responsive regions, which ultimately leads to the transcriptional suppression of rate-limiting enzymes for BA production like Cytochrome P450 (CYP)7A1 and Liver Receptor Homolog 1 (LRH-1). A transcription factor called LRH-1 plays a crucial role in regulating the balance of BA and cholesterol as well as in coordinating a number of other hepatic metabolic processes. Additionally, FXR promotes the production of Fibroblast Growth Factor-19 (FGF-19), which in turn works with the Fibroblast Growth Factor Receptor-4 (FGFR4) pathway in hepatocytes to suppress the expression of *CYP7A1* and *CYP8B1*. The aforementioned FXR/SHP and FXR/FGF19/FGFR4 pathways are therefore significant negative regulators of BA synthesis. Additionally, FXR suppresses hepatic BA absorption by inhibiting the Sodium Taurocholate Co-Transporting Polypeptide (*NTCP*) via SHP. A second mechanism underlying the anti cholestatic actions of FXR agonists is activated by FXR activation, which enhances the efflux of BAs from the liver to the canalicular lumen by targeting the transporter Bile Salt Export Pump (BSEP) and *Multidrug Resistance Protein-3* (*MDR3*). The organic solute transporters OST and are also expressed more frequently as a result of FXR activation, which improves BA efflux from the liver to the portal vein. It has been established that FXR-mediated signaling has a role in hepatic fibro genesis in addition to its crucial activity as a BA-responsive transcription regulator of BA production and metabolism, however contradictory results have been reported regarding this function. In light of the fact that FXR mutant animals eventually develop liver tumors, fibrosis, and inflammation, it has been shown that OCA-induced FXR activation reduces liver fibrosis in two separate experimental in vivo liver fibrosis models. Depending on the kind of damage, FXR in liver fibrosis models might be either harmful or inconsequential.

Notably, the key cell types responsible for initiating the fibro genesis process, cultured Hepatic Stellate Cells (HSCs), were not directly affected by FXR agonists. By focusing on the stimulation of both Liver Sinusoidal Endothelial Cells (LSECs) and Kupffer cells, OCA had anti-inflammatory and anti-fibrotic effects. OCA specifically decreases the amount of pro-inflammatory cytokines and chemokines (transforming growth factor, connective tissue growth factor, platelet-derived growth factor -receptor, and monocyte chemoattractant protein-1) produced by these two subtypes of sinusoidal cells, which in turn activates HSCs. Therefore, the NF-B signaling pathway is inhibited by upregulating its inhibitor I-B, which forms the basis of the anti-inflammatory action. In conclusion, OCA exerts its effects through a multifaceted method that includes the control of bile acid transport, a decrease in inflammation, and the manipulation of cellular pathways that initiate fibro genesis. OCA exerts more hepatoprotection than UDCA because it induces a signaling pathway that modifies the activity of Fibroblast Growth Factor-19 (*FGF-19*). Additionally, OCA stimulates the expression and release of hormones coming from the gut, such as *FGF-19*. Enterocytes take up and release this hormone into the portal blood, which then travels to the liver via the portal venous system. The above-mentioned anti-cholestatic processes in the liver involve *FGF-19*.

Pre-registration studies

PBC patients were included in a phase II research where OCA was investigated as monotherapy to determine its benefit in the absence of UDCA treatment. Following randomization, patients were given either a placebo (23 patients) or two doses of OCA (10 mg in 20 patients and 50 mg in 16 patients) for 3-months, with a 6-year open-label extension beyond that. The primary outcome of this trial was determined to be the ALP reduction, expressed as a percentage change from the baseline. When compared to the placebo, the therapy with both dosages significantly reduced ALP. Other plasma indicators, such as conjugated bilirubin, GGT, AST, and immunoglobulins, were therefore decreased in OCA-treated patients. In this study, 15% of patients treated with 10 mg and 38% of patients treated with 50 mg of OCA reported experiencing pruritus as a side effect following treatment.

A phase III research that included 216 patients and showed that around 59% of UDCA-non-responders benefited from a 1-year treatment with a combination of OCA and UDCA led to the first approval of OCA. These patients achieved the clinical endpoint, which was defined as an ALP level that was at least 15% lower than baseline and less than 1.67 times the upper limit of the normal range. An open-label extension phase of the research followed, during which 193 enrolled patients were switched to OCA therapy. Following a 3-year interim analysis, the findings revealed that OCA therapy was well tolerated and could be proven to sustain effectiveness over time. A posthoc study also showed that OCA caused a considerable drop in bilirubin, which was especially noticeable in patients with high baseline levels of direct bilirubin. Thus, this data supported the OCA therapy's positive outcomes in high-risk individuals. Additionally, a panel of histologic disease characteristics, including as ductular damage, fibrosis, and collagen morphometry, improved or stabilized in a subgroup of patients (n=17) who underwent histological analysis of liver biopsies at baseline and after 3-year treatment with OCA. Despite the small number of evaluated liver samples, this investigation further proved that OCA is successful in UDCA-non-responders. Pruritus and weariness were the side effects of OCA treatment that were most frequently mentioned, with 77% and 33% of patients, respectively. Only 8% of OCA-treated patients discontinued their medication due to pruritus during the open-label extension phase, and most patients reported mild-to-moderate pruritus. Patients who experienced severe pruritus were treated with a particular drug after consulting a doctor. Overall, the outcomes of this clinical trial show that 3-years of OCA treatment were effective in improving or stabilizing multiple histological characteristics of PBC in the majority of patients with a subpar UDCA response. These findings supported the FDA's 2016 approval of OCA.

Real-world data on OCA

OCA is currently offered in tablets with dosages of 5 mg and 10 mg under the trade name Ocaliva. The usual course of treatment for PBC patients begins with the administration of a starting dose of 5 mg once a day, which may be increased up to a daily maximum of 10 mg. Start with a dose of 5 mg once weekly for patients with advanced cirrhosis (Child-Pugh B or C), and if the medication is well tolerated, increase it to a maximum of 10 mg twice weekly.

In clinical trials, pruritus, tiredness, nausea, and headache have been described as the most important OCA therapy-related adverse events. Depression and hypersensitivity reactions have also been noted in small amounts. If patients are first given a modest dose of medication, which can then be progressively increased, pruritus seems to be less severe. In PBC patients receiving OCA, an increase in total serum lipid levels and a slight decline in High-Density Lipoprotein (HDL) have also been observed as a result of the altered lipid metabolism, which is brought on by other molecular signaling pathways triggered by FXR activation. However, these effects have not yet been linked to a long-term increase in cardiovascular risk. Real-world data are essential for determining treatment efficacy and safety in routine clinical practice, where patient characteristics are more variable in terms of sub-phenotypes, such as cirrhosis and overlap syndrome between PBC and AIH, and the treatment regimen may be less set in stone and more "personalized" by each treating physician. Numerous active post-registration clinical trials are taking patients.

Combined therapy with OCA and fibrates

Because of their well-documented positive effects on inflammation, cholestasis, and fibrosis, which are brought on by their activity as peroxisome Proliferator-Activated Receptor (PPAR) agonists, fibrates, well-known drugs with anti-lipidemic qualities, were suggested as a second-line treatment. The 3 primary PPAR isoforms, PPAR, PPAR/, and PPAR, have varied binding affinities for vertebrates, which enables them to activate various signaling pathways. For instance, the PPAR agonist fenofibrate stimulates the expression of the Multidrug Resistance Protein 3 (MDR3) when it binds to its receptor. Furthermore, it improves an established biomarker of cholestasis by increasing biliary phosphatidylcholine secretion. Bezafibrate functions as a dual agonist of PPAR and PPAR, as well as a PXR agonist.

The first placebo-controlled experiment examining the use of fibrates as a second-line treatment for PBC was the BEZURSO trial, a Phase III study that used bezafibrate in conjunction with UDCA. In this trial, a complete biochemical response could be attained with the help of the second-line combination therapy of bezafibrate and UDCA at a rate that was noticeably greater than that of patients who received UDCA and a placebo. The contemporaneous alleviation of the symptoms and surrogate markers of liver fibrosis was linked to this regression. Increased levels of creatinine, transaminases, and heartburn are the most often reported Adverse Drug Reactions (ADRs) of fibrates. Treatment with clofibrate can result in the development of gallstones and hypercholesterolemia because its primary mechanism of action is a reduction in BA synthesis, two side effects that have not been seen with fenofibrate or bezafibrate. A multicenter retrospective cohort of PBC patients received UDCA, OCA, and fibrates as part of a triple treatment. A regimen of UDCA (13–15 mg/day), OCA (5 mg/day–10 mg/day), and fibrates (200 md/day–400 mg/day of fenofibrate or bezafibrate) was used to treat 58 patients. Comparing this combination to dual therapy, the ALP level was significantly reduced (odds ratio for ALP normalization of 5.5).

Conclusion

The Food and Drug Administration updated its warning in May 2022 to limit the use of OCA in those with advanced cirrhosis. The term "advanced cirrhosis" refers to the presence of present or past signs of liver decompensation or portal hypertension, such as ascites, gastroesophageal varices, or persistent thrombocytopenia. The AASLD subsequently released a useful advice statement. The AASLD noted the FDA's contraindication on decompensated cirrhosis in this statement and also suggested careful monitoring of any patient with cirrhosis, even if it is not progressed, receiving OCA. The starting dose of OCA for suitable patients is 5 mg, and if it is well tolerated after 6 months, the amount can be increased to 10 mg. The AASLD also advises monitoring liver function both before and after starting OCA medication.

In conclusion, OCA represents a comprehensive intervention for the therapeutic management of those PBC patients who cannot be treated successfully with UDCA due to efficacy or safety concerns due to its complex and intriguing mechanism. To fully comprehend its pharmacological and toxicological characteristics, more empirical data are required.

Cite this article: Brown, E. First-Stage Biliary Cholangitis with Obeticholic Acid. J Health Med Res. 2022, 4 (5), 001-002