Obeticholic Acid: A Farnesoid X Receptor Agonist for Primary Biliary Cholangitis

Journal of Pharmacy Technology
2017, Vol. 33(2) 66–71
© The Author(s) 2017
Reprints and permissions:
sagepub.com/journalsPermissions.nav
DOI: 10.1177/8755122516687122
journals.sagepub.com/home/pmt

Susan M. Smith, PharmD, BCPS¹
and Angela H. Pegram, PharmD, BCPS, CDE¹

Abstract

Objective: To review the pharmacology, efficacy, and safety of obeticholic acid (OCA) and determine its clinical role relative to other agents in the treatment of patients with primary biliary cholangitis (PBC). **Data Sources:** A PubMed search (1946 to November 2016) was conducted using the terms *INT-747*, *obeticholic acid*, *OCA*, *farnesoid X receptor agonists*, *FXR agonists*, *primary biliary cirrhosis*, and *primary biliary cholangitis*. **Study Selection and Data Extraction:** Phase II and III studies evaluating the use of OCA in PBC patients were included in this review. **Data Synthesis:** OCA, a farnesoid X receptor (FXR) agonist, is indicated for adult patients with PBC in combination with ursodeoxycholic acid (UDCA) or as monotherapy if unable to tolerate UDCA. Two clinical trials were identified evaluating OCA for the treatment of PBC. Study end points utilized biochemical markers (alkaline phosphatase [ALP] and bilirubin). A phase II study ($n = 165$) to determine efficacy and safety of OCA at 3 different doses (10 mg, 25 mg, 50 mg) demonstrated statistically significant reductions in ALP ($P < .0001$ for all OCA groups versus placebo) after 12 weeks. A phase III trial ($n = 217$) assessed lower OCA doses (5 mg and 10 mg) with a longer study duration (12 months). Statistically significant differences ($P < .001$) between the 5 to 10 mg group (46%) and the 10 mg group (47%) compared to the placebo group (10%) were found. The primary adverse effect reported in both trials was pruritus. **Conclusions:** OCA is the first FXR agonist approved for the treatment of PBC. Ongoing research to evaluate clinical outcomes with OCA is currently underway.

Keywords

obeticholic acid, farnesoid X receptor, FXR agonist, primary biliary cirrhosis, primary biliary cholangitis

Introduction

Primary biliary cirrhosis, now known as primary biliary cholangitis (PBC), is a chronic autoimmune liver disease characterized by progressive destruction and inflammation of intrahepatic bile ducts.^{1,2} This destruction results in intrahepatic cholestasis, parenchymal injury due to bile acids, and eventually end-stage liver disease. The diagnosis of PBC is made on the presence of antimitochondrial antibodies (AMA) and a cholestatic biochemical profile of increased alkaline phosphatase ($ALP > 1.5 \times$ upper limit of normal) with absence of elevated serum aspartate aminotransferase ($AST < 5 \times$ upper limit of normal).³ PBC most commonly occurs in middle-aged women and tends to be closely associated with other autoimmune diseases.⁴ Changes in AMA titers do not predict prognosis or stage of PBC, and immunosuppressive therapy (ustekinumab and abatacept specifically) has not been found to be effective in treatment of the disease.⁵ The etiology of PBC is not understood and no causative agents have been found to date.⁶ Common symptoms of PBC are fatigue and pruritus, which are present in about 20% of patients at diagnosis.⁴

Historically, ursodeoxycholic acid (UDCA), a naturally occurring bile salt, was the only approved therapy for PBC.

However, 40% of PBC patients do not respond to UDCA. Therefore, a large percentage of patients have disease progression to end-stage liver disease.⁷ Many other agents have been trialed in treating this puzzling disease, including colchicine, fibrates, and methotrexate. However, these other therapies have not proven to be effective.^{8–10} Thus, there was a critical need for new pharmacotherapies to treat PBC and prolong survival from this disease. Obeticholic acid (OCA) is a new treatment for PBC that was recently approved by the Food and Drug Administration (FDA).

Data Sources

Clinical trials and review articles were located via literature search of PubMed and Google Scholar (1946 to November 2016). Key search terms included *INT-747*, *obeticholic*

¹Wingate University, Wingate, NC, USA

Corresponding Author:

Susan M. Smith, Wingate University School of Pharmacy, 515 N Main Street, Wingate, NC 28174, USA.
Email: su.smith@wingate.edu

Figure 1. The mechanism of action of OCA: OCA indirectly decreases bile acid synthesis by its action on ileal enterocyte FXRs to induce release of FGF-19, which enters the portal circulation to bind to FGFR-4. The expression of the CYP7A1 gene is inhibited, leading to decreased bile acid synthesis. In the liver, OCA directly stimulates the BSEP to downregulate bile acid uptake in the portal circulation. Abbreviations: ASBT, apical sodium-dependent bile acid transporter; BSEP, bile salt export pump; CYP7A1, cholesterol 7 α -hydroxylase; FGF-19, fibroblast growth factor-19; FGFR-4, fibroblast growth factor receptor-4; FXR, farnesoid X receptor; NTCP, Na⁺-taurocholate cotransporting polypeptide; OCA, obeticholic acid; OST α/β , organic solute transporter α and β .

acid, OCA, farnesoid X receptor agonists, FXR agonists, primary biliary cirrhosis, and primary biliary cholangitis with articles limited to English language. Other data sources included the product labeling of Ocaliva, news releases, and reference lists of pertinent articles to ensure all literature was located. Current ongoing trials using OCA were identified using clinicaltrials.gov.

Pharmacology

OCA is a semisynthetic analog derived from the naturally occurring bile acid chenodeoxycholic acid, the primary human bile acid and a natural ligand for the farnesoid X receptor (FXR).¹¹ FXRs are considered nuclear hormone receptors due to their action in the nucleus of hepatic and intestinal cells where they are predominantly expressed.^{2,11,12} In the enterocyte, FXR activity regulates bile acid synthesis by releasing fibroblast growth factor (FGF-19) into the portal circulation.¹ In the hepatocyte, FXRs are involved in the modulation of hepatic inflammation, fibrosis, metabolic pathways, and regeneration.¹³ By suppressing transcription

of CYP7A1, the enzyme necessary to convert cholesterol to bile acids, FXRs facilitate bile salt secretion through downregulation of the bile salt export pump, thereby promoting alternate routes of bile acid elimination.^{11,14} FXR agonists are important regulators of bile acid metabolism pathways involved in the regulation of hepatic bile acid production and flow.^{11,14}

OCA is a first-in-class agonist that selectively binds to the FXR. OCA works directly and indirectly to suppress bile acid production in the liver and increase bile flow, leading to reduced exposure of the liver to toxic levels of bile acids (Figure 1).^{1,14} These actions should clinically translate into decreased parenchymal liver injury caused by bile acids, resulting in improved biochemical enzyme profiles and decreased disease progression of PBC.¹⁴

Pharmacokinetics

OCA is an oral agent that is rapidly absorbed and reaches a peak plasma concentration 1.5 hours after administration of multiple doses of 10 mg daily. The drug is not affected by

administration of food. The mean volume of distribution is 618 L, and plasma protein binding is approximately 99% for OCA and its conjugates.¹⁵ At this time, it is not known what impact other highly protein bound drugs may have on the pharmacokinetic profile of OCA. Following ingestion, OCA is extensively metabolized by the liver into glycine and taurine via conjugation.^{11,15} Once the conjugates are secreted into the bile and absorbed by the small intestine, they enter into enterohepatic circulation where intestinal microbes deconjugate the metabolites and form OCA, which is then reabsorbed or excreted into the feces.

Clinical Trials

OCA was granted accelerated approval by the FDA on May 27, 2016, for the treatment of primary PBC in adult patients, either in combination with UDCA or as monotherapy when UDCA is not tolerated. Currently, only 2 randomized controlled trials evaluating OCA for the treatment of PBC utilizing biochemical markers such as ALP and bilirubin as predictors of efficacy are published in the clinical literature.¹¹ Trials that assess clinical outcomes have not yet been completed.

Phase II

A phase II randomized, double-blind, placebo-controlled study of patients with PBC was conducted to determine the efficacy and safety of OCA in patients who had an inadequate response to UDCA therapy.¹⁶ This dose-finding trial included 165 patients (95% female, 96% Caucasian) who were randomized 1:1:1:1 to receive OCA for 3 months at daily doses of 10 mg, 25 mg, or 50 mg, or placebo. Patients continued to receive their maintenance dose of UDCA at the approved dose range of 13-15 mg/kg/day. The mean mg/kg/day (standard deviation) doses were on the higher end of the dosing range at 15.9 (4.4), 15.9 (4.1), 15.6 (3.7), and 16.3 (5.2) in the placebo, OCA 10 mg, OCA 25 mg, and OCA 50 mg groups, respectively.¹⁶ The primary outcome was the change in ALP level from baseline to the end of the study.

The baseline demographics and clinical characteristics were not statistically different between the 4 groups. Patients receiving OCA, regardless of dose, demonstrated statistically significant reductions in ALP compared to placebo ($P < .0001$ for all OCA groups vs placebo). On average, ALP decreased 21% to 25% in the OCA groups compared to 3% in the placebo group. Secondary end points included evaluation of biochemical marker levels compared to baseline for liver enzymes (γ -glutamyl transpeptidase [GGT], alanine aminotransferase [ALT], aspartate aminotransferase [AST]), conjugated bilirubin, albumin, lipids (cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides), inflammatory markers (C-reactive

protein [CRP], immunoglobulin M [IgM], complement-4 [C4]), markers of FXR activation (fibroblast growth factor 19 [FGF-19]), and plasma bile acid levels. Significant reductions in GGT, ALT, AST, CRP, and IgM were noted in all treatment groups compared with placebo. Reduction in conjugated bilirubin was seen in all OCA treatment groups compared to a small increase in the placebo group. Significant increases in FGF-19 were seen in the 10 mg and 25 mg OCA groups, while significant reductions in C4 and bile acid levels were noted.

Following the 3-month double-blind study period, 78 patients were enrolled in a 12-month extension study in which ALP levels continued to decrease compared to baseline, thus maintaining the positive results seen in the randomized portion of the trial. The authors concluded that evaluation of biochemical surrogate markers has merit, but studies that evaluate clinical efficacy are needed.

Phase III

The Primary Biliary Cirrhosis Obeticholic Acid International Study of Efficacy (POISE) assessed improvement of 2 biochemical markers—ALP and total bilirubin levels—in patients with PBC.¹⁷ The goal was to assess longer term efficacy and safety of OCA for this disease. This randomized, double-blind, placebo-controlled trial enrolled 217 patients at 59 sites in 13 countries from March 2012 through December 2013.

Inclusion criteria required patients to be ≥ 18 years of age, have a diagnosis of PBC, an ALP level of at least 1.67 times the upper limit of the normal range, or a total bilirubin level of less than 2 times the upper limit of the normal range. Specific exclusion criteria were not described; therefore, it is unknown whether the study population included patients with concomitant chronic conditions.

Patients were randomized 1:1:1 to receive OCA 5 mg once daily with adjustment to 10 mg ($n = 71$) in 6 months, 10 mg once daily ($n = 73$), or placebo ($n = 73$) for 12 months. Concomitant use of oral UDCA (13-15 mg/kg/day) was permitted. Alternatively, patients experiencing unacceptable adverse effects from UDCA could receive OCA as monotherapy (a ≥ 3 -month washout period was required before enrollment).

The primary end point was an ALP level of less than 1.67 times the upper limit of the normal range, with a reduction of at least 15% from baseline, and a total bilirubin level at or below the upper limit of the normal range at 12 months. Secondary end points included levels of ALP, GGT, ALT, AST, total bilirubin, conjugated bilirubin, albumin, prothrombin time (PT), international normalized ratio (INR), plasma bile acid levels, FGF-19, CRP, tumor necrosis factor- α (TNF- α), interleukin-6 level, transforming growth factor- β (TGF- β), cleaved cytokeratin 18 level, and serum autotaxin. Another secondary end point included

assessment of symptoms according to the primary biliary cirrhosis-40 (PBC-40) quality-of-life questionnaire.¹⁸

The authors reported no significant differences among the 3 groups at baseline. The patients exhibited typical demographic characteristics of those who have PBC (91% female, 94% Caucasian, mean age 56 years). The majority of patients (93%) took UDCA at baseline and continued therapy throughout the trial. The presence of pruritus at baseline was reported by 59% of patients.

Patients receiving OCA had a positive response within 2 weeks of therapy that was sustained at each time point throughout the double-blind phase of the trial. A statistically significant difference ($P < .001$) between the 5 to 10 mg group (46%) and the 10 mg group (47%) compared to the placebo group (10%) was found in order to meet the primary end point. ALP showed greater improvement in both OCA groups versus placebo at all visits ($P < .001$), with reductions from baseline of -113 ± 14 U/L in the 5 to 10 mg group and -130 ± 15 U/L in the 10 mg group compared to -14 ± 15 U/L in the placebo group. There was a reduction in total bilirubin in all treatment groups compared to an increase in the placebo group. Statistically significant differences were seen for several of the secondary biochemical marker endpoints (GGT, ALT, AST, conjugated bilirubin, CRP, cleaved cytokeratin 18 level, TNF- α , and serum auto-taxon level), but the clinical significance is unknown. Consistent with FXR activation, plasma bile acid levels significantly decreased, and FGF-19 increased. There were no reported statistical differences between the 2 treatment groups and placebo group from baseline to the end of the study for change in albumin level, PT, INR, interleukin-6, and TGF- β . On the itch domain of the PBC-40 patient questionnaire, scores were significantly worse for the patients receiving OCA when compared to placebo ($P = .005$ at week 2 and $P < .001$ at month 3).

After completion of the 1-year double-blind study, 193 of 198 patients entered a long-term open-label extension phase, which is anticipated to last 5 years. Patients enrolled in this phase of the study were started on OCA 5 mg daily, regardless of their final dose (5 mg or 10 mg) in the double-blind portion of the trial. A dose increase to 10 mg was permitted in 3 months, as opposed to waiting until month 6 as required in the double-blind phase of the study.

An additional trial, Clinical Outcomes with Obeticholic Acid in Liver Treatment (COBALT), is currently enrolling patients.¹⁹ COBALT is a phase IIIb, double-blind, randomized, placebo-controlled, multicenter international study. It is anticipated that 350 patients with primary biliary cirrhosis will be enrolled and subsequently followed over an 8-year period. Patients will be randomized to either OCA 5 mg orally once daily or placebo orally once daily. The dose of OCA may be increased to 10 mg based on clinical judgment and patient tolerability. Primary end points of this study include death, liver transplant, model for end-stage

liver disease (MELD) score ≥ 15 , uncontrolled ascites, hepatocellular carcinoma, and hospitalization for new onset or recurrence of any of the following: variceal bleed, encephalopathy, or spontaneous bacterial peritonitis. Secondary end points include first occurrence of any of the criteria mentioned for the primary end point and changes from baseline of liver biomarkers. It is anticipated that the longer duration of this study will more clearly define clinical outcomes in patients receiving OCA who have more advanced liver disease.

Dosage and Administration

The recommended starting dose of OCA is 5 mg orally with or without food once daily in adult patients who are either intolerant to UDCA or have not achieved an adequate response to an appropriate dose of UDCA for at least 1 year. The dose may be increased to 10 mg orally once daily if the ALP or total bilirubin has not adequately decreased after 3 months of OCA therapy. In patients with hepatic impairment (Child-Pugh B or C), the dose is 5 mg weekly, which may be increased to twice weekly or 10 mg twice weekly depending on clinical response.¹⁵

Adverse Effects

Pruritus is the main side effect reported in OCA clinical trials. A dose-dependent relationship was found in phase II trials, with the incidence of pruritus increasing from 47% to 80% as the dose of OCA increased from 10 to 50 mg. However, it should be noted that the placebo group noted a 50% rate of pruritus.¹⁶ Pruritus is also a symptom of PBC, increasing in frequency over the duration of disease. Thus, it is difficult to distinguish medication adverse effects from disease-induced itching in all patients.¹ Clinical trials define pruritus related to OCA as a change in the characteristic itching from baseline. Although the pruritus was described as severe in 16% to 37% of patients, no discontinuations were noted in the double-blind portion of the phase II trial. However, the open label extension phase of the trial had a 13% discontinuation rate due to pruritus.¹⁶ Phase III trials attempted to address OCA-induced pruritus by using a dose titration arm (dose was dependent on tolerance and liver enzyme changes) and the addition of cholestyramine if needed for itching. Severity of itching decreased in this trial, with none of the placebo group and only 2% of the titration group withdrawing from the trial due to pruritus.¹⁷

High-density lipoprotein (HDL) reduction was observed in a phase II trial after 3 months of OCA therapy, regardless of dose.¹⁶ This effect is beneficial in patients with PBC, as their significant hyperlipidemia is primarily due to increased levels of HDL.¹⁵ Low-density lipoprotein (LDL) and triglyceride levels were unchanged during the 3-month period in a phase II trial.¹⁶ In a phase III trial, total cholesterol and

LDL both increased, but returned to baseline within 2 weeks of stopping OCA therapy.¹⁷ The clinical significance of these lipid changes has not yet been studied but may become important in proper patient selection for this agent.

Other adverse effects noted in clinical trials were fatigue (16% to 25%), abdominal pain (6% to 19%), rash (6% to 10%), clinically significant increases in liver function enzymes and worsening liver-related effects such as jaundice, ascites, or biliary obstruction (<10%).^{16,17}

Drug Interactions

Drug interactions with OCA are based on in vivo and in vitro studies conducted by Intercept Pharmaceuticals, manufacturer of Ocaliva. Three clinically relevant major interactions were found. Bile acid resins may be used to decrease pruritus, but also reduce absorption and efficacy of OCA. It is recommended to separate administration of these 2 agents by 4 hours or more. Warfarin was shown to have an 11% reduction of INR when co-administered with OCA. INR should be monitored and warfarin dosage adjusted to maintain therapeutic levels when given with OCA. CYP1A2 substrates (such as theophylline, caffeine, and tizanidine) have increased plasma AUC and C_{max} when co-administered with OCA. These agents should be carefully monitored; exaggerated responses to single doses may be seen.¹⁵

Clinical Considerations/Place in Therapy

As the only FDA-approved treatment for PBC in the past 20 years, UDCA has been the mainstay of therapy for this chronic condition.^{2,13,17,20,21} Treatment with UDCA improves hepatic biomarkers and delays the requirement for liver transplantation. Unfortunately, lifetime treatment for PBC is necessary, yet a significant percentage of patients either do not achieve a satisfactory clinical response (approximately 40%)¹¹ or do not tolerate UDCA (5% to 10%) due to diarrhea, constipation, or headache.²² The addition of OCA to UDCA has demonstrated a positive benefit in patients who had an inadequate response to UDCA alone, due to distinct yet complementary mechanisms of action. Currently, OCA is not recommended as a first-line agent; it is to be added to UDCA if an inadequate biochemical response is demonstrated after at least 1 year of UDCA therapy.^{15,23} Clinical experience and outcome trials may provide information as to whether OCA can be introduced earlier in the course of PBC and/or administered as first-line therapy.

OCA monotherapy is considered a viable alternative option for patients unable to tolerate UDCA. Although Nevens and colleagues reported that 93% of patients enrolled in the POISE trial received concomitant UDCA and OCA therapy, details on the 7% who received OCA monotherapy were not provided. Therefore, it is unclear

from this trial whether OCA monotherapy led to improvement in biochemical markers. Additionally, strategies for OCA monotherapy initiation are not clearly defined. Initiation of OCA monotherapy appears to occur once UDCA intolerance has been established. In other words, a decision is made to stop UDCA and then initiate OCA monotherapy. It is unclear whether OCA monotherapy resulting from the cessation of UDCA for reasons other than intolerance or lack of efficacy in patients who are taking concomitant therapy is a viable dosing strategy.

The biochemical response assessment is an integral part of the dose titration strategy. In the double-blind portion of the POISE trial, patients were treated with OCA 5 mg daily for 6 months before titration to 10 mg daily. In the open-label extension, a dose increase to 10 mg was permitted at an earlier point in time (at 3 months). Current product labeling also permits an increase to 10 mg if adequate reduction in ALP and/or total bilirubin has not been achieved after 3 months of therapy with 5 mg daily. It remains to be seen whether results of clinical outcome studies will offer guidance on even earlier dose titration.

Other medications that have been studied for use in PBC include colchicine, methotrexate and fibrates. Colchicine has been used in many trials, but has been very inconsistent in showing significant benefits in PBC (range of possibly decreasing mortality by 70% to increasing mortality by 344%).⁸ Bezafibrate shows significant decreases in ALP in clinical trials, but this fibrate is not available in the United States.⁹ Methotrexate trials show no difference in mortality or liver histology in PBC as compared to UDCA or placebo.¹⁰

Pruritus was the most common adverse event related to OCA in phase II and III studies, leading some patients to discontinue therapy. Noncompliance with OCA therapy is a potential concern that may be mitigated by decreasing the dose of OCA to the lowest effective dose. Of the 16 patients in the POISE trial who received OCA monotherapy, it is unknown what percentage of patients experienced pruritus or other adverse effects, or how many discontinued therapy.

Another important factor to consider when deciding the place in therapy of this agent is cost. It is estimated that the annual cost of OCA 5 mg daily or 10 mg daily is approximately \$82 000.²³ The cost of UDCA is variable as dosing is weight-based; however, a reasonable estimate is \$3500 to \$10 000 annually.²² Particularly when added to maintenance regimens of UDCA, the cost of OCA may be prohibitive for many patients with PBC. Financial assistance programs may be available for qualified patients.

Although PBC is a disease primarily of middle-aged Caucasian females, specific dosing recommendations do not exist for geriatric, non-Caucasian, or male patients. Additionally, specific recommendations for patients with concomitant acute or chronic disease states are not available.

Finally, while reductions in surrogate markers of cholestasis such as ALP and bilirubin seen with OCA seem promising, it is unknown whether these reductions translate into improved clinical outcomes.²¹

Summary

OCA is the first FDA-approved FXR agonist that reduces bile acid synthesis and hepatic damage caused by PBC. This new mechanism of action gives an alternative treatment for patients who are unable to tolerate UDCA, or may be used as an additive therapy to decrease ALP and other biochemical markers. Alternative medications to UDCA or OCA have been studied and have not been proven to be beneficial, thus are not recommended in the current American Association for the Study of Liver Diseases Practice guidelines for PBC.²⁰

Currently, OCA is considered second-line therapy at best, and questions regarding optimal dosing strategies and initiation of monotherapy remain unanswered at this time. While OCA has demonstrated efficacy in decreasing biochemical markers indicative of PBC, trials that examine the clinical outcomes of PBC patients treated with OCA over time are needed to fully assess this medication's place in therapy.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Mousa H, Lleo A, Invernizzi P, Bowlus CL, Gershwin ME. Advances in pharmacotherapy for primary biliary cirrhosis. *Expert Opin Pharmacother*. 2015;16:633-643. doi:10.1517/14656566.2015.998650.
2. Beuers U, Trauner M, Jansen P, Poupon R. New paradigms in the treatment of hepatic cholestasis: from UDCA to FXR, PXR and beyond. *J Hepatol*. 2015;62:S25-S37.
3. Zein CO, Angulo P, Lindor KD. When is liver biopsy needed in the diagnosis of primary biliary cirrhosis? *Clin Gastroenterol Hepatol*. 2003;1:89-95.
4. Carey EJ, Ali AH, Lindor KD. Primary biliary cirrhosis. *Lancet*. 2015;386:1565-1575. doi:10.1016/S0140-6736(15)00154-3.
5. Selmi C, Bowlus CL, Gershwin ME, Coppel RL. Primary biliary cirrhosis. *Lancet*. 2011;377:1600-1609. doi:10.1016/S0140-6736(10)61965-4.
6. Gershwin ME, Selmi C, Worman HJ, et al. Risk factors and comorbidities in primary biliary cirrhosis: a controlled interview-based study of 1032 patients. *Hepatology*. 2005;42:1194-1202.
7. Pares A, Caballeria L, Rodes J. Excellent long-term survival in patients with primary biliary cirrhosis and biochemical response to ursodeoxycholic acid. *Gastroenterology*. 2006;130:715-720. doi:10.1053/j.gastro.2005.12.029.
8. Gong Y, Gluud C. Colchicine for primary biliary cirrhosis. *Cochrane Database Syst Rev*. 2004;(2):CD004481. doi:10.1002/14651858.CD004481.pub2.
9. Rudic JS, Poropat G, Krstic MN, Bjelakovic G, Gluud C. Bezafibrate for primary biliary cirrhosis. *Cochrane Database Syst Rev*. 2012;(1):CD009145. doi:10.1002/14651858.CD009145.pub2.
10. Giljaca V, Poropat G, Stimac D, Gluud C. Methotrexate for primary biliary cirrhosis. *Cochrane Database Syst Rev*. 2010;(5):CD004385. doi:10.1002/14651858.CD004385.pub3.
11. Trivedi PJ, Hirschfield GM, Gershwin ME. Obeticholic acid for the treatment of primary biliary cirrhosis. *Expert Rev Clin Pharmacol*. 2016;9:13-26. doi:10.1586/17512433.2015.1092381.
12. Purohit T, Cappell MS. Primary biliary cirrhosis: pathophysiology, clinical presentation and therapy. *World J Hepatol*. 2015;7:926-941. doi:10.4254/wjh.v7.i7.926.
13. Sclair SN, Little E, Levy C. Current concepts in primary biliary cirrhosis and primary sclerosing cholangitis. *Clin Transl Gastroenterol*. 2015;6:e109. doi:10.1038/ctg.2015.33.
14. Ali AH, Carey EJ, Lindor KD. Recent advances in the development of farnesoid X receptor agonists. *Ann Transl Med*. 2015;3:5. doi:10.3978/j.issn.2305-5839.2014.12.06.
15. Obeticholic acid (Ocaliva) [Package insert]. New York, NY: Intercept Pharmaceuticals; 2016 May. https://ocaliva.com/ocaliva_pi.pdf. Accessed September 1, 2016.
16. Hirschfield GM, Mason A, Luketic V, et al. Efficacy of obeticholic acid in patients with primary biliary cirrhosis and inadequate response to ursodeoxycholic acid. *Gastroenterology*. 2015;148:751-761.e8. doi:10.1053/j.gastro.2014.12.005.
17. Nevens F, Andreone P, Mazzella G, et al. A placebo-controlled trial of obeticholic acid in primary biliary cholangitis. *N Engl J Med*. 2016;375:631-643. doi:10.1056/nejmoa1509840.
18. Jacoby A, Rannard A, Buck D, et al. Development, validation, and evaluation of the PBC-40, a disease specific health related quality of life measure for primary biliary cirrhosis. *Gut*. 2005;54:1622-1629. doi:10.1136/gut.2005.065862.
19. Intercept Pharmaceuticals. Phase 3 study of obeticholic acid evaluating clinical outcomes in patients with primary biliary cirrhosis (ClinicalTrials.gov identifier: NCT02308111). <https://clinicaltrials.gov/ct2/show/NCT02308111>. Accessed August 31, 2016.
20. Lindor KD, Gershwin ME, Poupon R, Kaplan M, Bergasa NV, Heathcote EJ. American Association for the Study of Liver Diseases Practice Guidelines: primary biliary cirrhosis. *Hepatology*. 2009;50:291-308.
21. Ali AH, Lindor KD. Obeticholic acid for the treatment of primary biliary cholangitis. *Expert Opin Pharmacother*. 2016;17:1809-1815. doi:10.1080/14656566.2016.1218471.
22. Lexicomp Online, Lexi-Drugs. Ursodeoxycholic acid. Hudson, OH: Lexi-Comp, Inc; Updated August 25, 2016.
23. Lexicomp Online, Lexi-Drugs. Obeticholic acid. Hudson, OH: Lexi-Comp, Inc; Updated May 31, 2016.