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Obeticholic Acid

Updated: December 10, 2019.

OVERVIEW

Introduction

Obeticholic acid (OCA) is a synthetically modified bile acid and potent agonist of the farnesoid X nuclear receptor (FXR) that is used to treat liver diseases including primary biliary cholangitis. Obeticholic acid has not been linked to elevations in serum enzyme levels during therapy, but has been linked to an increased rate of severe liver related adverse events such as ascites, jaundice and liver failure.

Background

Obeticholic (oh bet" i koe' lik) acid is a synthetically modified bile acid that is a potent agonist of the farnesoid X nuclear receptor (FXR), a nuclear receptor with major effects on bile acid synthesis and transport as well as lipid metabolism and glucose homeostasis. Obeticholic acid has been shown to improve serum enzymes in several diseases including nonalcoholic steatohepatitis (NASH) and primary biliary cholangitis (PBC, previously known as primary biliary cirrhosis). Obeticholic acid was given provisional approval for use in the United States for primary biliary cholangitis in 2016 and is currently under evaluation in other liver diseases including primary sclerosing cholangitis (PSC) and nonalcoholic steatohepatitis (NASH). Obeticholic acid is available as tablets of 5 and 10 mg under the brand name Ocaliva. The typical initial dose for primary biliary cholangitis is 5 mg once daily which can then be increased to a maximum of 10 mg daily. Patients with advanced cirrhosis (Child's Class B or C) are advised to start at a dose of 5 mg once weekly and increase thereafter based upon tolerance and effect to a maximum of 10 mg twice weekly. Side effects include pruritus, fatigue, nausea and headache. Symptoms of pruritus appear to be less if therapy is started at a low dose and increased gradually. Less common but potentially severe adverse reactions include hypersensitivity reactions and depression.

Hepatotoxicity

In multiple preregistration clinical trials, obeticholic acid was found to decrease serum enzyme elevations in a high proportion of patients with different liver diseases. Instances of paradoxical worsening of liver disease or further increases in serum ALT or AST were not reported. However, the product label for obeticholic acid includes warnings that serious liver related adverse events occurred more commonly with active therapy than with placebo treatment. In a pooled analysis of 3 placebo controlled trials in patients with primary biliary cholangitis, liver related adverse events were 5.2 per 100 patient exposure years with 10 mg and 2.4 with placebo. Even higher rates occurred with higher doses of obeticholic acid: 19.8 per 100 patient years for 25 mg daily and 54.5 for 50 mg daily. The clinical features, timing of onset, pattern of enzyme elevations and course of these events were not described in detail. Within a little over a year after approval of obeticholic acid as therapy for primary biliary cholangitis, the FDA published a warning letter stating that they had received notification of 19

deaths and 11 cases of severe liver injury in patients taking obeticholic acid, most but not all of whom had preexisting cirrhosis (Case 1). More recently, severe instances of hepatic decompensation have been reported in patients with both primary biliary cholangitis as well as primary sclerosing cholangitis, two similar chronic cholestatic liver diseases.

In patients with normal alkaline phosphatase levels, obeticholic therapy is associated with slight elevations in alkaline phosphatase, but without accompanying changes in serum aminotransferase levels, GGT or bilirubin, suggesting that the increases are due to alkaline phosphatase from other sources (bone, gastrointestinal tract). Therapy with OCA has been associated with development of pruritus in up to one-third of patients, but the appearance or worsening of itching is not usually associated with worsening of the underlying liver disease or increase in bilirubin or bile acid levels (other than OCA). Thus, obeticholic acid has apparent beneficial effects on liver test abnormalities, but has been linked to rare instances of worsening liver disease which may have clinical significance in patients with preexisting cirrhosis, particularly with use of higher doses of OCA.

Likelihood score: B (a rare but potentially severe cause of clinically apparent liver injury occurring mostly in patients with preexisting cirrhosis).

Mechanism of Liver Injury

The mechanism by which obeticholic acid might cause liver injury is unclear as it is a synthetic bile acid that is concentrated in the liver and interacts with the nuclear receptor FXR. Agonism of FXR leads to a decrease in bile acid synthesis and increase in bile acid and bilirubin transporters.

Outcome and Management

Patients on obeticholic acid should be monitored with liver tests, including serum bilirubin, ALT, AST and alkaline phosphatase, during the first few months of therapy to assess both its efficacy and safety. Patients with paradoxical worsening of the liver disease, with persistent worsening of serum enzyme elevations and particularly with evidence of hepatic decompensation, should discontinue obeticholic promptly. There does not appear to be cross sensitivity to liver injury or adverse events between obeticholic and other bile acid therapies such as ursodiol.

Other bile acids used in digestive diseases include chenodeoxycholic acid (chenodiol), cholic acid and ursodeoxycholic acid (ursodiol).

Drug Class: Gastrointestinal Agents, Bile Acids

CASE REPORT

Case 1. Hepatic decompensation during therapy of primary biliary cholangitis with obeticholic acid.(1)

A 59 year old Hispanic woman with primary biliary cholangitis (PBC) developed worsening jaundice and fatigue 3 months after starting obeticholic acid. She was known to have had autoimmune liver disease for at least 9 years and had been treated in the past with prednisone, mycophenolate mofetil, and ursodiol with only a partial response. Liver histology initially suggested an overlap syndrome of autoimmune hepatitis and PBC, but with time clinical features suggested that she had primary biliary cholangitis alone despite the absence of antimitochondrial antibody. On ursodiol, she had minimal symptoms, but laboratory tests showed alkaline phosphatase levels of 569 to 712 U/L, ALT 87 to 109 U/L and bilirubin of 2.3 to 2.7 mg/dL. Liver biopsy histology demonstrated significant fibrosis (stage 3 of 4) and paucity of bile ducts ("ductopenia"). In mid 2016, she was started on obeticholic acid (OCA) in a dose of 5 mg daily while maintaining a dose of ursodiol of 1.2 grams daily. She developed pruritus which responded minimally to cholestyramine and hydroxyzine.

Nevertheless, liver tests improved slightly, with alkaline phosphatase levels decreasing to 372 U/L, ALT to 53 U/L and bilirubin to 2.2 mg/dL (Table). Approximately 3 months after starting OCA, she was found to have worsening jaundice with a bilirubin of 7.6 mg/dL, but with little changes in serum enzymes. Obeticholic acid was stopped while ursodiol was continued. She had no history of previous drug allergies or exposure to viral hepatitis. She did not drink alcohol. She was managed as an outpatient, but serum bilirubin remained elevated and she developed evidence of ascites and mild hepatic encephalopathy. Upper gastrointestinal endoscopy showed small varices. She was treated with lactulose, diuretics, salt restriction and was monitored closely. Over the next six months, her serum bilirubin decreased to pretreatment values, but alkaline phosphatase levels remained high. Approximtely a year after onset, her itching and ascites resolved and she felt that she had returned to her pretreatment clinical status.

Key Points

Medication:	Obeticholic acid (5 mg daily)
Pattern:	Worsening jaundice
Severity:	4+ hepatic decompensation
Latency:	82 days
Recovery:	Incomplete at 6 months
Other medications:	Ursodiol, cholestyramine, hydroxyzine, bacloften, tramadol, alendronate, calcium, vitamin D

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
Pre	Pre	109	712	2.3	Ursodiol 1.2 g/d
• 2 mo	Pre	91	664	2.7	
0	Pre	Obeticholic acid started (5 mg daily)			
2 weeks	Pre	46	431	2.2	Itching
1 month	Pre	50	372	2.2	
2 months	Pre	52	382	2.6	
3 months	0	79	519	7.6	OCA stopped
	9 days	53	551	6.4	Ascites noted
4 months	30 days	51	651	6.2	EGD: Varices
5 months	50 days	83	959	4.2	INR 1.1
6 months	80 days	76	865	3.9	Lactulose started
9 months	6 months	89	743	2.7	
11 months	8 months	69	445	2.6	Itching resolved
14 months	11 months	52	362	2.4	Ascites resolved
Normal Values		**<35**	**<130**	**<1.2**	

Comment

A middle aged woman with primary biliary cholangitis with advanced fibrosis and an inadequate response to ursodiol was started on obeticholic acid shortly after its approval for this indication in the United States. She had an initial slight improvement in liver tests, but then developed jaundice and signs of hepatic decompensation 3 months after having started obeticholic acid. Despite stopping the medication, recovery was slow, and she

returned to her previous status only 8 to 11 months later. Sudden unexplained decompensation of liver disease has been described in several patients with chronic cholestatic liver disease such as primary biliary cholangitis and sclerosing cholangitis within a few weeks to several months after starting obeticholic acid. The cause is unknown, but may be dose related and is most frequent in patients with preexisting cirrhosis or advanced fibrosis. Patients with decompensated cirrhosis should be treated with caution, starting at a dose of 5 mg once weekly and advancing the dose gradually and with regular monitoring. The clinical presentation or phenotype of this injury resembles that of spontaneous hepatic decompensation or what is called "acute-on-chronic liver failure."

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Obeticholic Acid – Ocaliva®

DRUG CLASS

Gastrointestinal Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

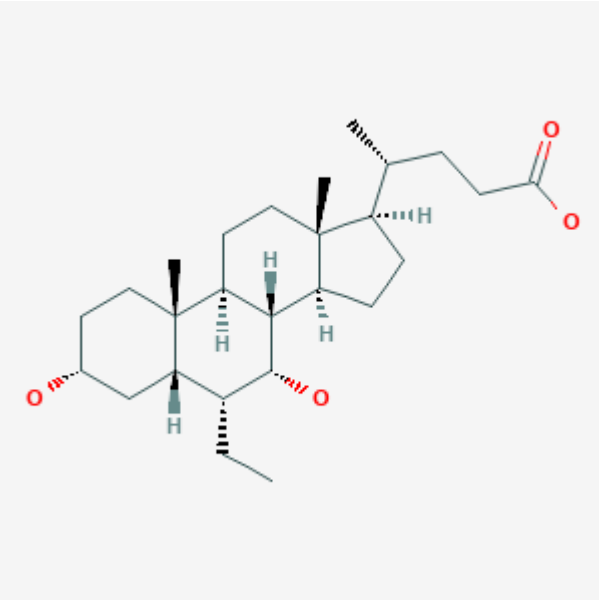
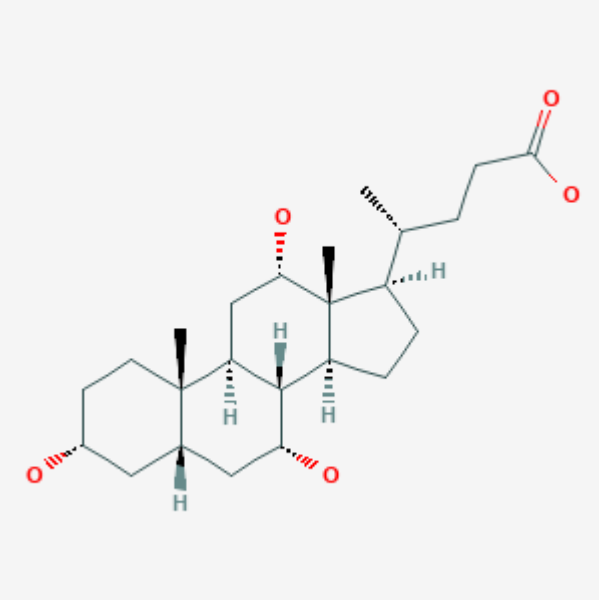
DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Obeticholic Acid	459789-99-2	C26-H44-O4	

Table continued from previous page.

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Cholic Acid	81-25-4	C24-H40-O5	

CITED REFERENCES

1. Data provided by Dr. A. Modi, Liver Consultants of Texas, Baylor Scott & White Medical Center.

ANNOTATED BIBLIOGRAPHY

References updated: 10 December 2019

Abbreviations used: FXR, farnesoid X receptor; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; OCA, obeticholic acid; PBC, primary biliary cirrhosis (cholangitis); PSC, primary sclerosing cholangitis.

Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999.

(Review of hepatotoxicity published in 1999 before the availability of obeticholic acid).

Chabner BA, Barnes J, Neal J, Olson E, Mujagic H, Sequist L, Wilson W, et al. Targeted therapies: tyrosine kinase inhibitors, monoclonal antibodies, and cytokines. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1731-54.

(Textbook of pharmacology and therapeutics).

Chen J, Raymond K. Nuclear receptors, bile-acid detoxification, and cholestasis. Lancet. 2006;367(9509):454–6. PubMed PMID: 16473109.

(Commentary on the nuclear receptor FXR, which acts as a bile acid receptor and mediates reduction in bile acid synthesis and increase in update of bile acids from the circulation as well as secretion of bile acids from hepatocytes).

Cipriani S, Mencarelli A, Palladino G, Fiorucci S. FXR activation reverses insulin resistance and lipid abnormalities and protects against liver steatosis in Zucker(fa/fa) obese rats. J Lipid Res. 2010;51:771–84. PubMed PMID: 19783811.

(In an animal model of obesity and fatty liver, FXR activation using a synthetic bile acid agonist led to less weight gain and reductions in fasting glucose, insulin, triglycerides and ALT levels as well as reduced hepatic fat when compared to placebo).

Mudaliar S, Henry RR, Sanyal AJ, Morrow L, Marschall HU, Kipnes M, Adorini L, et al. Efficacy and safety of the farnesoid X receptor agonist obeticholic acid in patients with type 2 diabetes and nonalcoholic fatty liver disease. Gastroenterology. 2013;145:574–82. PubMed PMID: 23727264.

(Among 64 patients with diabetes and fatty liver treated with OCA [25 or 50 mg] or placebo once daily for 6 weeks, OCA led to increases in insulin sensitivity and reductions in GGT [~50%] and ALT [~25%], but increases in Alk P and LDL cholesterol; 1 patient on placebo and one of OCA [50 mg] had ALT elevations above 3 times ULN and were withdrawn from therapy).

Neuschwander-Tetri BA, Loomba R, Sanyal AJ, Lavine JE, Van Natta ML, Abdelmalek MF, Chalasani N, et al; NASH Clinical Research Network. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis(FLINT): a multicentre, randomised, placebo-controlled trial. Lancet. 2015;385(9972):956–65. PubMed PMID: 25468160.

(Among 141 patients with NASH treated with OCA [25 mg] or placebo daily for 72 weeks, OCA was associated with greater improvements in ALT levels and liver histology, but without a significant increased rate of NASH resolution; pruritus arose in 33% vs 9% of patients, but there was no other evidence of hepatotoxicity or unexplained ALT elevations).

Hirschfield GM, Mason A, Luketic V, Lindor K, Gordon SC, Mayo M, Kowdley KV, et al. Efficacy of obeticholic acid in patients with primary biliary cirrhosis and inadequate response to ursodeoxycholic acid. Gastroenterology. 2015;148:751–61. PubMed PMID: 25500425.

(Among 165 patients with PBC and Alk P elevations despite ursodiol therapy who were treated with OCA [10, 25 or 50 mg] daily for 3 months, Alk P levels decreased more with OCA [20-25%] than placebo [<5%] and mean ALT, AST and conjugated bilirubin levels improved; side effects included pruritus, but no other liver related symptom or blood test result).

Rinella ME. Nonalcoholic fatty liver disease: a systematic review. JAMA. 2015;313:2263–73. PubMed PMID: 26057287.

(Review of the clinical features, epidemiology, risk factors, incidence, natural history, pathogenesis and therapy of NAFLD and NASH; mentions that OCA was found to have beneficial effects on liver histology, but the effect size was small and similar to that of vitamin E).

Fuchs CD, Traussnigg SA, Trauner M. Nuclear receptor modulation for the treatment of nonalcoholic fatty liver disease. Semin Liver Dis. 2016;36:69–86. PubMed PMID: 26870934.

(Review of the possible role of FXR modulation as therapy of fatty liver disease).

Pencek R, Marmon T, Roth JD, Liberman A, Hooshmand-Rad R, Young M. Effects of obeticholic acid on lipoprotein metabolism in healthy volunteers. Diabetes Obes Metab. 2016 Apr 25. Epub ahead of print. PubMed PMID: 27109453.

(Commentary on OCA from the sponsor focusing on effects of OCA in 68 healthy volunteers in two phase 1 trials that showed transient increases in total and LDL cholesterol and decreases in HDL, all of which reversed rapidly on discontinuation; no mention of ALT elevations or hepatotoxicity).

Parés A. Therapy of primary biliary cirrhosis: novel approaches for patients with suboptimal response to ursodeoxycholic acid. Dig Dis. 2015;33 Suppl 2:125–33. PubMed PMID: 26642350.

(Review of current and experimental therapies of PBC including use of OCA; no mention of hepatotoxicity).

Nevens F, Andreone P, Mazzella G, Strasser SI, Bowlus C, Invernizzi P, Drenth JP, et al; POISE Study Group. A placebo-controlled trial of obeticholic acid in primary biliary cholangitis. N Engl J Med. 2016;375:631–43. PubMed PMID: 27532829.

(Among 216 patients with PBC treated with OCA [5 to 10 mg daily] or placebo for 12 months, serum Alk P levels decreased by 35% and 41% with OCA but only by 4% with placebo, while symptoms of pruritus worsened and serious adverse event rates were more common with OCA [15% vs 4%]).

Center for Drug Evaluation and Research. Application 207999Orig1s00. Medical Review. pp: 212-26: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/207999Orig1s000MedR.pdf

(Medical review of clinical trials of obeticholic acid in primary biliary cholangitis; mentions a dose related increased rate of hepatic adverse events with therapy).

Obeticholic acid (Ocaliva) for primary biliary cholangitis. Med Lett Drugs Ther. 2017;59(1517):53–5. PMID. PubMed PMID: 28323811.

(Concise review of the mechanism of action, clinical efficacy and safety of OCA shortly after its approval in the US; mentions common side effects of pruritus, fatigue, abdominal pain, rash and arthralgia, and that pooled analyses of 3 controlled trials showed an increase in liver related adverse events per 100 patient years [from 2.4 with placebo to 5.2 with 10 mg, 19.8 with 25 mg and 54.6 with 50 mg daily]).

Markham A, Keam SJ. Obeticholic Acid: First Global Approval. Drugs. 2016;76:1221–6. PubMed PMID: 27406083.

(Review of the structure, mechanism of action, drug development, clinical efficacy and safety of OCA shortly after its approval as therapy of primary biliary cholangitis; mentions common side effects of pruritus [all degree in 56-68% and severe in 19-23%], fatigue, abdominal discomfort, rash, throat pain and arthralgia and rare instances of ascites or hepatic encephalopathy).

Issa D, Wattacheril J, Sanyal AJ. Treatment options for nonalcoholic steatohepatitis - a safety evaluation. Expert Opin Drug Saf. 2017;16:903–13. PubMed PMID: 28641031.

(Review of the safety of therapies for nonalcoholic steatohepatitis mentions that pruritus is a common dose related side effect of OCA and that rare instances of liver injury have been reported in clinical trials of ursodiol).

Quigley G, Al Ani M, Nadir A. Occurrence of jaundice following simultaneous ursodeoxycholic acid cessation and obeticholic acid initiation. Dig Dis Sci. 2018;63:529–32. PubMed PMID: 29305737.

(55 year old Hispanic woman with cirrhosis due to PBC treated was started on OCA simultaneous with stopping ursodiol and developed jaundice within 4-5 weeks [bilirubin rising from 0.8 to 13.0 mg/dL, ALT 20 to 42 U/L, Alk P 270 to 517 U/L], resolving with stopping OCA and restarting ursodiol and later tolerating reintroduction of OCA without worsening).

Hameed B, Terrault NA, Gill RM, Loomba R, Chalasani N, Hoofnagle JH, Van Natta ML. NASH CRN. Clinical and metabolic effects associated with weight changes and obeticholic acid in non-alcoholic steatohepatitis. Aliment Pharmacol Ther. 2018;47:645–56. PubMed PMID: 29333665.

(A secondary analysis of a randomized control trial of OCA in NASH found that the beneficial effects of weight loss on histology and serum enzyme elevations were additive to those of OCA but that other beneficial effects of weight loss did not occur in OCA treated subjects).

Kowdley KV, Luketic V, Chapman R, Hirschfield GM, Poupon R, Schramm C, Vincent C, et al; Obeticholic Acid PBC Monotherapy Study Group. A randomized trial of obeticholic acid monotherapy in patients with primary biliary cholangitis. Hepatology. 2018;67:1890–902. PubMed PMID: 29023915.

(Among 59 patients with PBC intolerant to ursodiol who were treated with OCA [10 or 50 mg daily] or placebo for 3 months, serum Alk P and GGT improved with OCA but not placebo, but pruritus was common occurring in 70% and 94% of OCA treated vs 35% of placebo recipients; 28 subjects were subsequently treated in an open label extension study and enzyme improvements were sustained while no new hepatic adverse events arose).

Al-Dury S, Wahlström A, Panzitt K, Thorell A, Ståhlman M, Trauner M, Fickert P, et al. Obeticholic acid may increase the risk of gallstone formation in susceptible patients. J Hepatol. 2019;71:986–91. PubMed PMID: 31254596.

(Among 20 patients with gallstones treated with obeticholic acid [25 mg] or placebo daily for 3 weeks before cholecystectomy, OCA was associated with higher FGF-19 and lower C4 and endogenous bile acid levels, resulting in a decreased biliary cholesterol saturation and greater bile acid hydrophobicity index suggesting an increased risk of gallstones with prolonged OCA therapy; gallbladder epithelial cells accounted for the increase in FGF-19 secretion).

Pockros PJ, Fuchs M, Freilich B, Schiff E, Kohli A, Lawitz EJ, Hellstern PA, et al. CONTROL: A randomized phase 2 study of obeticholic acid and atorvastatin on lipoproteins in nonalcoholic steatohepatitis patients. Liver Int. 2019;39:2082–93. PubMed PMID: 31402538.

(Among 84 adults with PBC treated with obeticholic acid [5, 10 or 25 mg] or placebo daily with addition of atorvastatin at week 4, serum LDL cholesterol increased with OCA treatment but levels fell to below baseline after addition of atorvastatin, while pruritus arose in 35% of those on 25 mg daily and one patient with cirrhosis on this dose died of multiorgan failure during the open label extension phase).

Bowlus CL, Pockros PJ, Kremer AE, Parés A, Forman LM, Drenth JPH, Ryder SD, et al. Long-term obeticholic acid therapy improves histological endpoints in patients with primary biliary cholangitis. Clin Gastroenterol Hepatol. 2019 Oct 10. Epub ahead of print. PubMed PMID: 31606455.

(Among 17 patients with PBC receiving ursodiol and OCA for 2-3 years while participating in an open label extension study of a randomized controlled trial [Trauner 2019], fibrosis stages worsened in 5 patients, were unchanged in 10 and improved in 2, although serum enzyme levels showed sustained improvement compared to baseline).

Trauner M, Nevens F, Shiffman ML, Drenth JPH, Bowlus CL, Vargas V, Andreone P, et al. Long-term efficacy and safety of obeticholic acid for patients with primary biliary cholangitis: 3-year results of an international open-label extension study. Lancet Gastroenterol Hepatol. 2019;4:445–53. PubMed PMID: 30922873.

(Among 193 patients with PBC entered into an open label extension study after a 48 week randomized controlled trial of OCA [Nevens 2016], serum enzyme improvements were sustained for up to 4 years and bilirubin levels were stable, although pruritus remained common [77%] and esophageal varices developed in 5% and ascites in 4%, but no patient died due to liver disease).

Eaton JE, Vuppalanchi R, Reddy R, Sathapathy S, Ali B, Kamath PS. Liver injury in patients with cholestatic liver disease treated with obeticholic acid. Hepatology. 2019. Epub ahead of print. PubMed PMID: 31680292.

(Case series of 8 patients, 4 each with PBC or PSC, who developed hepatic decompensation while on OCA treatment, four undergoing liver transplantation, the remaining improving slowly after stopping OCA).